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# Long-term safety and efficacy of high efficacy disease-modifying therapies in multiple sclerosis patients

Maya Zeineddine

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**Université de Limoges**

**ED 652 - Biologie, Chimie, Santé (BCS)**

U1094 Inserm U270 IRD EpiMaCT Épidémiologie des maladies chroniques en zone tropicale

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**Docteur de l'Université de Limoges**  
Santé Publique, Epidémiologie et Prévention

Présentée et soutenue par  
**Maya Zeineddine**

Le 2 décembre 2024

**Long-term Safety and Efficacy of High Efficacy Disease-Modifying Therapies in Multiple Sclerosis Patients**

Thèse dirigée par Farid BOUMEDIENE et Amal AI-HAJJE

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## **Dedication**

*To my beloved father, whose memory continues to inspire me every day.*

*To my mother, for her endless love and strength.*

*To my brother and sister, for their unwavering support.*

*To my husband, for his boundless encouragement.*

*And to my two boys, for being my greatest motivation and joy.*

*And to my beloved Lebanon, a country that has faced unimaginable hardships—from economic crisis and the COVID-19 pandemic to the Beirut port explosion and recent war in the South. Despite these challenges, the resilience and strength of my homeland have been a constant source of inspiration throughout this journey.*

*This work is as much yours as it is mine.*

***"The important thing is not to stop questioning. Curiosity has its own reason for existing."***

*— Albert Einstein*



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---

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I dedicate this work to the memory of my father, who passed away four years ago. His encouragement to pursue this PhD and his faith in my abilities were the foundations of my success. Every step I have taken in my academic and professional career has been influenced by his love, wisdom, and belief in me. I know he would be proud, and I am forever indebted to him for all that he has given me.

To my mother, whose unwavering love and support have been my constant source of strength. Her sacrifices, patience, and boundless encouragement have allowed me to chase my dreams with confidence. I owe much of this achievement to her nurturing care and belief in me, and for that, I am forever grateful.

Lastly, I wish to thank my family and friends, whose constant support and encouragement have carried me through the many challenges of this journey. Your love, understanding, and faith in me made this accomplishment possible, and I am blessed to have you all by my side.

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## Abbreviations

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ADL - Activities of Daily Living

AHSCT - Autologous Hematopoietic Stem Cell Transplantation

AI - Antibody Index

ARR - Annualized Relapse Rate

AUB - American University of Beirut

BBB - Blood-Brain Barrier

BMI - Body Mass Index

C - Concordance

CDP - Confirmed Disability Progression

CIS - Clinically Isolated Syndrome

CNS - Central Nervous System

COP – Coping

COVID-19 - Coronavirus Disease 2019

CSF - Cerebrospinal Fluid

CT - Computed Tomography

CVD - Cardiovascular Disease

DHOD - Dihydroorotate Dehydrogenase

DIS - Dissemination in Space

DIT - Dissemination in Time

DNA - Deoxyribonucleic Acid

DM - Diabetes Mellitus

DMT - Disease-Modifying Therapy

DMF - Dimethyl Fumarate

EBV - Epstein-Barr Virus

ECTRIMS - European Committee for Treatment and Research in Multiple Sclerosis

EDSS - Expanded Disability Status Scale

EMA - European Medicines Agency

FDA - Food and Drug Administration

Gd+ - Gadolinium Enhancing Lesions

GA - Glatiramer Acetate

HLA - Human Leukocyte Antigen

HRQOL - Health-Related Quality of Life

HTN - Hypertension

ICU - Intensive Care Unit

IFN - Interferon Beta  
IM - Intramuscular  
IRB - Institutional Review Board  
IVIG - Intravenous Immunoglobulin  
IVMP - Intravenous Methylprednisolone  
JCV - John Cunningham Virus  
KSA - Kingdom of Saudi Arabia  
LMP1 - Latent Membrane Protein 1  
LMICs - Low- and Middle-Income Countries  
MBP - Myelin Basic Protein

MENACTRIMS - Middle East and North Africa Committee for Treatment and Research in Multiple Sclerosis

MENA - Middle East and North Africa

MMPs - Matrix Metalloproteinases

MRI - Magnetic Resonance Imaging

MS - Multiple Sclerosis

MSIF - Multiple Sclerosis International Federation

MusiQoL - Multiple Sclerosis International Quality of Life Questionnaire

NEDA - No Evidence of Disease Activity

NTZ - Natalizumab

OCB - Oligoclonal Bands

OCR - Ocrelizumab

PML - Progressive Multifocal Leukoencephalopathy

PMS - Progressive Multiple Sclerosis

PI - Principal Investigator

PEG – Pegylated

PWB - Psychological Wellbeing Index

PwMS - People with Multiple Sclerosis

QOL - Quality of Life

RCTs - Randomized Controlled Trials

REJ – Rejection

RFa - Relationships with Family

Rfr - Relationships with Friends

RHCS - Relationships with Health Care System

RIS - Radiologically Isolated Syndrome

ROC - Receiver Operating Characteristic

RR – Relative Risk  
RRMS - Relapsing-Remitting Multiple Sclerosis  
RTX - Rituximab  
SARS-CoV-2 - Severe Acute Respiratory Syndrome Coronavirus 2  
SC - Subcutaneous  
SD - Standard Deviation  
S1PR - Sphingosine-1-Phosphate Receptor  
SPMS - Secondary Progressive Multiple Sclerosis  
SPT – Symptoms  
SSL - Sentimental and Sexual Life  
TNF – Tumor Necrosis Factor  
USA - United States of America  
UAE - United Arab Emirates  
VCAM-1 - Vascular Cell Adhesion Molecule 1  
WHO - World Health Organization

## Chapter I. Introduction

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### I.1. Multiple Sclerosis Definition

Multiple sclerosis (MS) is an inflammatory, autoimmune disease of the central nervous system, is the leading cause of disability in young adults, aside from trauma<sup>1</sup>. It attacks the myelinated axons in the CNS, destroying the myelin and the axons to varying degrees<sup>2</sup>. The course of MS is highly varied and unpredictable. In most patients, the disease is characterized initially by episodes of reversible neurological deficits, which is often followed by progressive neurological deterioration over time<sup>3</sup>.

### I.2. Immunopathogenesis

The pathogenesis of MS involves complex interactions between genetic, environmental, and immunological factors. Traditionally, MS was regarded as a condition primarily driven by activated T cells, with emerging evidence indicating a significant role played by B cells. The immune assault begins with the peripheral activation of auto-reactive T cells following a breakdown in self-tolerance towards myelin and other CNS antigens<sup>4</sup>. This breach could be triggered by an environmental antigen, such as a virus, resulting in the bystander activation of T cells, or by a cross-reactivity between an endogenous protein, like myelin basic protein, and a pathogenic exogenous protein, a phenomenon known as molecular mimicry<sup>5</sup>. Subsequently, auto-reactive T cells migrate across the blood-brain barrier<sup>6</sup>, facilitated by the expression and upregulation of various adhesion molecules, chemokines, and matrix metalloproteinases (MMPs)<sup>7</sup>. Upon entering the CNS, these auto-reactive T cells can be reactivated by local antigen-presenting cells (such as dendritic cells, macrophages, and B cells), triggering an inflammatory cascade characterized by the release of cytokines and chemokines<sup>7</sup>. This cascade leads to the recruitment of additional inflammatory cells, including T cells, monocytes, and B cells, and persistent activation of macrophages, resulting in loss of oligodendrocytes and myelin damage<sup>4</sup>. Epitope spreading occurs as a consequence of ongoing local inflammation, exposing additional targets for reactive T cells<sup>8</sup>. Additionally, axonal injury may occur during the early inflammatory stages or when repair mechanisms are overwhelmed by persistent activation of microglia/macrophages and complements, as well as the indirect effects of proinflammatory cytokines such as tumor necrosis factor (TNF)- $\alpha$ , nitric oxide, and MMPs<sup>4, 9</sup>.

Although B cells and antibodies have historically been ignored in MS research, intrathecal synthesis of oligoclonal immunoglobulins has long been recognized<sup>10</sup>. Clonal B cell proliferation has been observed both within the CNS and peripherally<sup>10</sup>. The identification of ectopic B cell follicles in the meninges of secondary progressive MS (SPMS) patients was an

early indication of B cell involvement in MS, suggesting sustained meningeal inflammation, particularly in progressive stages. This supports the hypothesis that cytotoxic factors diffusing from the meningeal compartment contribute to subpial cortical lesions (cortical demyelination) and subsequent increases in clinical disability<sup>11, 12</sup>. The role of B cells in MS pathogenesis is further supported by the success of B-cells depleting therapies<sup>13</sup>.

While demyelination stands as the primary feature of MS pathology, early axonal injury and subsequent loss also play a role in driving disability progression<sup>9</sup>. The precise mechanisms underlying both myelin and axonal damage remain incompletely understood, but are likely multifaceted, involving direct harm to myelin and oligodendrocytes, as well as axons by CD4+ and CD8+ T lymphocytes, activated microglia/macrophages, and/or antibodies and complement proteins. Additionally, indirect effects of proinflammatory cytokines such as IL-1beta, TNF- $\alpha$ , nitric oxide, and MMPs contribute to the pathology<sup>4, 12, 14</sup>. Meningeal inflammatory infiltrates observed in conjunction with subpial cortical lesions may also contribute to cortical inflammation and subsequent disability in certain cases<sup>15, 16</sup>.

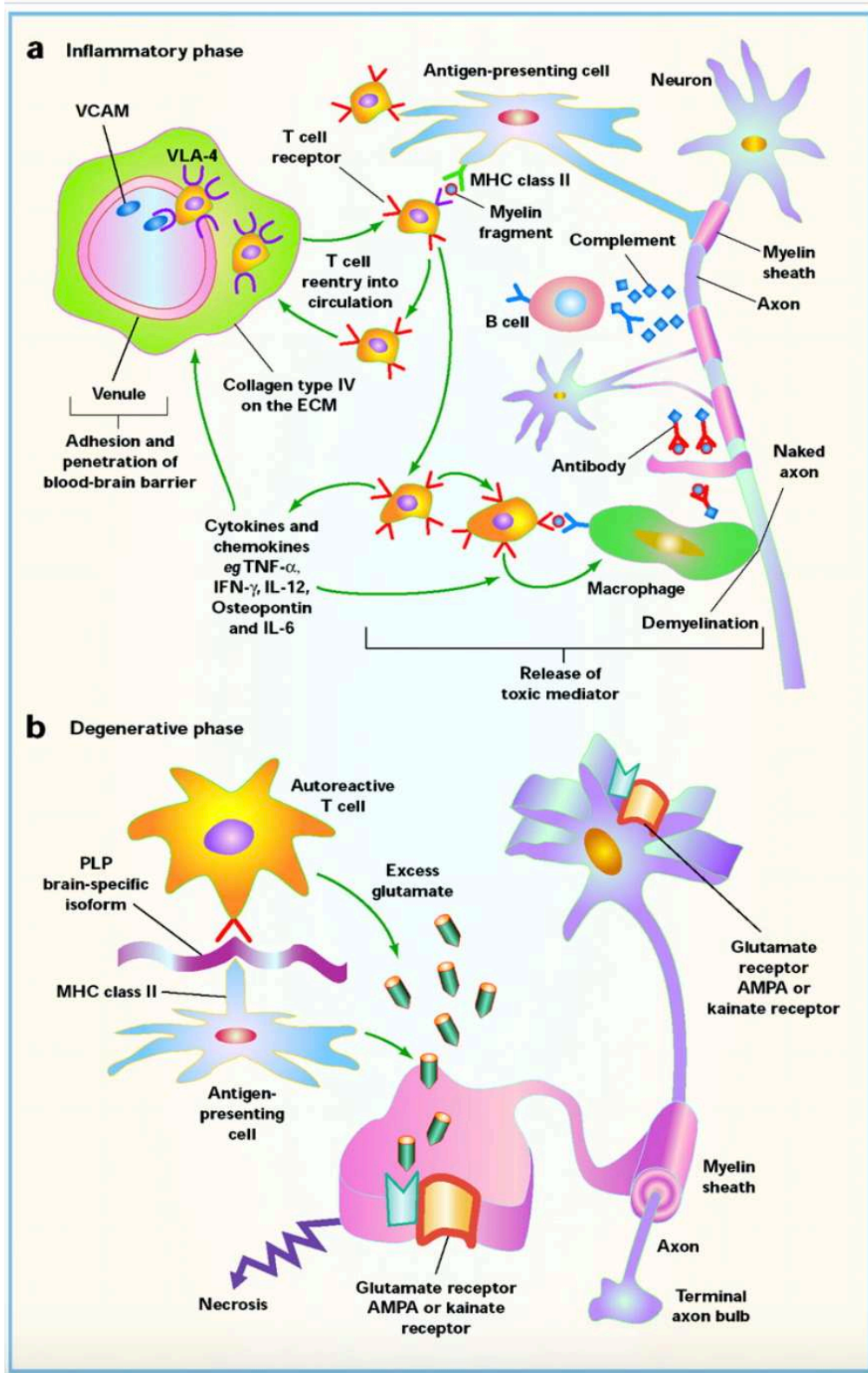


Image Adapted from Fox E et al. *Neurology* 63 (12): S3-S7. [https://doi.org/10.1212/WNL.63.12\\_suppl\\_6.S3](https://doi.org/10.1212/WNL.63.12_suppl_6.S3)

**Figure 1. Immunopathology of Multiple Sclerosis**

### **I.3. Etiology and Risk Factors**

The pathogenesis of MS presents a complex interplay of various factors, yet much of it remains unknown. While multiple risk factors have been identified, including geographical location, serum vitamin D levels, genetic predispositions, and viral infections, no single factor can fully account for the development of MS, indicating a multifaceted pathogenesis<sup>17</sup>.

#### **I.3.1. Genetic Factors**

While MS is not considered a hereditary condition, there is evidence of familial aggregation. The lifetime risk for first-degree relatives is notably higher than that of the general population, standing at 2.5%<sup>18</sup>. Twin studies have revealed interesting patterns, with the risk of MS for dizygotic twin pairs mirroring that of siblings, ranging from 3% to 5%, while monozygotic twins exhibit a substantially higher risk, estimated to be at least 20%<sup>19</sup>. Despite the identification of over 100 genetic variations associated with MS in various studies, the human leukocyte antigen (HLA) class II region, particularly the HLADRB1\*1501 allele on chromosome 6p21, stands out as strongly linked to MS risk<sup>20</sup>. The expansion of genome-wide association studies has further expanded our understanding, uncovering more than 20 additional risk loci and highlighting the significance of even modest genetic effects in increasing susceptibility to the disease<sup>21</sup>. Moreover, epigenetic modifications, such as alterations in deoxyribonucleic acid (DNA) methylation, have been linked to changes in gene expression associated with MS pathogenesis<sup>22</sup>.

#### **I.3.2. Environmental Factors**

Environmental factors including sex, viral infections, tobacco smoking, sunlight exposure, and vitamin D deficiency emerge as significant contributors to MS risk. Furthermore, factors such as childhood or adolescent obesity and gut microbium have been suggested as potential environmental influences for MS development. However, further investigation is required to elucidate the precise mechanisms underlying their interactions with the immune system in individuals with MS<sup>23-25</sup>.

##### **I.3.2.1. Sex**

MS is more common in women than men with a reported ratio of 3:1, suggesting that sex of the patient significantly influences the risk of developing the disease<sup>26</sup>. Moreover, factors such as puberty, especially early onset of menarche, contribute to the susceptibility to MS diagnosis<sup>27</sup>. However, it is unknown whether this is due to an increase in the levels of sex hormone. On the other hand, there is evidence suggesting that female sex hormones may exacerbate the progression of the disease. This hypothesis is supported by research showing improvement of MS symptoms during pregnancy<sup>28</sup> and a reduction in disability levels among pregnant women with MS<sup>29</sup>.



While female sex appears to be a contributing risk factor, robust evidence confirming a direct link between sex hormones and the onset of MS pathogenesis remains lacking<sup>26</sup>. Thus, sex is considered as a contributing factor to the development of MS in combination with other risk factors. This assumption is supported by the results of Irizar et al. study which demonstrated an association between female sex and the HLA-DRB115:01 haplotype<sup>30</sup>. Additionally, Chao et al. illustrated that the combination of HLA-DRB115:01, a well-established MS risk factor, with female sex is more likely to be transmitted from mother to daughter than to son<sup>31</sup>.

Female sex hormones have been shown to modulate the immune response by promoting the development of regulatory T cells (Tregs), reducing the activity of Th1 and Th17 cells, and supporting the differentiation of Th2 lymphocytes<sup>32</sup>. The anti-inflammatory effects of estrogens have also been confirmed using experimental autoimmune encephalomyelitis (EAE), an animal model of MS<sup>33, 34</sup>.

### **1.3.2.2. Viral Infections**

The role of viral infection as a risk factor for MS has been extensively studied and supported by epidemiological evidence. Notably, individuals infected with Epstein-Barr virus (EBV) and diagnosed with infectious mononucleosis have shown a higher risk of developing MS<sup>35</sup>. Seropositivity for EBV antibodies, indicating prior exposure, consistently correlates with MS onset across different demographics<sup>36</sup>.

A study conducted by Bjornevik et al. in 2022 provided compelling evidence of a causal relationship between EBV infection and MS<sup>37</sup>. Analyzing over 10 million young adults in the US military, the study identified 955 individuals diagnosed with MS during their service period. The risk of MS increased 32-fold following EBV infection, with no change observed after infection with other viruses. Serum levels of neurofilament light chain, indicative of nerve degeneration in MS, rose only after EBV infection. These findings suggest that EBV may be the primary cause of MS, as they cannot be attributed to any known MS risk factors. However, the exact mechanisms by which EBV contributes to MS pathogenesis remain largely unknown. It is theorized that EBV may inhibit the production of antiviral cytokines and proteins, interfere with antigen processing and presentation, and stimulate the production of autoreactive immune cells<sup>38, 39</sup>. Evidence of cross-reactivity between antibodies targeting myelin basic protein (MBP) and EBV latent membrane protein 1 (LMP1) suggests a potential link between EBV and MS<sup>40</sup>. This cross-reactivity is attributed to the homology between MBP and LMP1, with further support for the role of LMP1 in MS pathogenesis demonstrated by its ability to induce myelin-reactive antibodies *in vivo*<sup>40</sup>. The compelling evidence implicating EBV in MS underscores the need for

further research to elucidate the precise mechanisms and explore potential preventive or therapeutic interventions.

### **I.3.2.3. Smoking**

Smoking has been consistently identified as a risk factor for MS across various studies. Research by Manouchehrinia et al. found that "ever-smokers" had a 41% higher likelihood of MS diagnosis compared to "never smokers"<sup>41</sup>. This habit impacts the immune system by inducing oxidative stress, releasing pro-inflammatory cytokines, and increasing nitric oxide levels<sup>42</sup>. Furthermore, smoking influences the differentiation and activation of lymphocyte populations, promoting the development of auto-aggressive T cells that cross-react with central nervous system antigens in MS<sup>42, 43</sup>.

The association between smoking and MS risk extends beyond individual studies. Population-based research, such as that by Hedström et al., has demonstrated a higher incidence of MS among smokers, with both duration and intensity of smoking correlating with increased risk<sup>44</sup>. Smokers are 1.5 times more likely to develop MS, and even passive smokers face a heightened risk compared to non-smokers<sup>45</sup>. The precise mechanism linking smoking to MS remains uncertain, but it likely involves the multitude of toxic substances found in cigarette smoke, including nicotine and nitric oxide. These substances may irritate lung tissue, triggering a pro-inflammatory response via Toll-like receptors<sup>45</sup>. Moreover, smoking-associated damage to the blood-brain barrier facilitates the entry of T cells into the brain, where they target myelin, leading to its destruction and subsequent autoimmune responses against nervous system antigens<sup>45</sup>. Overall, smoking contributes to MS pathogenesis through a combination of inflammatory processes, barrier disruption, and autoimmune mechanisms.

### **I.3.2.4. Vitamin D deficiency**

Serum vitamin D levels are among the extensively documented risk factors associated with MS. Vitamin D is believed to exert a protective effect on MS owing to its immunomodulatory role within the CNS<sup>46</sup>. It exhibits anti-inflammatory properties by suppressing macrophage activity and modulating cytokine levels. Additionally, vitamin D plays a role in safeguarding myelin integrity by stimulating oligodendrocytes and influencing the behavior of T lymphocytes. Numerous studies have established an inverse correlation between sun exposure<sup>47</sup>, ultraviolet radiation exposure<sup>48</sup>, or serum vitamin D levels<sup>49</sup>, and the risk or prevalence of MS. Conversely, some studies<sup>50, 51</sup> have indicated that these factors are inversely associated with disease activity in individuals already diagnosed with MS.

### **I.3.2.5. Childhood Obesity**

Obesity has recently emerged as a risk factor for MS. Studies<sup>52, 53</sup> have indicated that childhood obesity increases the likelihood of MS diagnosis, with a higher body mass index (BMI) correlating with elevated odds ratios for MS diagnosis, particularly in extremely obese individuals. Interestingly, this association appears to be more pronounced in girls than in boys<sup>54</sup>. Moreover, while adolescence is also identified as a critical period where obesity heightens MS risk, its impact during childhood versus adolescence may vary depending on the metrics used to assess obesity<sup>54</sup>.

Obese individuals commonly exhibit chronic inflammation, characterized by elevated levels of inflammatory cytokines such as IFN- $\gamma$  and TNF- $\alpha$ <sup>55</sup>. This inflammatory state may be exacerbated by disruptions in the gut microbiome, frequently observed in obese individuals, which can skew the balance between regulatory T cells (Tregs) and pathogenic Th17 cells. This imbalance in turn has implications for MS pathogenesis, as Th17 cells have been implicated in the development of the disease.

Furthermore, obesity is associated with lower levels of vitamin D, another established risk factor for MS<sup>54</sup>. Collectively, these findings suggest that the increased risk of MS associated with obesity may arise from a combination of factors, including chronic inflammation, Th17 cell activation, and decreased vitamin D levels induced by obesity.

### **I.3.2.6. Gut Microbiome**

The gut microbiome plays a significant role in modulating both innate and adaptive immune responses, potentially influencing the pathogenesis of immune-mediated disorders like MS. Several studies<sup>56-58</sup> have demonstrated alterations in the microbiome composition in MS patients, with these changes linked to disease activity and progression. Different forms of MS exhibit distinct microbial profiles, with reductions in beneficial short-chain fatty acid-producing bacteria observed in relapsing-remitting MS (RRMS) and an increase in bacteria associated with DNA oxidation in SPMS<sup>57</sup>.

These alterations in the gut microbiome have been shown to impact lymphocyte activation and differentiation<sup>59</sup>. For instance, MS-associated microbiota can hinder the interaction between specific immune cell receptors, leading to a reduction in circulating CD4+ T cells. Moreover, an imbalance in certain bacterial ratios, such as *Firmicutes/Bacteroidetes*, correlates with increased disease activity, likely mediated by heightened Th17 cell frequency. Conversely, the depletion of beneficial bacterial species, such as *Clostridia*, has been observed in primary progressive MS (PPMS), potentially contributing to disease pathogenesis<sup>60</sup>.

Experimental studies using MS models have highlighted the therapeutic potential of short-chain fatty acids derived from gut bacteria in promoting the development of Tregs, which can suppress autoimmune responses<sup>6,60</sup>. Dysbiosis, characterized by specific alterations in microbial species, including increased *Methanobrevibacter* and *Akkermansia* coupled with decreased *Butyricimonas*, has been linked to MS pathogenesis, with certain species implicated in promoting inflammation and exacerbating disease activity<sup>61</sup>.

In summary, MS is characterized by dysregulation of the gut microbiome, which may lead to a reduction in Tregs and the promotion of pathogenic Th17 lymphocytes, ultimately contributing to inflammation and disease progression.

#### **I.4. Epidemiology of MS**

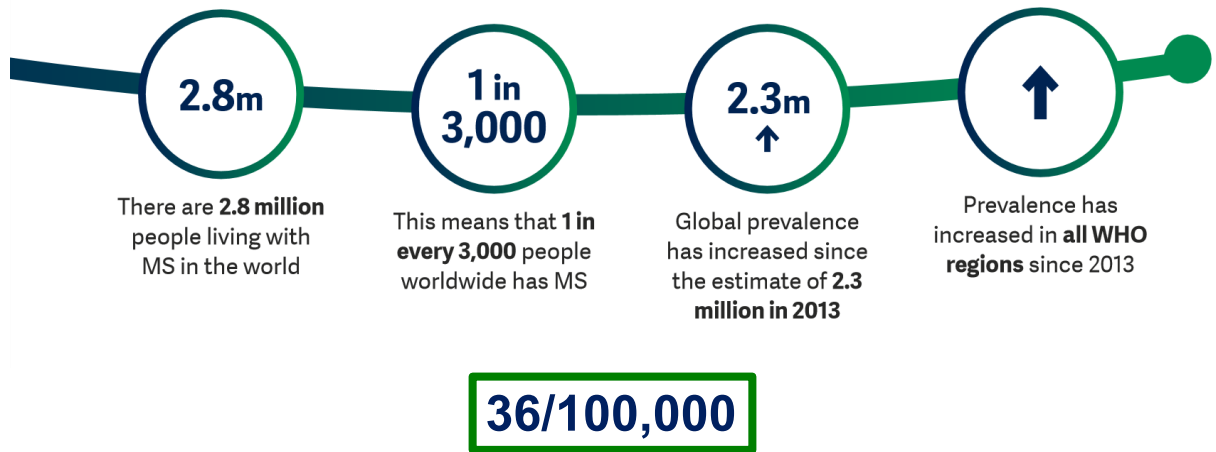
The global epidemiology of MS is undergoing shifts, alongside evolving insights into its immunopathogenesis and natural progression. Recent evidence suggests a complex origin involving a combination of environmental and genetic factors<sup>62</sup>.

##### **I.4.1. Global Epidemiology**

Review of recent medical literature and meta-regression analyses has uncovered a global increase in both the prevalence and incidence rates of MS in the past few decades. According to the most recent Atlas released by the Multiple Sclerosis International Federation (MSIF) in 2020, the estimated number of individuals affected by MS has risen by 9.5% between 2013 and 2020, reaching 2.8 million worldwide<sup>63</sup>.

## Main findings

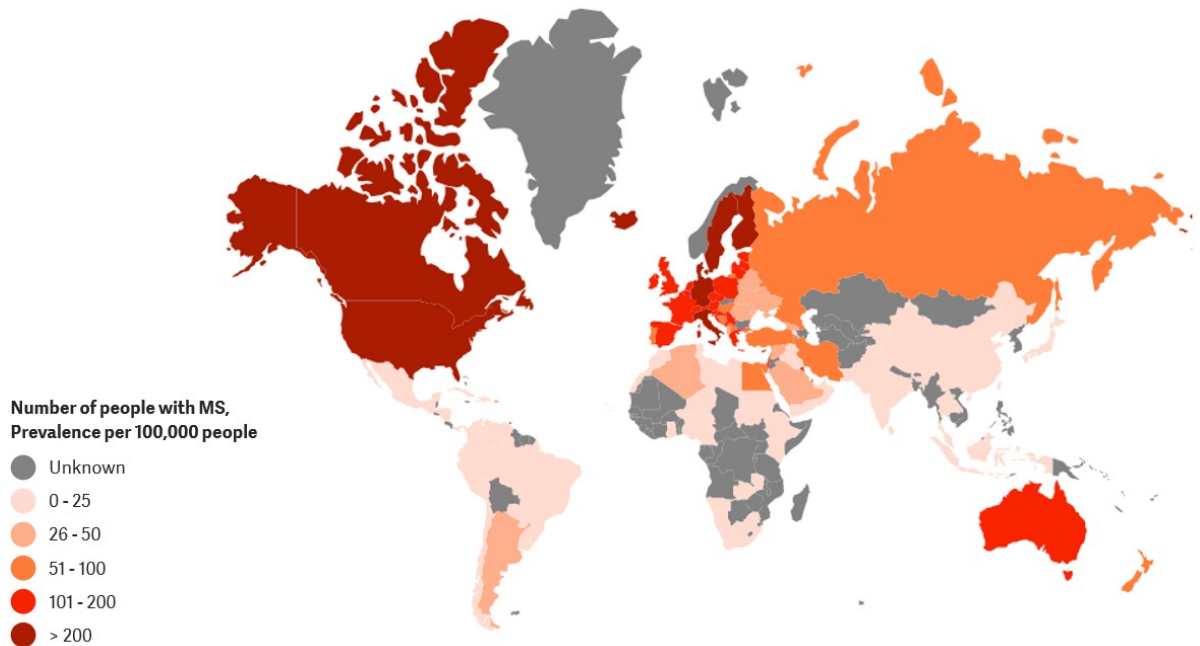
### The number of people with MS around the world (prevalence of MS)



### Figure 2: Global MS Prevalence

Image Adapted from Atlas of MS 2020 available at: <https://www.msif.org/resource/atlas-of-ms-2020/#:~:text=The%20Atlas%20of%20MS%20is,to%202.8%20million%20in%202020.>

The prevalence of MS displays significant disparities worldwide. Notably, European regions such as San Marino, Germany, and Denmark exhibit the highest prevalence rates, standing at 337 per 100,000, 303 per 100,000, and 282 per 100,000, respectively<sup>63</sup>. Following closely is the United States of America<sup>64</sup> with a prevalence rate of 288 per 100,000. Conversely, regions like the Eastern Mediterranean, Southeast Asia, Africa, and the Western Pacific report estimated prevalence rates below 40 per 100,000<sup>63</sup>.



**Figure 3: MS Prevalence Per 100,000 People**

*Image Adapted from Atlas of MS 2020 available at: <https://www.msif.org/resource/atlas-of-ms-2020/#:~:text=The%20Atlas%20of%20MS%20is,to%202.8%20million%20in%202020.>*

Various factors may have contributed to these discrepancies in prevalence, including different study methodologies (e.g., national MS registries versus hospital- or community-based studies), disparities in the accessibility and availability of disease-modifying therapies (DMTs), and socio-economic variations. Epidemiological evidence suggests that racial and ethnic differences significantly affect the distribution of MS worldwide<sup>65, 66</sup>. Conversely, cultural practices such as wearing protective clothing and exposure to sunlight could have indirectly influenced geographical variations<sup>67</sup>.

Regional differences in MS incidence rates (measured per 100,000 individuals per year) typically mirror the prevalence trends<sup>68</sup>. Europe exhibits the highest documented incidence at 6.8, followed by the Americas at 4.8. South East Asia and Africa report the lowest documented incidence rates of 0.4.

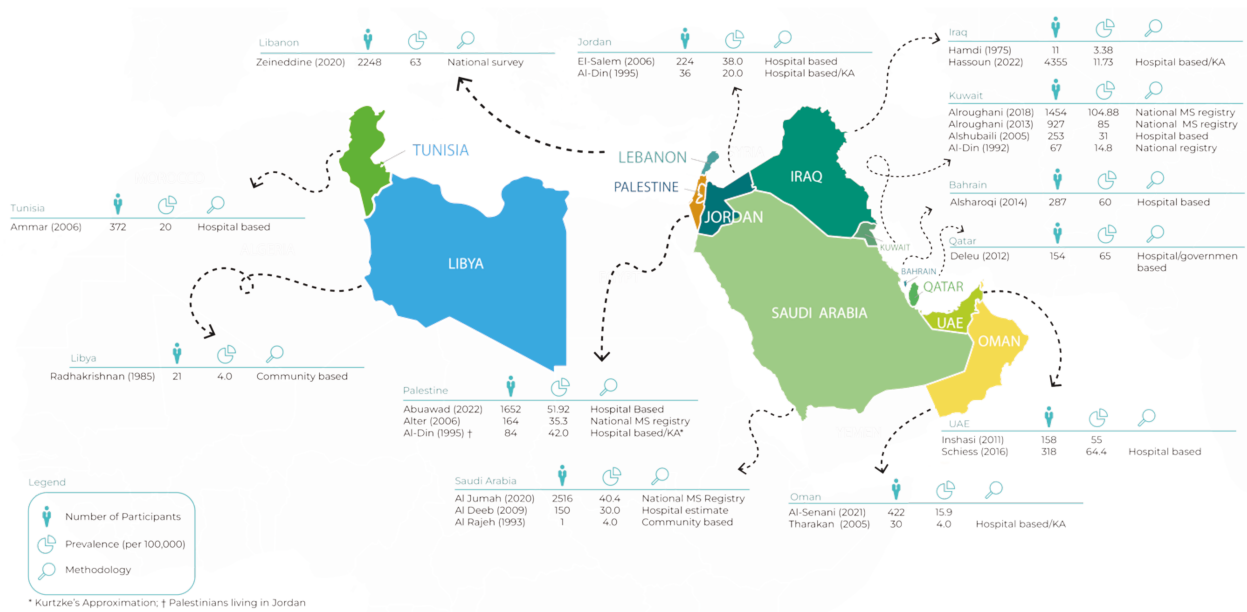
MS demonstrates a higher prevalence among women compared to men<sup>63</sup>. A systematic review spanning from 1955 to 2000 discovered that the estimated female-to-male ratio of MS incidence escalated from 1.4:1 to 2.3:1<sup>69</sup>. Recent investigations indicate that this high prevalence among females is even more pronounced in the Western Pacific and Southeast

Asia regions, where the ratio of females to males exceeds threefold. Moreover, intra-regional variations in gender ratios exist, as observed in the Eastern Mediterranean region, where the average female-to-male ratio stands at 2:1<sup>63</sup>. However, in several countries including Egypt, Iran, the Palestinian Authority, and Sudan, females with MS outnumber males at a ratio of 3 or even 4 to 1<sup>63</sup>.

As for the age of disease onset, MS is diagnosed between the ages of 20 and 40 years, although less than 1% of cases may occur in childhood and approximately 2–10% after the age of 50<sup>63</sup>.

#### **I.4.2. Epidemiology in the Middle East and North Africa Region**

The Middle East and North Africa<sup>70</sup> region is characterized by a low-to-moderate prevalence of MS. Epidemiological studies conducted before 2000 indicated low prevalence rates ranging from 3 to 20/100,000, predominantly from countries such as Saudi Arabia, Iraq, Libya, Kuwait, Tunisia, and Jordan<sup>71</sup>. However, prevalence rates began to rise in the early 21st century. Studies from Kuwait<sup>72</sup> (31/100,000), Saudi Arabia<sup>73</sup> (30/100,000), Palestine<sup>74</sup> (35.3/100,000) and Jordan<sup>75</sup> (38/100,000) reported rates between 30 and 38/100,000. Recent data from Kuwait<sup>76</sup> (105/100,000), Qatar<sup>77</sup> (65/100,000), Lebanon<sup>78</sup>, Bahrain<sup>79</sup> (60/100,000) and United Arab Emirates<sup>80</sup> (64.4/100,000) showed a further increase, with prevalence rates now ranging between 65 and 105/100,000. Oman, on the other hand, maintained a consistently low prevalence rate of 16/100,000 in 2021, possibly due to genetic differences compared to neighboring Arab countries<sup>81</sup>. A study from Egypt in 2013 reported a prevalence of 13.7/100,000, reflecting the lower rates seen in African countries<sup>82</sup>. Notably, Iran consistently exhibited the highest disease prevalence in the region, rising from 51.9 in 2010 to 162.4/100,000 in 2019, possibly due to genetic factors associated with the diverse ethnic makeup of the Iranian population<sup>83, 84</sup>. It is important to recognize that the methodologies for calculating prevalence varied widely among these studies, ranging from national registry-based to hospital or community-based approaches, with some older studies employing the Kurtzke approximation method.



**Figure 4. Prevalence of MS in the Arab World**

### I.4.3. Reasons for Increased Prevalence of MS

The global rising trends in the prevalence of MS could be explained by the availability of modern diagnostic techniques particularly advanced magnetic resonance imaging (MRI), the introduction of the new 2017 McDonald Criteria<sup>85</sup> which allowed better and earlier diagnosis, an increase awareness about the disease for both public and physicians, and longer survival of MS patients. Improved survival in MS, possibly due more frequent use of advanced DMTs<sup>86</sup>, was probably the most important factor related to the observed increase in prevalence. Goodin et al.<sup>86</sup> concluded that early treatment with interferon beta 1b was associated with a 47% reduction in the hazard ratio for all-cause mortality over 21 years compared with placebo treatment. Similarly, a recent study demonstrated that the use of MS DMTs mainly beta-interferon for  $\geq 3$ -years was significantly associated with increase survival<sup>87</sup>. The improved survival may also be attributed to a general increase in life expectancy during the last decades<sup>88</sup>.

However, these factors alone could not be responsible for such a large increment. Changing in environmental exposures such as urbanization, improved hygiene, decreased sun exposure, higher consumption of dietary salt intake and smoking were significant players in the sharp increase of the MS prevalence<sup>71</sup>.

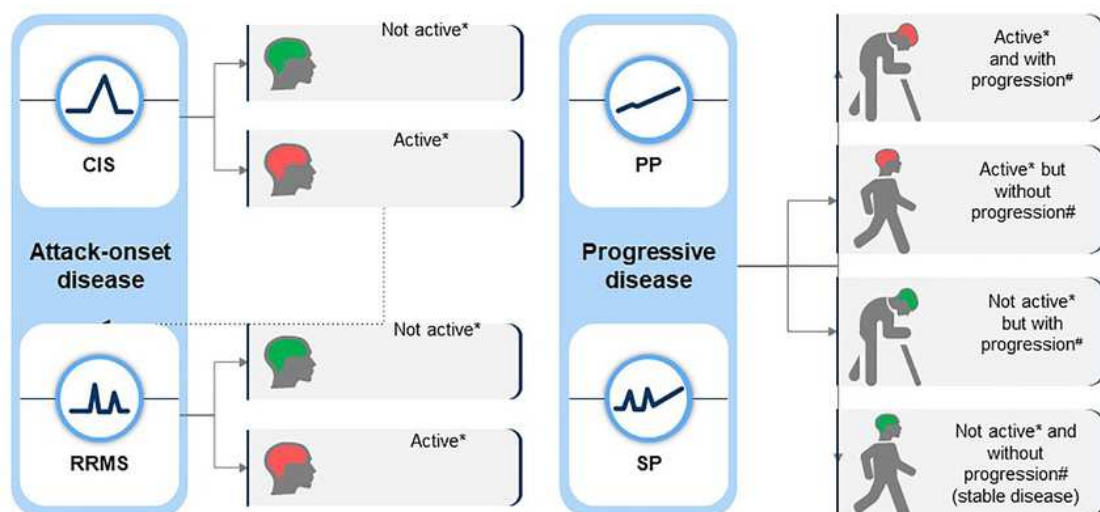
### I.5. Clinical Features and Phenotypes

The clinical manifestations of MS can vary widely and may result from the impairment of sensory, motor, visual, and brainstem pathways, depending on the areas of the brain and spinal cord affected<sup>89</sup>. The first clinical presentation most frequently manifest as optic neuritis,



myelitis, or a brainstem syndrome (characterized by symptoms such as diplopia, oscillopsia, facial sensory loss, vertigo, and dysarthria)<sup>89</sup>. However, sensory loss, spasticity, gait instability, dysarthria, nystagmus, trigeminal neuralgia, fatigue, pain, cognitive decline, depression, bladder and bowel dysfunction, and sexual dysfunction are all prevalent symptoms of MS. These symptoms can vary among individuals and may even fluctuate within the same patient over time.

As for the clinical course of the disease, MS can be categorized into three main phenotypes: clinically isolated syndrome, RRMS, and progressive MS (PMS)<sup>90</sup>. CIS is characterized by a single episode of neurological symptoms lasting at least 24 hours, resulting from inflammation and demyelination in the CNS. RRMS is the most prevalent phenotype, with approximately 70 to 80% of patients experiencing relapses followed by periods of stability. A relapse is defined as the onset of new neurological symptoms or the worsening of existing ones lasting at least 24 hours, unrelated to fever, infection, or environmental triggers<sup>91</sup>. PMS includes PPMS and SPMS. PPMS, observed in 10–15% of patients, is defined as a continuous decline in neurological function and disability accumulation from symptom onset, without distinct relapses or remissions<sup>90</sup>. Approximately 25 to 40% of RRMS patients transition to SPMS within 15 years of diagnosis<sup>92</sup>. SPMS is characterized by progressive neurological deterioration over time, although some patients may experience superimposed relapses during this phase<sup>93</sup>. According to the revised Lublin phenotypes<sup>93</sup>, progressive MS at onset (PPMS) or transitioning from relapsing forms (SPMS) can be classified as active or inactive based on clinical and radiological assessments.



**Figure 5. Lublin 2013 MS Phenotypes**

Image Adapted from Giovannoni G et al. *Ther Adv Neurol Disord* 2022 (15): 1–18  
<https://doi.org/10.1177/17562864211066751>

The advances in brain MRI have led to the frequent identification of incidental white matter lesions in asymptomatic patients. In 2009, the term radiologically isolated syndrome was introduced to describe patients with typical MS demyelinating lesions on MRI but without any clinical symptoms<sup>94</sup>. Although these patients are at risk of future demyelinating events, there are currently no universally accepted guidelines for monitoring and treating this evolving phenotype.

## **I.6. Diagnosis**

The diagnosis of MS continues to heavily depend on medical history and neurological examination, despite advancements in diagnostics and the introduction of various radiological and neuroimmunological markers. Paraclinical assessments such as MRI, evoked potential studies, and cerebrospinal fluid (CSF) analysis to detect the presence of oligoclonal bands (OCB), which are considered an inflammatory marker, may support the diagnosis<sup>95</sup>. Moreover, a thorough differential diagnosis is essential to prevent misdiagnosis with other conditions that share some diagnostic features with MS, including neurobrucellosis, neuro-Behcet, acute disseminated encephalomyelitis, neuromyelitis optica, and other neurological diseases<sup>95</sup>.

The primary goal of all defined MS diagnostic criteria since the 1950s has been to establish the dissemination in space and time (DIT) of lesions within the CNS responsible for the clinical manifestations in CIS patients<sup>95</sup>. However, current diagnostic criteria necessitate the consideration of both clinical and paraclinical measures, as delineated in the McDonald criteria, initially developed in 2001 and subsequently revised in 2005, 2010, and most recently in 2017. Diagnosis of MS can be confirmed with at least two typical clinical attacks or a single typical demyelinating event, accompanied by evidence of DIS and DIT on MRI<sup>95</sup>. DIS is defined as the presence of neurological lesions in at least two of four CNS regions (cortical-juxtacortical, periventricular, infratentorial, and spinal cord), while DIT indicates the occurrence of neurological damage at multiple time points. DIT criteria are met with the identification of new T2 and/or gadolinium-enhancing lesions on follow-up MRI or the concurrent presence of gadolinium-enhancing and non-enhancing lesions at any point in time.

The major differences in the 2017 McDonald criteria<sup>96</sup> compared to the earlier versions are the allowance for OCB presence to substitute the requirement of demonstrating DIT when DIS criteria are met, the inclusion of cortical lesions in DIS determination alongside juxtacortical lesions, and the consideration of both symptomatic and asymptomatic lesions in DIS and DIT determination.

## **I.7. Treatment**

### **I.7.1. Goals of Therapy**

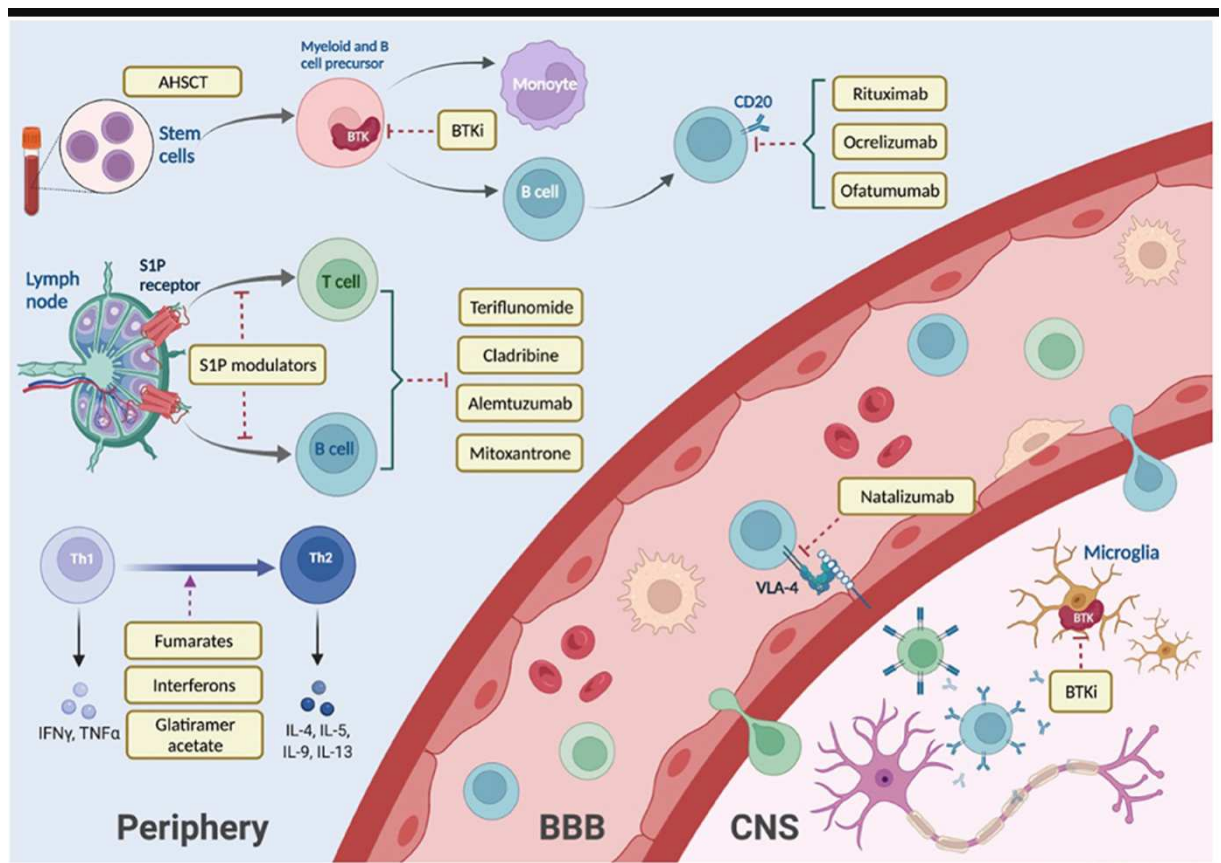
While there is currently no cure for MS, the goals of therapy revolve around treating acute exacerbations, stopping the progression of the disease, and improving symptoms<sup>97</sup>.

### **I.7.2. Treatment of Acute Relapses**

The preferred treatment for acute exacerbations remains high doses of methylprednisolone, administered either orally or intravenously. Studies have confirmed the efficacy of intravenous methylprednisolone (IVMP), and a Cochrane meta-analysis has indicated that both oral and IV routes of administration lead to a reduction in disease progression within the initial 5 weeks of treatment<sup>98</sup>. For patients who do not respond adequately to methylprednisolone, plasmapheresis may be considered based on clinical evidence from two randomized clinical trials<sup>99, 100</sup>. According to the American Academy of Neurology guideline, plasmapheresis should be considered in patients experiencing severe relapses that do not respond to high-dose steroids<sup>101</sup>. While there is limited evidence regarding the effectiveness of intravenous immunoglobulin (IVIG) for treating acute MS relapses, it may be administered to patients who cannot tolerate corticosteroids and plasmapheresis<sup>102, 103</sup>.

### **I.7.3. Disease-Modifying Therapies: Safety and Efficacy**

Currently, over twenty DMTs have received approval for treating RRMS, with additional options being introduced annually. These DMTs operate through various mechanisms, such as immunomodulation, disruption of cell trafficking, and depletion of diverse immune cells.



**Figure 6. DMTs Mechanisms of Action**

Image Adapted from Yang JH et al. *Front. Neurol* 2022 (13), Sec. Multiple Sclerosis and Neuroimmunology available at <https://doi.org/10.3389/fneur.2022.824926>

### I.7.3.1. Interferons Beta and Glatiramer Acetate

Interferons-beta (IFN-beta) and glatiramer acetate are approved for the treatment of RRMS, supported by class I evidence from numerous multicenter randomized controlled trials (RCTs)<sup>104-108</sup>. IFN-beta can influence T and B cell activity, cytokine secretion, and T regulatory cells, whereas GA specifically modulates T regulatory cells. Both treatments have demonstrated moderate efficacy, reducing the risk of relapse and disability progression by approximately 30%. Pegylated (PEG) interferon-beta-1a allows for once-every-two-weeks dosing and exhibits similar efficacy and adverse event profiles to other IFNs<sup>109</sup>. Additionally, double-dose (40 mg) GA administered three times weekly has shown comparable efficacy in recent trials<sup>86, 110</sup>. The long-term safety data spanning more than two decades is a significant advantage of both treatments. However, their route of administration may lead to poor adherence due to acute adverse events such as injection site reactions and flu-like symptoms<sup>111</sup>. Treatment should be personalized based on patient preferences, although the use of injectables has declined in recent years due to the availability of various treatment options.

### **I.7.3.2. Teriflunomide**

Teriflunomide acts as a reversible inhibitor of the mitochondrial enzyme dihydro-orotate dehydrogenase (DHODH), essential for de novo pyrimidine synthesis in rapidly proliferating immune cells<sup>112, 113</sup>. It was approved by the Food and Drug Administration (FDA) based on the results of the phase III trials in RRMS patients, namely the TOWER and TEMSO trials<sup>114, 115</sup>. In these trials, a daily dose of 14mg reduced the annualized relapse rate by 36.3% and 31%, along with decreasing the risk of disability progression by 31.5% and 30%, respectively, compared to placebo. Generally well tolerated, teriflunomide presents mild adverse events such as hair thinning, elevated serum liver enzymes, and mild leucopenia. It can be rapidly eliminated from the body within 11 days using oral cholestyramine or charcoal. Long-term follow-up studies, including the TEMSO extension study over nine years and the TOPIC extension study, have not revealed any new safety concerns, maintaining consistency with the core trial results<sup>116, 117</sup>.

### **I.7.3.3. Dimethyl Fumarate**

Dimethyl Fumarate (DMF) is also an oral medication approved for the treatment of RRMS. It is a modified fumaric acid ester known to stimulate anti-inflammatory and cytoprotective actions, partly through the Nrf2 antioxidant response pathway<sup>118</sup>. An integrated analysis of phase III trials, DEFINE and CONFIRM, revealed that DMF administered at 240 mg twice daily led to a substantial reduction in ARR (49%) and disability progression (32%) compared to placebo<sup>119</sup>. Overall, DMF exhibited favorable safety and tolerability profiles, with flushing and gastrointestinal adverse events being most common. The ENDORSE study, an open-label extension of the initial trials, reported no new adverse events during six years of follow-up<sup>120</sup>.

### **I.7.3.4. Fingolimod**

Fingolimod is a modulator of sphingosine1-phosphate receptor (S1PR), hindering the egress of lymphocytes from lymph nodes. This mechanism reduces the infiltration of potentially auto-aggressive lymphocytes into the CNS<sup>121, 122</sup>. Fingolimod was the first oral DMT approved for RRMS, endorsed following two phase III clinical trials<sup>123, 124</sup>. It decreased the ARR by 55% compared to placebo and by 52% in comparison to intramuscular IFN-beta 1a, along with reducing the risk of disability progression by 30% compared to placebo. In a subgroup analysis of patients with highly active disease despite prior IFN treatment, fingolimod demonstrated a 61% reduction in ARR compared to IFN-beta 1a IM, alongside decreases in the number of lesions and brain volume loss<sup>125</sup>. Despite its efficacy, vigilant monitoring is essential due to several safety concerns, including bradycardia, macular edema, and infections.

### **I.7.3.5. Ponesimod**

Ponesimod is as a selective modulator of S1PR1, possessing pharmacological properties that are rapidly reversible<sup>126</sup>. It exhibits a shorter half-life and faster elimination, typically occurring within one week, in contrast to fingolimod<sup>127</sup>. In 2021, the FDA granted approval for ponesimod as an oral once-daily medication for treating adults with RRMS, CIS, and active secondary SPMS. In the phase III OPTIMUM trial<sup>128</sup>, ponesimod (20 mg/day) demonstrated a 30.5% reduction in the ARR and a 56% decrease in active lesions per year on MRI compared to teriflunomide. However, there was no statistically significant reduction in confirmed disability accumulation compared to teriflunomide. The adverse event profile of ponesimod was similar to other S1PR modulators, with lower rates of bradycardia and long-term lymphopenia in comparison to fingolimod<sup>129</sup>.

### **I.7.3.6. Siponimod**

Siponimod is also a selective modulator of S1P1 and S1P5. Its mode of action parallels that of fingolimod, yet with enhanced selectivity towards S1P receptors, improved penetration of the blood-brain barrier, and a shorter half-life, resulting in quicker recovery of lymphocyte counts to baseline levels within 10 days of discontinuation<sup>130</sup>. FDA-approved for CIS, RRMS, and active SPMS, in the BOLD phase II trial, siponimod at a 2 mg/day dosage significantly reduced new and enhancing (Gd+) lesions by 72% and ARR by 66% compared to placebo over six months<sup>131</sup>. This effect persisted during a 24-month dose-blinded extension of the study<sup>132</sup>. Siponimod's adverse event profile is similar that of other drugs in its class, including liver enzyme elevation, macular edema, hypertension, seizures, and varicella-zoster reactivation. Particularly, it is contraindicated in patients with a homozygous CYP2C9\*3 genotype due to potential long-term safety concerns, with adjusted dosing recommended for patients with specific genotypes<sup>133</sup>.

### **I.7.3.7. Cladribine**

Cladribine, a nucleoside analogue of deoxyadenosine, accumulates within cells, inhibiting DNA synthesis and repair, leading to subsequent apoptosis, with a prominent effect on lymphocytes<sup>134</sup>. It was approved in Europe in 2017 as a first-line therapy for RRMS patients with high disease activity or those unresponsive to other DMTs, and as second-line therapy in the United states of America<sup>64</sup> in 2019 for RRMS patients failing other DMTs or with active SPMS. Administered orally at a dose of 3.5 mg/kg over four cycles of five-day duration each, during months 1, 2, 13, and 14 of the two-year trial, cladribine reduced the ARR by 58% and the risk of confirmed disability progression over six months by 47% compared to placebo<sup>135</sup>. Moreover, in the extension trial, patients shifted to placebo for the subsequent two years

maintained treatment efficacy, with a considerable proportion remaining relapse-free<sup>135</sup>. Consequently, cladribine was approved for two treatment courses during the initial two years, with no further therapy required in years 3 and 4. Despite inducing transient lymphopenia, which typically resolves within six months post-dose, cladribine demonstrated a favorable safety profile, with infection and severe infection rates similar to placebo, except for a slight increase in herpes zoster infections.

#### **I.7.3.8. Natalizumab**

Natalizumab, the first monoclonal antibody approved for RRMS, is a selective adhesion molecule inhibitor that inhibits the influx of inflammatory cells into the brain<sup>136</sup>. It achieves this by binding to the  $\alpha 4$  subunit of  $\alpha 4\beta 1$  integrin found on immune cells' surface, thus impeding its interaction with vascular cell adhesion molecule (VCAM1) on endothelial cells<sup>136</sup>. In the phase III AFFIRM trial, natalizumab showcased a 68% reduction in ARR and a 42% decrease in sustained disability progression compared to placebo<sup>137</sup>. Post-marketing data further supported its efficacy, particularly in patients transitioning from first-line therapies due to inadequate response. However, its usage is often reserved for patients failing initial therapy or those with aggressive disease due to the associated risk of progressive multifocal leukoencephalopathy (PML), estimated at approximately 4.22 per 1000 patients<sup>138</sup>. Factors such as seropositivity for *John Cunningham virus* (JCV) antibodies, prior immunosuppressant use, and treatment duration exceeding 2 years elevate PML risk<sup>138</sup>. While the prevalence of JCV antibodies in MS patients ranges from 50-60%, with an annual seroconversion rate of 8.5-11.7%<sup>139, 140</sup>, the risk of PML can be stratified further using serum antibody levels, measured as the antibody index<sup>141</sup>. Natalizumab, despite its PML risk, remains well-tolerated with a low incidence of hypersensitivity reactions. Recent findings suggest that extending the dosing interval up to 6-8 weeks maintains efficacy and potentially reduces PML risk<sup>95</sup>. Thus, extended interval dosing may be considered, although long-term safety data is lacking.

#### **I.7.3.9. Alemtuzumab**

Alemtuzumab, a humanized monoclonal antibody approved for RRMS treatment, targets the CD52 surface protein predominantly found on T and B lymphocytes, with minor presence on other immune cells. In two phase III randomized controlled trials (CARE-MS I and II), including treatment-naïve individuals or those experiencing relapses on IFN-beta/GA, alemtuzumab at a 12 mg/day dosage exhibited a 55% and 49% reduction in relapse risk compared to IFN-beta 1a subcutaneously<sup>142, 143</sup>. Among patients with prior relapses on IFN-beta/GA, there was a 42% reduction in disability progression risk versus IFN-beta. A 9-year follow-up from both trials

revealed that 62% of patients experienced no confirmed disability worsening over 6 months, while 50% exhibited confirmed disability improvement<sup>64</sup>. Its side effects include infusion-related reactions, an increase in infection rates, and the occurrence of delayed secondary autoimmune events, peaking in the third treatment year. These events encompassed thyroid disease (40%), immune thrombocytopenia (1-2%), and sporadic cases of anti-glomerular basement membrane disease<sup>144</sup>. Recent reports have highlighted additional adverse events associated with alemtuzumab, including stroke, listeria meningitis, acute coronary syndrome, acute pneumonitis, and other autoimmune disorders<sup>145, 146</sup>. Consequently, its utilization has been constrained to third-line therapy.

### **I.7.3.10. Ocrelizumab**

Ocrelizumab (OCR), a recombinant humanized monoclonal antibody, targets the CD20 protein present on B lymphocytes, leading to their selective depletion through various mechanisms<sup>147</sup>. It is administered intravenously as two initial doses of 300 mg given two weeks apart, followed by 600 mg every six months. FDA and European Medications Agency approvals were granted for both RRMS and PPMS in 2017. In two phase III trials (Opera I and II) involving RRMS patients, ocrelizumab reduced ARR by 46-47% and lowered the risk of confirmed disability progression over 24 weeks by 37-43% compared to IFN-beta 1a 44 ug 3x/week<sup>147</sup>. Ocrelizumab exhibited favorable safety profiles, with lower rates of serious infections compared to IFN-beta and comparable overall incidence of serious adverse events. While a slight increase in breast cancer incidence was noted in the ocrelizumab group, it fell within the expected range for age-matched controls in various international MS registries<sup>148</sup>. Similar to rituximab, ocrelizumab use was linked to heightened risk of coronavirus disease 2019 (COVID-19) infection and diminished humoral response to vaccination<sup>149</sup>.

### **I.7.3.11. Ofatumumab**

Ofatumumab is a human IgG1 kappa anti-CD20 monoclonal antibody that has also been approved for RRMS treatment. Unlike other anti-CD20 therapies, ofatumumab is entirely human-derived, administered monthly via SC injections at 20 mg doses. Compared to teriflunomide, ofatumumab demonstrated superiority in two phase-3 randomized controlled trials ASCLEPIOS I and II, each enrolling 900 patients<sup>150</sup>. Both trials indicated a significant reduction in ARR among patients receiving ofatumumab (0.11 and 0.10) compared to those on teriflunomide (0.22 and 0.25). Furthermore, ofatumumab-treated patients showed a significant decrease in the confirmed disability worsening at 3 and 6 months, with a hazard ratio of 0.7. Significant differences were also observed in gadolinium-enhancing lesions and



new T2 lesions, favoring ofatumumab. Injection site reactions and injection-related systemic reactions were the most common adverse events in phase III clinical trials (11% and 20%, respectively).

Similar to other chronic B cell-depleting DMTs, patients on ofatumumab may experience reduced humoral response to immunizations. Recently, a study reported the safety outcomes of 1969 patients treated with SC ofatumumab every four weeks in Phase III clinical trials<sup>151</sup>. The median duration at risk, spanning from the first dose of ofatumumab until 100 days after the last, was 21 months (ranging from 0.0 to 51.8). Approximately 5.8% of patients discontinued treatment due to adverse events. Infections were reported in 54% of patients, primarily nasopharyngitis, upper respiratory tract infections, and COVID-19 infections. Moreover, around 3% of patients experienced serious infections. Malignancies occurred in 11 patients (0.6%) during the observation period. As anticipated, serum immunoglobulin levels were reduced, with approximately 23% and 1.5% of patients exhibiting IgM and IgG levels below the lower limit of normal, respectively.

#### **I.7.3.12. Rituximab**

Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody renowned for its B lymphocyte-depleting properties, officially approved for various conditions such as B-cell malignancies, rheumatoid arthritis, Wegener granulomatosis, and microscopic polyarthritis<sup>152</sup>. Its off-label usage extends to systemic and neurological immune-mediated disorders, including neuromyelitis optica and myasthenia gravis. The use of RTX in MS has considerably emerged, specifically after a phase 2 trial demonstrated its efficacy in RRMS patients<sup>153</sup>. Subsequent open-label or observational studies from Sweden and other regions have supported RTX's effectiveness and safety compared to alternative DMTs in MS patients<sup>154-157</sup>.

A pivotal multicenter randomized phase 3 trial (RIFUND-MS) comparing RTX versus dimethyl fumarate, showed a significant decrease in relapse rates in the RTX cohort (3% versus 16%,  $p=0.0060$ )<sup>158</sup>.

Rituximab has gained widespread use in the Middle East. In an observational study conducted by Yamout et al.<sup>159</sup>, they presented their findings on 89 patients (59 with RRMS and 30 with PMS) treated with RTX. They noted a significant reduction in ARR from baseline to 0.11 in RRMS ( $p < 0.0001$ ) and from 0.25 to 0.16 in PMS patients ( $p = 0.593$ ). Additionally, they observed no clinical or radiological activity in 74% of patients after one year of RTX treatment. Despite the absence of phase III controlled trials, RTX's use for MS is rapidly expanding,

particularly in countries like Sweden<sup>160</sup>. RTX offers advantages such as wider availability, extensive long-term safety data, and lower cost compared to recently approved anti-CD20 medications. These factors, coupled with its convenient dosing regimen, make RTX widely prescribed in regions where newer, more expensive DMTs may not be accessible or affordable, especially among refugee populations or areas affected by political or economic instability or conflict<sup>160, 161</sup>. The dosing of RTX typically involves an induction dose of 1000mg followed by maintenance doses of 500-1000 mg every 6 months, as commonly practiced. RTX is generally well tolerated, with a low incidence of infusion reactions and minimal elevation of liver function tests. However, due to its profound B lymphocyte depletion, the risk of hypogammaglobulinemia and infections increases, as evidenced by population-wide observational studies<sup>162</sup>. Notably, during the COVID-19 pandemic, MS patients on RTX generally recovered well, yet exhibited an increased risk of severe infection and hospitalization compared to non-CD20 targeting DMTs<sup>163, 164</sup>. Humoral response to COVID-19 vaccines was compromised in rituximab- and ocrelizumab-treated patients, although cellular response remained relatively intact<sup>165</sup>.

#### **I.7.4. Treatment Algorithms for Relapsing-Remitting Multiple Sclerosis**

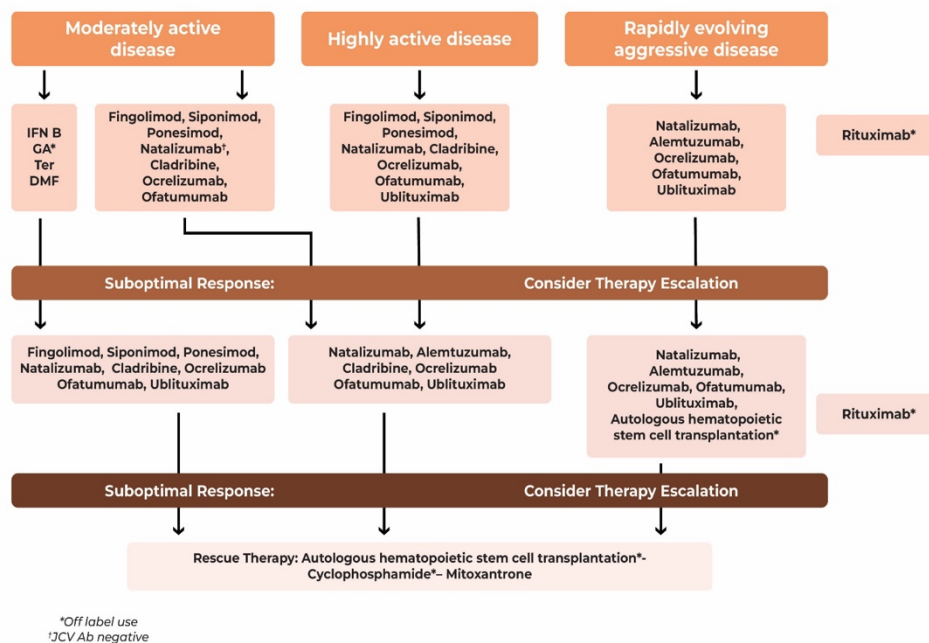
The Middle East and North Africa Committee for Treatment and Research in Multiple Sclerosis have recently published guidelines aiming to provide evidence-based recommendations to guide clinicians in the treatment of MS<sup>95</sup>. The MENACTRIMS guidelines recommends the below for the management of RRMS:

- In treatment-naïve patients with moderately active disease, initiating moderate efficacy DMTs like IFN-beta, GA, teriflunomide, or DMF is appropriate.
- For patients with highly active disease, initiating S1PR modulators, cladribine, B-cell depleting therapies, or natalizumab (high-efficacy DMTs) should follow thorough risk assessment and consideration of comorbidities.
- In cases of rapidly evolving aggressive disease, recommendations include natalizumab, B-cell depleting therapies, or alemtuzumab after comprehensive risk assessment and evaluation of comorbidities.
- Rituximab may be utilized off-label across activity levels, particularly in special populations like refugees or in regions where other suitable options are either unavailable or financially inaccessible.
- DMTs efficacy should be assessed after one year of treatment. Suboptimal response to a continuous DMT is defined as patients experience one or more relapses, disability progression, or two or more active MRI lesions (Gd+ and/or new T2

lesions), with the baseline being an MRI conducted six months after treatment initiation.

- For patients with moderately active disease showing suboptimal response to first-line therapies, considering escalation to S1PR modulators, natalizumab, B-cell depleting therapies, or cladribine is recommended.
- In cases of highly active disease with suboptimal response to DMTs, escalating to natalizumab, B-cell depleting therapies, cladribine, or alemtuzumab should be considered.
- Patients with rapidly evolving aggressive disease and suboptimal response to initial DMT may consider a lateral shift among alemtuzumab, B-cell depleting therapies, natalizumab, or autologous hematopoietic stem cells transplantation (AHSCT), with decision factors including risk stratification based on anti-JCV antibody status, prior immunosuppressant use, and comorbidities.
- For breakthrough disease on second-line medications, lateral switching based on risk stratification or AHSCT should be considered before resorting to third-line therapies such as cyclophosphamide or mitoxantrone.

### MENACTRIMS 2023 Algorithm for Treatment of RRMS



**Figure 7. MEMACTRIMS RRMS Treatment Algorithm**

Image Adapted from Yamout B et al. *Mult Scler Relat Disord* 2024 (83):105435. doi: 10.1016/j.msard.2024.105435.

### **I.7.5. Treatment of Progressive MS**

The treatment options for progressive MS are limited, but recent trials have shown promising results with certain drugs<sup>166</sup>. Mitoxantrone, although effective in reducing disability progression and relapse rate in the short term (2 years), is currently less likely used due to significant adverse events like cardiotoxicity (12%) and leukemia (0.8%)<sup>167</sup>.

Ocrelizumab is the only FDA-approved drug for PPMS, demonstrating a 25% reduction in the risk of disability progression compared to placebo<sup>168</sup>.

Siponimod, a second-generation S1P receptor modulator, has shown significant efficacy in reducing disability progression and brain atrophy in SPMS patients<sup>169</sup>, leading to its FDA approval for active SPMS.

Other immunosuppressants like cyclophosphamide, methotrexate, and mycophenolate have shown some potential in short-term disability progression, but their effects haven't been confirmed by large-scale trials<sup>170-172</sup>.

Therefore, the current treatment guidelines suggest the below for the treatment of progressive MS<sup>95</sup>:

- Consider siponimod or B-cell depleting therapies for active SPMS patients under 60 years old with an Expanded Disability Status Score  $\leq 6.5$ .
- Ocrelizumab is recommended for PPMS patients under 55 years old with EDSS  $\leq 6.5$  and disease duration  $\leq 10-15$  years. If ocrelizumab is unavailable, other B-cell depleting therapies can be considered.
- Autologous hematopoietic stem cell transplantation is an option for active progressive MS patients not responding to siponimod or ocrelizumab.
- For ambulatory SPMS patients not responding to recommended treatments or lacking access, a trial of cyclophosphamide, methotrexate, or mycophenolate may be considered.

### **I.8. Quality of life and Burden of the Disease**

MS poses significant economic and social challenges due to its impact on various aspects of life, including quality of life, employment, social relationships, and productivity<sup>195</sup>. While the economic burden of MS in high-income countries has been extensively studied, there is limited information available on the costs of MS in low- and middle-income countries (LMICs). To address this gap, a systematic literature review was conducted to gather prevalence or incidence-based cost data of MS in LMICs<sup>173</sup>. This review identified economic data from ten

countries: Latin America, Argentina, Colombia, Mexico, Brazil, Turkey, Thailand, Jordan, Iran, China, and Russia. The annual cost per patient varied widely, ranging from 463 to 58,616 USD. Discrepancies in costs were observed across studies and countries, primarily due to variations in the inclusion of DMTs, cost items, methodological approaches for estimating healthcare resource consumption, and accounting for informal care and productivity losses. The total costs escalated with increasing disease severity, with moderate MS being 1–1.5 times more costly than mild MS, and severe MS being approximately twice as expensive as mild MS. In less severe cases, MS drug costs were the primary cost driver, while direct nonmedical costs and indirect costs became more significant with greater disease severity. Consequently, MS imposes a considerable economic burden on healthcare systems and societies in LMICs.

## Chapter II. Research Context and Objectives

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### II.1. Rationale and Aims

Over the past decade, there has been a significant expansion in the therapeutic options available for MS. New and more potent DMTs with diverse mechanisms of action are increasingly being administered early in the course of the disease. These newer DMTs have shown promising efficacy and a favorable safety profile in Phase III clinical trials. However, their long-term benefits and potential adverse events are still not fully understood. Additionally, in the current landscape of MS treatment, determining the most suitable therapy for each patient remains a topic of debate. There is a lack of evidence supporting the superiority of one DMT over another, as well as a shortage of biomarkers to accurately predict which patients will benefit most from specific medications. Clinical trials often involve cohorts that may not accurately represent the general population, and the monitoring process within these trials may not reflect real-world conditions. Furthermore, there is a scarcity of head-to-head trials comparing newer DMTs. Specifically in the MENA region, there is a lack of studies investigating the long-term safety and efficacy of DMTs. Consequently, clinicians cannot solely rely on RCTs to determine the most appropriate DMT for each patient, resulting in a lack of clear recommendations in clinical practice guidelines when sufficient data-driven evidence is lacking.

On the other hand, there is a lack of consensus on the definition of treatment failure, and the absence of agreement on various outcomes that could predict the future course of the disease further complicates treatment decision-making. Choosing between high-efficacy DMTs for MS treatment is often a complex decision that necessitates personalized discussions between patients and healthcare providers, taking into account the potential benefits and risks associated with each option in the context of the patient's individual disease course.

Therefore, the objective of this project was to evaluate the long-term safety and efficacy of high-efficacy DMTs among MS patients in the MENA region.

To achieve this goal, we first examined the availability and accessibility of DMTs across different countries in the MENA region and identified barriers to MS treatment (Study #1). Subsequently, we conducted an in-depth investigation into the accessibility of DMTs in Lebanon, a MENA country experiencing critical medication shortages due to an economic crisis since 2019 (Study #2).

Having established the landscape of available therapies and identified access barriers in the MENA region, we then proceeded to assess the long-term safety of these therapies, with a particular focus on infections such as COVID-19 (Study #3) and PML a rare viral brain infection

associated with natalizumab (Study #4). Regarding long-term efficacy, we evaluated the effectiveness of high-efficacy DMTs in patients after natalizumab cessation (Study #4) and compared the effectiveness of natalizumab versus anti-CD20 monoclonal antibodies (Study #5) using data from the MENACTRIMS registry.

To sum up, the main objectives of this project were:

1. To identify the different disease-modifying drugs available for the treatment of MS and the barriers to access treatment in each country of the MENA region
2. To assess the quality of life (QOL) among a cohort of Lebanese MS patients and identify barriers to treatment during the economic recession
3. To evaluate the severity of COVID-19 infection among MS patients treated with high-efficacy DMTs
4. To determine the most effective and tolerable DMTs to switch to after natalizumab treatment discontinuation due to positive serum JCV antibody
5. To compare the effectiveness and safety of natalizumab and anti-CD20 monoclonal antibodies

## **II.2. The MENACTRIMS Registry**

The MENA region is located at the crossroads of Africa, Asia, and Europe. Geographically, it spans from the easternmost part of North Africa, including countries along the Mediterranean Sea such as Morocco, Algeria, Tunisia, Libya, and Egypt, to the westernmost part of Asia, encompassing countries in the Middle East such as Lebanon, Syria, Iraq, Jordan, Palestine, and Saudi Arabia<sup>174</sup>. The region is bordered by the Mediterranean Sea to the north, the Red Sea to the northeast, the Arabian Sea and Indian Ocean to the southeast, and the Atlantic Ocean to the west.

The MENACTRIMS is an independent, non-profit organization dedicated to fostering collaboration among clinicians and scientists. Its primary goal is to advance research and improve clinical outcomes for MS within the MENA region<sup>70</sup>. MENACTRIMS focuses on several key objectives, including the establishment of National and Regional MS registries, the development of updated diagnostic and therapeutic guidelines, the organization of bi-annual congresses, the encouragement of young researchers, and collaboration with relevant regional associations.

Established on March 16, 2016, the MENACTRIMS Registry stands as the largest MS registry in the MENA region, encompassing over 12,000 patients with an average follow-up duration of 10 years<sup>175</sup>. Participating countries in the registry include Egypt, Iran, Saudi Arabia, Kuwait, Lebanon, Tunisia, Oman, UAE, and Algeria. Each participating center is required to have at least one principal investigator responsible for maintaining data accuracy and conducting local registry audits, with assigned PIs completing iMED training.

Data entry into the MENACTRIMS Registry is facilitated through licensed software such as iMed, which integrates collected patient data. Assigned PIs in each center enter patient information into the database, which is then uploaded to a central server and incorporated into the MSBase global registry. Notably, patient data remains under the ownership of investigators, with each individual having the ability to extract their own database. Patient confidentiality is maintained through the assignment of unique identification codes, with no identifiable information uploaded to the MSBase Registry.

Ethical requirements for data entry include obtaining ethics approval/exemption and securing patient consent, either verbally or in writing. The system generates patient reports as needed, and physician-specific statistical analyses can be extracted at any time through MSBase.

The MENACTRIMS Registry captures comprehensive data on various aspects of MS, including demographics, past medical history, disease characteristics, symptoms, diagnostic findings, laboratory tests, visits, relapse details, and treatment regimens.

To ensure the quality of data and oversee registry operations, a MENACTRIMS registry committee has been established. This committee is responsible for auditing data quality, allocating funds, and preparing annual progress reports, thus ensuring the integrity and effectiveness of the registry in advancing MS research and treatment within the MENA region.

### **II.3. Methodological Aspects**

The first study was a descriptive, survey-based study whereby we extracted data collected, between October 2019 and April 2020, for countries in the MENA region by the MSIF through their Atlas of MS survey. The aim of the third Atlas of MS was to provide comprehensive, globally accessible information regarding MS epidemiology and management, with particular emphasis on barriers to healthcare and DMTs accessibility. Data covering the following topics was collected via an international survey (**Appendix 1**) completed by experts from diverse countries worldwide during the specified timeframe: diagnostic criteria used, barriers to diagnosis, types of DMTs used and barriers to accessing them, symptomatic therapies, rehabilitation, number of health care professionals in the country, national guidelines and standards for MS diagnosis and treatment. For our study, only data related to DMTs and barriers to accessibility was extracted and analyzed.



Similarly, the second study was also a survey-based, cross-sectional study conducted in Lebanon between June and September 2022. During this study, a structured questionnaire (**Appendix 2**) was administered by two trained investigators via phone calls to randomly selected Lebanese MS patients. Patients' demographics, medical information, QOL assessment using the MS International QOL (MusiQoL), and information related to barriers in accessing MS therapies were collected and analyzed. This study was approved by the Institutional Review Board (IRB) of the Lebanese University.

As for the studies assessing the long-term safety and efficacy of DMTs, data was extracted from the MENACTRIMS registry using standardized data collection sheets for each study. The MENACTRIMS registry was approved by the IRB of the American university of Beirut (**Appendix 3**).



**Figure 8. Project Summary**

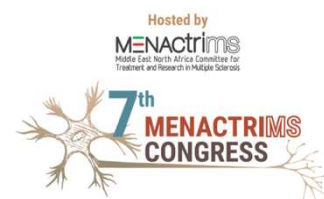
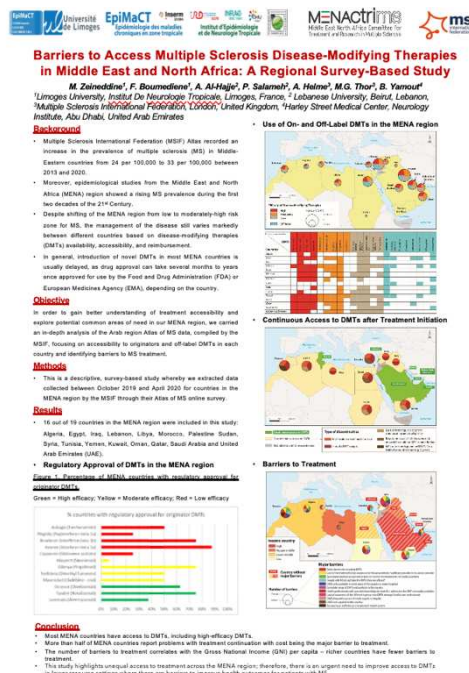
# Chapter III. Barriers to Accessing Multiple Sclerosis Disease-modifying Therapies in the Middle East and North Africa region: A Regional Survey-based Study

## III.1. Background

MS is a debilitating neurological disorder that requires timely and effective treatment to manage its progression. However, access to DMTs remains a significant challenge, particularly in the MENA region, where socioeconomic disparities impact healthcare availability.

Given the critical role of timely and effective MS treatment in improving patient outcomes, it is essential to understand and address the barriers to accessing DMTs. This research study was conducted to evaluate the accessibility of DMTs across the MENA region, identify the key barriers to treatment access, and propose recommendations for enhancing the availability of MS therapies. By shedding light on the regional disparities in MS treatment, this study aims to contribute to the development of targeted strategies that can improve healthcare equity and outcomes for people with MS (PwMS) in the MENA region.

This work was published in Multiple Sclerosis and Related Disorders (MSARD) journal (**Appendix 4**), and its significance was further highlighted in an editorial written after its publication (**Appendix 5**). Moreover, it was presented as a poster presentation in European Committee for Research and Treatment in Multiple Sclerosis (ECTRIMS) and MENACTRIMS congresses in October and November 2022, respectively.



## Abstract

**Background:** Multiple sclerosis (MS) management varies markedly between different countries of the Middle East and North Africa (MENA) region based on the availability and accessibility of disease-modifying therapies (DMTs).

**Objective:** To evaluate the accessibility to DMTs in each MENA country, identify barriers to treatment and make recommendations for improved access to DMTs across the region.

**Methods:** This is a descriptive, survey-based study whereby we extracted data collected, between October 2019 and April 2020, for countries in the MENA region by the Multiple Sclerosis International Federation (MSIF) through their Atlas of MS survey.

**Results:** 16 out of 19 countries in the MENA region were included in this study. Sudan and Syria did not have any originator DMTs approved. Interferons were the most widely low-efficacy originator approved DMTs. Three countries did not have any high efficacy DMTs approved. Moreover, follow-on DMTs were approved in half (50%) of the countries. Cost of treatment was the most important barrier, reported in nearly half (47%) of the MENA countries.

**Conclusion:** Although most MENA countries have access to DMTs, more than half of countries report problems with treatment continuation, highlighting the need for a targeted regional strategy to address the variations in access to MS treatments.

**Keywords:** barriers, access, treatment, multiple sclerosis, disease-modifying therapies, MENA

## III.2. Introduction

The MENA is a diverse and large region encompassing more than 20 countries in North Africa and the Middle East. There has been a worldwide increase in the incidence and prevalence of MS over the past decades, including the MENA region. The estimated global number of PwMS increased by 21.7% between 2013 and 2020 according to the latest Atlas of MS published by the Multiple Sclerosis International Federation (MSIF)<sup>1</sup>. The Atlas of MS recorded an increase in the prevalence of MS in Middle-Eastern countries from 24 per 100,000 to 33 per 100,000 between 2013 and 2020. Moreover, epidemiological studies<sup>2,3</sup> from the MENA region showed a rising MS prevalence during the first two decades of the 21st Century, with studies from Lebanon<sup>4</sup>, United Arab Emirates (UAE)<sup>5,6</sup>, Qatar<sup>7</sup> and Bahrain<sup>8</sup> showing rates in the range of 55–65/100,000. Even higher prevalence rates were reported from Kuwait<sup>9</sup> and Iran<sup>10-11</sup> ranging between 104 and 151/100,000.

Despite shifting of the MENA region from a low to moderately-high prevalence zone for MS and publication of the MENACTRIMS consensus recommendations for diagnosis and treatment<sup>12</sup>, management of the disease still varies markedly between countries based on DMTs availability, accessibility, and reimbursement. In general, introduction of novel DMTs in most MENA countries is usually delayed, as drug approval can take several months to years once approved for use by the US FDA or EMA, depending on the country.

To our knowledge, there are no published studies assessing the accessibility to DMTs across different countries of the MENA region. In order to gain better understanding of treatment accessibility and explore potential common areas of need in the MENA region, we carried out an in-depth analysis of the Arab region Atlas of MS data, focusing on accessibility to originator, follow-on and off-label DMTs in each country and identified barriers to MS treatment.

## III.3. Methods

In April 2021, MSIF published the third Atlas of MS<sup>1</sup> with the aim of providing open-source, global information on MS epidemiology and management with particular emphasis on barriers to healthcare and DMTs accessibility. Data covering the following topics was collected via an international survey (**Appendix 1**) completed by experts from different countries around the world between October 2019 and April 2020: diagnostic criteria used, barriers to diagnosis, types of DMTs used and barriers to accessing them, symptomatic therapies, rehabilitation, number of health care professionals in the country, national guidelines and standards for MS diagnosis and treatment. English, Spanish, and French versions of the survey were available to encourage greater response rates and collaboration with all national experts. The survey was piloted prior to launch to test clarity, understanding and ease of completion. All MS experts

provided consent to participate in the survey. As no patient data was included, no ethical approval was required.

Country coordinators, typically representatives from MS organizations, neurologists, epidemiologists or researchers with expertise in MS, were identified in each country and asked to complete the survey by making use of all possible sources of information available to them including publications, presentations, registries, government/health system statistics, administrative data sets, electronic medical records, and through collaboration with other experts in the country where possible and/or necessary (expert opinion). Survey responses covered 85%–91% of the population in each World Health Organization (WHO) region (Europe (89%), Americas (89%), South East Asia (90%), Eastern Mediterranean (91%), Western Pacific (85%), except for Africa with only 42% of the population represented<sup>1</sup>. A glossary of terms (**Appendix 6**) was provided within the survey, to improve uniformity and comparability of the information received.

This is a descriptive, survey-based study in which we extracted data from the Atlas of MS relevant to countries in the MENA region. Only answers for questions 11 to 32 in the full survey, which related to DMTs and barriers to accessibility, were entered into an Excel Spread sheet and analyzed using frequencies.

We assessed the local regulatory approval of originators versus follow-on DMTs in each MENA country. Originator DMT was defined as the product that was first authorized worldwide for marketing (typically patented) on the basis of documentation of its efficacy, safety, and quality according to requirements at the time of authorization<sup>13</sup>. Follow-on DMT was defined as a medication similar to a pre-existing DMT - but with some minor modifications, creating slight changes in drug action or adverse effects - used to treat the same condition which is MS in this case<sup>14</sup>. We also investigated the use of on-label versus off-label DMTs across the region. On-label DMT is a drug used for a condition for which it has been officially approved. Off-label use is the use of drugs for an unapproved indication. Interferons beta 1a and 1b, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, siponimod, cladribine, natalizumab, ocrelizumab, alemtuzumab and mitoxantrone are US FDA and EMA approved for the treatment of MS<sup>15,16</sup>. Conversely, rituximab, azathioprine, cyclophosphamide, fludarabine, fumadern, leflunomide, methotrexate, and minocycline are used off-label<sup>17</sup>. For the purpose of this analysis, DMTs were divided into three categories based on their presumed efficacy: low, moderate or high efficacy. This was based on either head to head trials<sup>18-21</sup> or real world evidence based on propensity score matching comparisons<sup>22-24</sup>. The different barriers to treatment reported were stratified by Gross National Income (GNI) per capita. GNI is defined and reported by the World Bank and allows classification of countries into high, upper middle, lower middle, and low income. In the MENA region, Kuwait, Oman, Qatar, Bahrain, Saudi

Arabia, and UAE are considered high-income countries. Iraq, Lebanon and Libya are upper-middle income. Algeria, Egypt, Morocco, Palestine, and Tunisia are lower-middle income and Sudan, Syria, and Yemen are low-income countries<sup>25</sup>.

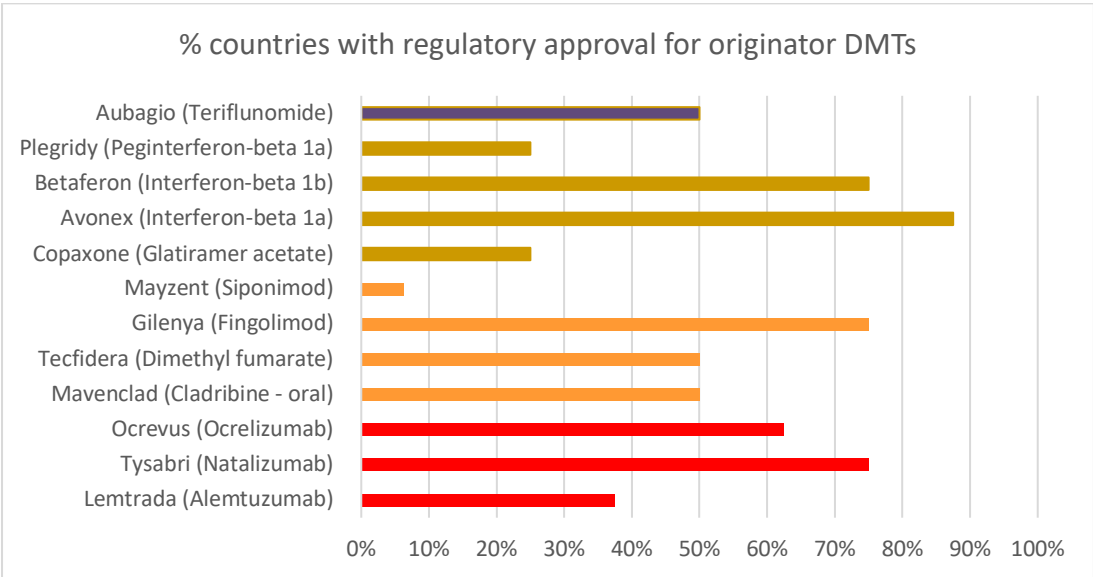
**III.4. Results**

**III.4.1. Participating Countries**

16 countries in the MENA region that contributed data to the Atlas of MS were included in this study: Algeria, Egypt, Iraq, Lebanon, Libya, Morocco, Palestine, Sudan, Syria, Tunisia, Yemen, Kuwait, Oman, Qatar, Saudi Arabia, and UAE. Although very limited data was provided by Yemen, such data were included where available. The Gulf countries in this study refer to Kuwait, Oman, Qatar, Saudi Arabia, and UAE.

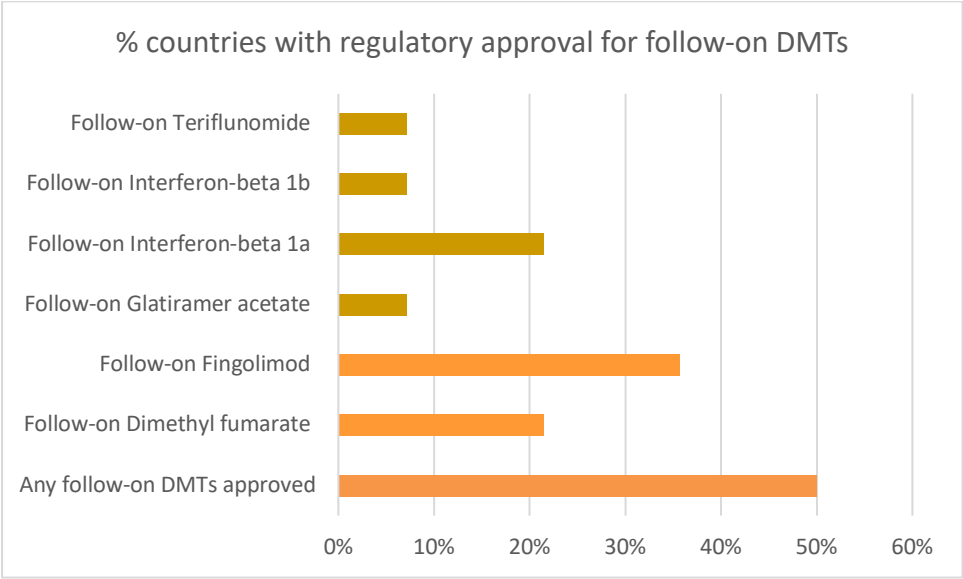
**III.4.2. Regulatory Approval of DMTs in the MENA Region**

Two countries did not have any originator DMTs approved (Sudan and Syria). Among low efficacy originator DMTs, interferons were the most widely approved DMTs (14/16 or 88% of countries) followed by glatiramer acetate (50%) and pegylated interferon (25%) (**Figure 1**). As for the moderate-efficacy DMTs, fingolimod was approved in 12 out of 16 countries (75%) followed by dimethyl-fumarate and cladribine, each approved in 8/16 countries (50%). Siponimod was only approved in Kuwait at the time of this analysis. Three countries (19%) did not have any high efficacy DMTs (natalizumab, ocrelizumab and alemtuzumab) approved. Natalizumab and ocrelizumab were approved in 12/16 (75%) and 10/16 (63%) of countries, respectively and alemtuzumab in 6/16 (38%).



MENA = Middle East and North Africa; DMTs= Disease-Modifying Therapies  
**Figure 1. Percentage of MENA countries with Regulatory Approval for Originator DMTs**  
 Green = High efficacy; Yellow = Moderate efficacy; Red = Low efficacy

On the other hand, follow-on DMTs (generic or copy) were approved in half (50%) of the MENA countries (**Figure 2**). Follow-on fingolimod received approval in 5 countries (36%): Libya, Syria, Tunisia, Saudi Arabia and United Arab Emirates. Follow-on dimethyl fumarate and intramuscular interferon beta 1a were each approved in 3 countries (21%). Follow-on glatiramer acetate was only approved in Tunisia and follow-on interferon beta 1b and teriflunomide were both approved in Syria.



MENA = Middle East and North Africa; DMTs= Disease-Modifying Therapies

**Figure 2. Proportion of MENA countries with Regulatory Approval for Generic and Follow-on DMTs**

Yellow = Moderate efficacy; Red = Low efficacy

**III.4.3. Use of On- and Off-Label DMTs in the MENA Region**

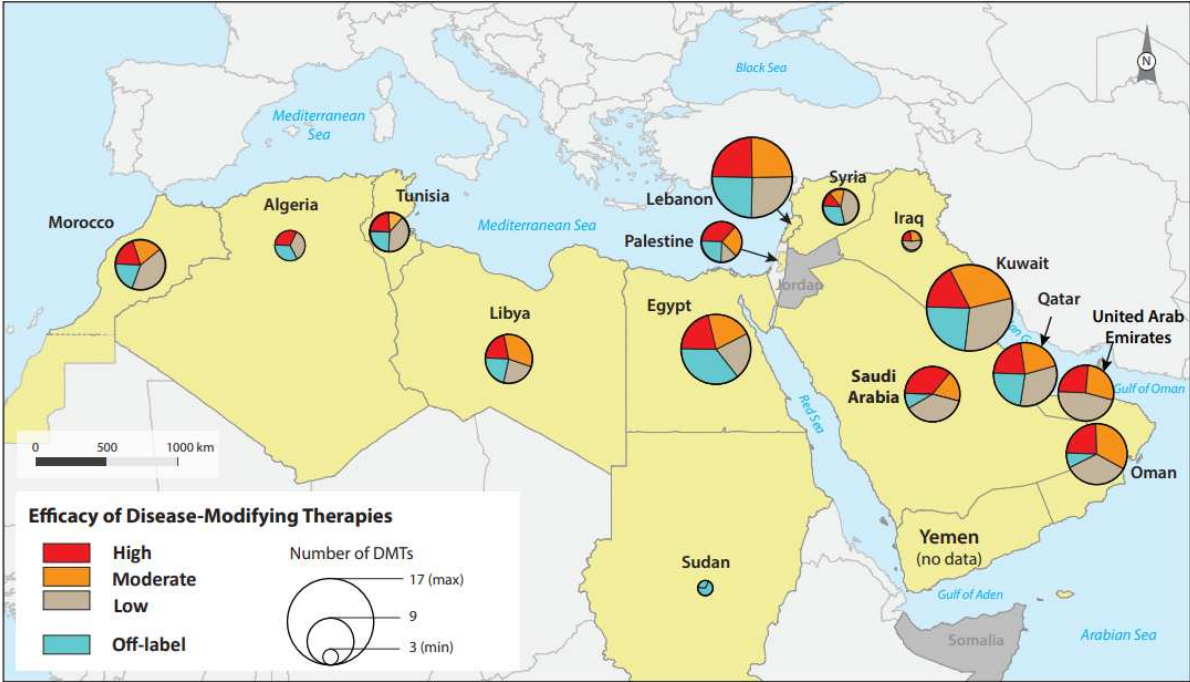
Thirteen countries in the MENA region reported the use of off-label DMTs (**Figure 3**), including: rituximab, azathioprine, cyclophosphamide, fludarabine, fumaderm, leflunomide, methotrexate, and minocycline.

Sudan reported lack of access to any approved DMT, but did report access to off-label DMTs; however, no high efficacy DMTs, either on- or off-label, were available. Sudan is the only country in the MENA region lacking access to any high efficacy DMT.

In Syria, none of the on-label high efficacy DMTs were available, but report access to rituximab, an off-label high efficacy DMT widely used in MS worldwide. Overall, rituximab was used in 11/15 (73%) countries.

The most commonly used on-label DMTs in the MENA region countries were natalizumab (87%) as high efficacy DMT, fingolimod (87%) as moderate efficacy DMT and interferons (beta 1a and 1b, 93% and 87% respectively) as low efficacy DMTs. Among off-label DMTs, azathioprine (low efficacy) and rituximab (high efficacy) were the two most widely used (73% of both) (Figure 3).

**Figure 3: DMTs in Use in MENA by Country**



**Figure 3A: Number of DMTs Available in Each Country with Proportions of On-label DMT Efficacy and Off-label DMT use Indicated**



Treatment availability Countries	DMTs																						
	Alemtuzumab	Mitoxantrone	Natalizumab	Ocrelizumab	Cladribine (IV)	Cladribine (oral)	Dimethyl fumarate	Fingolimod	Siponimod	Glatiramer acetate	Interferon beta 1a	Interferon-beta 1b	Peginterferon-beta 1a	Teriflunomide	Azathioprine	Cyclophosphamide	Fludarabine	Fumaderm	Leflunomide	Methotrexate	Minocycline	Rituximab	
Algeria																							
Egypt																							
Iraq																							
Lebanon																							
Libya																							
Morocco																							
Palestine																							
Sudan																							
Syria																							
Tunisia																							
Kuwait																							
Oman																							
Qatar																							
Saudi Arabia																							
United Arab Emirates																							

\* Yemen did not provide answers for this question  
 MENA = Middle East and North Africa; DMTs= Disease-Modifying Therapies; IV= Intravenous

**Figure 3B: List of DMTs in Use by Country**

### III.4.4. Barriers to Treatment

The major barriers for PwMS to access DMTs sorted by country and GNI per capita are shown in **Figure 4**. Overall, 9 countries (56%) reported some barriers to treatment access.

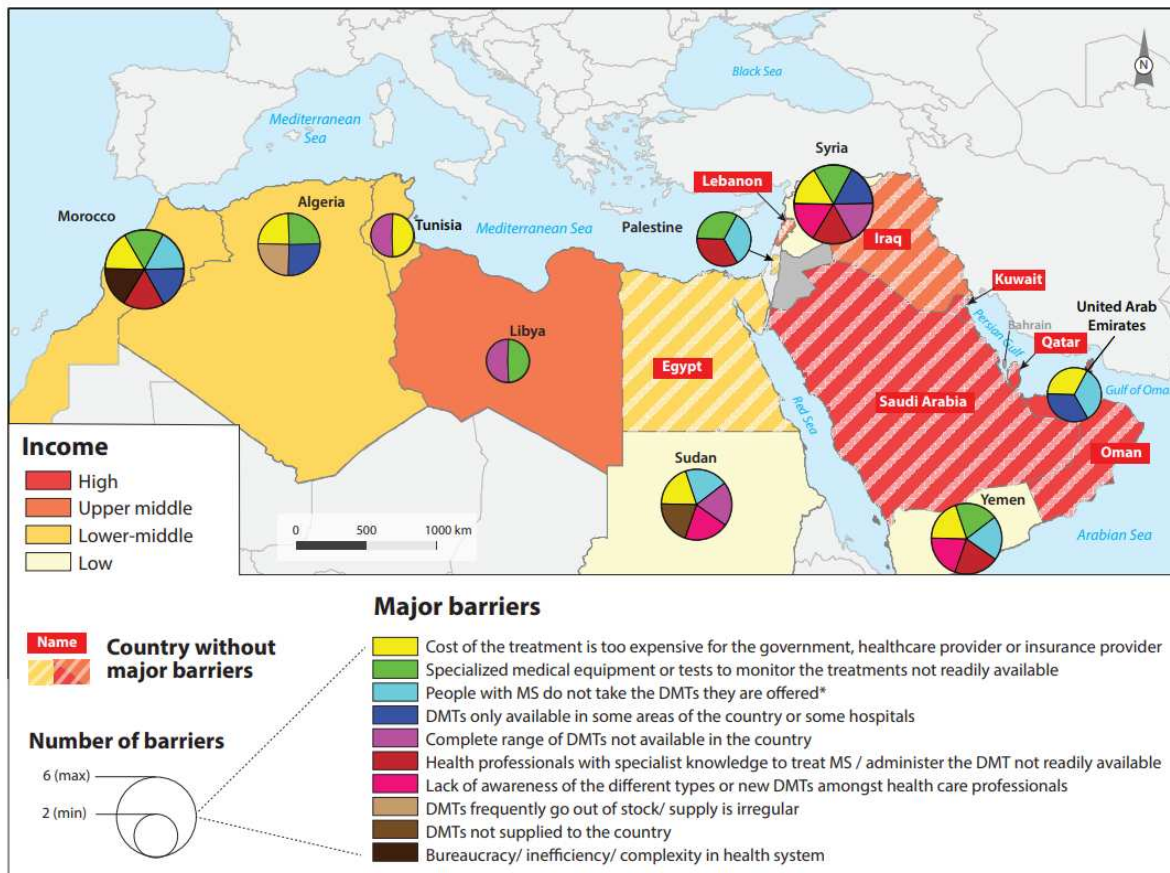
Cost of treatment, which refers to cost for governments, healthcare providers, or insurance providers, was the most important barrier, reported by nearly half (47%) of the countries.

Access to specialized medical equipment or tests to monitor treatment were readily available in all Gulf countries, but 40% (6/16) of MENA countries reported lack of specialized medical equipment and tests.

Around a third of the countries (5/16) reported poor adherence to prescribed DMTs, primarily due to high out of pocket cost, inability to travel, or fear of adverse effects.

Other reasons for non-accessibility to DMTs included: availability of DMTs only in some areas of the country or in few hospitals (4/16), non-availability of the complete range of DMTs (4/16), lack of neurologists specialized in MS (4/16), and lack of awareness among health care professionals regarding the safety, efficacy and administration of DMTs (3/16).

Based on the reports given, the number of barriers to treatment access appears to be linked with GNI per capita. High income countries (Gulf countries) report the fewest barriers, while low income countries report the highest number of barriers.



**\*Main reasons: Cost is too high / people can't travel / concern about side effects**  
 GNI= Gross national income; DMTs= Disease-Modifying Therapies; MS=Multiple Sclerosis

**Figure 4. Major Barriers to Treatment by Country, sorted by GNI per Capita**

### III.4.5. Cost of DMTs

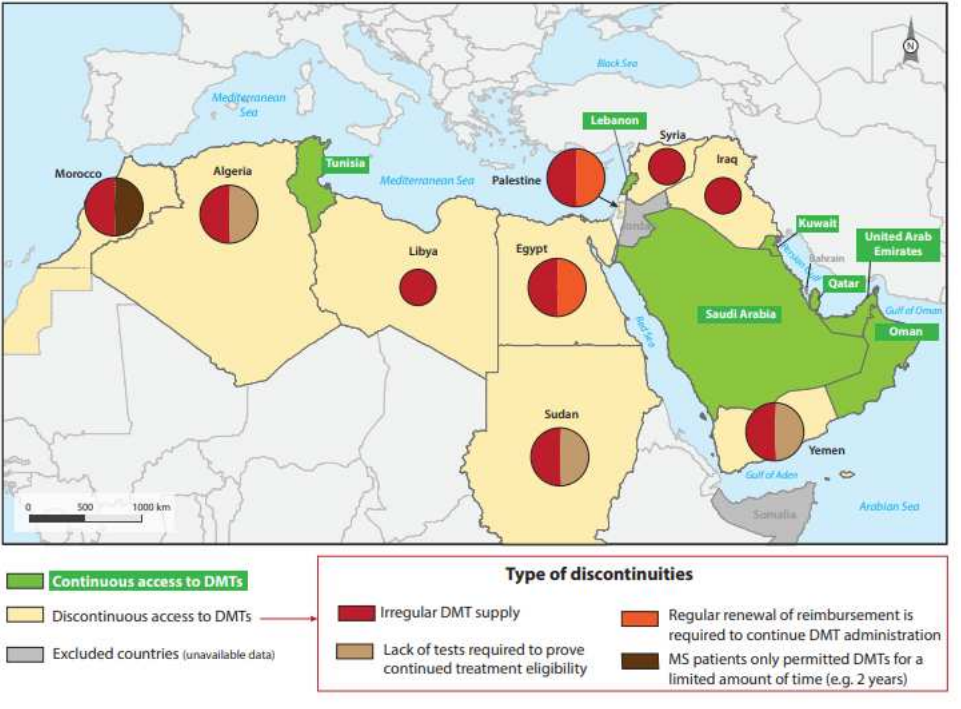
The most commonly reported barrier to treatment access in the MENA region was treatment cost for governments, healthcare providers and insurance providers. On the other hand, in 67% (10/15) of countries, PwMS are required to pay for a proportion of their treatment. In 4 of these countries (Morocco, Sudan, Qatar and Palestine), over half of them have to contribute towards the cost of DMTs, while in the remaining 6 countries the proportion is  $\leq 25\%$ . In most MENA countries however, MS patients who do contribute to DMT payment, typically pay less than 25% of the total cost except for Sudan where it can reach 75% and Egypt and the UAE where it can go up to 50%.

There are different reasons why PwMS pay towards the cost of DMTs. It is either due to lack of health insurance (Morocco, Oman and UAE), or lack of coverage of DMTs by their health insurance (Sudan and UAE). In other cases, health insurance covers DMTs, but the

recommended DMT is not on the approved list of therapies or they do not meet the eligibility criteria (Egypt, Morocco, Palestine, and UAE).

**III.4.6. Continuous Access to DMTs after Treatment Initiation**

More than half (56%) of the MENA region countries reported issues with continuing treatment due to irregular supply (9/16), lack of monitoring tests required to prove continued eligibility for treatment continuation (3/16), need for regular renewal of reimbursement (2/16) or time-limited supply of DMTs (1/16) (**Figure 5**). The most common barrier to treatment continuation was irregular supply of DMTs, reported by 56% of countries. Algeria, Sudan, and Yemen require proof of eligibility to continue treatment. Morocco is the only country reporting a time-limited supply of DMTs. Lebanon, Tunisia and the Gulf countries are the only countries with continuous access to MS treatments after treatment initiation.



DMTs= Disease-Modifying Therapies; MS=Multiple Sclerosis

**Figure 5. Continuous Access to DMTs after Treatment Initiation**

**III.5. Discussion**

The treatment of MS has evolved exponentially over the last three decades with the introduction of high efficacy DMTs targeting different immunological pathways. This is the first study evaluating access to MS therapies in the region.

This study showed that DMTs, including high-efficacy DMTs, are used in most MENA countries. However, there were significant disparities across the region with some countries

having access to most DMTs such as Kuwait, Oman, Saudi Arabia, UAE and Qatar, while for others such as Tunisia, Algeria, Syria, Iraq and Sudan, the therapeutic options were limited, especially for high efficacy DMTs. This disparity is likely due to the considerable disparities in socioeconomic status across countries of the MENA region. According to a 2018 study by the World Inequality Lab<sup>26</sup>, the Middle East is the most unequal region in the world with a regional economic inequality as high as that measured within some of the most unequal countries, such as Brazil and South Africa. Other potential factors contributing to this disparity are political instability and wars in countries like Syria, Sudan, Palestine, Libya and Yemen. Inequity to accessing DMTs within countries is also an important factor to consider; availability and affordability of DMTs can vary greatly depending on which DMTs are covered by a particular health system scheme or insurance.

Compared to other parts of the world, 88% of MENA countries reported having access to approved originator DMTs which is similar to Southeast Asia (83%) and Western Pacific (89%) but lower than Europe (98%) and the USA (94%) according to the latest Atlas of MS<sup>1</sup>. Follow-on DMTs are also available in half of the MENA countries, which is slightly lower than the global average of 64% as per global MSIF data<sup>1</sup>. Follow-on DMTs are important, especially in low income countries, due to their lower price and local production in some cases. In that respect, they might fill an important gap in treatment access for PwMS.

The high accessibility to DMTs across the MENA region is due to multiple factors including increased number of specialized MS neurologists, emergence of multidisciplinary MS Centers which are now participating in global multicenter clinical trials, the foundation of MENACTRIMS which created a regional organization that has gradually become the most significant stimulus for clinical education, research and awareness about MS among health care professionals and patients' societies, the publication of regional treatment guidelines<sup>12</sup>, and the establishment of the MENACTRIMS registry<sup>27</sup>.

The proportion of countries that reported using off-label DMTs in the MENA region was similar to the global average (87%). Among off-label DMTs, azathioprine and rituximab were the most commonly used. The main reasons for the use of off-label DMTs were lack of availability of similar approved DMTs in countries such as Syria where rituximab was the only available high-efficacy DMT, or the unaffordability of originator DMTs. An example highlighting the use of off-label DMTs in the MENA region is the Lebanese experience in treating refugees<sup>28</sup>. Zeineddine et al.<sup>29</sup> reported the use of rituximab and off-label immunosuppressive medications, such as mycophenolate mofetil, cyclophosphamide, azathioprine, and methotrexate, in Syrian and Palestinian refugees who had no insurance coverage for their chronic medications and could not afford expensive DMTs. In fact, rituximab was the most cost-effective therapy for refugees. The use of off-label DMTs was further encouraged by the recent publication of the MSIF

guidelines for the use of off-label azathioprine and rituximab for the treatment of MS in low-resource settings<sup>29</sup>.

The most important barrier to MS treatment reported in the MENA region as well as worldwide<sup>30,31</sup> was treatment cost to governments, healthcare system and insurance providers, cited by experts in around half of all reporting countries. In addition, it was not uncommon for PwMS to pay part of the cost of their DMTs. This was reported in 63% of the MENA countries which is slightly higher than the global rate of 57%. Although in most MENA countries contribution to DMT payment was less than 50% of the total cost, this co-payment could be considerable given the high price of most DMTs, making treatment unaffordable for many PwMS. In fact, the prices of DMTs have risen dramatically over the last 15 years, far outpacing inflation, with a current mean price of more than \$86,000 per year to treat one person<sup>32</sup>. Similar to our findings, a study from the USA<sup>33</sup> showed that half of the PwMS reported difficulty accessing DMTs due to high out-of-pocket costs and approval requirements by insurance. The second most common barrier to MS treatment was access to specialized medical equipment or tests to monitor treatment, reported by 40% of MENA countries, which was higher than the global rate (27%)<sup>1</sup>.

Our study showed that the number of barriers to treatment appeared to be linked to the GNI per capita. High income countries (Gulf countries) reported the fewest, while low income countries reported the most barriers to access to DMTs. This can be explained by the fact that MS is a chronic disease with huge economic burden on healthcare systems and societies, with direct costs of prescription drugs and indirect productivity loss being important cost drivers<sup>34</sup>. A recent study from Lebanon<sup>35</sup> reported an average per-person annual medical cost of \$25,645 with DMTs accounting for the largest proportion of this cost.

Furthermore, more than half (56%) of the MENA region countries reported problems with continuous provision of DMTs, which was higher than the global average of 48%<sup>1</sup>. The most common barrier to continuous access to treatment was irregular supply of DMTs, reported by 56% of countries, which is much higher compared to the global average, where only 27% of countries reported such issue<sup>1</sup>.

There are several limitations to our study which used data collected via the Atlas of MS international survey. Although the Atlas of MS is one of the most comprehensive global data sources on clinical management of MS, the initially collected data relied on expert opinions of clinicians or specialists in each country since few peer-reviewed publications exist on the availability and access to DMTs in the MENA region. However, we improved confidence in the data collected by asking country coordinators to collaborate with other local experts when submitting answers to the survey and to report data sources if available. Moreover, for relevant

questions in the survey, country coordinators were asked to indicate the source of their information. Crucially, for the data presented in this article, most countries referenced independent evidence such as data from academic papers or patient data (surveys or registries). Another limitation is the fact that data collected is at a national level and might not reflect disparities and barriers to treatment access within the country.

### **III.6. Conclusion**

In conclusion, our study shows that although most MENA countries have access to some DMTs, whether originator, follow-on, or off-label, more than half of them report problems with treatment access and continuation, especially in low and middle income countries. Recognizing and addressing barriers to treatment access encountered by PwMS is essential to improve their quality of life and disease outcomes. Our study can support the development of a comprehensive strategy for MS care in MENA countries which is a fundamental step to improve person-centered management and promote the health of PwMS. Such targeted regional strategy needs to address the variations in access to treatment for PwMS. A greater investment in healthcare infrastructure devoted to MS is required in many MENA countries. Since affordability was a key barrier to accessing DMTs, local reimbursement decisions should be based on policies that improve affordability of a range of DMTs and continuity of treatment. Given the widespread use of off-label DMTs, evidence-based guidance on the use of off-label DMTs should be made available to support clinical decision-making and reimbursement decisions.

In addition, local MS registries and databases need to be further developed in order to provide epidemiological and clinical data to help assess, compare and enhance the status of PwMS across the MENA region. Finally, local MS patients' societies should be supported, and their role enhanced, as they can provide key services such as programs or resources to help PwMS navigate the complexity of accessing DMTs. Such strategies will allow better access to DMTs in our MENA region, leading to significant benefits to PwMS and the whole healthcare system.

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## **Chapter IV. Quality of life and Access to Treatment of Patients with Multiple Sclerosis in Times of Economic crisis: The Lebanese Experience**

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### **IV.1. Background**

Following the comprehensive analysis of barriers to accessing DMTs across the MENA region, it became evident that socio-economic disparities significantly impact the availability and continuity of MS treatment. The findings of the first study underscored the need for targeted strategies to enhance treatment access, particularly in low- and middle-income countries where economic constraints exacerbate healthcare inequities. Building on these insights, the subsequent study focuses on the specific context of Lebanon, a country currently facing a severe economic crisis that has further constrained access to essential MS treatments. This study explores how the ongoing economic crisis has adversely affected the QOL of Lebanese MS patients, with a particular emphasis on how treatment accessibility during this crisis has compounded the challenges faced by this population. By linking the broader regional challenges identified in the first study with the more focused analysis of Lebanon, this second study collectively highlights the critical importance of addressing economic and healthcare barriers to improve outcomes for MS patients both regionally and globally.

Similarly, to the first study, the results of this work was presented as a poster presentation during the 7<sup>th</sup> MENACTRIMS Congress on November 11-12, 2022 in Cairo, Egypt.

Furthermore, the manuscript was submitted for publication in the Multiple Sclerosis journal (MSJ) and is currently under review.

## **Abstract**

**Background:** Multiple sclerosis (MS) is a demyelinating disease of the central nervous system that can lead to lifelong disability, significantly impacting patient's quality of life (QOL). The current Lebanese economic crisis led to limited accessibility to MS therapies and had a major impact on QOL.

**Objective:** The aim of this study was to assess QOL in a cohort of Lebanese MS patients, and its association with socio-demographic factors, disease characteristics, and treatment accessibility.

**Methods:** A cross-sectional, survey-based study was conducted between June and September 2022 in Lebanese patients with confirmed MS diagnosis as per the 2017 McDonald criteria. Structured questionnaires were used to obtain (1) socio-demographic and medical information, (2) QOL assessment using the MS International QOL questionnaire (MusiQoL), and (3) information related to barriers in accessing MS therapies. All questionnaires were administered via telephone call.

**Results:** A total of 350 MS patients were included in the study. Most participants (92.3%) were diagnosed with relapsing-remitting MS and were females (65.1%) with a mean age of  $39.45 \pm 11.43$  years. The mean MusiQol global index was  $69.25 \pm 11.53$ . In the multivariate analysis, younger age, higher level of education, being employed, being married, living outside the capital Beirut, and having no physical disability were significantly associated with higher MusiQol global index scores. A total of 216 Lebanese MS patients (61.7%) had no access to MS treatments due to the economic crisis. Treatment discontinuation and lack of governmental or private insurance were significant predictors of lower MusiQol scores ( $p < 0.05$ ).

**Conclusion:** The economic crisis and resultant recession in Lebanon had a significantly negative impact on QOL and treatment accessibility of MS patients. Socio-demographic factors, disease characteristics and treatment accessibility were strong predictors of QOL.

**Keywords:** quality of life, MusiQol, accessibility, disease-modifying therapies, multiple sclerosis, economic crisis, Lebanon

## **IV.2. Introduction**

Multiple sclerosis (MS) is a chronic autoimmune disease affecting the CNS and characterized mainly by demyelination and neuronal loss. It predominantly affects patients aged 20 to 40 years<sup>1</sup>. MS is associated with clinical manifestations that can influence the patient's personal life and have considerable impact on their QOL<sup>1</sup>.

Health-related QOL (HRQOL) is an important concept whereby the patient's health is evaluated through physical, emotional, mental, and social components<sup>2</sup>. These QOL components can be affected by several sociodemographic and clinical factors<sup>3</sup>. Most studies have shown that patients with MS have lower QOL compared to either healthy individuals or even patients with other chronic diseases such as diabetes, congestive heart failure, myocardial infarction and hypertension<sup>4,5</sup>. Disability, fatigue, depression, anxiety, quality of sleep, pain, high medical costs and inability to work or carry-on usual life functions are some of the determinants of poor QOL in MS patients<sup>6</sup>. A cross-sectional retrospective study conducted in 16 countries, showed that, in France, fatigue and cognitive impairment had the worst impact on QOL in patients with MS<sup>7</sup>. Another European multi-country cross-sectional study<sup>8</sup> showed that disability status and primary progressive phenotype were negatively correlated with HRQOL. In a cross-sectional analysis involving 949 MS patients, Berrigan et al.<sup>9</sup> demonstrated that increased disability, depression, anxiety, fatigue, and physical comorbidities were associated with decreased HRQOL in MS. Similarly, a study from Saudi Arabia (KSA) identified psychological state, pain, vitality, sexual dysfunction, fatigue, financial problems, employment difficulties, and the perception of MS within the community as risk factors affecting QOL in patients with MS<sup>10</sup>.

In Lebanon, the economic crisis that started in 2019 and is still ongoing, led to unemployment, poverty, business closures, inflation, limited access to foreign exchange and imports, and most importantly critical shortage of medications. As a result, QOL of the Lebanese population in general was negatively impacted, but more so for patients suffering from chronic diseases including MS. The aim of this study was (1) to assess the QOL of Lebanese MS patients during this economic crisis and (2) to determine the association of QOL with socio-demographic factors, disease characteristics and treatment accessibility.

## **IV.3. Methods**

### **IV.3.1. Study Design and Inclusion/Exclusion Criteria**

This cross-sectional study was conducted among Lebanese MS patients over a period of 3 months. Patients older than 18 years, diagnosed with MS (RRMS or PMS) according to the 2017 McDonald criteria<sup>11</sup> by a specialized neurologist and residing in Lebanon were included.

Patients receiving their treatment outside Lebanon, those perceived to have clinically significant cognitive deficits, and those who refused to fill the questionnaire were excluded.

### IV.3.2. Data Collection

Data were acquired between July and September 2022, through a questionnaire completed by two pharmacists for each MS patient via phone calls lasting 15-20 minutes. Prior to data collection, a pilot study was conducted on 10 MS patients to estimate the time needed for completion of the survey and to standardize the interview process. Patients were randomly selected from the authors' neurology clinics, all of whom experienced in MS management and treatment. After a thorough explanation of the study's purpose and assurance of anonymity, confidentiality, and the right to withdraw from the study at any time, verbal informed consent was obtained from every subject. The study was approved by the IRB of the Lebanese University.

### IV.3.3. Study Questionnaire

The questionnaire (**Appendix 2**) was constructed based on previous questionnaires adapted in studies from Middle Eastern countries including Saudi Arabia<sup>10</sup>, Oman<sup>2</sup>, Iran<sup>12</sup>, and from international studies<sup>13</sup>. It was developed in English and translated into Arabic, then back to English for language validation. It consisted of 34 questions divided into three major sections. Section one included sociodemographic (gender, age, district of residence, educational level, marital status, employment, monthly income, family history, type of insurance and treatment provider) and clinical variables (disease phenotype, disease duration, physical disability, and presence of comorbidities). Section two consisted of the MusiQol questionnaire to assess HRQOL. The MusiQoL is a multi-dimensional tool including 31 items divided into 9 dimensions: activity of daily living (ADL); psychological well-being (PWB); symptoms (SPT); relationships with friends (Rfr); relationships with family (Rfa); relationships with health care system (RHCS); sentimental and sexual life (SSL); coping (COP); and rejection (REJ). The items were answered using a five-point Likert scale, defined as '1 – Never/Not at all', '2 – Rarely/A little', '3 – Sometimes/Somewhat', '4 – Often/A lot', '5 – Always/Very much' and each item is given a score from 1 to 5<sup>14</sup>. Nine standardized scores of the dimensions and one global index ranging from 0 to 100 can be derived. The higher the MusiQol score, the better the patient's HRQOL. A score of up to 40 was considered poor HRQOL, a score of 40.01-80 was considered moderate HRQOL, and a score  $\geq 80.01$  was considered good HRQOL<sup>2</sup>. It can be applied internationally based on previous testing of the construct validity, internal consistency, reproducibility, and external consistency of the score. Internal consistency was satisfactory for all dimensions where Cronbach's alpha coefficients ranged from 0.68 to 0.92<sup>14</sup>. To have access to the Arabic version (**Appendix 7**)<sup>15</sup>, a request was submitted to the developer who

approved its use. The final section of the questionnaire assessed treatment accessibility. If patients had no access to their MS treatment locally, two more questions were asked: the first one regarding exit strategy: whether the patient was buying a DMT from abroad, substituting it with other available MS treatments, modifying the dosage through skipping doses, or discontinuing treatment altogether. The second question assessed the main reason for non-accessibility to DMTs.

#### **IV.3.4. Sample Size Calculation**

The Epi Info™ version 7.2.5.0 category "Population Survey" was used to calculate the sample size. The Lebanese MS population size was fixed at 2437 based on the latest study conducted in 2018 to evaluate the incidence and prevalence of MS in Lebanon<sup>16</sup>. The expected frequency was fixed at 51.4% based on the cross-sectional survey conducted in 2019 on 177 Omani patients with MS using the MusiQoL instrument in which 51.4% of patients had poor QOL, 48.6% had moderate QOL, and none had a good QOL<sup>2</sup>. The acceptable margin of error was fixed at 5%, and the design effect and clusters were fixed to 1.0. With a 95% confidence interval, a minimal sample size of 332 was needed to represent the Lebanese MS population.

#### **IV.3.5. Statistical Analysis**

The Statistical Package for Social Science (SPSS) version 23.0 was used for data entry and data analysis. For accuracy, the data was audited by two investigators. Descriptive summaries of sociodemographic and clinical characteristics were performed to describe the sample. Count and percentage were used for categorical variables and median and range for numerical data. In the bivariate analysis, group comparisons of MusiQoL were performed using independent t-tests and one-way analysis of variance (ANOVA) with post-hoc (Bonferroni) test. Pearson correlations and simple linear regression were used to assess associations with quantitative variables. Non-parametric Kruskal-Wallis H and Mann-Whitney U tests were used when the normality of quantitative variables and/or homogeneity of variances conditions were not satisfied. Variables showing a p-value < 0.2 on those sets of tests were then entered as predictors into the forward multiple regression analysis. The unstandardized coefficient ( $\beta$ ), p-value ( $p$ ), standardized coefficient ( $\beta$ ), adjusted R<sup>2</sup>, and VIF were recorded.

The confidence interval (CI) was set at 95% with a 5% margin of error. A p-value < 0.050 was considered statistically significant for all tests.

## IV.4. Results

### IV.4.1. Baseline Characteristics

Out of 597 MS patients contacted, 350 consented to participate in the study. The mean age was  $39.4 \pm 11.4$ , years and 65.1% (228) were females. One hundred sixteen (33.2%) patients lived in the capital Beirut, and more than half ( $n=204$ , 58.3%) achieved college education. The majority of recruited patients ( $n=219$ ; 62.6%) were married and employed ( $n=167$ ; 47.7%). Regarding clinical characteristics, 92.3% had RRMS ( $n=323$ ), 77.4% had no physical disabilities ( $n=271$ ), and 78.8% had no concomitant comorbidities (**Table 1**).

**Table 1: Baseline Characteristics of Patients**

Characteristic	All (n=350)
Age, years, mean (SD)	39.4 (11.4)
Disease duration, years, mean (SD)	8.5 (6.2)
Females, n (%)	228 (65.1)
Residency, n (%)	
• Beirut	116 (33.2)
• Bekaa	48 (13.7)
• Mount Lebanon	61 (17.4)
• South	26 (7.4)
• North	99 (28.3)
Marital Status, n (%)	
• Single	101 (28.8)
• Married	219 (62.6)
• Divorced	24 (6.9)
• Widowed	6 (1.7)
Educational Level, n (%)	
• Elementary School	15 (4.3)
• High School	125 (35.7)
• University	204 (58.3)
• Uneducated	6 (1.7)
Employment, n (%)	
• Employed	167 (47.7)
• Unemployed	181 (51.7)
• Retired	2 (0.6)
Monthly Income Level in USD, n (%)	
• 600-2,499	79 (22.6)
• 2,500-3,999	32 (9.2)
• 4,000-6,999	26 (7.4)
• 7,000-12,999	12 (3.4)
• $\geq 13,000$	49 (14.0)
• No answer	152 (43.4)
Family History for MS, n (%)	
• Yes	59 (16.9)
• No	291 (83.1)
Treatment Provider, n (%)	
• Family Physician	3 (0.8)
• Neurologist	227 (64.9)
• Specialized Neurologist/MS Center	120 (34.3)

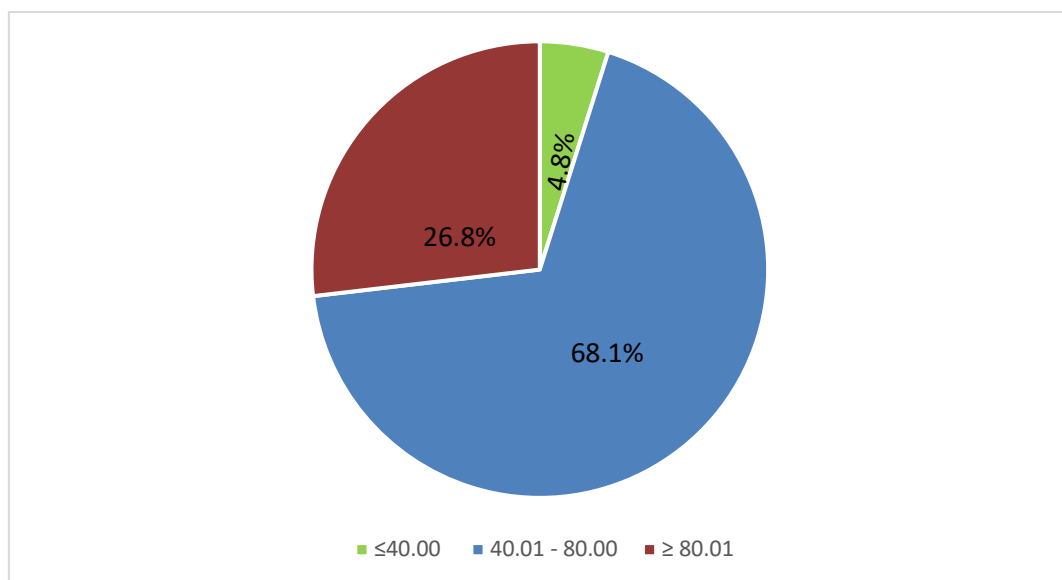


<b>Insurance Type, n (%)</b>	
• Governmental Insurance	232 (66.3)
• Private Insurance	48 (13.7)
• Self-Payers	70 (20.0)
<b>MS Phenotype, n (%)</b>	
• RRMS	323 (92.3)
• PMS	27 (7.7)
<b>Physical Disability, n (%)</b>	
• With any disability	79 (22.6)
• No disability	271 (77.4)
<b>Comorbidities, n (%)</b>	
• None	276 (78.8)
• CVD/HTN	17 (4.9)
• Diabetes	4 (1.1)
• Pulmonary diseases	2 (0.6)
• Hepatic diseases	3 (0.9)
• Autoimmune diseases	14 (4.0)
• Malignancy	6 (1.7)
• HTN and Diabetes	5 (1.4)
• Psychiatric diseases	14 (4.0)
• Others	9 (2.6)

CVD: cardiovascular disease; HTN: hypertension; MS: multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; PMS: progressive multiple sclerosis; SD: standard deviation; USD: U.S. Dollar

#### IV.4.2. MusiQol Scores

The reported mean MusiQol global index was  $69.20 \pm 11.50$ . Following categorization of the global index, 68.1% had a MusiQol score ranging between 40.01 and 80.00, 26.8 % had a score  $\geq 80.01$ , and 4.8% had a score  $\leq 40.00$  (**Figure 1**).



**Figure 1: Percentage of MS Patients in Each Category of the MusiQol Global Index**

The “COP” and “REJ” MusiQol dimensions recorded the highest scores ( $80.50 \pm 28.60$  and  $93.80 \pm 18.10$ , respectively), while the “Rfr” dimension scored the lowest ( $42.76 \pm 38.20$ ) (**Table 2**).

**Table 2: Mean of MusiQol Global Index and Dimension Scores**

Dimensions of MusiQol	Mean $\pm$ SD
1. ADL	65.00 $\pm$ 28.70
2. PWB	66.10 $\pm$ 26.40
3. SPT	69.00 $\pm$ 24.10
4. Rfr	42.76 $\pm$ 38.20
5. Rfa	77.20 $\pm$ 26.90
6. SSL	51.60 $\pm$ 35.10
7. COP	80.50 $\pm$ 28.60
8. REJ	93.80 $\pm$ 18.10
9. RHCS	77.10 $\pm$ 24.10
<b>Global MusiQol score</b>	<b>69.20 <math>\pm</math> 11.50</b>

*ADL: Activities of daily living; COP: Coping; MusiQoL: Multiple Sclerosis International Quality of Life; PWB: Psychological wellbeing; REJ: Rejection; RHCS: Relationship with the healthcare system; Rfa: Relationship with family; Rfr: Relationship with friends; SD: standard deviation; SPT: Symptoms; SSL: Sentimental and sexual life.*

#### IV.4.3. Access to DMTs

Unfortunately, the majority of MS patients residing in Lebanon ( $n=216$ , 61.5%) had no access to treatment during the economic crisis. The two main reasons for inaccessibility were unaffordable high cost of the medications ( $n=100$ , 28.5%) and medication shortage ( $n=98$ , 27.9%). Patients unable to access their medications chose to discontinue treatment ( $n=87$ , 40.3%), buy medications from outside Lebanon ( $n= 55$ , 15.7%), shift to other available MS medications ( $n= 54$ , 15.4%), or skip doses to avoid treatment discontinuation ( $n=20$ , 5.7%).

#### IV.4.4. Sociodemographic and Clinical Factors Associated with MusiQoL

The MusiQol global index was significantly associated with many of the socio-demographic, clinical and treatment accessibility factors (**Table 3**). In bivariate linear regression analysis, older age was associated with lower MusiQol scores ( $\beta= -0.42$ ,  $p< 0.001$ ). Men had higher scores compared to women (mean  $\pm$  SD,  $72.06 \pm 15.10$  vs  $67.74 \pm 15.57$ ,  $p= 0.013$ ). Higher education (mean  $\pm$  SD,  $74.34 \pm 13.92$ ,  $p<0 .001$ ), being married (mean  $\pm$  SD,  $70.78 \pm 14.32$ ,  $p< 0.001$ ), being employed (mean  $\pm$  SD,  $75.32 \pm 11.54$ ,  $p< 0.001$ ), receiving treatment at a specialized MS center (mean  $\pm$  SD,  $72.14 \pm 16.97$ ,  $p= 0.039$ ) and having no comorbidities (mean  $\pm$  SD,  $70.30 \pm 14.94$ ,  $p= 0.001$ ) were significantly associated with a higher MusiQol score. Lower MusiQol scores were associated with having PMS compared to RRMS (mean  $\pm$  SD,  $57.79 \pm 15.04$  vs  $70.20 \pm 15.20$ , respectively,  $p< 0.001$ ), and with physical disability (mean  $\pm$  SD,  $58.43 \pm 15.10$  vs  $72.38 \pm 14.22$  respectively,  $p< 0.001$ ).

Regarding accessibility to DMTs, the MusiQoL score was significantly higher in patients who had access to therapy compared to those who did not (mean  $\pm$  SD, 72.14  $\pm$ 13.97 vs 67.33 $\pm$ 16.20 respectively,  $p= 0.005$ ). In patients with no access to treatment, MusiQoL score was lowest among patients who discontinued their medication (mean  $\pm$  SD, 60.80  $\pm$  15.04,  $p <0.001$ ).

**Table 3: Associations between MusiQoL Global Index and Patients’ Socio-demographic and Clinical Factors: A Bivariate Analysis**

Variables	MusiQoL Global Index, mean (SD)	p-value
Age (Years)	39.45(11.43)	< 0.001
Disease duration (Years)	8.54 (6.16)	0.062
Gender	Male	72.06 (15.10)
	Female	67.74 (15.57)
Residency	Beirut	69.38 (16.49)
	Bekaa	62.85 (14.99)
	Mount Lebanon	75.53 (17.76)
	South	67.60 (13.58)
	North	68.74 (12.08)
Marital Status	Single	69.94 (15.61)
	Married	70.78 (14.32)
	Divorced	57.39 (19.01)
	Widowed	49.01 (8.32)
Educational Level	Elementary school	52.63 (20.22)
	High school	63.45 (13.81)
	University	74.34 (13.92)
	Uneducated	58.29 (14.63)
Employment	Employed	75.32 (11.54)
	Unemployed	63.98 (16.49)
	Retired	38.42 (0.01)
Monthly Income Level in USD	600-2,499	66.49 (15.59)
	2,500-3,999	67.32 (15.59)
	4,000-6,999	76.65 (9.30)
	7,000-12,999	70.59 (12.36)
	$\geq 13,000$	78.05 (11.63)
	No answer	66.87 (15.30)
Treatment/Care Location	At residency	67.63 (15.30)
	Away from residency	72.62 (15.52)
Insurance Type	Governmental Insurance	66.87 (15.30)
	Private insurance	72.62 (15.52)
	Self-payers	72.62 (15.52)
MS Phenotype	RRMS	70.20 (15.20)
	PMS	57.79 (15.04)
Physical disability	With any disability	58.43 (15.10)
	No disability	72.38 (14.22)
Comorbidities	None	70.30 (14.94)
	CVD/HTN	61.64 (12.68)
	Diabetes	72.45 (5.07)
	Pulmonary diseases	59.60 (0.00)
	Hepatic diseases	30.43 (31.47)

	Autoimmune diseases	74.00 (16.60)	
	Malignancy	61.30 (4.02)	
	HTN and diabetes	63.05 (29.49)	
	Psychiatric diseases	61.67 (11.60)	
<b>Access to DMT</b>	Yes	72.14 (13.97)	<b>0.005</b>
	No	67.33 (16.20)	

Values are mean (standard deviation); p-values calculated using student t-test, Pearson's correlation coefficient, One-Way ANOVA, and Kruskal-Wallis test.  $p < 0.05$  indicates significant association/ MusiQol: Multiple Sclerosis International Quality of Life; CVD: cardiovascular disease; HTN: hypertension; MS: multiple sclerosis; PMS: Progressive multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis DMT: disease modifying therapy; SD: Standard deviation

#### IV.4.5. Predictors of HRQOL in MS

Multiple linear regression was run for each dependent variable, the MusiQol index and its dimensions to determine the main predictors of HRQOL. When evaluating the MusiQol index, the variables entered in the model predicted 45.3% of the variance ( $R^2 = 0.453$ ). Younger age ( $\beta = -0.235$ ,  $p = 0.004$ , 95% CI [-0.394- -0.075]), higher level of education ( $\beta = 8.357$ ,  $p < 0.001$ , 95% CI [4.671-12.043]), being employed ( $\beta = 5.097$ ,  $p = 0.014$ , 95% CI [1.027-9.166]), being married ( $\beta = 6.975$ ,  $p < 0.001$ , 95% CI [3.471-10.480]), living outside Beirut ( $\beta = -5.596$ ,  $p < 0.001$ , 95% CI [-9.259- -1.933]), and having no physical disability ( $\beta = 9.631$ ,  $p = 0.017$ , 95% CI [5.205-14.058]) were significantly associated with a higher MusiQol index (**Table 4**).

Treatment discontinuation ( $\beta = -4.711$ ,  $p = 0.011$ , 95% CI [-8.333- -1.088]) and lack of insurance, whether governmental or private ( $\beta = -5.598$ ,  $p = 0.017$ , 95% [-10.191- -1.006]) were significant predictors of lower MusiQol scores.

**Table 4. Predictors of MusiQoL Global Index: Multiple Regression Analyses**

Variables	MusiQol Global Index		
	$\beta$	95% CI	p-value
<b>Age (Years)</b>	-0.235	-0.394 – -0.075	<b>0.004</b>
<b>Residency (0 outside Beirut, 1 inside Beirut)</b>	-5.596	-9.259 – -1.933	<b>0.003</b>
<b>Marital status (0 single/divorced/widowed, 1 married)</b>	6.975	3.471 – 10.480	<b>&lt; 0.001</b>
<b>Educational level (0 non-educated/ below university, 1 university level)</b>	8.357	4.671 – 12.043	<b>&lt; 0.001</b>
<b>Employment (0 unemployed, 1 employed)</b>	5.097	1.027 – 9.166	<b>0.014</b>
<b>Insurance type (0 private or governmental insurance, 1 self-payers)</b>	-5.598	-10.191 – -1.006	<b>0.017</b>
<b>Physical disability (0 Yes, 1 No)</b>	9.631	5.205 – 14.058	<b>&lt; 0.001</b>
<b>What to do to access DMT during shortage (0 others, 1 discontinue medications)</b>	-4.711	-8.333 – -1.088	<b>0.011</b>

Significant association:  $p < 0.05$

VIF < 10 for all variables indicating no collinearity between them/  $\beta$ : unstandardized beta coefficient (represents the change in standard deviation units in QoL score resulting from a change of one standard deviation in the different independent variables).

CI: Confidence Interval; DMT: Disease-modifying Therapy; Multiple Sclerosis International Quality of Life

Regarding the different MusiQol dimensions, ADL was associated with the highest number of independent variables: disability, employment, insurance type, Body Mass Index (BMI), education, current treatment, disease type, and comorbidities. In addition, 70% ( $R^2 = 0.69$ ) of the variability of ADL was explained by these variables, in which for every one-unit increase in disability, employment, or education, the QOL dimension improved by 38.71 ( $p < 0.001$ ), 9.458 ( $p = 0.001$ ), and 10.154 ( $p < 0.001$ ) units respectively. The PWB dimension had 23% of its variance explained by the variables entered. It was negatively associated with disease type ( $\beta = -28.18$ ,  $p < 0.001$ ), residency ( $\beta = -15.82$ ,  $p < 0.001$ ), comorbidities ( $\beta = -11.29$ ,  $p = 0.005$ ), and family history ( $\beta = -12.82$ ,  $p = 0.006$ ), and only positively associated with educational level ( $\beta = 17.55$ ,  $p < 0.001$ ). The SPT dimension was positively associated with educational level ( $\beta = 9.79$ ,  $p < .001$ ) and negatively associated with presence of comorbidities ( $\beta = -9.19$ ,  $p = 0.003$ ). For every one-unit increase in educational level and comorbidities (presence of comorbidities), there was 9.79 folds improvement and 9.19 folds deterioration in MS-symptom related QOL, respectively. Regarding the SSL dimension, being younger and female were associated with better SSL scores ( $\beta = -0.729$ ,  $p < 0.001$ ,  $\beta = -21.95$ ,  $p < .001$ , respectively), and those who were married had better scores compared to single/divorced/widowed MS patients ( $\beta = 26.59$ ,  $p < 0.001$ ). For the COP dimension, it improved with university level education ( $\beta = 15.47$ ,  $p < 0.001$ ) and being married ( $\beta = 18.31$ ,  $p < 0.001$ ) and worsened with living inside Beirut ( $\beta = -12.93$ ,  $p = 0.002$ ), and having PMS ( $\beta = 19.00$ ,  $p = 0.003$ ). When evaluating the RHCS dimension, receiving treatment was associated with 24.28 ( $p < 0.001$ ) folds increase in this QOL dimension. Since the REJ dimension had no normal distribution, the non-parametric general linear model was used to evaluate its association with the independent variables. We found no association between REJ and any of the entered variables ( $p > 0.05$ ).

#### **IV.5. Discussion**

To the best of our knowledge, this is the first study to assess HRQOL, QOL predictors, and barriers to treatment accessibility in MS patients during an economic crisis. Since October 2019, Lebanon has been facing a major socioeconomic crisis that led, coupled with the COVID-19 pandemic, to serious medications shortage, impacting the optimal medical management and QOL of patients<sup>17,18</sup>. Although several generic and disease-specific instruments were developed and validated to assess HRQOL in MS patients, the MusiQol questionnaire has several advantages over the others: It can be applied internationally as it has been validated in 20 countries and 14 languages and is much shorter compared to other MS-specific instruments<sup>13</sup>. In this study, the estimated mean MusiQol global index ( $69.25 \pm 11.53$ ) reflected a moderate HRQOL with the majority of patients scoring between 40.01 and 80.00. Similar results were obtained in a study conducted in Oman where all patients had a MusiQol score in the moderate to low HRQOL category<sup>2</sup>. Interestingly, "COP" and "REJ" dimensions recorded

the highest scores among the MusiQol dimensions score. What supported this result, was the moderate to high level of HRQOL in the components of “Rfa” and “RHCS” in our cohort of MS patients, reflecting successful coping strategies that could reduce the impact of disability on QOL, and improve orienting therapeutic interventions. In a study conducted by the Isfahan MS Association in Iran, positive thinking, exercise, social support, and social organizations were associated with high scores in these dimensions<sup>12</sup>. In another study conducted in 2016 in Lebanese MS patients, psychological interventions such as mindfulness, cognitive behavioral therapy, self-management and self-control, in addition to emotional stability, planning problem solving, and positive reappraisal were all coping factors leading to better QOL<sup>19</sup>.

The multivariate analysis in this cross-sectional study showed that the HRQOL of MS patients was determined by multiple factors. Younger age, higher level of education, being employed, being married, living outside the capital Beirut, and having no physical disability were significantly associated with better HRQOL, whereas treatment discontinuation and lack of governmental or private insurance to cover treatment cost were significant predictors of lower HRQOL. Older age was significantly associated with lower MusiQol global index, SSL, and RHCS scores. Fernandez et al.<sup>13</sup> showed that older age was significantly correlated with worse MusiQoL global index and ADL and SSL scores. Similarly, a Canadian population-based study examining HRQOL among MS patients found better physical HRQOI in younger patients<sup>20</sup>. Interestingly, living in the capital Beirut was associated with lower HRQOL as reflected by a low MusiQol global index and low “PWB”, “Rfr” and “COP” scores. Unlike our findings, a North American study assessing the impact of rural–urban residency on HRQOL of MS patients living in the USA, showed that rural areas tended to report lower HRQOL among MS patients<sup>21</sup>. This could be explained by to the fact that living in urban areas facilitate receiving MS-focused care at specialized MS clinics<sup>22</sup>. However, this might not be applicable to Lebanon which is a small country with a total area of 10,400 square kilometers where MS patients have access to clinics and medications across all districts<sup>16</sup>. In the multivariate analysis, physical disability was the only disease characteristic associated with HRQOL. Presence of physical disability was associated with worse MusiQol global index and “ADL” dimension score. A study conducted to identify the impact of socio-demographic and clinical factors on HRQOL of Lebanese patients with MS showed that higher EDSS was associated with lower MusiQoL global index and “ADL” dimension score<sup>3</sup>. Similarly, a study conducted in Kuwait, found a negative correlation between HRQOL and EDSS scores among Kuwaiti MS patients<sup>23</sup>. Two other studies conducted in Iran, and Germany showed as well, the significant deterioration of HRQOL with worsening physical disability<sup>24,25</sup>. We found a significant association between marital status and HRQOL, whereby being married was associated with higher MusiQol global index, “SSL” and “COP” dimensions scores. Similar results were obtained in other studies<sup>13,26</sup>.

Improved QOL in married individuals can be linked to the presence of family support as evidenced by the high mean “Rfa” dimension score among married MS patients (79.45 ±25.94). Regarding employment status, being employed was significantly associated with better HRQOL (higher MusiQol global index and ADL dimension score). Although this finding was not consistent with a study from Oman which did not show any difference in HRQOL among employed versus unemployed Omani MS patients(2), another observational cross-sectional study found that being employed had a positive impact on both physical and mental health status and HRQOL in MS patients<sup>27</sup>. Likewise, a study, conducted in the USA on 101 MS patients, showed that patients who remained employed had better self-reported QOL compared to those who lost their work<sup>28</sup>. MS patients face challenging work lives and are more likely to report unemployment or part-time work participation with lower income compared to the general population and other patients with chronic diseases such as arthritis, type-2 diabetes or depression<sup>29</sup>. The improved QOL among employed MS patients can be linked to the availability of economic resources, work benefits such as health insurance, sense of personal and professional identity, and social participation and interactions<sup>30</sup>. Higher level of education was also associated with higher MusiQol global index and all dimension scores except for “Rfa”, “REJ”, and “RHCS”. Several previous studies supported the association between higher educational level and improved level of QOL<sup>10,26,31</sup>. This is probably due to the fact that health literacy is one of the most important strategies for improving one’s health which in turn improves QOL<sup>32</sup>.

The majority of the patients had no access to treatment due to shortage of medications in the country or inability to afford buying DMTs. As a result, a large proportion of patients discontinued treatment, which was significantly associated with reduced HRQOL. The economic crisis in Lebanon led to crumbling of the entire health care system. The shortage of basic medical supplies and essential medications was one of the most critical issues that Lebanese patients, including patients with MS, had to face. In addition, the ongoing crisis made private healthcare prohibitively expensive, leaving more patients reliant on the public health sector, which got even more devastated with time<sup>33</sup>. All of those factors can explain the negative association between being self-payer with neither private nor public insurance and having a worse HRQOL.

Our study is unique in that it assessed the impact of a severe economic crisis with the resultant medications’ shortage, unemployment and loss of income and or/insurance on the QOL of MS patients. Another strength of the study is the lack of information bias since no missing data was reported especially that the questionnaire was filled via telephone call. In addition, we were able to recruit the needed sample size, which was representative of the Lebanese MS population. The data was collected from MS patients visiting different clinics in different regions

of the country, which helped reducing selection bias. The main limitation of this study was its cross-sectional design which did not allow to establish causal relationships. Another limitation is the presence of two different investigators administering the questionnaire which might have been a possible cause for investigator bias; however, this was minimized by piloting the questionnaire before administering it to patients.

#### **IV.6. Conclusion**

This study was conducted in Lebanon during the current economic crisis and showed that Lebanese MS patients have a moderate HRQOL determined by many factors including age, education, employment, area of residency, treatment accessibility, and disability. The findings emphasize the importance of governmental and healthcare authorities' role in implementing more effective care strategies for MS patients during periods of economic crisis. Governmental interventions are necessary to ensure accessibility and funding of MS medications, especially for low-income uninsured patients.

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## Chapter V. Disease-Modifying Therapies, Outcomes, Risk Factors and Severity of COVID-19 in Multiple Sclerosis: A MENACTRIMS Registry Based Study

### V.1. Background

Building on the examination of barriers to accessing DMTs in the MENA region and the specific impact of the Lebanese economic crisis on MS patients' quality of life and treatment accessibility, the next critical area of focus is the intersection between MS treatments and the global COVID-19 pandemic. The unprecedented spread of COVID-19 posed significant challenges for PwMS, particularly those on immunosuppressive therapies. Given the increased susceptibility of PwMS to infections due to both their disease and DMTs, it was essential to evaluate how these treatments influenced COVID-19 outcomes in this population. Moreover, this study was pivotal in addressing the overarching objective of this thesis, which is to assess the long-term safety of high-efficacy DMTs. Infections represent a major safety concern with the prolonged use of these potent therapies. Thus, the third study aimed to assess not only the severity of COVID-19 among MS patients in the MENA region but also to identify the risk factors associated with worse outcomes, particularly the role of high-efficacy DMTs. Using the MENACTRIMS registry, this research provides critical insights into the safety profile of these therapies in the context of a global pandemic, advising safer long-term clinical practices for MS management.

The significance of this study was recognized through its publication in the Multiple Sclerosis and Related Disorders (MSARD) journal (**Appendix 8**) and its presentation as an oral session at the 7th MENACTRIMS Congress held in Cairo on November 11-12, 2022.



## Abstract

**Background:** There is a lack information regarding risk factors associated with worse COVID-19 outcomes in patients with multiple sclerosis (MS) in the MENA region.

**Methods:** This is a multicenter, retrospective cohort study that included all MS patients with a suspected or confirmed COVID-19 infection using the MENACTRIMS registry. The association of demographics, disease characteristics, and use of disease-modifying therapies (DMTs) with outcomes and severity of COVID-19 were evaluated by multivariate logistic model.

**Results:** A total of 600 MS patients with confirmed (n=542) or highly suspected (n=58) COVID-19 were analyzed. Seventy-three patients (12.2%) had a COVID-19 severity score of  $\geq 3$  on a 7-point ordinal scale (ranging from 1 [not hospitalized with no limitations on activities] to 7 [death] with a cutoff at 3 [hospitalized and not requiring supplemental oxygen]), and 15 patients (2.5%) died. Out of 73 patients with a severity score  $\geq 3$ , 90.4% were on DMTs; 50.6% of them were on anti-CD20, including ocrelizumab and rituximab. Multivariate logistic regression showed that older age (odds ratio per 10 years, 1.4 [95%CI, 1.0-1.8]), disability (OR for EDSS 3.0-5.5, 2.9 [95%CI, 1.5-5.7], OR for EDSS  $\geq 6.0$ , 2.3 [95%CI, 1.0-5.1]), obesity (OR, 3.0 [95%CI, 1.5-6.0]), and treatment with rituximab (OR, 9.0 [95%CI, 3.1-25.3]) or off-label immunosuppressive medications (OR, 5.6 [95%CI, 1.1-27.8]) were risk factors for moderate or severe COVID-19.

**Conclusion:** In this registry-based study of MS patients, age, sex, EDSS, obesity, progressive MS were risk factors for severe COVID-19. Moreover, there was an association found between exposure to anti-CD20 DMTs and COVID-19 severity.

**Keywords:** risk factors; severity; COVID-19; multiple sclerosis; disease-modifying therapies

## V.2. Introduction

The COVID-19 pandemic has raised concerns regarding the risk of infection and its effects on patient populations, particularly PwMS as they may be more vulnerable to infections due to disability and/or treatment with DMTs that alter the immune response<sup>1</sup>. In the general population, risk factors for poorer outcomes with COVID-19 include older age, male sex, and comorbidities such as obesity, diabetes, hypertension, coronary heart disease, chronic pulmonary or kidney disease, and cancer<sup>2-4</sup>. The current evidence suggests that MS does not increase the risk of COVID-19 infection nor does it worsen clinical outcomes compared to people without MS<sup>5,6</sup>. Several studies evaluating the epidemiology of COVID-19 severity have been published and generally reported mixed results<sup>7-10</sup>. The COVISEP, a French clinical registry-based study which included 347 PwMS with confirmed or highly suspected COVID-19, found that age, disability and obesity were risk factors for severe infection, but not exposure to DMTs<sup>7</sup>. In contrast, Sormani et al. reported the results of the national Musc-19 Italian registry study on 593 suspected and 191 confirmed COVID-19 infection<sup>8</sup>. This study showed that progressive MS course, recent corticosteroids use, and anti-CD20 DMTs (ocrelizumab and rituximab) were significantly associated with an increased risk of severe COVID-19 course. These results were replicated in the pooled analysis of the MS Global Data-Sharing Initiative comprising 5,648 PwMS with suspected or confirmed COVID-19 diagnosis, concluding that anti-CD20 DMTs, ocrelizumab and rituximab, were associated with greater frequency of hospital admission, Intensive Care Unit (ICU) admission, need for artificial ventilation and death compared to glatiramer acetate and other DMTs<sup>9</sup>. Moreover, in the United States/Canada, Salter and colleagues conducted a large, multicenter, registry-based cross-sectional study which included 1626 patients<sup>10</sup>. They identified increased disability, older age, black race, cardiovascular comorbidities and recent use of corticosteroids as risk factors for worse COVID-19 outcomes. The authors also found that compared with untreated PwMS, ocrelizumab and rituximab were associated with a higher risk of hospitalization; however, only rituximab showed positive trends for ICU admission, artificial ventilation and death<sup>10</sup>.

In the MENA region, studies identifying clinical characteristics of MS associated with worse COVID-19 outcomes are lacking. Accordingly, we conducted a large, MENACTRIMS registry-based study to determine whether the outcomes of these global studies were applicable to our MS population in the MENA region. The purpose of this study was to identify clinical and DMTs-related risk factors for severe COVID-19 in PwMS in the MENA region.

## **V.3. Methods**

### **V.3.1. Data Collection**

This was a multicenter, retrospective, observational cohort study of patients with confirmed or highly suspected COVID-19 infection. Data were collected from the MENACTRIMS registry, local COVID-19 registries and cohorts from nine Middle Eastern countries, including Algeria, Egypt, Iraq, Iran, Kuwait, Lebanon, Oman, Tunis and UAE. The MENACTRIMS registry, the largest MS patients' registry in the MENA region<sup>11</sup>, received approval from the IRB of the AUB (**Appendix 3**) for collection and use of confidential electronically processed patient data. Study data were collected for patients diagnosed with COVID-19 between March 01,2020 and February 01,2021, before the introduction of any COVID-19 vaccine in the MENA region.

### **V.3.2. Inclusion Criteria**

A confirmed diagnosis of MS with at least one of the following 4 criteria: (1) a confirmed COVID-19 diagnosis based on a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test, (2) Typical abnormalities on thoracic computed tomography (CT) scan manifested as ground-glass opacities, (3) sudden onset of anosmia or ageusia in the absence of rhinitis or nasal obstruction, and (4) typical COVID-19 symptoms (triad of cough, fever, and asthenia) in an epidemic area of COVID-19.

### **V.3.3. Study Variables**

Demographic variables collected were sex, age, country at time of infection, smoking status, alcohol consumption, and employment status. Comorbidities were queried, including obesity, hypertension (HTN), cardiovascular disease (CVD), diabetes mellitus (DM), thyroid disease, chronic lung disease, chronic kidney disease, chronic liver disease and cancer. Obesity was defined as a body mass index (BMI)  $\geq 30$ <sup>12</sup>.

Disease characteristics captured included MS phenotype (CIS, RRMS, SPMS or PPMS)<sup>13</sup>, and disease duration. Disability was assessed by the EDSS which was dichotomized into 3 categories:  $<3.0$ ,  $3.0-5.5$ ,  $\geq 6.0$ , and by the ambulation milestones (fully ambulatory, walks with assistance, non-ambulatory)<sup>14,15</sup>. DMT use at the time of COVID-19 infection was recorded as one of the following: alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate (GA), interferons, natalizumab, ocrelizumab, ofatumumab, rituximab, siponimod, teriflunomide, other DMTs (off-label use of azathioprine, mycophenolate mofetil or methotrexate), or none. Data on DMT dose and duration were not documented. Additionally, the use of glucocorticoids during the prior 1-month was recorded.

Regarding COVID-19, we collected symptoms and diagnostic data (PCR for SARS-CoV-2, serological tests and CT chest findings).

#### **V.3.4. Definition of Study Endpoints**

The primary endpoint was the patient's clinical status at the most severe point of their COVID-19 course, referred to as the COVID-19 severity score<sup>16</sup>. This is a 7-point ordinal scale where 1 indicates the patient was not hospitalized and had no limitations on activities; 2, the patient was not hospitalized but had limitations on activities; 3, the patient was hospitalized but did not require supplemental oxygen; 4, the patient was hospitalized and required supplemental oxygen; 5, the patient was hospitalized and received noninvasive ventilation or high flow oxygen; 6, the patient was hospitalized and received invasive mechanical ventilation or extracorporeal membrane oxygenation; and 7, death.

#### **V.3.5. Statistical Analysis**

Patients' demographic and clinical characteristics were summarized using count and percentage for categorical variables and median and range for numerical data such as duration of hospitalization. Severity score by DMT type was reported using frequency and percent and statistical significance was tested using Pearson chi-square. Difference in age and EDSS according to hospitalization, ICU and living status, were reported based on median and tested using the Mann Whitney U test, where differences in distribution of phenotypes for same outcomes were tested using Pearson's chi-square. Any 2-sided p-value < 0.05 was considered statistically significant.

Logistic regressions were performed at the univariate and multivariate level predicting severity score ( $\geq 3$ ). Coefficients produced by the logistic regression were exponentiated to produce odds ratios (ORs) and 95% confidence interval (CI). In the multivariate analysis, Receiver Operating Characteristic (ROC) curves and Concordance (C) statistics were done to show the model discrimination capacity in predicting the severity of COVID-19 infection<sup>17</sup>. Predicted probabilities were used to draw a calibration line. The produced model was repeated using severity score  $\geq 4$  as a sensitivity analysis. Statistical analyses were conducted using SPSS software version 27.

### **V.4. Results**

#### **V.4.1. Study Population**

As of February 2021, 600 PwMS were included in the study. Five-hundred forty-two (542) patients had a positive SARS-CoV-2 PCR result. One patient had a negative SARS-CoV-2 PCR result but a chest CT showing typical lesions of COVID-19. For the remaining 57 patients with unavailable SARS-CoV-2 PCR results, 27 had positive SARS-CoV-2 serology, 7 had ground-glass opacity on thoracic CT scan, and 23 presented with typical COVID-19 symptoms.

#### V.4.2. Demographics and Clinical Characteristics

The mean (Standard Deviation [SD]) age was 36.4 (10.2) years, 414 (69.0%) were women, and the mean (SD) disease duration was 8.3 (6.6) years. Obesity (n=77, 12.8%), HTN (n=41, 6.8%), and CVD (n=41, 6.8%) were the most frequently reported comorbidities. The majority of patients had RRMS (n=495, 82.5%) and were full ambulatory (n=494, 82.3%). The median EDSS was 2.0 (range, 0.0 – 9.0), and 559 patients (93.2%) were receiving DMT but 107 (19.4%) withheld their MS treatment at onset of the infection (**Table 1**).

Seventy-three patients (12.2%) had a COVID-19 severity score  $\geq 3$  (needed hospitalization), and 15 patients (2.5%) died of COVID-19. Among hospitalized patients, 26 (4.3%) required ICU, 52 (8.7%) required oxygen, and 18 (3.0%) required mechanical ventilation. The most frequently recorded symptoms for COVID-19 were fever (n=318, 53.0%), cough (n=226, 37.7%), anosmia/ageusia (n=203, 33.8%), and fatigue (n=179, 29.8%).

**Table 1. Demographic and Clinical Characteristics of Patients with Multiple Sclerosis Diagnosed with Coronavirus Disease 2019**

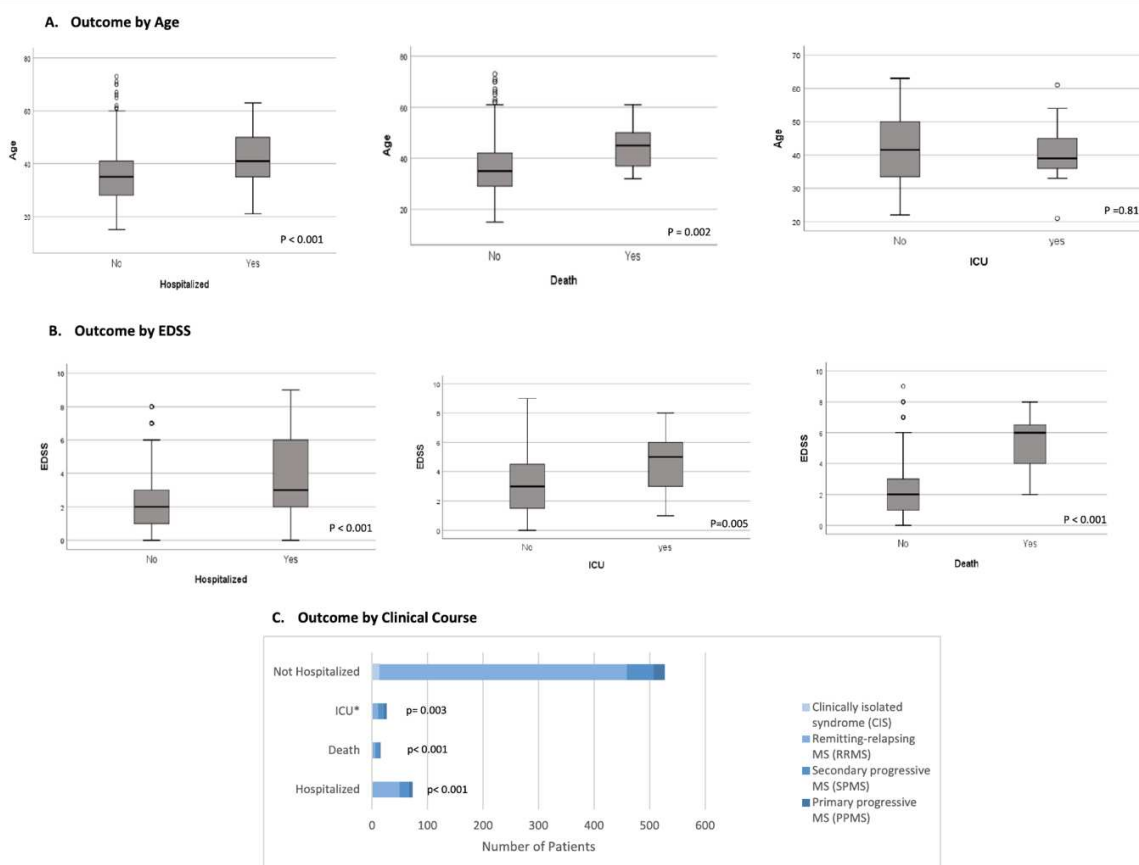
Characteristics	N.	%
Number. of patients with MS	600	
<b>Demographics</b>		
Age, mean (SD) in years	36.4 (10.1)	
Gender		
Male	186	31.0
Female	414	69.0
Current Smoker	121	20.2
Former Smoker	27	4.5
Alcohol Consumer	92	15.3
<b>Disease Course</b>		
Clinically isolated syndrome (CIS)	13	2.2
Relapsing-relapsing MS (RRMS)	495	82.5
Secondary progressive MS (SPMS)	66	11.0
Primary progressive MS (PPMS)	26	4.3
<b>Disease Duration in years, mean (SD)</b>	8.3 (6.6)	
<b>Expanded Disability Severity Scale Score, median (range)</b>	2.0 (0.0-9.0)	
<b>Ambulatory Status</b>		
Non-Ambulatory	37	6.2
Walk with Assistance	64	10.7
Full Ambulatory	494	82.3
<b>Used Steroids in the Last Month</b>	16	2.7
<b>Disease-modifying therapies</b>		
None	41	6.8
Interferon beta	159	26.5
Teriflunomide	17	2.8
Dimethyl Fumarate	46	7.7



Cladribine	4	0.7
Fingolimod/Siponimod	112	18.7
Natalizumab	50	8.3
Ocrelizumab	47	7.8
Rituximab	96	16.0
Ofatumumab	1	0.2
Alemtuzumab	6	1.0
Glatiramer Acetate (GA)	6	1.0
Others*	15	2.5
<b>DMT withheld at COVID-19 onset</b>	<b>107</b>	<b>19.4</b>
<b>Comorbid Conditions</b>		
Obesity (BMI $\geq$ 30)	77	12.8
Hypertension	41	6.8
Cardiovascular Disease	41	6.8
Diabetes Mellitus	17	2.8
Thyroid Disease	12	2.0
Chronic Lung Disease	5	0.8
Anemia	4	0.7
Active Malignancy	3	0.5
Malignancy Remission	2	0.3
Renal Disease	1	0.2
Liver Disease	1	0.2
<b>COVID-19 Diagnosis</b>		
SARS-CoV-2 PCR	543	90.5
Serological Test, without fulfilling the criteria	148	24.7
Thoracic CT, without fulfilling the criteria	184	30.7
<b>Covid-19 Symptoms</b>		
Fever	318	53.0
Cough	226	37.7
Anosmia/ageusia	203	33.8
Fatigue	179	29.8
Sore Throat	136	22.7
Pain	124	20.7
Dyspnea	85	14.2
Runny Nose	78	13.0
Headache	66	11.0
Diarrhea	31	5.2
Nausea/Vomiting	6	1.0
Others	11	1.8
<b>Inclusion Criteria for COVID19cases</b>		
Positive SARS-CoV-2 PCR	542	90.3
Positive Serological Test, without fulfilling the criteria	27	4.5
Ground-glass opacity on thoracic CT, without fulfilling the criteria	8	1.3
Typical COVID-19 symptoms without fulfilling the criteria	23	3.8
<b>Abbreviations:</b> MS, multiple sclerosis; SD, Standard Deviation; BMI, body mass index; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction; CT, Computerized tomography; COVID-19, coronavirus disease 2019.		
*Other treatments for patients with multiple sclerosis: mycophenolate mofetil, azathioprine and methotrexate.		

### V.4.3. Factors Associated with COVID-19 Severity

Comparing patients that required hospitalization to those that did not, patients requiring hospitalization were older (median [range] age, 41.4 [21-61] years vs 35.0 [15-73] years;  $p < 0.001$ ), had a higher EDSS (median [range], 3.0 (0.0-9.0) vs 2.0(0.0-8.0);  $p < 0.001$ ), and were more likely to have a progressive course (17/66 [25.8%] SPMS and 7/26 [26.9%] PPMS vs 49/495 [9.9%] RRMS;  $p < 0.001$ ) (**Figure 1**). There was no statistically significant difference between males and females. Although, ICU admission was not associated with older age (median [range], 39.0 [21-61] vs 41.5 [22-63];  $p = 0.818$ ), ICU patients had a higher EDSS (median [range], 5.0 [1.0-8.0] vs 3.0 [0.0-9.0];  $p = 0.005$ ) and a higher likelihood of a progressive clinical course (10/17 (58.8%) SPMS and 5/7 (71.4%) PPMS vs 11/49 (22.4%) RRMS;  $p < 0.003$ ). Similarly, older age (median [range], 45.0 [32-61] vs 35.0 [15-73];  $p = 0.002$ ), higher EDSS (median [range] 6.0 [2.0-8.0] vs 2.0 [0.0-9.0];  $p < 0.001$ ), and progressive course (7/66 [10.6%] SPMS and 2/26 [7.7%] PPMS vs 6/495 [1.2%] RRMS) were associated with death due to COVID-19.



**Figure 1. Characteristics of COVID19 and MS Patients stratified by Not Hospitalized, Hospitalized, Admitted to the Intensive Care Unit (ICU) or Died**

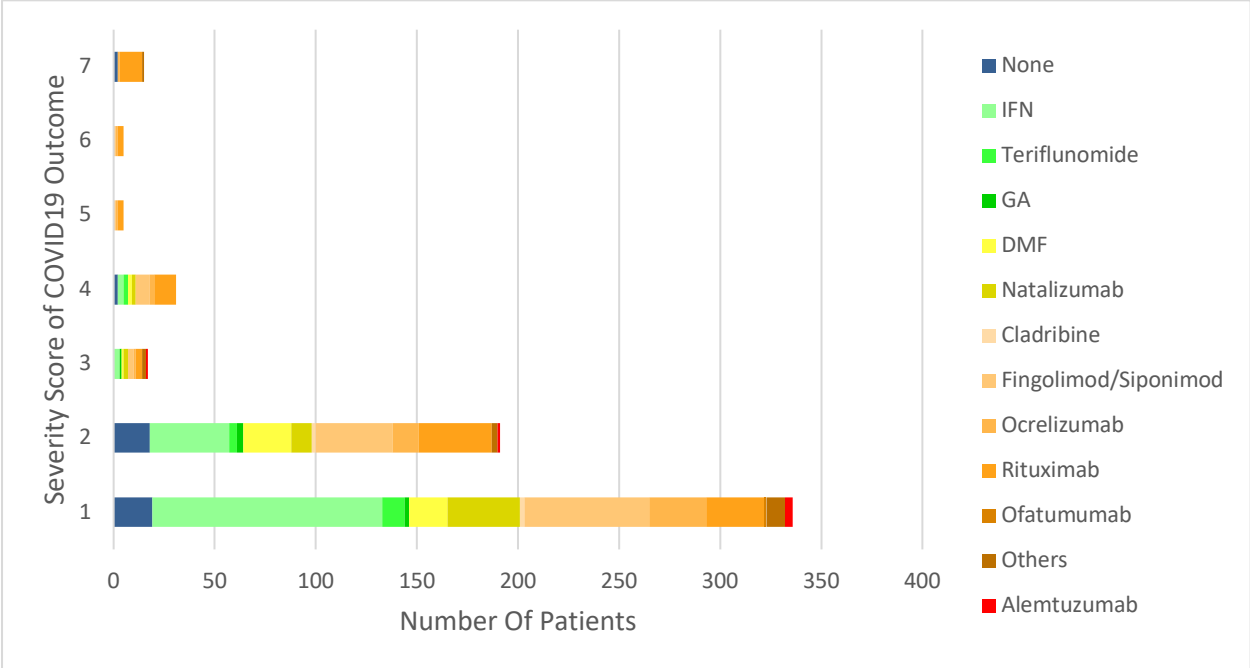
**Abbreviations:** EDSS, Expanded Disability Severity Scale (EDSS); ICU, Intensive Care Unit

\*Among hospitalized patients, the p-values were obtained from Mann-Whitney U tests for age and EDSS group differences (Figures 1A and 1B) and Pearson Chi-square tests for clinical course distribution differences (Figure 1C)

Having at least one comorbidity was significantly associated with increased risk of severe COVID-19. The proportion of patients with at least one comorbidity was lower in non-hospitalized patients (61 of 527 [11.6%] vs 17 of 73 [23.3%]; p=0.005). Hypertension and cardiovascular comorbidities were significantly associated with more severe COVID-19 (11 of 73 [15.1%] vs 30 of 527 [5.7%]; p= 0.003).

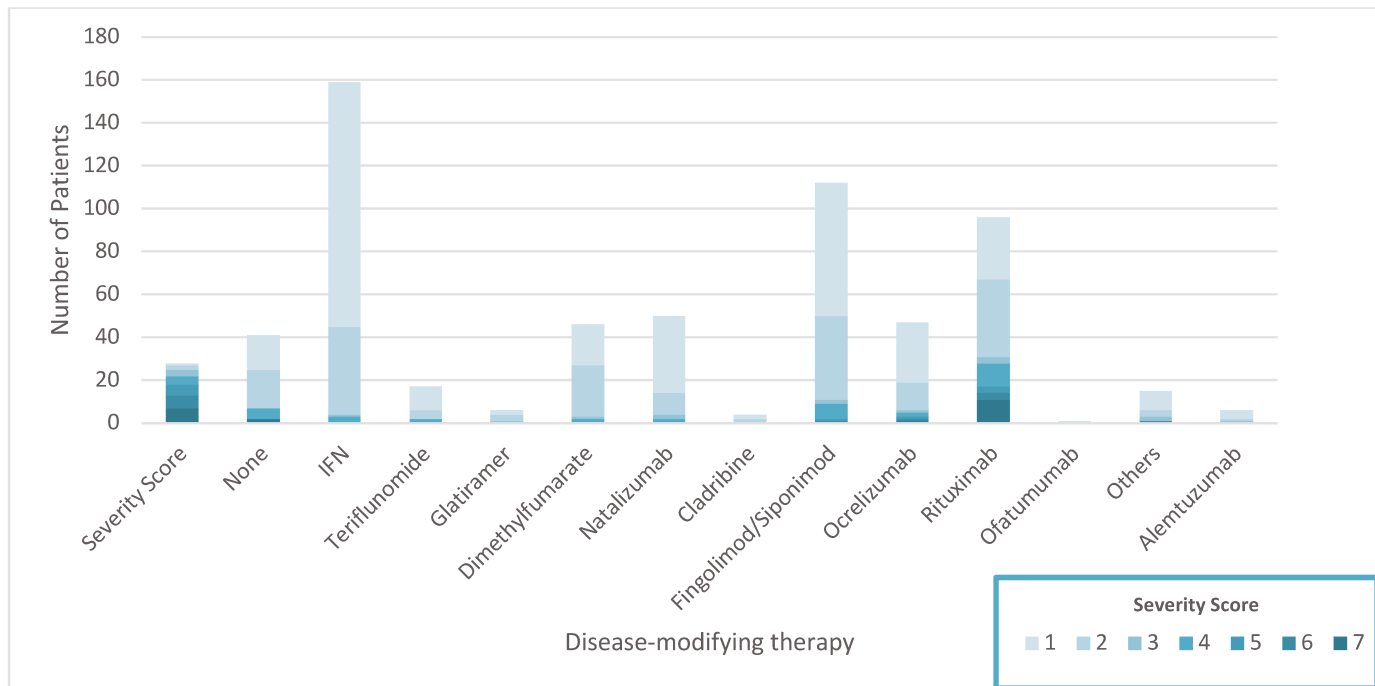
Sixty-six out of the 73 (90.4%) hospitalized patients were maintained on DMTs. The majority (n=37; 50.6%) were on anti-CD20s (ocrelizumab, rituximab or ofatumumab) compared to 20.1% (n=107) of the non-hospitalized patients receiving treatment (p <0.001). The distribution of clinical severity for COVID-19 according to the different DMTs is presented in **Figure 2**.

**A. Patients Grouped by Severity of COVID-19 Outcome**



1: Not hospitalized, no limitations on activities; 2: Not hospitalized, limitation on activities; 3: Hospitalized, not requiring supplemental oxygen; 4: Hospitalized, requiring supplemental oxygen; 5: Hospitalized, or noninvasive ventilation or high-flow oxygen devices; 6: Hospitalized, on invasive mechanical ventilation or ECMO; 7: Death

## B. Patients Grouped by Disease-modifying Therapy



**Abbreviations:** COVID-19: Coronavirus Disease 2019; IFN, Interferon beta; GA: Glatiramer acetate; DMF: Dimethyl Fumarate  
<sup>†</sup>Other treatments for patients with multiple sclerosis: mycophenolate mofetil, azathioprine and methotrexate.  
<sup>\*</sup> $p < 0.001$  using the Pearson Chi-square  $X^2=143.86$   $df=72$

### **Figure 2. Clinical Severity of Coronavirus Disease 2019 (COVID-19) and Disease-Modifying Therapies in Patients with Multiple Sclerosis**

- (A) Patients Grouped by Severity of COVID-19 Outcome  
 (B) Patients Grouped by Disease-modifying Therapy

#### V.4.4. Multivariate Logistic Regression Models of Severe COVID-19

A multivariate logistic regression analysis was performed to assess variables independently associated with severe COVID-19 (severity score  $\geq 3$ ) (**Table 2**).

Results showed that older age (OR per 10 years, 1.4 [95%CI, 1.0-1.8]), disability (OR for EDSS 3.0-5.5, 2.9 [95%CI. 1.5-5.7], OR for EDSS  $\geq 6.0$ , 2.3 [95%CI. 1.0-5.1]), obesity (OR, 3.0 [95%CI, 1.5-6.0]), and treatment with rituximab (OR, 9.0 [95%CI, 3.1-25.3]) or off-label immunosuppressive medications such as azathioprine, mycophenolate mofetil or methotrexate (OR, 5.6 [95%CI. 1.1-27.8]) were risk factors for severe COVID-19 requiring hospitalization.

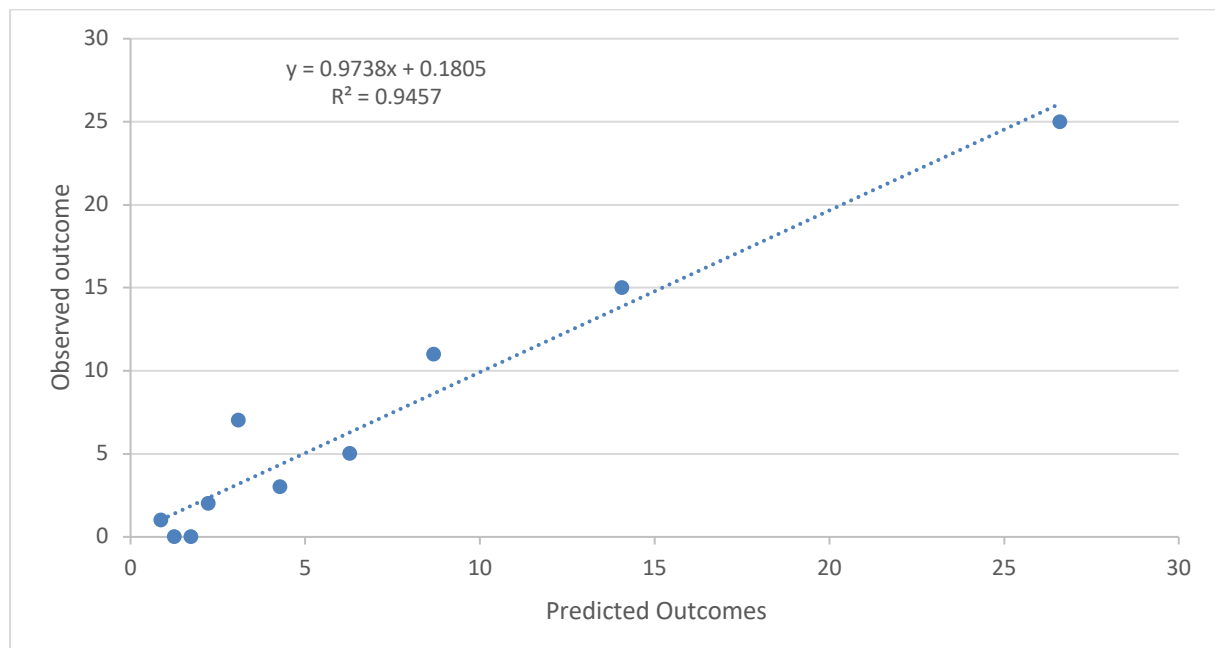
**Table 2. Associated Risk Factors of Severe Coronavirus Disease 2019 (COVID-19) among Multiple Sclerosis (MS) Patients**

	Severe COVID-19 (Severity Score $\geq 3$ )			
	OR <sub>c</sub> (95% CI)	P-value	OR <sub>a</sub> (95% CI)	P-value
Age per 10 years	1.67(1.33-2.10)	<b>&lt;0.001</b>	1.38 (1.04-1.83)	<b>0.025</b>
Male	1.77(1.07-2.92)	<b>0.025</b>	--	<b>NS</b>
Obesity	2.60 (1.43-4.72)	<b>0.002</b>	3.02 (1.52-6.01)	<b>&lt;0.001</b>
Cardiovascular comorbidity	2.94 (1.40-6.16)	<b>0.004</b>	--	<b>NS</b>
Hypertension	2.94 (1.40-6.16)	<b>0.004</b>	--	<b>NS</b>
Diabetes Mellitus	2.29 (0.73-7.23)	0.157	--	NS
Smoking	0.99 (0.53-1.84)	0.962	--	NS
Progressive Course				
- SPMS	3.16 (1.69-5.90)	<b>&lt;0.001</b>	--	<b>NS</b>
- PPMS	3.35 (1.34-8.38)	<b>0.010</b>	--	<b>NS</b>
Disease Duration per 10 years	1.66 (1.20-2.29)	<b>0.002</b>	--	<b>NS</b>
EDSS score <3 ( <i>reference</i> )				
EDSS score 3-5.5	3.73 (2.05-6.79)	<b>&lt;0.001</b>	2.93 (1.50-5.74)	<b>0.002</b>
EDSS score $\geq 6$	5.67 (2.92-10.99)	<b>&lt;0.001</b>	2.31 (1.04-5.15)	<b>0.040</b>
DMT (IFN/GA <i>reference</i> )				
Teriflunomide	4.27 (0.76-23.9)	0.099	3.17 (0.53-18.93)	0.206
Dimethyl Fumarate (DMF)	2.23 (0.51-9.71)	0.284	1.91 (0.42-8.65)	0.399
Fingolimod/Siponimod	3.49 (1.18-10.33)	<b>0.024</b>	2.28 (0.74-7.04)	0.153
Natalizumab	2.78 (0.72-10.79)	0.139	1.69 (0.41 -6.90)	0.466
Ocrelizumab	4.68 (1.36-16.11)	<b>0.014</b>	2.04 (0.55 -7.67)	0.289
Rituximab	15.26 (5.69-40.97)	<b>&lt;0.001</b>	9.0 (3.12 -25.36)	<b>&lt;0.001</b>
Others	8.00 (1.70-37.58)	<b>0.008</b>	5.58 (1.12-27.84)	<b>0.036</b>
None	6.59 (1.97-22)	<b>0.002</b>	1.85 (0.42-8.20)	0.419
Full Ambulatory ( <i>reference</i> )	NA			
Non-Ambulatory	5.40 (2.58-11.34)	<b>&lt;0.001</b>	--	<b>NS</b>
Walk With Assistance	2.79 (1.43-5.44)	<b>0.003</b>	--	<b>NS</b>
DMT Withheld at COVID-19 onset	2.40 (1.35-4.23)	<b>0.003</b>	--	<b>NS</b>

**Abbreviations:** COVID-19, Coronavirus Disease 2019; ORc, Crude Odds Ratio; ORa Adjusted Odds Ratio; CI, Confidence Interval; SPMS, Secondary Progressive; Multiple Sclerosis; PPMS, Primary Progressive MS; EDSS, Expanded Disability Severity Status; NA, Not Applicable; DMT, Disease-Modifying Therapy

To validate our results, a post hoc analysis with a threshold of 4 for COVID-19 severity score was performed. Results were similar in both cases indicating that the model used showed sensitivity. In the sensitivity analysis, obesity (OR, 3.7 [95% CI, 1.7-7.8],  $p=0.001$ ), higher EDSS (EDSS score 3.0-5.5 OR, 3.62 [95% CI, 1.7-7.7],  $p=0.001$ ; EDSS score  $\geq 6.0$  OR, 2.8 [95% CI, 1.2-6.7],  $p=0.021$ ), and treatment with rituximab (rituximab, 12.5 [95% CI, 3.5 - 44.6],  $p<0.001$ ) were retained as independent variables associated with severe COVID-19. Unlike the first model, off-label immunosuppressive medications such as azathioprine, mycophenolate mofetil or methotrexate and older age were not significantly associated with higher COVID-19 severity score although higher age showed a trend toward significance (OR, 1.3 [95% CI, 1.0-1.8],  $p=0.061$ ).

The model was checked for calibration in for its predictive capacity. The predicted probability of severity was regressed against the observed probability, and a linear model was produced with a coefficient of 0.97 and an  $R^2$  of 94.6% indicating a good calibrated model. C statistics was 0.81 [95% CI, 0.8-0.9], indicating a good discrimination capacity of the model in predicting high and low severity (**Figure 3**). Including only PCR+ cases in the logistic regression model (543/600) led to identical results.



**Figure 3. Calibration Plot for the Logistic Regression**

#### **V.4.5. Death Rate in Patients with Multiple Sclerosis Hospitalized for COVID-19**

Fifteen patients (2.5%) in this study died due to COVID-19. Compared to surviving patients, they were older (OR, 1.9 [95% CI, 1.2-2.9],  $p < 0.004$ ), non-ambulatory (OR, 13.5 [95% CI, 4.3-42.5],  $p < 0.001$ ) with at least one comorbidity (OR, 8.4 [95% CI, 2.9-23.9],  $p < 0.001$ ), a progressive course (ORs, SPMS, 9.7 [95% CI, 3.1-29.7],  $p < 0.001$ ; PPMS, 6.8 [95% CI, 1.3-35.4],  $p = 0.023$ ), higher EDSS (ORs, EDSS 3.0-5.5, 8.9 [95% CI, 1.7-46.7],  $p = 0.009$ ; EDSS  $\geq 6.0$ , 26.9 [95% CI, 5.6-129.8],  $p < 0.001$ ) and longer disease duration (OR per 10 years, 2.0 [95% CI, 1.1-3.5],  $p = 0.013$ ).

#### **V.5. Discussion**

Our study showed that COVID-19 symptoms in PwMS were similar to what has been described in the general population. In our cohort, fever, cough, anosmia/ageusia and fatigue were the most frequently recorded symptoms. Similarly, a cross-sectional study of the general population conducted in seven MENA region countries (Algeria, Egypt, Iraq, Lebanon, Libya, Tunisia, and the United Arab of Emirate) showed that more than half of the participants reported fever, cough, and fatigue as the most frequent symptoms during the course of infection<sup>18</sup>.

Univariate logistic regression models showed that older age, male sex, comorbidities, progressive MS, longer disease duration, higher EDSS, deteriorated ambulation, and withholding DMT were associated with COVID-19 severity scores of 3 or more. Our results were similar to other international COVID-19 registries, mainly the COVISEP French registry<sup>7</sup>, and the MS Global Data Sharing Initiative study<sup>9</sup> that showed that older age, higher EDSS, progressive MS course and male sex were associated with more severe COVID-19 infection. It is of note that male sex was not a risk factor in our cohort.

Similar to the North American Registry-based cohort<sup>10</sup>, our study demonstrated a significant association between hypertension and cardiovascular comorbidities with worse COVID-19 infection. A retrospective case study conducted throughout China involving 11791 MS patients with confirmed COVID-19 also showed that hypertension and cardiac disease were among the most common comorbidities associated with poorer prognosis<sup>19</sup>.

Given the possible interaction between the independent variables, we carried out a multivariate logistic regression analysis. Only older age, higher EDSS, obesity and off-label use of immunosuppressive medications such as azathioprine, mycophenolate mofetil or methotrexate remained as risk factors for severe COVID-19 infection.

The increased severity of COVID-19 among MS patients with higher EDSS can be linked to the fact that respiratory dysfunction is common in such patients and is linked to expiratory muscles weakness and cough impairment<sup>20</sup>. These findings should lead to improving preventive measures to limit the risk of COVID-19 infection in older patients and in patients with advanced disability.

Obesity was associated with 3-fold increased odds of severe COVID-19 infection. This is compatible with the results of a meta-analysis from China that showed that patients with obesity have a greater risk of infection, hospitalization, severe disease, mechanical ventilation, ICU admission, and mortality due to COVID-19<sup>21</sup>. Petrilli et al.<sup>22</sup>, in a large prospective analysis of 5279 COVID-19 patients in the United States demonstrated as well that obese patients have greater tendency to develop adverse events, including respiratory failure, admission to ICU, and invasive mechanical ventilation. Obesity-related respiratory dysfunction is probably the main cause of severe COVID-19 infection in those patients<sup>23</sup>.

Surprisingly, diabetes mellitus was not associated with increased COVID-19 severity in our study. However, several published studies indicated that type 2 diabetes mellitus is a significant risk factor for COVID-19 severity, and mortality. A large meta-analysis involving 78,874 confirmed COVID-19 hospitalized patients showed that pre-existing diabetes is significantly associated with a greater risk of severe/critical illness and in-hospital mortality in patients admitted to hospital with COVID-19<sup>24</sup>.

Multiple studies evaluated the impact of DMT use on COVID-19 infection in PwMS. Given their anti-viral effect, patients treated with interferon beta and teriflunomide were at a lower risk of COVID-19 infection and disease severity<sup>25</sup>. The French<sup>7</sup> and Italian<sup>8</sup> cohorts showed no association between interferon beta, glatiramer acetate and dimethyl fumarate use and COVID-19 severity. In other studies, fingolimod<sup>7,8</sup>, natalizumab<sup>26</sup>, alemtuzumab<sup>27,28</sup>, cladribine<sup>29</sup>, and corticosteroids<sup>30</sup> were not associated with COVID-19 severity. Our results were similar, showing no impact of interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, sphingosine-1-phosphate (S1P) receptor modulators, natalizumab and alemtuzumab on COVID-19 severity.

The MENA cohort, however; showed that exposure to rituximab and immunosuppressive medications such as azathioprine, mycophenolate mofetil and methotrexate increased the risk of severe COVID-19. Rituximab use was associated with a 9-folds increase in risk of severe COVID-19 infection. This was consistent with the findings of Simpson-Yap et al.<sup>9</sup> who reported on 2340 MS patients with COVID-19 infection from 28 countries and showed a significant



association between rituximab and increased risk of hospitalization, ICU admission, and need for artificial ventilation. The same outcomes were replicated in the pooled analysis studies from Italy and France<sup>7,8</sup>.

We found no association between ocrelizumab and COVID-19 increased severity, despite a trend towards higher severity of infection. Although both rituximab and ocrelizumab are anti-CD20 therapies, this discrepancy might be due to different molecular structure or mechanism of cytotoxicity. Another possible explanation is that ocrelizumab was only recently introduced in the MENA region, and therefore the duration of treatment with rituximab was probably longer, knowing that hypogammaglobulinemia and infections increase with the treatment duration of anti-CD20 drugs. Socioeconomic factors might have also played a role, since rituximab is usually prescribed to patients without health insurance, especially refugees in the Middle East. Although this result is compatible with the interim report published by Roche-the pharmaceutical company producing ocrelizumab-, it does not harmonize with some other cohort studies<sup>26</sup>. The Italian cohort study showed an increased risk in severe forms of COVID-19 in MS patients treated with ocrelizumab<sup>8</sup>. The French cohort did not show any association between the use of DMTs and COVID-19 severity, but reported acute respiratory distress syndrome in two patients treated with ocrelizumab<sup>7</sup>. This discrepancy might be due to the small number of ocrelizumab-treated patients in our cohort.

The overall mortality rate of COVID-19 in our MS cohort was 2.5%, similar to the fatality rate of 3.5 % reported by Louapre et al. in the COVISEP registry-based study<sup>7</sup>. Older age, having at least one co-morbidity, progressive MS, higher disability and a longer disease duration were risk factors for mortality in patients with COVID-19 infection. The global average mortality rate of COVID-19 infection in the general population is 2.7%, which is similar to the mortality rate detected in our MS population<sup>31</sup>. This suggests no increased risk of death in patients with MS compared to the general population, but still needs to be confirmed with further epidemiological studies. Two Regional studies from Iran showed similar risk factors for mortality due to COVID-19 infection in the general population, namely older age, obesity and comorbidities<sup>32,33</sup>.

Limitations of this analysis include a potential selection bias as reporting was voluntary by health care professionals, which may have led to selection of more severe cases. Since this study was based on data collected retrospectively from the MENACTRIMS registry and other local registries, we were not able to collect some potentially relevant information like DMT dosage, frequency and duration, and other risk factors beyond those investigated. Some immunosuppressive treatments like ofatumumab, cladribine and alemtuzumab, were not commonly used in our region, limiting the possibility of detecting any association between their

use and COVID-19 severity. Our study strengths include its large sample size and the sensitivity analysis that confirmed the results.

## V.6. Conclusion

COVID-19 has significantly impacted the medical practice, and it is likely to remain an issue for several years to come with annual waves. It is therefore crucial to identify the risk factors for more severe infection in Middle-Eastern PwMS who may have different genetic predisposition compared to other populations leading to improvement in the clinical management of MS patients with COVID-19 infection in our region. This is the largest registry-based cohort study in our region and its outcomes were consistent with those described in other international studies. In patients with MS, we identified age, sex, disability, obesity progressive MS and rituximab exposure as independent risk factors for severe COVID-19. We found no association between all other DMTs and severe COVID-19 which should reinforce the recommendation of keeping PwMS and COVID-19 on their DMT and avoid delaying treatment initiation.

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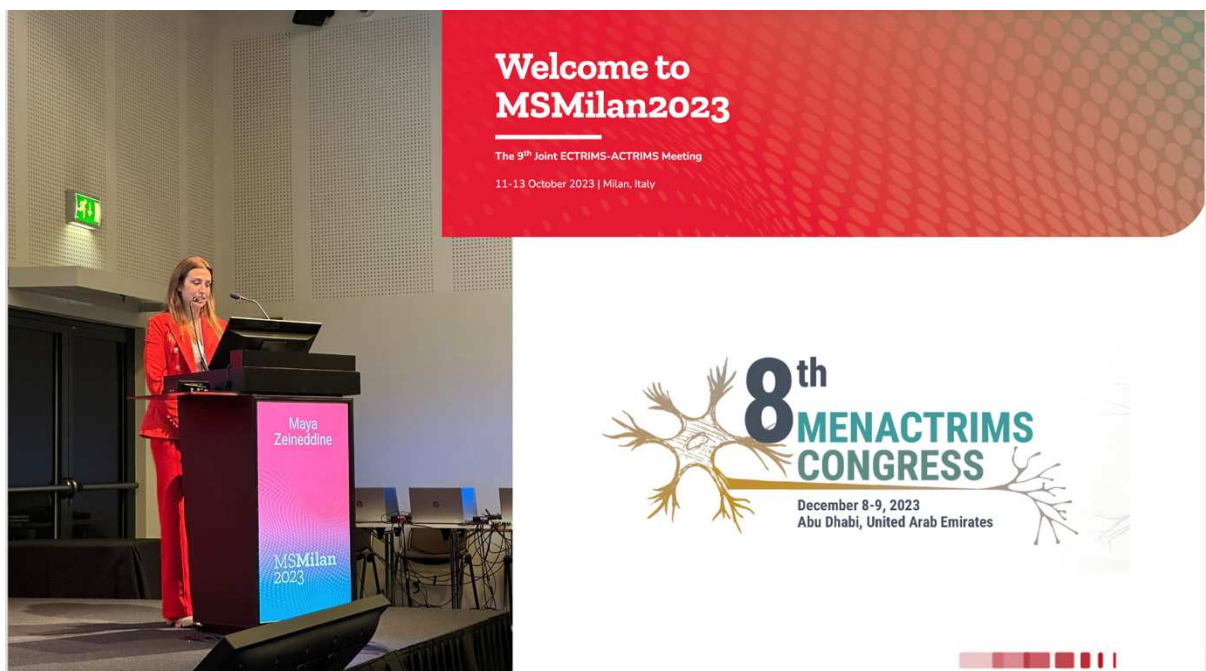
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## Chapter VI. Safety and Effectiveness of Disease Modifying Therapies after Switching from Natalizumab

### VI.1. Background

The first three studies in this thesis highlighted significant challenges in accessing DMTs in the MENA region and emphasized the importance of safety in long-term MS treatment, particularly during the COVID-19 pandemic. Building on these findings, the fourth study explores how to safely and effectively transition patients from natalizumab, a highly effective but risky treatment due to its association with PML. This study focuses on evaluating the safety and effectiveness of alternative high-efficacy DMTs, specifically rituximab/ocrelizumab, fingolimod, and alemtuzumab, when switching from natalizumab in patients with JCV antibody positivity. By comparing these therapies, the study aims to identify the most effective and safest options for patients at high risk of PML, thereby contributing to the overarching thesis objective of optimizing long-term MS treatment strategies in the MENA region.

The findings of this research were presented as an oral session at both the 9th ECTRIMS Congress in Milan, Italy, in October 2023, and the 8th MENACTRIMS Congress in Abu Dhabi, UAE, in December 2023. Furthermore, this study was published in the Multiple Sclerosis Journal (**Appendix 9**).



## **Abstract**

**Introduction:** One strategy to mitigate progressive multifocal leukoencephalopathy (PML) risk is to switch to other highly effective disease-modifying therapies (DMT). However, the optimal switch DMT following NTZ discontinuation is yet to be determined.

**Objective:** To determine the most effective and tolerable DMTs to switch to following NTZ discontinuation due to John Cunningham Virus (JCV) antibody positivity.

**Methods:** This is a multi-center observational cohort study that included all stable relapsing-remitting MS patients who were treated with NTZ for at least 6 months before switching therapy due to JCV antibody positivity.

**Results:** Out of 321 patients, 255 switched from NTZ to rituximab/ocrelizumab, 52 to fingolimod, and 14 to alemtuzumab, with higher ARR in fingolimod switchers (0.193) compared to rituximab/ocrelizumab or alemtuzumab (0.028 and 0.032, respectively). Fingolimod switchers also had increased disability progression ( $p=0.014$ ) and a higher proportion developed MRI lesions compared to rituximab/ocrelizumab (62.9% versus 13.0%,  $p<0.001$ , and 66.6% versus 24.0%,  $p < 0.001$ , respectively). Mean drug survival favored rituximab/ocrelizumab or alemtuzumab over fingolimod ( $p < 0.001$ ).

**Conclusion:** Our study shows superior effectiveness of rituximab/ocrelizumab and alemtuzumab compared with fingolimod in stable patients switching from natalizumab due to JC virus antibody positivity.

**Keywords:** natalizumab; switching; PML; multiple sclerosis; fingolimod; rituximab

## VI.2. Introduction

Natalizumab (NTZ) is a monoclonal antibody approved for treating RRMS. It blocks  $\alpha 4\beta 1$  integrin on leukocytes, preventing mononuclear cell trafficking across the blood-brain barrier (BBB)<sup>1</sup>. Phase III clinical trials<sup>2-3</sup> and observational studies<sup>4-6</sup> have confirmed its long-term efficacy and safety in RRMS.

The most significant risk with NTZ is PML, especially in patients treated for over two years, those with prior immunosuppressive therapy exposure, or those who are JCV antibody positive with a high index<sup>7-8</sup>.

With the availability of high-efficacy DMTs, the risk of PML in NTZ-treated patients can be mitigated by switching treatments. However, NTZ is associated with a rebound phenomenon and severe disease reactivation risk<sup>9</sup>. The RESTORE trial showed that switching from NTZ to less efficacious DMTs, such as interferons, glatiramer acetate, or methylprednisolone, led to clinical relapses in 15–29% of patients, with MRI activity detected as early as 12 weeks post-treatment cessation<sup>10</sup>. Similarly, real-world studies found breakthrough disease in patients switched from NTZ to dimethyl fumarate<sup>11</sup> or teriflunomide<sup>12</sup>.

Only few small observational studies<sup>13-16</sup> looked at efficacy and safety of fingolimod, ocrelizumab (OCR), rituximab (RTX) or cladribine after natalizumab cessation.

The aim of this study was to compare the effectiveness, safety and drug survival of switching from natalizumab to other high efficacy DMTs due to JCV Ab positivity.

## VI.3. Methods

### VI.3.1. Study Setting and Population

We conducted a multicenter retrospective observational study of patients with RRMS treated with NTZ for at least 6 months before switching to high-efficacy DMTs due to JCV Ab positivity. Patient data was obtained from the MENACTRIMS registry, the largest regional MS registry<sup>17</sup>, and local national registries from different countries in the MENA region including Kuwait, Lebanon, UAE, Iraq, Oman, Algeria and Tunis. Data was extracted and analysed between October 2022 and March 2023. All patients diagnosed with RRMS according to the 2010<sup>18</sup> or 2017<sup>19</sup> Mc Donald criteria and fulfilling the following inclusion criteria were included in the study: age between 18 and 65 years, EDSS between 0-6, treated with natalizumab for at least 6 months before switching to another DMT due to positive serum JCV Ab or high AI, and a follow up period on the new DMT of at least 1 year or until drug discontinuation whichever



comes first. Patients who discontinued natalizumab treatment for other reasons than a positive JCV Ab or shifted to other DMTs after a wash out period longer than 3 months were excluded.

### **VI.3.2. Outcomes**

The study outcomes were: ARR, time to first relapse, confirmed disability progression, new MRI activity after switching to the new DMT, no evidence of disease activity (NEDA-3) defined as absence of relapses, new MRI lesions or disability progression, drug survival and adverse events. The study baseline was defined as the date of initiation of the new DMT.

Relapse was defined as new or recurrent neurological symptoms lasting for more than 24 hours without fever or infection<sup>20</sup>. ARR was calculated by dividing the total number of relapses by the total number of person-years at risk<sup>21</sup>.

The EDSS obtained within 6 months before or 3 months after switching to the new DMT was chosen as baseline. Disability progression was defined as 3 or 6 months sustained EDSS increase by  $\geq 1$  point for a baseline EDSS between 2 and 5.5, or 0.5 points for an EDSS above 5.5, or 1.5 points for an EDSS between 0 and 1.5<sup>22</sup>.

Baseline MRI was defined as the MRI scan performed at least 3 months after initiating the new DMT. Enhancing lesions and new T2 lesions on MRIs were calculated as proportion of patients with positive scans among patients with valid baseline and follow-up MRIs.

Registered adverse events were: severe infections requiring medications, persistent lymphopenia for  $> 3$  months, increased liver enzymes  $\geq 3$  times upper limit of normal, bradycardia, autoimmune disorders, hypersensitivity reactions, PML and malignancies. The date of discontinuation of the new DMT was recorded as the date of last administration. Drug survival was defined as persistence on the new DMT during the observational period. Alemtuzumab treatment discontinuation was defined as beginning of an alternative DMT within the first year or when the decision against administration of the second treatment course was made<sup>23</sup>.

### **VI.3.3. Data Collection**

Patient data were recorded during routine clinic visits at participating centers via the locally installed iMed or MDS software programs. Data was collected from the MENACTRIMS and local MS registries using a standardized data collection sheet.

#### **VI.3.4. Standard Protocol Approvals**

Ethical approval for the MENACTRIMS registry was granted by the American University of Beirut Ethics Committee (**Appendix 3**). Approvals from local ethical committees in participating centers were also obtained.

#### **VI.3.5. Statistical Analyses**

Patient data was coded and entered for analysis in SPSS V28. Sample characteristics were summarized using frequency, proportion for categorical variable, mean and standard deviation or median and interquartile range for numerical data.

Number of relapses were counted and normalized per year duration to produce ARR, followed by multivariable modeling using the Poisson distribution to produce Relative Risk (RR), 95% confidence intervals CI, and p-value.

Kaplan-Meier survival analysis was utilized to look at time for first relapse after switching to the new DMT. Log Rank test produced p-value comparing the different DMT.

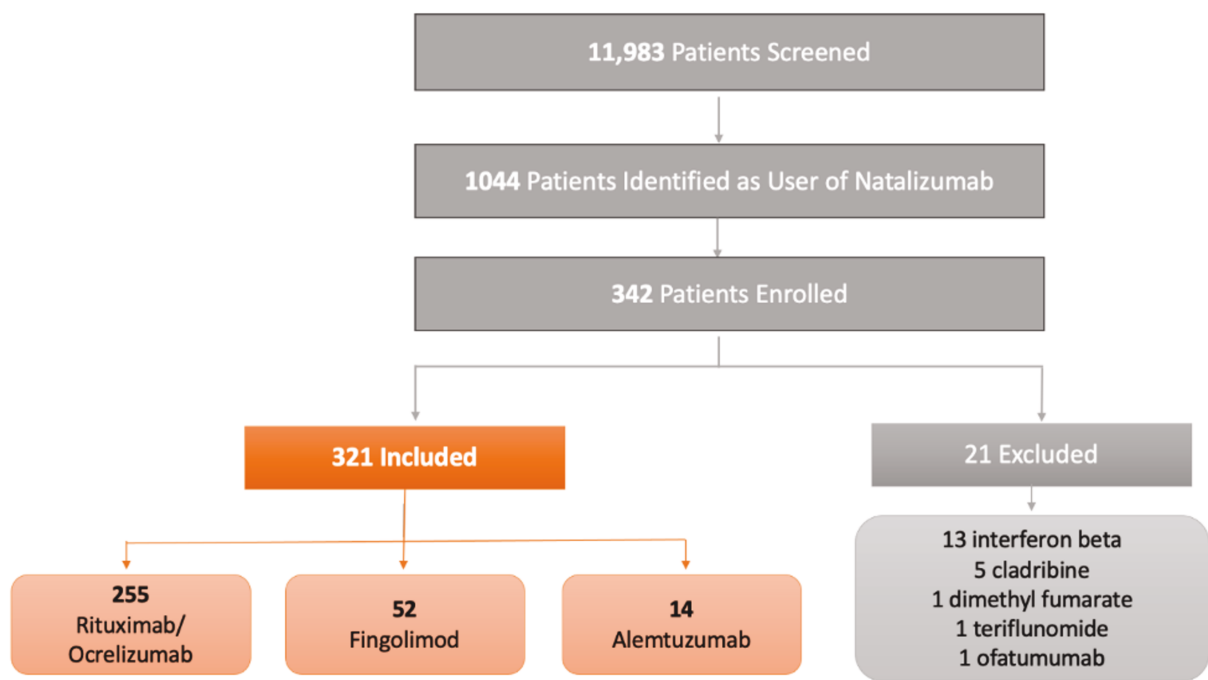
Confirmed disability progression CDP at 3-month and 6-month were computed. Crude and adjusted Odds Ratio (OR) were computed using univariate and multivariable regression models adjusting for other statistically significant covariates.

MRI activity outcomes, new T2 lesions and gadolinium enhancing lesions, were also counted and compared between the different DMT using the Pearson Chi-square, and subsequently followed by the multivariable logistic regression to compute OR, 95% CI adjusted for the following confounding variables: age, sex, disease duration, washout period, baseline EDSS, EDSS upon initiating NTZ, ARR in the year preceding NTZ treatment and duration of follow-up on the new DMT. All analyses were carried out at the 0.05 significant level.

### **VI.4. Results**

#### **VI.4.1. Study Population**

In total, 342 patients switched from NTZ due to JCV Ab positivity. We excluded 15 patients switching to low-efficacy DMTs (13 to interferon beta and 2 to teriflunomide and dimethyl fumarate). Six patients switching to cladribine and one to ofatumumab were also excluded due to small numbers. A total of 321 patients were included in the final analysis: 255 on rituximab (RTX)/Ocrelizumab (OCR), 52 on fingolimod and 14 on alemtuzumab (**Figure 1**).



**Figure 1: Flow chart of the Included/Excluded Patients**

Baseline characteristics of the study population are shown in **Table 1**. The mean duration of follow-up on the new DMT was 2.4, 4.3 and 4.0 years on RTX/OCR, fingolimod and alemtuzumab, respectively.

**Table 1: Baseline Characteristics of the Study Population**

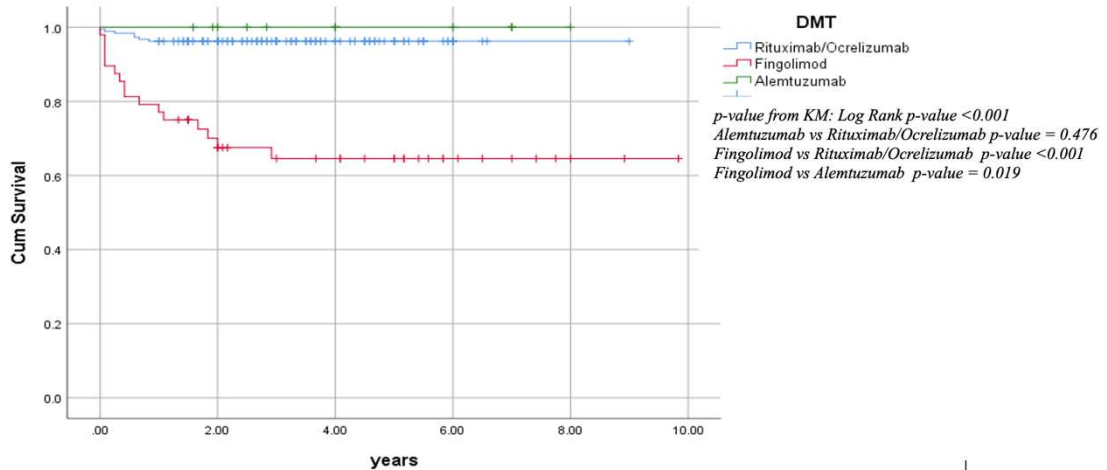
	Rituximab/Ocrelizumab (n=255)	Fingolimod (n=52)	Alemtuzumab (n=14)
<b>Sex</b>	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
Male	79 (31)	20 (38.5)	4 (28.5)
Female	176 (69)	32 (61.5)	10 (71.4)
<b>Age (years)</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>	<b>Mean ± SD</b>
	38.3 ± 8.5	40.1 ± 9.2	38.6 ± 6.1
<b>Age of diagnosis (years)</b>	26.4 ± 7.9	26.3 ± 7.4	25.6 ± 6.5
<b>Age at initiation of NTZ (years)</b>	32.1 ± 8.6	30.6 ± 8.8	30.8 ± 5.6
<b>Total disease duration (years)</b>	11.9 ± 5.5	13.8 ± 5.6	12.9 ± 5.4
<b>Number of relapses in the year prior starting NTZ</b>	1.5 ± 0.8	1.3 ± 0.6	1.4 ± 0.6
	<b>Median (IQR)</b>	<b>Median (IQR)</b>	<b>Median (IQR)</b>
<b>Washout period (weeks)</b>	4.0 (2 – 6)	6.0 (4 – 11)	4.5 (4 – 9)
<b>EDSS upon initiating NTZ</b>	2.0 (1 - 4)	2.0 (1 - 3)	2.0 (1 - 5.6)
<b>EDSS upon initiating the new DMT</b>	2.0 (1 - 4)	2.0 (1 - 4.4)	2.3 (1 - 6)
<b>Duration of follow up on DMT (years)</b>	2.4 (1.5 - 4)	4.3 (2 - 6.4)	4 (2.4 - 7)

*SD = standard deviation; IQR = Interquartile Range; NTZ = natalizumab; EDSS = Expanded Disability Status Score; DMT = Disease-modifying therapy*

## VI.4.2. Effectiveness

### VI.4.2.1. Clinical Relapses

Switching to RTX/OCR was associated with a statistically significant reduction in ARR compared to fingolimod (0.028 vs 0.193; p-value <0.001). No significant difference in ARR was found between patients shifting to RTX/OCR vs alemtuzumab (0.028 vs 0.032; p-value=0.987). Similar results were obtained when adjusting for the following confounding variables: age, sex, disease duration, washout period, baseline EDSS, EDSS upon initiating NTZ, ARR in the year preceding NTZ treatment and duration of follow-up on the new DMT. The time to first relapse was significantly shorter in patients switching to fingolimod as compared to RTX/OCR, with a mean time of 6.7±0.6 and 8.7±0.1 years (p-value <0.001), respectively (**Figure 2**). There was no significant difference in time to first relapse between patients switching to RTX/OCR vs alemtuzumab. Only 1 patient had a relapse on the latter. The results were similar after adjusting for the selected confounding variables.



	Mean Time to First Relapse (years)	Standard Deviation
<b>Rituximab/Ocrelizumab</b>	8.7	0.1
<b>Fingolimod</b>	6.7	0.6
<b>Alemtuzumab*</b>	-	-

\*Only 1 patient had a relapse on alemtuzumab

**Figure 2: Time to first relapse on the new Disease-Modifying Therapy**

#### VI.4.2.2. Disability Progression

Compared with RTX/OCR, switching to fingolimod was associated with a significant increase in risk of 3- and 6-month confirmed disability progression, even after adjusting for confounding variables (Adjusted OR, 3.28; 95%CI 1.06-10.09 and 2.89; 95%CI 1.06-7.87, respectively). Patients switching to alemtuzumab were not included in the disability progression analysis due to the small sample size (**Table 2**).

**Table 2: Confirmed 3- and 6-month Disability Progression on the New DMT**

Odds-Ratio of 3-month and 6-month CDP by DMT Type						
3-month CDP	Unadjusted			Adjusted*		
	OR	95% CI	p-value	OR	95% CI	p-value
Rituximab/Ocrelizumab			1.00 (ref)			
Fingolimod	3.29	1.27 – 8.51	0.014	3.28	1.06 – 10.09	0.039
6-month CDP						
Rituximab/Ocrelizumab			1.00 (ref)			
Fingolimod	2.29	1.03- 5.06	0.041	2.89	1.06 – 7.87	0.038

\*Adjusted for Age, Sex, Disease duration, washout period, EDSS baseline, EDSS upon initiating NTZ, ARR before NTZ treatment

CDP = Confirmed disability progression; OR = Odds Ratio; CI = Confidence Interval; DMT = Disease-modifying therapy; EDSS – Expanded Disability Status Score; ARR= Annualized Relapse Rate; NTZ= Natalizumab  
*Alemtuzumab was removed from the analysis because the number of patients was too low.*

#### VI.4.2.3. MRI Activity

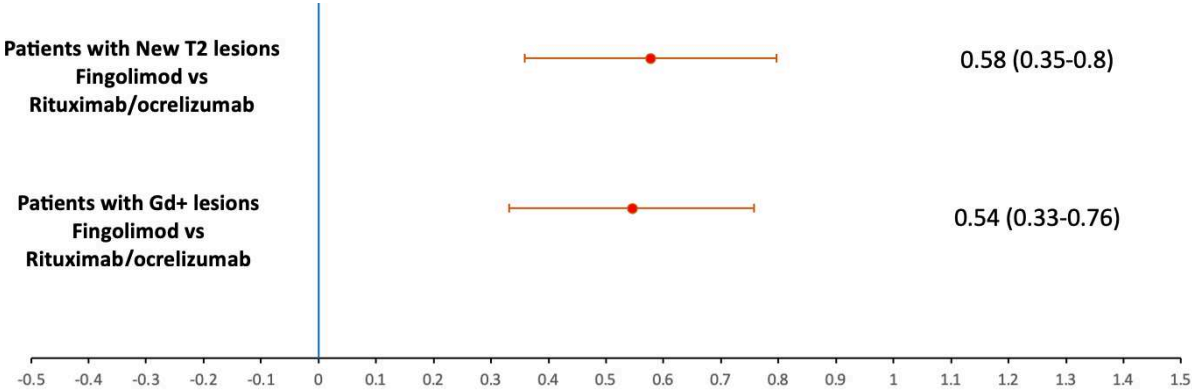
Due to the small number of patients with valid MRI scans in the alemtuzumab group (n=3), alemtuzumab was not included in the MRI analysis. A higher proportion of patients with new T2 lesions was detected in patients shifting to fingolimod compared to RTX/OCR (66.6% vs 24.0%; p-value<0.001) (**Table 3**). Similar results were obtained for Gd+ lesions with a higher proportion of patients with Gd+ lesions on fingolimod compared to RTX/OCR (62.9% vs 13.0%, p-value< 0.001).

**Table 3: MRI Outcomes on the New DMT**

	Rituximab/Ocrelizumab (n=100)		Fingolimod (n=27)		p-value
	N	%	N	%	
<b>Number of Patients with new T2 lesions</b>	24	24.0	18	66.6	<0.001
<b>Number of New T2 Lesions</b>					
0	76	76.0	9	33.3	<0.001
1	22	22.0	5	18.5	
2	2	2.0	5	18.5	
3	0	0.0	6	22.2	
4+	0	0.0	2	7.4	
<b>Number of Patients with Gd+ lesions</b>	13	13.0	17	62.9	<0.001
<b>Number of Gd+ Lesions</b>					
0	87	87.0	10	37.0	<0.001
1	12	12.0	6	22.2	
2	1	1.0	6	22.2	
3	0	0.0	5	18.5	

DMT = Disease-modifying therapy; GD+ = Gadolinium Enhancing  
*Alemtuzumab was removed from the analysis because the number of MRI scans in this group was too low.*

**Figure 3** shows that, after adjusting for confounding variables, the proportion of patients with new T2 or Gd+ lesions was still lower on RTX/OCR compared to fingolimod (OR 0.58; 95%CI 0.35-0.80 and 0.54; 95%CI 0.33-0.76, respectively).



*\*Adjusted for sex, age, washout period, baseline EDSS, and EDSS scores at initiation of NTZ, number of relapses in year prior to NTZ, disease duration, and DMT duration*

*Alemtuzumab was removed from the multivariate regression analysis due to low number of patients with valid scans.*

*MRI= Magnetic Resonance Imaging; Gd+= Enhancing Lesions; EDSS= Expanded Disability Status Scale; NTZ= Natalizumab; DMT= Disease Modifying Therapy*

**Figure 3: Forest Plot for MRI Activity after Adjusting For Confounding Factors\***

**VI.4.2.4. NEDA-3**

The alemtuzumab group was not included in the NEDA-3 analysis due to the small number of patients with MRI. A higher proportion of patients on RTX/OCR achieved NEDA-3 compared to fingolimod: 74.9% (191/255) vs. 40.4% (21/52); p-value< 0.001.

**VI.4.3. Safety**

Patients on alemtuzumab experienced the highest frequency of adverse events (4/14 patients with autoimmune thyroiditis) compared to fingolimod and RTX/OCR (28.6%, 21.2%, and 8.6%, respectively) Lymphopenia, increased liver enzymes and bradycardia were more commonly seen in patients on fingolimod. There was one case of PML (considered a carry-over from NTZ) and one case of breast cancer on RTX and OCR, respectively (**Table 4**).

**Table 4: Adverse Events**

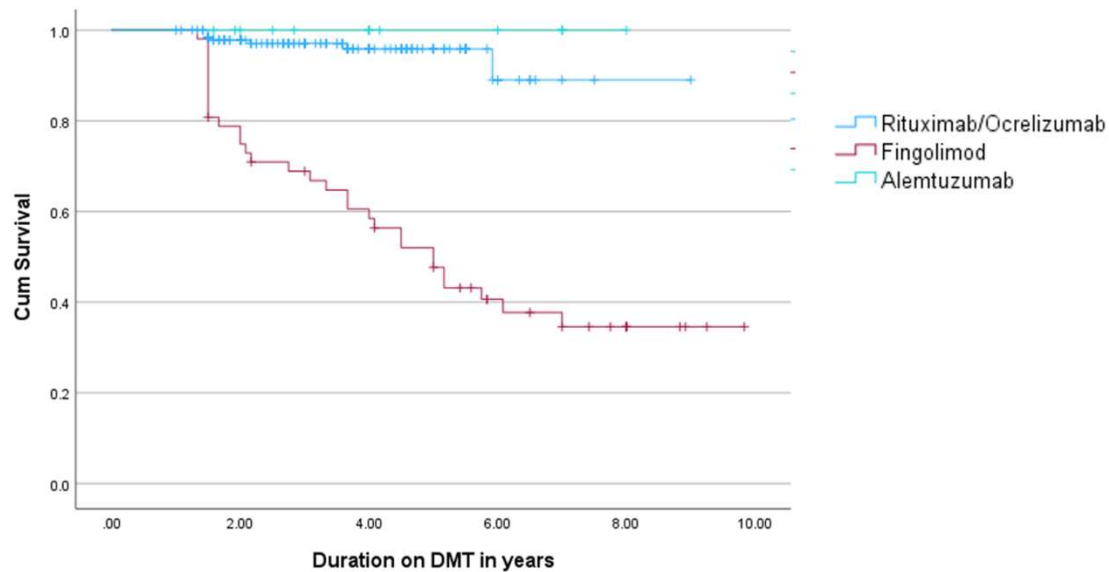
Adverse Events	Rituximab/Ocrelizumab (n=255)		Fingolimod (n=52)		Alemtuzumab (n=14)	
	N	%	N	%	N	%
Yes	22	8.6	11	21.2	4	28.6
Infections	9	3.5	5	9.6	0	0.0
Hypersensitivity Reactions	7	2.7	0	0.0	0	0.0
Asymptomatic Bradycardia	0	0.0	1	1.9	0	0.0
Persistent lymphopenia	0	0.0	3	5.8	0	0.0
Increase in Liver Enzymes $\geq 3X$ ULN	1	0.4	2	3.8	0	0.0
Autoimmune Thyroiditis	0	0.0	0	0.0	4	28.6
PML	1	0.4	0	0.0	0	0.0
Breast Cancer	1	0.4	0	0.0	0	0.0

UTI= Urinary Tract Infection; ULN= Upper Limit of Normal; PML= Progressive Multifocal Leukoencephalopathy; DMT= Disease Modifying Therapy

#### VI.4.4. Drug Survival

A total of 31/52 patients (59.6%) on fingolimod discontinued treatment compared to 8/255 (3.1%) on RTX/OCR. The mean drug survival was 8.5 years on RTX/OCR compared to 5.6 years on fingolimod (p-value < 0.001) (**Figure 4**). The reasons for discontinuation of fingolimod were: treatment failure (20/31 [64.5%]), adverse events (7/31 [22.6%]) and pregnancy (4/31 [12.9%]), and for RTX/OCR: patient preference (3/8 [37.5%]), treatment failure (2/8 [25%]), adverse events (2/8 [25%]) and pregnancy (1/8 [12.5%]). None of the patients on alemtuzumab fulfilled the criteria for treatment discontinuation, but 3 patients received a third cycle due to breakthrough disease.





*KM Log-rank p-value <0.001*  
*Alemtuzumab vs Rituximab/Ocrelizumab p-value = 0.458*  
*Fingolimod vs Rituximab/Ocrelizumab p-value <0.001*  
*Fingolimod vs Alemtuzumab p-value = 0.004*

**Figure 4: DMT Survival**

## VI.5. Discussion

In this observational retrospective cohort study, we compared the effectiveness, safety and drug survival of RTX/OCR, fingolimod and alemtuzumab after switching from NTZ due to JCV Ab positivity. Compared to fingolimod, RTX/OCR and alemtuzumab were associated with significant reduction in ARR and time to first relapse and had a longer drug survival. Patients switching to RTX/OCR had less disability progression, fewer new T2 and Gd+ lesions and higher rates of NEDA-3 compared to fingolimod. The results were similar after adjusting for the selected confounding variables. Due to the low number of patients switching to alemtuzumab, the latter was not included in the disability progression, NEDA-3 and MRI activity analyses. The safety profile also favored RTX/OCR vs both fingolimod and alemtuzumab with higher rate of infections, liver toxicity and lymphopenia on fingolimod and autoimmune thyroiditis on alemtuzumab. It is of note however, that there was one case of PML and one case of breast cancer on RTX and OCR, respectively. The better drug survival of RTX/OCR and alemtuzumab compared to fingolimod was mainly due to a higher rate of treatment failure on fingolimod.

To our knowledge, this is the first study comparing the effectiveness, safety and drug survival of RTX/OCR, alemtuzumab and fingolimod after switching from NTZ. It is of note that to date,

no randomized controlled trial comparing the efficacy and safety of switching from NTZ to high efficacy DMTs due to JCV Ab positivity has been performed.

In a Swedish multicenter study of 256 patients switching from NTZ to rituximab or fingolimod due to JCV Ab positivity, rituximab was associated with significantly lower relapse rates (1.8% vs. 17.6%), Gd+ lesions (1.4% vs. 24.2%), and treatment discontinuation rates (1.8% vs. 28.2%) during 1.5 years of follow-up<sup>24</sup>. Our study showed similar results when comparing RTX/OCR to fingolimod over a longer follow-up period (2.4-4.3 years)<sup>25</sup>. Similar outcomes were reported in a large retrospective observational MSBase registry study<sup>25</sup> comparing the effectiveness and treatment discontinuation rates in patients switching from NTZ to dimethyl fumarate, fingolimod, or OCR. Patients on fingolimod had higher annualized relapse rates (ARR) (OR=4.33; 95% CI, 3.12-6.01), increased risk of disability progression (49%), and higher treatment discontinuation rates (OR=2.57; 95% CI, 1.74-3.80) compared to OCR. In a retrospective French study<sup>26</sup>, 48 patients on OCR were compared to 54 on fingolimod after NTZ cessation. Patients on OCR had a significantly lower ARR after one year (0.12 vs. 0.41, p=0.026), similar to our findings.

A retrospective multicenter German study<sup>27</sup> compared 101 patients on fingolimod to 42 on alemtuzumab after NTZ cessation. Patients on fingolimod had higher relapse rates (OR=2.24; 95% CI, 1.12-4.50), disability progression (OR=4.84; 95% CI, 1.74-13.47), and MRI progression (OR=2.41; 95% CI, 1.26-4.60). Adverse events were more common in fingolimod compared to alemtuzumab (OR=7.78; 95% CI, 1.04-57.95). However, follow-up was only for one year, whereas the most common adverse events of alemtuzumab, autoimmune disorders, peak in the third year of treatment.

In a recent study, Santiago-Setien et al. assessed clinical outcomes in 30 patients maintained on NTZ extended interval dosing or shifted to OCR. There was no significant differences in AAR, radiological activity, or disability progression between the 2 groups<sup>28</sup>.

Our study has several limitations. The retrospective observational design could have introduced a selection bias. However, adjusting for multiple confounding variables did not alter the outcomes. Combining both B-cell depleting therapies (OCR and RTX) into a single group might have obscured any differential effects between them, but most studies have shown similar effectiveness and safety profiles for both DMTs. For instance, a retrospective multicenter Italian study found that OCR and RTX had similar reductions in ARR and MRI activity in patients switching from NTZ. Additionally, we could not determine the JCV Ab index due to inconsistent reporting in the registries. We also lacked detailed information on the

dosage and interval dosing of natalizumab and the B-cell depleting therapies. Some patients on rituximab received doses ranging from 500 to 1000 mg at intervals of 6 to 12 months, a common practice in the MENA region. However, previous studies have indicated that such variations in dosing or treatment interval did not affect the effectiveness of RTX<sup>30-32</sup>.

The strengths of this study include the large number patients and long follow-up duration compared to most previous studies. It is also, to our knowledge, the first study to compare RTX/OCR, fingolimod and alemtuzumab as potential exit strategies in patients on NTZ and JCV Ab positivity.

## **VI.6. Conclusion**

Our study showed that in patients switching from NTZ due to JCV Ab positivity, RTX/OCR showed higher effectiveness and better safety profile compared to fingolimod. Compared to alemtuzumab, RTX/OCR had similar effectiveness but better safety profile.

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## Chapter VII. General Discussion

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### VII.1. Main Findings

This thesis aimed to evaluate the long-term safety and efficacy of high-efficacy DMTs among MS patients in the MENA region.

The first objective focused on evaluating the availability and accessibility of DMTs across the MENA region. The findings revealed significant disparities in access to both low-efficacy and high-efficacy DMTs, with high-income countries generally having better access compared to low-income countries. For instance, countries such as Kuwait and Saudi Arabia had a broad range of available DMTs, while countries like Sudan and Syria struggled with limited access due to both economic and infrastructural barriers. These findings align with the broader global patterns observed in studies by the MSIF<sup>63</sup>, which have highlighted significant discrepancies in MS care depending on national income levels.

Comparing these results to studies from other regions, this research showed that access to DMTs in the MENA region is similar to areas like Southeast Asia and the Western Pacific but remains lower than in Europe and the USA<sup>63</sup>. Moreover, it emphasized the widespread use of off-label DMTs in MENA, aligning with global trends, especially in low-resource settings<sup>176</sup>. This study also indicated that barriers to treatment access, such as cost and availability, are more significant in MENA compared to other regions, highlighting the economic disparities within the area. This observation is consistent with findings from other regions, such as Latin America, where similar challenges are present<sup>177</sup>. However, the extent of the disparity within the MENA region, where some countries have near-complete access while others have almost none, is particularly striking and suggests that regional efforts to address these gaps are urgently needed.

Building on these findings, the next study explored the specific situation in Lebanon, a country grappling with a severe economic crisis that has further restricted access to MS treatments. In the context of the ongoing economic crisis in Lebanon, this second study examined how the country's financial instability has affected MS patients' access to treatment and overall quality of life. The study found that many patients experienced interruptions in their treatment regimens, leading to worsened health outcomes and reduced QOL. This is consistent with the findings from global studies that have linked economic crises to deteriorations in chronic disease management, as seen in Greece during its financial crisis, where access to healthcare significantly declined, resulting in poorer health outcomes<sup>178</sup>.

Furthermore, the Lebanese study showed that higher levels of education, being employed, and being married are associated with better HRQOL, similarly the results of studies from Oman<sup>179</sup> and Kuwait<sup>180</sup>. Notably, physical disability negatively impacted HRQOL, aligning with research from Iran<sup>181</sup>, Germany<sup>182</sup>, and Kuwait<sup>180</sup>, which also demonstrated that worsening disability correlates with lower quality of life. The association between marital status and improved quality of life, found in this study, mirrors similar findings in other research, where family support plays a crucial role<sup>183, 184</sup>. In contrast, living in urban areas, specifically Beirut, was linked to lower HRQOL, which differs from North American studies showing better outcomes for urban residents<sup>185</sup>, possibly due to the unique healthcare landscape in Lebanon.

Overall, both studies (1 and 2) underscored the profound impact of external factors, economic crises and healthcare access, on the QoL and health outcomes for MS patients. In the broader MENA region and specifically in Lebanon, financial barriers, such as the high cost of DMTs and lack of insurance, were shown to significantly hinder patients' ability to maintain their treatment regimens, which in turn directly impacts their QoL. To sum up, the studies collectively highlighted the urgent need for targeted healthcare strategies and policies to address economic barriers and improve treatment access, which are crucial for enhancing the QoL of MS patients in resource-constrained settings.

After assessing the accessibility of DMTs in the MENA region with a particular emphasis on Lebanon, the next critical focus was the intersection of MS treatments and the global COVID-19 pandemic. The unprecedented spread of COVID-19 introduced significant challenges for PwMS, especially those undergoing immunosuppressive therapies. Due to their increased susceptibility to infections, it became crucial to evaluate the effects of these treatments on COVID-19 outcomes within this population. Thus, the third study addressed the safety concerns related to the use of high-efficacy DMTs during the COVID-19 pandemic. Consistent with global studies, this research identified older age, higher disability scores EDSS, and comorbidities like obesity as significant risk factors for severe COVID-19 outcomes in PwMS. The association between these risk factors and severe COVID-19 was also observed in the COVISEP French registry<sup>186</sup> and the MS Global Data Sharing Initiative<sup>149</sup>, which reported similar associations in their populations. Unlike some studies<sup>164, 187</sup>, this study found no significant association between ocrelizumab and increased COVID-19 severity, although a trend was noted, possibly due to the relatively recent introduction of ocrelizumab in the MENA region. Moreover, the study also highlighted that rituximab and other off-label immunosuppressive treatments were associated with a higher risk of severe COVID-19, aligning with findings from other international registries like those from Italy<sup>164</sup> and France<sup>186</sup>. The mortality rate among the cohort was similar to that observed in the general population,



suggesting no increased risk of death from COVID-19 specifically due to MS, although this requires further epidemiological confirmation. This suggests that while high-efficacy DMTs are effective in controlling MS, they necessitate careful monitoring and risk assessment during infectious disease outbreaks. These findings contribute to the broader discussion on the safety profiles of MS treatments in the context of global pandemics, highlighting the need for updated treatment guidelines that reflect these risks.

For a better understanding of the safety and efficacy of high-efficacy DMTs in PwMS, the fourth study investigated the comparative safety and effectiveness of these therapies for patients transitioning from natalizumab, particularly those at risk for PML. This research found that rituximab/ocrelizumab offers superior outcomes in reducing relapse rates and MRI activity compared to fingolimod, along with a better safety profile. Alemtuzumab, while effective, was associated with autoimmune thyroiditis as a significant adverse event. These results align with those from Swedish multicenter<sup>188</sup> and MSBase registry studies<sup>189-191</sup>, reinforcing the preference for rituximab/ocrelizumab over fingolimod post-natalizumab discontinuation. However, similarly to the third study, this research highlighted some concerns regarding the long-term safety of these high-efficacy DMTs, particularly in relation to infection risks, which is consistent with findings from studies on B-cell depleting agents<sup>192</sup>. This suggests that while these therapies are effective alternatives, their use should be carefully managed, particularly in patients with additional risk factors for infections. Together, these studies (3 and 4) emphasize the crucial need for careful DMT selection in MS management, ensuring that patients receive treatment that maximizes efficacy while minimizing risks, particularly in situations like the COVID-19 pandemic.

## **VII.2. Clinical Practice Recommendations and Implications**

This research underscored the multifaceted challenges faced by MS patients in the MENA region, particularly in low-resources countries and during times of crisis. The barriers to treatment, whether due to economic instability or a global pandemic, significantly impact patient outcomes. The consistent finding across all these studies is that access to safe and effective DMTs is crucial in managing MS and maintaining QoL. Based on these results, several recommendations and implications for clinical practice can be drawn:

### **1. Enhancing Access to DMTs in Low- and Middle-Income Countries**

The disparities in access to DMTs across the MENA region highlight the urgent need for targeted interventions to improve accessibility in low- and middle-income countries. Health authorities and policymakers should consider implementing national and regional strategies to address these disparities. This could include negotiating with pharmaceutical companies for

lower drug prices, encouraging the local production of generics, and establishing funding mechanisms to subsidize the cost of treatment for patients who cannot afford it. Additionally, increasing awareness and training among healthcare providers about the available DMTs and their appropriate use could help improve treatment coverage in underserved areas.

## **2. Addressing Economic Barriers to Continuous MS Care**

The impact of economic crises on MS treatment continuity, as evidenced by the situation in Lebanon, underscores the need for resilient healthcare systems that can maintain the supply of essential medications during financial downturns. Governments should explore creating emergency healthcare funds or partnering with international organizations to ensure that patients with chronic conditions like MS continue to receive necessary treatments despite economic challenges. For clinical practice, it is crucial to prioritize the most cost-effective therapies that can maintain efficacy while being financially sustainable during crises.

## **3. Incorporating Infection Risk Management in High-Efficacy DMT Protocols**

The increased risk of severe infections, particularly during the COVID-19 pandemic, among patients on high-efficacy DMTs like anti-CD20 monoclonal antibodies, suggests that infection risk management should be a critical component of MS treatment protocols. Clinicians should assess patients' infection risk before initiating these therapies and consider alternative treatments for those at higher risk. Additionally, patients on these therapies should receive regular monitoring for infections, and clinicians should be prepared to modify treatment plans in response to emerging infectious threats. Vaccination strategies, including timing and choice of vaccines, should be optimized for patients on immunosuppressive therapies.

## **4. Regular Reevaluation of Treatment Strategies Based on Individual Patient Responses**

The comparative effectiveness of therapies post-natalizumab suggests that regular reevaluation of treatment strategies is necessary to ensure optimal outcomes. Clinicians should not only rely on initial treatment choices but should continuously assess patient responses and adjust therapies accordingly. This could involve transitioning patients between therapies based on their evolving risk profiles or emerging evidence about the safety and efficacy of different DMTs. Incorporating biomarkers and other predictive tools into routine practice could further enhance the ability to tailor treatments to individual patients.

## **5. Educating Patients on the Risks and Benefits of High-Efficacy DMTs**

Given the complexity of treatment decisions in MS, especially regarding high-efficacy DMTs, it is crucial to involve patients in their care decisions through comprehensive education. Patients should be informed about the potential risks and benefits of different therapies, including the possibility of severe infections and the need for regular monitoring. This shared decision-making process will empower patients to make informed choices about their treatment and could improve adherence and overall outcomes.

## **6. Strengthening Regional Collaboration and Data Sharing**

This research leveraged data from the MENACTRIMS registry, highlighting the value of regional collaboration and data sharing in advancing MS care. Expanding the registry to include more comprehensive data from all MENA countries could enhance understanding of regional treatment patterns and outcomes, leading to better-informed clinical practices. Clinicians and healthcare providers across the region are encouraged to contribute to and utilize this shared resource to improve MS care and patient outcomes collectively.

### **VII.3. Strengths and Limitations**

The thesis demonstrates several strengths, mainly its comprehensive evaluation of DMTs accessibility and long-term safety and efficacy in the MENA region, a typically underrepresented area in global MS research. By analyzing DMT availability, accessibility, and clinical outcomes across multiple countries with varying income levels, it provides valuable insights into the unique challenges faced by neurologists and patients. The use of a large sample size, particularly through the MENACTRIMS registry, enhances the reliability and generalizability of the findings, allowing for more precise estimates of treatment effects and robust subgroup analyses. Furthermore, the use of real-world data from one of the largest MS registries in the region ensures that the findings are highly relevant to everyday clinical decision-making. The focus on the long-term safety and efficacy of high-efficacy DMTs, especially in the context of the MENA region, significantly contributes to understanding the risks associated with these therapies, including during the COVID-19 pandemic. This research also adds to the global understanding of how chronic conditions and their treatments interact with emerging infectious diseases. The use of validated tools, rigorous statistical analysis, and collaboration across multiple centers further enhance the study's robustness and applicability to a broader population of MS patients beyond the MENA region.

However, this research also has some limitations, primarily its reliance on registry data, which, while valuable, may lack the granularity needed for certain analyses and be subject to

inconsistencies in data collection and reporting across centers and countries. This reliance introduces potential selection bias, as the data might disproportionately represent patients from larger, more resource-rich centers, leading to an overestimation of treatment access and outcomes. Additionally, information bias and data quality issues may arise from inconsistent data entry and variability in reporting, potentially affecting the reliability of the results. The observational nature of the registry data also poses a risk of confounding factors which could influence the observed associations between treatments and outcomes. Moreover, the cross-sectional and retrospective designs of the studies, while useful for identifying associations and trends, limit the ability to establish causality, necessitating longitudinal studies for a more comprehensive understanding of the long-term effects of the economic crisis, pandemic, and treatment decisions on MS outcomes.

## Chapter VIII. Future Research Perspectives

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While this research has provided important insights into MS management in the MENA region, several areas require further investigation to continue advancing the field.

### **VIII.1. The Comparative Effectiveness of Natalizumab and Anti-CD20 Monoclonal Antibodies in Relapsing-Remitting Multiple Sclerosis: A Real-World based Study**

The fifth objective of this thesis, which focuses on comparing the effectiveness of high-efficacy monoclonal antibodies in MS, is currently under finalization. In fact, natalizumab and anti-CD20 monoclonal antibodies are among the most potent DMTs used, either as escalation therapy or in cases of highly active disease. However, there is a lack of head-to-head comparisons of their efficacy and safety, particularly in real-world settings. This study, which aims to compare the effectiveness and safety of natalizumab versus ocrelizumab/rituximab in a real-world cohort of RRMS patients, addresses this gap by providing valuable data that could guide clinicians in optimizing treatment strategies for MS patients, particularly in the MENA region, aligning with the main thesis objective. This registry-based, retrospective, multicenter study was carried out in 7 Middle Eastern countries (Iraq, Kuwait, Lebanon, Oman, Saudi Arabia, Tunisia, and UAE) by analyzing data from the MENACTRIMS registry and local MS registries in the MENA region. All adults RRMS patients treated with natalizumab, rituximab or ocrelizumab and maintained on treatment for at least 12 months were included. Patients were matched using propensity scores to minimize selection bias and ensure balanced baseline characteristics between patients treated with natalizumab and those treated with anti-CD20 monoclonal antibodies. Primary outcomes were clinical relapses measured as ARR, confirmed disability progression and improvement and MRI activity. Secondary outcomes included NEDA-3 (no relapses, no confirmed disability progression, and no MRI activity), adverse events and drug survival. A subgroup analysis comparing rituximab to ocrelizumab will also be conducted.

A total of 1954 RRMS patients were identified: 677 were treated with NTZ and 1277 with anti-CD20 therapies. Natalizumab and anti-CD20 groups were matched by means of propensity scores using age, sex, time since first symptoms, baseline EDSS, relapses in previous year and number of previous DMT. This resulted in 677 cases of Natalizumab and 587 anti CD20 cases matched. The results of this study will be presented as an oral presentation during the 40<sup>th</sup>ECTRIMS Congress on September 19, 2024 in Copenhagen, Demark (**Appendix 10**).

## **VIII.2. Longitudinal Studies on the Impact of Socioeconomic and Healthcare Disparities on MS Care**

The research highlighted significant barriers to accessing MS treatments in the MENA region. Future research should explore strategies to overcome these barriers, such as cost-effective treatment options, improved healthcare infrastructure, and policy changes. Furthermore, studies should investigate the impact of these interventions on patient outcomes.

## **VIII.3. Personalized Medicine in MS Treatment**

As the thesis has highlighted the importance of personalized treatment strategies, future research should aim to identify and validate biomarkers that can predict treatment response and disease progression in MS patients. This would enable more tailored treatment approaches, improving outcomes and reducing the risk of adverse effects associated with high-efficacy DMTs.

## **VIII.4. Longitudinal Studies on Treatment Discontinuation**

The thesis provided insights into the outcomes following natalizumab discontinuation. Future research should conduct longitudinal studies to understand better the long-term effects of stopping or switching DMTs, including the risk of disease rebound and strategies to mitigate such risks.

## **VIII.5. Expanding the MENACTRIMS Registry**

The MENACTRIMS registry has proven to be a valuable resource for understanding MS in the MENA region. Future research should focus on expanding the registry to include more countries and more comprehensive data on patient demographics, treatment outcomes, and long-term follow-up. Enhancing the quality and scope of the data collected will allow for more detailed analyses and provide a high-quality resource for ongoing research into MS in the MENA region.

## Chapter IX. Conclusion

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This research evaluated the long-term safety and efficacy of high-efficacy DMTs MS patients in the MENA region. It revealed significant disparities in access to these therapies, driven by socioeconomic and political challenges. In Lebanon, the study highlighted how the ongoing economic crisis has severely impacted continuous treatment for MS patients.

The findings emphasized the need for improved access to high-efficacy therapies and tailored guidelines for the MENA region. Additionally, the research provided valuable insights into the safety risks associated with DMTs, such as COVID-19 and PML, which are crucial for guiding clinical decisions. Moreover, this study highlighted the complexities of transitioning patients from natalizumab to other high-efficacy DMTs, contributing to the broader understanding of how to optimize long-term treatment strategies for MS patients.

This project contributes to a better understanding of MS treatment in the MENA region and calls for future efforts to address the healthcare disparities and improve patient outcomes.

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# Appendices

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## Appendix 1. Study 1 Questionnaire

### Atlas of MS – 3<sup>rd</sup> Edition - Questionnaire B: Clinical Management of MS

Final issue updated 13-10-19

**COUNTRY:** Please indicate the country you are providing data for:

#### **INTRODUCTION:**

This survey is conducted by the MS International Federation (MSIF) and their trusted partner McKing Consulting Corporation (McKing). The purpose of the survey is to collect information for the Atlas of Multiple Sclerosis (MS). The Atlas is a key tool for organizations, health professionals and individuals when advocating for better access to treatment, care and support, and has been widely cited in the research literature.

Your participation is voluntary, and refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled, and you may discontinue participation at any time.

Your personal data may be used by MSIF or McKing in relation to the Atlas project (for example for validation purposes, invitations to participate in future updates, advice or reporting etc.).

MSIF and McKing take our duty to protect your personal information seriously. Any personal information you provide will be collected, transferred and/or stored in compliance with MSIF's privacy policy <https://www.msif.org/privacy-policy/>. We will retain this information for the duration of the Atlas project. The data that we collect from you may be transferred to, and stored at locations both inside or outside the European Economic Area ("EEA") or Switzerland, including the USA.

To agree to the above terms and conditions and proceed with the survey please select "I agree" below: w

1. I agree  
 2. I do not agree

#### **CONTACT DETAILS**

Thank you for agreeing to contribute data to the Atlas of MS - you are part of a global movement to create this important data source that will be used to improve the situation for people with MS worldwide. We cannot do this without you!

When answering the questions in this survey, please focus on the diagnosis, treatment and clinical management of Multiple Sclerosis (MS) only. Please do not include other demyelinating conditions such as Neuromyelitis Optica (NMO).

It is important that the answers provided are as accurate as possible. To help with validation and interpretation some questions ask for sources of evidence for the data. However, we appreciate that you may not have evidence to support the answer - for these, it would be useful to consult with others in the country to ensure confidence in the answers and that best estimates are provided for the country (so they are not just based on one person's opinion). To help with the collaboration we have provided a PDF version of the survey that you can use to share and discuss with colleagues or collect data from multiple sources before inputting the data into the online survey.

Once you have started completing the online questionnaire, all entered data will be saved as you go, so it is possible to pause and return to it at a later time.

**CONTACT DETAILS:** Please provide the contact information for the lead person completing this questionnaire and coordinating the response for the country

*By providing this information, you are consenting for MSIF and their trusted partners to securely hold this data for the duration of the Atlas project and to contact you in connection with the project.*

Full Name:

Title (Dr, Prof, Mr, Ms.  
etc...):

Current Position/job title:


Organization:

Email:

**Diagnosis of MS**

***The first few questions are about the diagnosis of MS, the criteria used and the barriers to diagnosis.***

**QB1.** Please indicate all the MS diagnostic criteria that you are aware are used in the country?  
*Please indicate all that apply.*

- 1. McDonald criteria – 2017 version
- 2. McDonald criteria – 2010 version
- 3. McDonald criteria – 2001 or 2005 version
- 4. Poser criteria
- 5. Schumacher criteria
- 6. Other (please specify: \_\_\_\_\_)
- 7. Not sure

**QB2.** And which ONE criteria do you think is currently the most commonly used to diagnose MS in the country?

- 1. McDonald criteria – 2017 version
- 2. McDonald criteria – 2010 version
- 3. McDonald criteria – 2001 or 2005 version
- 4. Poser criteria
- 5. Schumacher criteria
- 6. Other (please specify: \_\_\_\_\_)
- 7. Not sure

**QB3.** Please include the types of source(s) you consulted to provide this information.  
*If you have estimated this information or it is based on your opinion – please mention this under the “Your personal opinion” code and indicate any assumptions or data you used.*

*Please indicate all sources used.*

- 1. Published academic paper or a poster/platform presentation at a scientific conference
- 2. Patient data (*patient register, government or health service report/statistics, electronic medical records, insurance claims data, patient survey*)
- 3. My personal opinion
- 4. Opinion of others
- 5. Other (please specify: \_\_\_\_\_)

Please specify any assumptions or data you have taken into account when providing opinions. Please also provide further details or links to any public academic papers or patient data that you have consulted.



**QB4.** If the 2017 version of the McDonald criteria is not being used or not being used all the time or by all neurologists in the country, why do you think that is? *Please indicate all that apply.*

- |                          |                                                                                                                                                                       |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Neurologists lack awareness or are not trained to use the 2017 criteria                                                                                            |
| <input type="checkbox"/> | 2. Health professionals (lab assistants, radiographers, neurologists) with specialist knowledge to diagnose MS (run or interpret the tests) are not readily available |
| <input type="checkbox"/> | 3. Magnetic Resonance Imaging (MRI) machines are not readily available                                                                                                |
| <input type="checkbox"/> | 4. Specialist equipment for detecting oligoclonal bands in cerebrospinal fluid are not readily available                                                              |
| <input type="checkbox"/> | 5. The cost of the diagnostic tests required by the 2017 McDonald criteria are <u>too expensive for the government, health provider or insurance provider</u>         |
| <input type="checkbox"/> | 6. The cost of the diagnostic tests required by the 2017 McDonald criteria are too expensive <u>for people suspected of having MS</u>                                 |
| <input type="checkbox"/> | 7. People suspected of having MS do not take all the diagnostic tests required for the 2017 McDonald criteria (for reasons other than cost)                           |
| <input type="checkbox"/> | 8. <b>Not applicable</b> – 2017 McDonald criteria used by all neurologists/all the time                                                                               |
| <input type="checkbox"/> | 9. Other (please specify _____ )                                                                                                                                      |
| <input type="checkbox"/> | 10. Not sure                                                                                                                                                          |

**QB5.** What procedures are typically used to diagnose people suspected as having MS in the country? *Please indicate all that apply.*

- |                          |                                                                   |
|--------------------------|-------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Neurological examination                                       |
| <input type="checkbox"/> | 2. Magnetic Resonance Imaging (MRI)                               |
| <input type="checkbox"/> | 3. Spinal tap/lumbar puncture (e.g., to detect oligoclonal bands) |
| <input type="checkbox"/> | 4. Evoked potentials                                              |
| <input type="checkbox"/> | 5. Optical Coherence Tomography (OCT)                             |
| <input type="checkbox"/> | 6. Other (please specify _____ )                                  |

### **Barriers to diagnosis**

**The next few questions are to help provide a picture of the barriers to early diagnosis in the country. The first question is to ascertain the broad categories of barriers and the follow-up questions will delve into some of these in more detail.**

**QB6.** Please indicate the **major** barriers in the country that prevent individuals from receiving a MS diagnosis as early as possible. *Please indicate all major barriers that apply.*

- |                          |                                                                                                                                                                      |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. <b>No major barriers</b> - everyone gets diagnosed promptly                                                                                                       |
| <input type="checkbox"/> | 2. Lack of awareness of MS symptoms among the general public ( <i>leads to delays contacting health professionals</i> )                                              |
| <input type="checkbox"/> | 3. Lack of awareness of MS symptoms among health care professionals ( <i>leads to misdiagnosis or delays in referral</i> )                                           |
| <input type="checkbox"/> | 4. Health professionals (lab assistants, radiographers, neurologists) with specialist knowledge to diagnose MS not readily available                                 |
| <input type="checkbox"/> | 5. Specialist medical equipment or tests to diagnose MS not readily available (e.g.: MRI machines, equipment for detecting oligoclonal bands in cerebrospinal fluid) |
| <input type="checkbox"/> | 6. Cost of providing diagnosis is too expensive for the government, health provider or insurance provider                                                            |
| <input type="checkbox"/> | 7. People suspected of having MS do not take the diagnostic tests (for cost or personal reasons)                                                                     |
| <input type="checkbox"/> | 8. Bureaucracy/inefficiency/complexity in health system ( <i>leading to delays in referral between parts of system</i> )                                             |
| <input type="checkbox"/> | 9. Other (please specify _____ )                                                                                                                                     |
| <input type="checkbox"/> | 10. Not sure                                                                                                                                                         |

### **PLEASE ANSWER QB7 IF YOU MENTIONED HEALTH PROFESSIONALS NOT READILY AVAILABLE (QB6 code 4)**

**QB7.** You mentioned that health professionals with specialist knowledge to ensure that MS is diagnosed at an early stage are not readily available in the country. Which of the following aspects related to this do you think are the major barriers? *Please indicate all major barriers that apply.*

- |                          |                                                              |
|--------------------------|--------------------------------------------------------------|
| <input type="checkbox"/> | 1. Neurologists not readily available                        |
| <input type="checkbox"/> | 2. Specialist MS neurologists not readily available          |
| <input type="checkbox"/> | 3. Radiologists / Neuro-radiologists not readily available   |
| <input type="checkbox"/> | 4. Other staff not readily available (please specify _____ ) |
| <input type="checkbox"/> | 5. Not sure                                                  |

### **PLEASE ANSWER QB8 IF YOU MENTIONED EQUIPMENT OR TESTS NOT READILY AVAILABLE (QB6 code 5)**

**QB8.** You mentioned that specialist medical equipment or tests needed to diagnose MS are not readily available in the country. Which of the following aspects related to this do you think are the major barriers?

*Please indicate all major barriers that apply.*

- |                          |                                       |
|--------------------------|---------------------------------------|
| <input type="checkbox"/> | 1. MRI machines not readily available |
|--------------------------|---------------------------------------|

- |                          |                                                                                                                                            |
|--------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 2. Specialist laboratory equipment/tests for accurate diagnosis (e.g. checking spinal fluid for oligoclonal banding) not readily available |
| <input type="checkbox"/> | 3. Other medical equipment or tests not readily available (please specify_____)                                                            |
| <input type="checkbox"/> | 4. Not sure                                                                                                                                |



**PLEASE ANSWER QB9 IF YOU MENTIONED PEOPLE DO NOT TAKE THE DIAGNOSTIC TESTS**

(QB6 code 7)

**QB9.** You mentioned that some people suspected as having MS in the country do not take the diagnostic tests. Which of the following aspects related to this do you think are the major barriers? Please indicate all major barriers that apply.

- |                          |                                                                                                                                                                             |
|--------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Cost of diagnostic tests is too high for the people suspected as having MS (e.g. lack of health insurance, or tests not covered/fully covered by health insurance, etc.) |
| <input type="checkbox"/> | 2. They are not able to travel to access the diagnostic tests (e.g. live too far away, cannot afford transport costs, not physically able to travel etc.)                   |
| <input type="checkbox"/> | 3. They are worried about the social stigma related to having a confirmed diagnosis of MS                                                                                   |
| <input type="checkbox"/> | 4. They are worried about the diagnostic procedures/tests (e.g. concern over side effects / pain / claustrophobia)                                                          |
| <input type="checkbox"/> | 5. Other reasons people do not to take the tests needed for diagnosis (please specify:<br>_____ )                                                                           |
| <input type="checkbox"/> | 6. Not sure                                                                                                                                                                 |

**EVERYONE ANSWERS HERE**

**QB10.** Please include the types of source(s) you consulted to provide this information regarding the **barriers to diagnosis**.

*If you have estimated this information or it is based on your opinion – please mention this under the “Your personal opinion” code and indicate any assumptions or data you used.*

*Please indicate all sources used.*

- |                          |                                                                                                                                                                |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Published academic paper or a poster/platform presentation at a scientific conference                                                                       |
| <input type="checkbox"/> | 2. Patient data ( <i>patient register, government or health service report/statistics, electronic medical records, insurance claims data, patient survey</i> ) |
| <input type="checkbox"/> | 3. My personal opinion                                                                                                                                         |
| <input type="checkbox"/> | 4. Opinion of others                                                                                                                                           |
| <input type="checkbox"/> | 5. Other (please specify:<br>_____ )                                                                                                                           |

Please specify any assumptions or data you have taken into account when providing opinions. Please also provide further details or links to any public academic papers or patient data that you have consulted.

--

**Disease Modifying Therapies (DMTs)**

***The next section is about the use of disease modifying therapies (DMTs) for the treatment of MS and any barriers to accessing DMTs in the country.***

*A disease modifying therapy (DMT) is a treatment or drug that can modify the course of MS by reducing the number of relapses or slowing down any worsening of disability or symptoms. Drugs used for the treatment of symptoms or relapses are excluded from this category.*

**QB11.** Are any type of disease modifying therapies (DMTs) available in the country **at the moment**? Please indicate if they are DMTs that have been approved for the treatment of MS in the country or off-label DMTs that are used for the treatment of MS. *Please indicate all that apply.*

1. Yes – DMTs approved for the treatment of MS in the country are available
2. Yes – Off label DMTs used for the treatment of MS in the country are available
3. No (*please skip to QB18*)

**PLEASE ANSWER QB12 IF APPROVED DMTs AVAILABLE IN THE COUNTRY** (QB11 code 1)

**QB12.** Please estimate the percentage of people diagnosed with MS who are currently being treated with disease modifying therapies (DMTs) that have been **approved** for use in the country.

- |                          |                  |
|--------------------------|------------------|
| <input type="checkbox"/> | 1. 0 percent     |
| <input type="checkbox"/> | 2. 1-25 percent  |
| <input type="checkbox"/> | 3. 26-50 percent |
| <input type="checkbox"/> | 4. 51-75 percent |
| <input type="checkbox"/> | 5. 76-99 percent |
| <input type="checkbox"/> | 6. 100 percent   |
| <input type="checkbox"/> | 7. Not sure      |

**PLEASE ANSWER QB13 IF OFF LABEL DMTs AVAILABLE IN THE COUNTRY** (QB11 code 2)

**QB13.** Please estimate the percentage of people diagnosed with MS in the country, who are currently being treated with **off-label** disease modifying therapies (DMTs).

- |                          |                  |
|--------------------------|------------------|
| <input type="checkbox"/> | 1. 0 percent     |
| <input type="checkbox"/> | 2. 1-25 percent  |
| <input type="checkbox"/> | 3. 26-50 percent |
| <input type="checkbox"/> | 4. 51-75 percent |
| <input type="checkbox"/> | 5. 76-99 percent |
| <input type="checkbox"/> | 6. 100 percent   |
| <input type="checkbox"/> | 7. Not sure      |

**PLEASE ANSWER QB14 IF APPROVED DMTs OR OFF LABEL DMTs AVAILABLE** (QB11 code 1 or 2)

**Source - Percent treated with DMT**

**QB14.** Please include the types of source(s) you consulted to provide this information regarding the **percentage of people treated with approved or off label DMTs.**

*If you have estimated this information or it is based on your opinion – please mention this under the “Your personal opinion” code and indicate any assumptions or data you used.*

*Please indicate all sources used.*

- |                          |                                                                                                                                                                |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Published academic paper or a poster/platform presentation at a scientific conference                                                                       |
| <input type="checkbox"/> | 2. Patient data ( <i>patient register, government or health service report/statistics, electronic medical records, insurance claims data, patient survey</i> ) |
| <input type="checkbox"/> | 3. My personal opinion                                                                                                                                         |
| <input type="checkbox"/> | 4. Opinion of others                                                                                                                                           |
| <input type="checkbox"/> | 5. Other (please specify: _____)                                                                                                                               |

Please specify any assumptions or data you have taken into account when providing opinions. Please also provide further details or links to any public academic papers or patient data that you have consulted.

--

**PLEASE ANSWER QB15 IF APPROVED DMTs AVAILABLE IN THE COUNTRY** (QB11 code 1)

**QB15.** Please indicate which of these **originator brands** of disease modifying therapies (DMTs), if any, are **approved** by a national regulatory authority in the country for the treatment of MS?

*An originator brand of DMT is the product that was first authorized worldwide for marketing (normally as a patented product) on the basis of the documentation of its efficacy, safety, and quality.*

*Please only indicate originator DMTs that are approved for use for MS by the regulatory authority in the country. There is a subsequent question that will ask about follow-on/copy/generic/bio-similar DMTs (so please do not include these here) and another question that looks at all DMTs that people with might be treated with (including off-label).*

*It is important the data is as accurate as possible, so please consult published information to verify which originator DMTs are approved for the treatment of MS in the country when answering this question.*

*Please indicate all approved.*

- |                          |                                                     |
|--------------------------|-----------------------------------------------------|
| <input type="checkbox"/> | 1. Lemtrada® [Alemtuzumab, ATC: L04AA34]            |
| <input type="checkbox"/> | 2. Mavenclad® [Cladribine (oral), ATC: L04AA40]     |
| <input type="checkbox"/> | 3. Tecfidera® [Dimethyl fumarate, ATC: N07XX09]     |
| <input type="checkbox"/> | 4. Gilenya® [Fingolimod, ATC: L04AA27]              |
| <input type="checkbox"/> | 5. Copaxone® [Glatiramer acetate, ATC: L03AX13]     |
| <input type="checkbox"/> | 6. Avonex® [Interferon-beta 1a, ATC: L03AB07]       |
| <input type="checkbox"/> | 7. Betaferon® [Interferon-beta 1b, ATC: L03AB08]    |
| <input type="checkbox"/> | 8. Novantrone® [Mitoxantrone, ATC: L01DB07]         |
| <input type="checkbox"/> | 9. Tysabri® [Natalizumab, ATC: L04AA23]             |
| <input type="checkbox"/> | 10. Ocrevus® [Ocrelizumab, ATC: L04AA36]            |
| <input type="checkbox"/> | 11. Plegridy® [Peginterferon-beta 1a, ATC: L03AB13] |
| <input type="checkbox"/> | 12. Mayzent® [Siponimod, ATC: L04AA42]              |
| <input type="checkbox"/> | 13. Aubagio® [Teriflunomide, ATC: L04AA31]          |
| <input type="checkbox"/> | 14. Other (specify _____)                           |
| <input type="checkbox"/> | 15. None approved by the regulatory authority       |
| <input type="checkbox"/> | 16. Not sure                                        |

Please provide a link to the website where this information was found

**PLEASE ANSWER QB16 IF APPROVED DMTs AVAILABLE IN THE COUNTRY** (QB11 code 1)

**QB16.** Are any follow-on (generic, biosimilar, or “copy”) disease modifying therapies (DMTs) **approved** by a national regulatory authority in the country for the treatment of MS?

*Follow-on, generic, copy or biosimilar DMTs are DMTs that are made by a different manufacturer after the expiration of the original patent and marketing exclusivity of an original innovative DMT.*

- |                          |             |
|--------------------------|-------------|
| <input type="checkbox"/> | 1. Yes      |
| <input type="checkbox"/> | 2. No       |
| <input type="checkbox"/> | 3. Not sure |

**PLEASE ANSWER QB17 IF FOLLOW-ON DMTs AVAILABLE IN THE COUNTRY** (QB16 code 1)  
**QB17.** Which follow-on (generic, biosimilar, or “copy”) disease modifying therapies (DMTs) are **approved** by a national regulatory authority for the treatment of MS in the country?

*It is important the data is as accurate as possible, please consult published information to verify which follow-on (generic, biosimilar or copy) DMTs are approved for the treatment of MS in the country when answering this question.*

*Please indicate all approved*

- |                          |                                        |
|--------------------------|----------------------------------------|
| <input type="checkbox"/> | 1. Follow-on Dimethyl fumarate         |
| <input type="checkbox"/> | 2. Follow-on Fingolimod                |
| <input type="checkbox"/> | 3. Follow-on Glatiramer acetate        |
| <input type="checkbox"/> | 4. Follow-on Interferon-beta 1a        |
| <input type="checkbox"/> | 5. Follow-on Interferon-beta 1b        |
| <input type="checkbox"/> | 6. Follow-on Teriflunomide             |
| <input type="checkbox"/> | 7. Other Follow-on DMT (specify _____) |
| <input type="checkbox"/> | 8. Not sure                            |

Please provide a link to the website where this information was found

**EVERYONE ANSWERS HERE**

**QB18.** In some countries, the DMTs used to treat MS can differ from those approved for use, due to the use of off-label drugs or drugs imported from other countries. Which disease modifying therapies (DMTs) are **used for the treatment** of MS in the country? (Please exclude any drugs used just to treat symptoms or relapses)

*Please indicate all DMTs used (including off-label). If you do not have a source of evidence for this question, please consult with other health professionals in the country to ensure the data is a complete representation for the country.*

- |                          |                                         |
|--------------------------|-----------------------------------------|
| <input type="checkbox"/> | 1. Alemtuzumab, ATC: L04AA34            |
| <input type="checkbox"/> | 2. Azathioprine, ATC: L04AX01           |
| <input type="checkbox"/> | 3. Cladribine (IV), ATC: L01BB04        |
| <input type="checkbox"/> | 4. Cladribine (oral), ATC: L04AA40      |
| <input type="checkbox"/> | 5. Cyclophosphamide, ATC: L01AA01       |
| <input type="checkbox"/> | 6. Dimethyl fumarate, ATC: N07XX09      |
| <input type="checkbox"/> | 7. Fingolimod, ATC: L04AA27             |
| <input type="checkbox"/> | 8. Fludarabine, ATC: L01BB05            |
| <input type="checkbox"/> | 9. Fumaderm, ATC: D05AX01               |
| <input type="checkbox"/> | 10. Glatiramer acetate, ATC: L03AX13    |
| <input type="checkbox"/> | 11. Interferon-beta 1a, ATC: L03AB07    |
| <input type="checkbox"/> | 12. Interferon-beta 1b, ATC: L03AB08    |
| <input type="checkbox"/> | 13. Leflunomide, ATC: L04AA13           |
| <input type="checkbox"/> | 14. Methotrexate, ATC: L04AX03          |
| <input type="checkbox"/> | 15. Minocycline, ATC: J01AA08           |
| <input type="checkbox"/> | 16. Mitoxantrone, ATC: L01DB07          |
| <input type="checkbox"/> | 17. Natalizumab, ATC: L04AA23           |
| <input type="checkbox"/> | 18. Ocrelizumab, ATC: L04AA36           |
| <input type="checkbox"/> | 19. Peginterferon-beta 1a, ATC: L03AB13 |
| <input type="checkbox"/> | 20. Rituximab, ATC: L01XC02             |
| <input type="checkbox"/> | 21. Siponimod, ATC: L04AA42             |
| <input type="checkbox"/> | 22. Teriflunomide, ATC: L04AA31         |
| <input type="checkbox"/> | 23. Other (specify _____)               |

- 24. None
- 25. Not sure

### Source - DMT use in the country

**QB19.** Please include the types of source(s) you consulted to provide this information regarding **DMTs used to treat people with MS in the country.**

*If you have estimated this information or it is based on your opinion – please mention this under the “Your personal opinion” code and indicate any assumptions or data you used.*

*Please indicate all sources used.*

- |                          |                                                                                                                                                                |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Published academic paper or a poster/platform presentation at a scientific conference                                                                       |
| <input type="checkbox"/> | 2. Patient data ( <i>patient register, government or health service report/statistics, electronic medical records, insurance claims data, patient survey</i> ) |
| <input type="checkbox"/> | 3. My personal opinion                                                                                                                                         |
| <input type="checkbox"/> | 4. Opinion of others                                                                                                                                           |
| <input type="checkbox"/> | 5. Other (please specify:<br>_____ )                                                                                                                           |

Please specify any assumptions or data you have taken into account when providing opinions. Please also provide further details or links to any public academic papers or patient data that you have consulted.

--

### Barriers to Accessing DMTs

***The next few questions are to help provide a picture of the barriers to getting disease modifying therapies (DMTs) in the country. The first question is to ascertain the broad categories of barriers and the follow-up questions will delve into some of these in more detail.***

**QB20.** Please indicate **the major** reasons why people with MS in the country **do not** get treated with disease modifying therapies (DMTs) they meet the clinical eligibility criteria for.

*Please indicate all major barriers that apply.*

- |                          |                                                                                                                                                                                                                                                 |
|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. <b>No major barriers</b> – everyone who meets the clinical eligibility criteria for disease modifying therapies is treated with a DMT appropriate for their personal circumstances                                                           |
| <input type="checkbox"/> | 2. Lack of awareness of the different types or new DMTs amongst health care professionals (leading to a reduced number of DMT options or the most appropriate DMT not being recommended)                                                        |
| <input type="checkbox"/> | 3. Health professionals with specialist knowledge to treat MS / administer the DMT not readily available (leading to long wait times or not enough time to provide information to patients/discuss changes in condition/alternative treatments) |
| <input type="checkbox"/> | 4. Specialized medical equipment or tests to monitor the treatments (e.g. JCV testing) not readily available                                                                                                                                    |
| <input type="checkbox"/> | 5. Cost of the treatment is too expensive for the government, healthcare provider or insurance provider                                                                                                                                         |
| <input type="checkbox"/> | 6. People with MS do not take the DMTs they are offered (for cost or other reasons)                                                                                                                                                             |
| <input type="checkbox"/> | 7. DMTs only available in some areas of the country or some hospitals                                                                                                                                                                           |
| <input type="checkbox"/> | 8. DMTs frequently go out of stock/supply is irregular                                                                                                                                                                                          |
| <input type="checkbox"/> | 9. DMTs not supplied to the country (i.e. by pharmaceutical companies)                                                                                                                                                                          |
| <input type="checkbox"/> | 10. Complete range of DMTs not available in the country                                                                                                                                                                                         |

<input type="checkbox"/>
<input type="checkbox"/>
<input type="checkbox"/>

11. Bureaucracy/inefficiency/complexity in health system (leading to delays in referral between parts of system)

12. Other reason (specify \_\_\_\_\_)

13. Not sure



**PLEASE ANSWER QB21 IF YOU MENTIONED HEALTH PROFESSIONALS NOT READILY AVAILABLE** (QB20 code 3)

**QB21.** You mentioned that health professionals with specialist knowledge to ensure people with MS get disease modifying therapies (DMTs) are not readily available in the country. Which of the following aspects related to this are the major barriers?

*Please indicate all major barriers that apply.*

- |                          |                                                                                            |
|--------------------------|--------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Neurologists not readily available                                                      |
| <input type="checkbox"/> | 2. Specialist MS neurologists not readily available                                        |
| <input type="checkbox"/> | 3. Radiologists/neuro-radiologists not readily available (for treatment monitoring by MRI) |
| <input type="checkbox"/> | 4. Nurses not readily available                                                            |
| <input type="checkbox"/> | 5. Specialist MS nurses not readily available                                              |
| <input type="checkbox"/> | 6. Other staff not readily available (please specify _____)                                |
| <input type="checkbox"/> | 7. Not sure                                                                                |

**PLEASE ANSWER QB22 IF YOU MENTIONED EQUIPMENT OR TESTS NOT READILY AVAILABLE** (QB20 code 4)

**QB22.** You mentioned that specialist medical equipment to ensure people with MS have access to disease modifying therapies (DMTs) is not readily available in the country. Which of the following aspects related to this are the major barriers?

*Please indicate all major barriers that apply.*

- |                          |                                                                                  |
|--------------------------|----------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. MRI machines not readily available                                            |
| <input type="checkbox"/> | 2. Infusion centres not readily available                                        |
| <input type="checkbox"/> | 3. JCV (John Cunningham virus) testing not readily available                     |
| <input type="checkbox"/> | 4. Other medical equipment or tests not readily available (please specify _____) |
| <input type="checkbox"/> | 5. Not sure                                                                      |

**PLEASE ANSWER QB23 IF YOU MENTIONED PEOPLE DO NOT TAKE DMT's OFFERED** (QB20 code 6)

**QB23.** You mentioned that some people with MS do not take the disease modifying therapies (DMTs) they are offered in the country. Which of the following aspects related to this are the major barriers?

*Please indicate all major barriers that apply.*

- |                          |                                                                                                                                                 |
|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Cost of DMTs is too high for the person with MS (e.g. lack of health insurance, or DMTs not covered/fully covered by health insurance, etc.) |
| <input type="checkbox"/> | 2. Not able to travel to access the DMTs (e.g. live too far away, cannot afford transport costs, not physically able to travel etc.)            |
| <input type="checkbox"/> | 3. Concern about the side effects of DMTs                                                                                                       |
| <input type="checkbox"/> | 4. Concern regarding the efficacy of DMTs (e.g. don't feel the drugs give enough of an improvement etc)                                         |
| <input type="checkbox"/> | 5. Choose to take alternative or traditional medicines instead of DMTs                                                                          |
| <input type="checkbox"/> | 6. Prefer to use diet/other lifestyle choices such as exercise to manage their MS instead of taking DMTs                                        |
| <input type="checkbox"/> | 7. Other reasons for people choosing not to take the DMTs (specify _____)                                                                       |
| <input type="checkbox"/> | 8. Not sure                                                                                                                                     |

**EVERYONE ANSWERS HERE**

**Source - Barriers to DMTs**

**QB24.** Please include the types of source(s) you consulted to provide this information regarding the **barriers for DMTs**.

*If you have estimated this information or it is based on your opinion – please mention this under the “Your personal opinion” code and indicate any assumptions or data you used.*

*Please indicate all sources used.*

- 1. Published academic paper or a poster/platform presentation at a scientific conference
- 2. Patient data (*patient register, government or health service report/statistics, electronic medical records, insurance claims data, patient survey*)
- 3. My personal opinion
- 4. Opinion of others
- 5. Other (please specify:  
\_\_\_\_\_ )

Please specify any assumptions or data you have taken into account when providing opinions. Please also provide further details or links to any public academic papers or patient data that you have consulted.

**QB25.** Do people who are taking DMTs experience any issues with continuing their treatment?

*Please indicate all that apply.*

- 1. Yes – because the supply of the DMT in the country is irregular
- 2. Yes – because people have to have tests to prove they are still eligible for treatment
- 3. Yes – because reimbursement for the DMT has to be renewed at regular intervals
- 4. Yes – because people are only allowed DMTs for a limited amount of time (e.g. 2 years)
- 5. Yes – for a different reason (please specify:  
\_\_\_\_\_ )
- 6. No – there are no issues with continuation of treatment
- 7. Not sure

**QB26.** Are there any issues around the quality of DMTs in the country?

- 1. Yes (please specify what these issues are:  
\_\_\_\_\_ )
- 2. No
- 3. Not sure

**QB27.** Please provide your best estimate of the proportion of people with MS in the country who have to pay any part of the cost of their disease modifying therapies (DMTs) themselves?

- 1. 0 percent
- 2. 1-25 percent
- 3. 26-50 percent
- 4. 51-75 percent
- 5. 76-99 percent

- 6. 100 percent
- 7. Not sure

**Source - Percent paying for DMT**

**QB28.**Please include the types of source(s) you consulted to provide this information regarding paying for DMTs.

*If you have estimated this information or it is based on your opinion – please mention this under the “Your personal opinion” code and indicate any assumptions or data you used.*

*Please indicate all sources used.*

- |                          |                                                                                                                                                                |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Published academic paper or a poster/platform presentation at a scientific conference                                                                       |
| <input type="checkbox"/> | 2. Patient data ( <i>patient register, government or health service report/statistics, electronic medical records, insurance claims data, patient survey</i> ) |
| <input type="checkbox"/> | 3. My personal opinion                                                                                                                                         |
| <input type="checkbox"/> | 4. Opinion of others                                                                                                                                           |
| <input type="checkbox"/> | 5. Other (please specify: _____ )                                                                                                                              |

Please specify any assumptions or data you have taken into account when providing opinions. Please also provide further details or links to any public academic papers or patient data that you have consulted.

--

**PLEASE ANSWER QB29 IF PEOPLE HAVE TO PAY ANY PART OF THEIR DMT COST (QB27 cods 2-6)**

**QB29.** Thinking about disease modifying therapies (DMTs) that people pay any or part of the cost for, what is the estimated average proportion of the cost that they pay themselves?

- |                          |                  |
|--------------------------|------------------|
| <input type="checkbox"/> | 1. 1-25 percent  |
| <input type="checkbox"/> | 2. 26-50 percent |
| <input type="checkbox"/> | 3. 51-75 percent |
| <input type="checkbox"/> | 4. 76-99 percent |
| <input type="checkbox"/> | 5. 100 percent   |
| <input type="checkbox"/> | 6. Not sure      |

**PLEASE ANSWER QB30 IF PEOPLE HAVE TO PAY ANY PART OF THEIR DMT COST (QB27 cods 2-6)**

**Source - Percent of cost that people have to pay**

**QB30.**Please include the types of source(s) you consulted to provide this information regarding the proportion of the cost of DMTs that people pay themselves.

*If you have estimated this information or it is based on your opinion – please mention this under the “Your personal opinion” code and indicate any assumptions or data you used.*

*Please indicate all sources used.*

- |                          |                                                                                                                                                                |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Published academic paper or a poster/platform presentation at a scientific conference                                                                       |
| <input type="checkbox"/> | 2. Patient data ( <i>patient register, government or health service report/statistics, electronic medical records, insurance claims data, patient survey</i> ) |
| <input type="checkbox"/> | 3. My personal opinion                                                                                                                                         |
| <input type="checkbox"/> | 4. Opinion of others                                                                                                                                           |
| <input type="checkbox"/> | 5. Other (please specify: _____ )                                                                                                                              |

Please specify any assumptions or data you have taken into account when providing opinions. Please also provide further details or links to any public academic papers or patient data that you have consulted.

**PLEASE ANSWER QB31 IF PEOPLE HAVE TO PAY ANY PART OF THEIR DMT COST** (QB27 cods 2-6)

**QB31.** You mentioned that some people have to pay some or all of the costs themselves for disease modifying therapies (DMTs), what are the major reasons for this? Please indicate all major reasons that apply.

- |                          |                                                                                                                                                                                                                                          |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. They don't have health insurance                                                                                                                                                                                                      |
| <input type="checkbox"/> | 2. They do have health insurance but DMTs are not covered                                                                                                                                                                                |
| <input type="checkbox"/> | 3. They do have health insurance but the specific DMT recommended/they want is not included on the approved list of therapies or they don't meet the eligibility criteria to cover the payment of DMT (i.e. dependent on the EDSS score) |
| <input type="checkbox"/> | 4. Government/healthcare provider or insurance provider requires a co-payment or will only pay part of the cost of the DMT                                                                                                               |
| <input type="checkbox"/> | 5. Other reasons (please specify _____)                                                                                                                                                                                                  |
| <input type="checkbox"/> | 6. Not sure                                                                                                                                                                                                                              |

**EVERYONE ANSWERS HERE**

**QB32.** Is Hematopoietic stem cell transplantation (HSCT) available for people with MS in the country? Please indicate all that apply.

- |                          |                                                                                |
|--------------------------|--------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Yes - as part of a clinical trial                                           |
| <input type="checkbox"/> | 2. Yes - by paying for it themselves                                           |
| <input type="checkbox"/> | 3. Yes - paid for by the government / healthcare provider / insurance provider |
| <input type="checkbox"/> | 4. Yes - by some other way (please specify: _____)                             |
| <input type="checkbox"/> | 5. No - HSCT not available for people with MS                                  |
| <input type="checkbox"/> | 6. Not sure                                                                    |

**Rehabilitation**

***The next few questions are about rehabilitation and palliative care for people with MS.***

**QB33.** Please indicate which symptoms people with MS are **typically** able to **access** rehabilitation or other types of therapy (e.g. medication) for **when they need them?**

*Please indicate all that apply.*

- |                          |                                         |
|--------------------------|-----------------------------------------|
| <input type="checkbox"/> | 1. Fatigue                              |
| <input type="checkbox"/> | 2. Heat sensitivity                     |
| <input type="checkbox"/> | 3. Difficulty walking                   |
| <input type="checkbox"/> | 4. Stiffness and spasms                 |
| <input type="checkbox"/> | 5. Bladder problems                     |
| <input type="checkbox"/> | 6. Memory and other cognitive problems  |
| <input type="checkbox"/> | 7. Pain and other unpleasant sensations |
| <input type="checkbox"/> | 8. Emotional and mood problems          |
| <input type="checkbox"/> | 9. Vision problems                      |
| <input type="checkbox"/> | 10. Dizziness or vertigo                |

- 11. Bowel problems
- 12. Tremors
- 13. Sexual problems
- 14. Difficulty moving arms/hands
- 15. Swallowing problems
- 16. Speech problems
- 17. Seizures
- 18. Other (please specify \_\_\_\_\_)
- 19. Not sure which rehabilitation therapies are available to people with MS

**QB34.** In your opinion, are rehabilitation therapies available quickly enough for all people with MS who need them in the country?

- |                          |             |
|--------------------------|-------------|
| <input type="checkbox"/> | 1. Yes      |
| <input type="checkbox"/> | 2. No       |
| <input type="checkbox"/> | 3. Not sure |

**QB35.** In your opinion, do people with MS who need rehabilitation therapies ever experience rationing or restrictions on the number of the treatments or therapies which prevents them getting access (e.g. only have access to a restricted number of treatment sessions irrespective of their need)?

- |                          |             |
|--------------------------|-------------|
| <input type="checkbox"/> | 1. Yes      |
| <input type="checkbox"/> | 2. No       |
| <input type="checkbox"/> | 3. Not sure |

**PLEASE ANSWER QB36 IF REHABILITATION THERAPIES ARE NOT AVAILABLE QUICKLY ENOUGH (QB34 NO) OR IF THEY ARE RATIONED/RESTRICTED (QB35 YES)**

**QB36.** Please indicate the major reasons why people with MS might not be able to access all the rehabilitation therapies they need.

*Please indicate all major barriers that apply.*

- |                          |                                                                                                                                                                                                                                     |
|--------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Lack of awareness of the different types of rehabilitation therapies available amongst health care professionals ( <i>leading to a reduced number of therapy options offered or the most appropriate not being recommended</i> ) |
| <input type="checkbox"/> | 2. Health professionals with specialist knowledge to provide the rehabilitation therapies not readily available ( <i>leading to long delays/limited places available/ reduced number of therapy options or sessions offered</i> )   |
| <input type="checkbox"/> | 3. Specialist equipment used in rehabilitation therapies is not readily available                                                                                                                                                   |
| <input type="checkbox"/> | 4. Cost of the rehabilitation therapies too expensive for the government, health provider or insurance provider                                                                                                                     |
| <input type="checkbox"/> | 5. Cost of the rehabilitation therapies too expensive for people with MS (e.g. don't have health insurance or not covered by health insurance)                                                                                      |
| <input type="checkbox"/> | 6. People with MS do not take the rehabilitation therapies offered (for reasons other than cost) – (please specify: _____)                                                                                                          |
| <input type="checkbox"/> | 7. Rehabilitation therapies are not available in all parts of the country                                                                                                                                                           |
| <input type="checkbox"/> | 8. Rehabilitation therapies are not available consistently over time                                                                                                                                                                |
| <input type="checkbox"/> | 9. Bureaucracy/inefficiency/complexity in health system (leading to delays in referral between parts of system)                                                                                                                     |
| <input type="checkbox"/> | 10. Other (specify _____)                                                                                                                                                                                                           |
| <input type="checkbox"/> | 11. Not sure                                                                                                                                                                                                                        |

### **Palliative Care**

**EVERYONE ANSWERS HERE**

**QB37.** Does palliative care for people with MS exist in the country?

*The goal of palliative care in MS is to achieve the best quality of life for the person with MS and their families once their symptoms no longer respond effectively to treatment or management. It includes management of pain and other symptoms, and of psychological, social and spiritual problems.*

- |                          |                                            |
|--------------------------|--------------------------------------------|
| <input type="checkbox"/> | 1. Yes – general palliative care           |
| <input type="checkbox"/> | 2. Yes – specialist palliative care for MS |
| <input type="checkbox"/> | 3. No                                      |
| <input type="checkbox"/> | 4. Not sure                                |

Please specify any other comments to do with palliative care you wish to share below:

### **Health Care Professionals, Guidelines, Types of data collected**

***The next section is about the number of health care professionals in the country, the availability of national guidelines relating to MS, the type of data collected to monitor the diagnosis/treatment of MS and the use of Telemedicine.***

**QB38.** Please indicate below the estimated number of people in each profession in the country.

*If you can't provide absolute numbers but you have the data as ratios (i.e. 1.3 neurologist per 100,000 people), please provide the data in this format instead*

**Number of Neurologists:**

**Number of Neurologists with a special interest in MS**

*A 'special interest in Multiple Sclerosis' means a neurologist who has more experience in diagnosing/treating MS. There is no standard definition but they may work in specialist MS Centres or Clinics; they make focus only on MS and no other neurological conditions; they may have undertaken additional training relevant to MS; they may be conducting research into MS alongside their clinical work.*

**Number of Pediatric specialist Neurologists**

**Number of Nurses with a special interest in MS (MS Nurses)**

*A nurse with a 'special interest in Multiple Sclerosis' means a nurse who has more experience in the care or treatment of people with MS. There is no standard definition but they may work in specialist MS Centres or Clinics; they make focus only on MS and no other neurological conditions; they may have undertaken additional training relevant to MS. They may be involved in conducting research into MS.*

**Number of Neurology nurses**

*A Neurology Nurse is a licensed/registered nurse whose professional interests and activities are related exclusively / specifically to the care of people with neurological disorders*

**Number of Radiologists**

**Number of Neuro-radiologists**

*A Neuro-radiologist focuses on the diagnosis and characterization of abnormalities of the central and peripheral nervous system, spine, and head and neck using neuroimaging techniques.*





**Source - Number of health care professionals**

**QB39.** Please include the types of source(s) you consulted to provide this information regarding the **number of health professionals in the country.**

*If you have estimated this information or it is based on your opinion – please mention this under the “Your personal opinion” code and indicate any assumptions or data you used.*

*Please indicate all sources used.*

- 1. Published academic paper or a poster/platform presentation at a scientific conference
- 2. Patient data (*patient register, government or health service report/statistics, electronic medical records, insurance claims data, patient survey*)
- 3. My personal opinion
- 4. Opinion of others
- 5. Other (please specify: \_\_\_\_\_)

Please specify any assumptions or data you have taken into account when providing opinions. Please also provide further details or links to any public academic papers or patient data that you have consulted.

**QB40.** Does the country have any national health plan(s) or guidelines that cover aspects of diagnosis, treatment or living with MS? *Please indicate all that apply.*

- 1. Yes – diagnosis
- 2. Yes – treatment
- 3. Yes – something else (please specify: \_\_\_\_\_)
- 4. No
- 5. Not sure

Please provide a link to any documents or guidelines.

**QB41.** Are there any **national** standards or targets set relating to the diagnosis, treatment or monitoring of MS patients in the country?

- 1. Yes
- 2. No

**PLEASE ANSWER QB42 IF HAVE NATIONAL STANDARDS OR TARGETS (QB41 YES)**

**QB42.** What aspects of the diagnosis, treatment or monitoring of MS patients in the country have targets or standards (e.g.: receiving DMTs within a specific time period, or having a clinical review at least once a year)

*Please indicate that apply.*

- 1. Speed of diagnosis
- 2. Speed of receiving DMT treatment
- 3. Frequency of receiving MRI scans
- 4. Frequency of receiving a clinical review (checking they are on the right DMT, the status of their disease course, whether there has been any new disease activity etc.)
- 5. Wait times to see professionals/or have relevant tests/procedures/scans

6. Other metrics to do with the diagnosis, treatment or monitoring of MS  
(please specify: \_\_\_\_\_)

Please provide details on the standards/targets set below (including timeframes)

**QB43.** The MS Brain Health initiative has produced evidence-based international consensus standards (*Brain health: time matters in multiple sclerosis*) which recommend a strategy to maximize lifelong 'brain health' and include targets on timelines for diagnosis, treatment and review. Are you familiar with these standards?

1. Yes  
 2. No

**PLEASE ANSWER QB44 IF AWARE OF THE BRAIN HEALTH REPORT (QB43 Yes)**

**QB44.** Has a regulatory authority or nationally recognized group in the country endorsed the standards set by this MS brain health initiative to be followed in the country?

1. Yes – following the consensus standards completely  
 2. Yes – following the consensus standards but modified the timelines  
 3. Yes – following some of consensus standards but not all of them  
 4. No – but we have plans to develop standards based on the MS Brain Health initiative  
 5. No – we do not have national standards  
 6. No – we recognize different standards  
(specify: \_\_\_\_\_)  
 7. Not sure

**EVERYONE ANSWERS HERE:**

**QB45.** In the country which of the following data, if any, are captured or collected (either by the government, the health system, insurance company or other scientific studies)?

*Please indicate all that apply.*

1. Speed of diagnosis (time taken from first reporting a possible MS symptom to a health care professional to receiving a diagnosis, or the proportion of people who receive a diagnosis within a certain time period)  
 2. Speed of receiving DMT treatment (time taken from receiving an MS diagnosis to receiving DMT treatment, or the proportion of people who start DMT treatment within a certain time period)  
 3. Proportion of people with MS currently being treated with DMTs  
 4. Frequency of receiving MRI scans  
 5. Frequency of clinical review by a health professional (checking someone is on the right DMT, the status of their disease course, whether there has been any new disease activity etc.)  
 6. Wait times experienced by people with MS (to see health care professionals or to receive tests/procedures/scans for diagnosis, treatment or monitoring)  
 7. Proportion of people who have MS but are not officially diagnosed  
 8. Other metrics to do with the diagnosis, treatment or monitoring of MS  
(please specify: \_\_\_\_\_)  
 9. None – there is no data captured in relation to the diagnosis, treatment or monitoring of MS in the country

Please provide details on the type of data collected (and include any relevant links)

**QB46.** In the country, has an organization or group adopted a recognized model for multi-disciplinary coordinated care for the treatment of MS?

- |                          |                                                            |
|--------------------------|------------------------------------------------------------|
| <input type="checkbox"/> | 1. Yes (please provide link to the definition here: _____) |
| <input type="checkbox"/> | 2. No                                                      |
| <input type="checkbox"/> | 3. Not sure                                                |

**QB47.** Does the country use Telemedicine in the diagnosis, treatment or monitoring of MS?

*Telemedicine is defined as the use of technology to provide access to clinical care when distance separates patients and providers. Telemedicine can be used in place of what would otherwise be an in person visit to provide a diagnosis, consultation, or treatment using interactive audio, video or other electronic media.*

- |                          |                                                                       |
|--------------------------|-----------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Yes – and is an accepted part of clinical practice                 |
| <input type="checkbox"/> | 2. Yes – but only used for one off cases/experimental settings/trials |
| <input type="checkbox"/> | 3. No                                                                 |
| <input type="checkbox"/> | 4. Not sure                                                           |

Please provide further comments about the use of Telemedicine in the country and links to any examples or case-studies

**Source - Telemedicine**

**QB48.** Please include the types of source(s) you consulted to provide this information on the use of Telemedicine.

*If you have estimated this information or it is based on your opinion – please mention this under the “Your personal opinion” code and indicate any assumptions or data you used.*

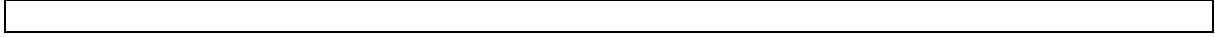
*Please indicate all sources used.*

- |                          |                                                                                                                                                                |
|--------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <input type="checkbox"/> | 1. Published academic paper or a poster/platform presentation at a scientific conference                                                                       |
| <input type="checkbox"/> | 2. Patient data ( <i>patient register, government or health service report/statistics, electronic medical records, insurance claims data, patient survey</i> ) |
| <input type="checkbox"/> | 3. My personal opinion                                                                                                                                         |
| <input type="checkbox"/> | 4. Opinion of others                                                                                                                                           |
| <input type="checkbox"/> | 5. Other (please specify:<br>_____ )                                                                                                                           |

Please specify any assumptions or data you have taken into account when providing opinions. Please also provide further details or links to any public academic papers or patient data that you have consulted.

**QB49.** Do you have any additional comments concerning the diagnosis or clinical management of MS in the country?

**QB50.** Please provide any additional information here to help explain any changes to the clinical management or diagnosis of MS in the country since the last Atlas of MS update in 2013 (e.g.: changed criteria used to diagnose MS, National health insurance now covers DMTs etc.)



**Collaborators and Acknowledgments**

**QB51.** Please indicate whom else you have consulted or collaborated with in order to provide the answers to these questions to ensure a comprehensive picture of the clinical management of MS in the country.

Please indicate all that apply

<input type="checkbox"/>	1. Other clinicians based in the country or with experience of working in the country
<input type="checkbox"/>	2. Other experts in the country (please specify what type of role/expertise they have: _____ )
<input type="checkbox"/>	3. Didn't consult anyone else – no other experts with knowledge of the clinical management of MS in the country
<input type="checkbox"/>	4. Didn't consult anyone else – you lacked time to consult any other clinicians or experts in the country
<input type="checkbox"/>	5. Didn't consult anyone else – you tried to approach other experts but they lacked time to take part
<input type="checkbox"/>	6. Other (please specify _____ )

**QB52** Would you like your name to appear in the list of contributors to the Atlas of MS update?

*We will not make public any personal information without your permission, and the information displayed will be limited to your name and country.*

<input type="checkbox"/>	1. Yes (Please specify below)
<input type="checkbox"/>	2. No (Please skip to QB53)

Please specify how you would like your name to appear in the list of contributors, including any titles.

--

**QB53.** Is there anyone else who you have collaborated with to complete this survey who would like to appear in the list of named contributors to the Atlas of MS update and have agreed for their name to be passed to MSIF and McKing?

*Please ensure that you have consent to provide us with their name and for us to publish this in our report (the information displayed will be limited to their name and country).*

<input type="checkbox"/>	1. Yes (Please specify details below)
<input type="checkbox"/>	2. No (Please skip to QB54)

Please specify the contact name (including any titles) and email address for each collaborator below.

*Please ensure that you have consent to provide us with their name and for us to publish this in our report (the information displayed will be limited to their name and country).*

	Name (including any titles)	Email address
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
9.		
10.		

## **Thank You**

Thank you very much for completing this survey – we are very grateful for your help.

You can find out more about MSIF's work by signing up to our newsletters: <https://www.msif.org/get-involved/our-newsletters/>



## Appendix 2. Study 2 Questionnaire

### **Part I: Demographics**

#### **1- Gender**

- Male
- Female

#### **2- Age in years:**

#### **3- Place of residence**

- Beirut
- Bekaa
- Mount Lebanon
- North Lebanon
- South Lebanon

#### **4- Highest degree of education**

- Up to elementary school
- High school and high secondary
- University education
- None of the above

#### **5- Marital status**

- Single
- Married
- Divorced
- Widowed

#### **6- Occupation**

- Employed, if yes type of employment:
- Unemployed
- Retired

**7- Monthly income in USD (average):**

- Less than 600
- 1600-2,499
- 2,500-3,999
- 4,000-6,999
- 7,000-12,999
- $\geq 13,000$
- No answer

**8- Family history:**

- Yes
- No

**9- Where do you get your treatment?**

- At the family doctor clinic
- At a general neurology clinic
- At a specialized MS center

**10- Do you get your treatment at your place of residence?**

- Yes
- No, if no specify where:

**11- Type of insurance?**

- Governmental Insurance
- Private Insurance
- None (self-payers)

**12. What is the disease type?**

- Relapsing-Remitting
- Progressive MS

**13. What is the duration of your disease (years)?**

**14. Do you have physical disability?**

- Yes  
 No

**15. Do You have any other comorbidities? If Yes, Specify**

**Part II: MUSIQOL: Multiple Sclerosis International QOL Questionnaire**

You are invited to complete this questionnaire concerning different aspects of your life with MS. It is anticipated that this will help towards a better understanding of the real impact of your health problems.

Please answer the questions by ticking () or checking () the box that describes best your feelings **during the last 4 weeks**. Some questions relate to your private life; these are necessary to evaluate all aspects of your health. However, if you think that a question is not relevant to you, or if you do not want to answer a question, please move on to the next one.

**Pr. Pascal Auquier, Dr Karine Baumstarck**

Aix Marseille Université, France. Email : pascal.auquier@univ-amu.fr,  
karine.baumstarck@univ-amu.fr

---

**Due to your MS, during the past 4 weeks, have you...**

<b>IX.5.1. For each question, check the response that is closest to your feelings</b>	Never Not at all	Rarely A little	Someti mes Somew hat	Often A lot	Always Very much
1 had difficulty walking or moving outside?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 had difficulty with outdoor activities: i.e. shopping, going out to a movie...?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3 had difficulty walking or moving around at home?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4 been troubled by your balance or walking problems?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5 had difficulty with leisure activities at home: i.e. do-it-yourself, gardening...?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6 had difficulty with your occupational activities: i.e. integration, interruption, limitation...?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7 been quickly tired?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8 been short of energy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9 felt anxious?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 felt depressed or gloomy?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 felt like crying?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 felt nervous or irritated by a few things or situations?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

---

**Due to your MS, during the past 4 weeks, have you...**

<b>IX.5.1. For each question, check the response that is closest to your feelings</b>	Never Not at all	Rarely A little	Someti mes Somew hat	Often A lot	Always Very much
1 been troubled by loss of memory?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 had difficulty concentrating: i.e. when reading, watching a film, following a discussion...?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 been troubled by your vision: worsened or 5 unpleasant?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 experienced unpleasant feelings: i.e. hot, cold...?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1 talked with your friends?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

---


1	felt understood by your friends?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	felt encouraged by your friends?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	talked with your spouse/partner or your family?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	felt understood by your spouse/partner or your family?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	felt encouraged by your spouse/partner or your family?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Due to your MS, during the past 4 weeks, have you...**

<b>IX.5.1. For each question, check the response that is closest to your feelings</b>	Never Not at all	Rarely A little	Someti mes Somew hat	Often A lot	Always Very much	
2	felt satisfied with your love life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	felt satisfied with your sex life?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	felt that your situation is unfair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	felt bitter?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	been upset by the stares of other people?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	been embarrassed when in public?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2 9	been satisfied with the information on your disease or the treatment given by the doctors, nurses, psychologists... taking care of your MS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	felt understood by the doctors, nurses, psychologists... taking care of your MS?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	been satisfied with your treatments?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>



### Appendix 3. IRB Approval for the MENACTRIMS Registry

 <b>AMERICAN UNIVERSITY OF BEIRUT</b>	<b>Institutional Review Board</b> لجنة الأخلاقيات
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**APPROVAL OF RESEARCH  
CONTINUING REVIEW**

October 2, 2023

Samia Khoury, MD  
American University of Beirut Medical Center  
Email Address: [sk88@aub.edu.lb](mailto:sk88@aub.edu.lb)

Dear Dr. Khoury,

On October 2, 2023, the IRB reviewed the following protocol:

Type of Review:	Continuing, Expedited
Project Title:	Multiple Sclerosis Patient Registry
Investigator:	Dr. Samia Khoury
IRB ID	IM.BY.10
Documents reviewed:	Received on August 2, 2023: <ul style="list-style-type: none"><li>The continuing review form.</li></ul>

The IRB reviewed the Continuing Review and granted you approval to the study, from October 2, 2023 to October 11, 2024 inclusive.

Before August 11, 2024 or within 30 days of study close, whichever is earlier, you are to submit a completed "FORM: Continuing Review Progress Report" and required attachments to request continuing approval or study closure.

If continuing review approval is not granted before the expiration date of October 12, 2024, approval of this research expires on that date.

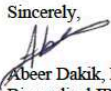
This is to acknowledge the removal of Ali Ezzeddine from the team of the study.

Kindly note that this approval does not grant permission for contacting patients who were enrolled in previous studies, unless it is specified in the signed consent form or if the principal investigator or research team member has a primary patient-physician relationship. In all other circumstances, the IRB needs to grant approval for alternative mechanisms.

HRPP/IRB Compliance and Auditing office will be auditing all clinical trials, and randomly selected other studies, on a quarterly basis to comply with the updated JCI standards regarding the Human Research Protection for accreditation as an Academic Medical Center.

*The American University of Beirut and its Institutional Review Board, under the Institution's Federal Wide Assurance with OHRP, comply with the Department of Health and Human Services (DHHS) Code of Federal Regulations for the Protection of Human Subjects ("The Common Rule") 45CFR46, subparts A, B, C, and D, with 21CFR56; and operate in a manner consistent with the Belmont report, FDA guidance, Good Clinical Practices under the ICH guidelines, and applicable national/local regulations.*

Sincerely,


  
Abeer Dakik, MSc, CIM  
Biomedical IRB Administrator

Cc: Rami Mahfouz, MD, MPH  
Professor of Pathology and Laboratory Medicine

American University of Beirut  
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Page 1 of 2

Template Revision: October 2,

 <b>AMERICAN UNIVERSITY OF BEIRUT</b>	<b>Institutional Review Board</b> لجنة الأخلاقيات
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Chairperson of the IRB  
Ali K. Abu-Alfa, MD, FASN, FASH  
Professor of Medicine

## Appendix 4. Publication : Barriers to accessing multiple sclerosis disease-modifying therapies in the Middle East and North Africa region: A regional survey-based study

Multiple Sclerosis and Related Disorders 79 (2023) 104959

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: [www.elsevier.com/locate/msard](http://www.elsevier.com/locate/msard)

Original article

Barriers to accessing multiple sclerosis disease-modifying therapies in the Middle East and North Africa region: A regional survey-based study

Maya Zeineddine<sup>a,b,\*</sup>, Amal Al-Hajje<sup>c,d</sup>, Pascale Salameh<sup>c,d,e,f</sup>, Anne Helme<sup>g</sup>, Michael Gunnar Thor<sup>h</sup>, Farid Boumediene<sup>a</sup>, Bassem Yamout<sup>b</sup>

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<sup>d</sup> National Institute of Public Health, Clinical Epidemiology and Toxicology (INSPECT-LB), Beirut, Lebanon  
<sup>e</sup> School of Medicine, Lebanese American University, Byblos, Lebanon  
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ARTICLE INFO

Keywords:  
Barriers  
Access  
Treatment  
Multiple sclerosis  
Disease-modifying therapies  
MENA

ABSTRACT

**Background:** Multiple sclerosis (MS) management varies markedly between different countries of the Middle East and North Africa (MENA) region based on the availability and accessibility of disease-modifying therapies (DMTs).

**Objective:** To evaluate the accessibility to DMTs in each MENA country, identify barriers to treatment and make recommendations for improved access to DMTs across the region.

**Methods:** This is a descriptive, survey-based study whereby we extracted data collected, between October 2019 and April 2020, for countries in the MENA region by the Multiple Sclerosis International Federation (MSIF) through their Atlas of MS survey.

**Results:** 16 out of 19 countries in the MENA region were included in this study. Sudan and Syria did not have any originator DMTs approved. Interferons were the most widely low-efficacy originator approved DMTs. Three countries did not have any high efficacy DMTs approved. Moreover, follow-on DMTs were approved in half (50%) of the countries. Cost of treatment was the most important barrier, reported in nearly half (47%) of the MENA countries.

**Conclusion:** Although most MENA countries have access to DMTs, more than half of countries report problems with treatment continuation, highlighting the need for a targeted regional strategy to address the variations in access to MS treatments.

1. Introduction

The Middle East and North Africa region (MENA) is a diverse and large region encompassing more than 20 countries in North Africa and the Middle East. There has been a worldwide increase in the incidence and prevalence of multiple sclerosis (MS) over the past decades, including the MENA region. The estimated global number of people with MS (PwMS) increased by 21.7% between 2013 and 2020 according to the latest Atlas of MS published by the Multiple Sclerosis International Federation (MSIF) (Multiple Sclerosis International Federation 2023). The Atlas of MS recorded an increase in the prevalence of MS in Middle-Eastern countries from 24 per 100,000 to 33 per 100,000 between 2013 and 2020. Moreover, epidemiological studies (Heydarpour et al., 2015, Yamout et al., 2020) from the MENA region showed a rising MS prevalence during the first two decades of the 21<sup>st</sup> Century, with studies from Lebanon (Zeineddine et al., 2021), United Arab Emirates (UAE) (Inshasi and Tharke, 2011, Schiess et al., 2016), Qatar (Deleu et al., 2012) and Bahrain (Alsharoqi et al., 2014) showing rates in the

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range of 55–65/100,000. Even higher prevalence rates were reported from Kuwait (Alroughani et al., 2019) and Iran (Mirmosayyeb et al., 2022, Eskandarieh et al., 2020) ranging between 104 and 151/100,000.

Despite shifting of the MENA region from a low to moderately-high prevalence zone for MS and publication of the Middle East and North Africa Committee for the Treatment and Research in MS (MENACTRIMS) consensus recommendations for diagnosis and treatment (Yamout et al., 2020), management of the disease still varies markedly between countries based on DMTs availability, accessibility, and reimbursement. In general, introduction of novel DMTs in most MENA countries is usually delayed, as drug approval can take several months to years once approved for use by the US Food and Drug Administration (FDA) or European Medicines Agency (EMA), depending on the country.

To our knowledge, there are no published studies assessing the accessibility to disease-modifying therapies (DMTs) across different countries of the MENA region. In order to gain better understanding of treatment accessibility and explore potential common areas of need in the MENA region, we carried out an in-depth analysis of the Arab region Atlas of MS data, focusing on accessibility to originator, follow-on and off-label DMTs in each country and identified barriers to MS treatment.

## 2. Methods

In April 2021, MSIF published the third Atlas of MS (Multiple Sclerosis International Federation 2023) with the aim of providing open-source, global information on MS epidemiology and management with particular emphasis on barriers to healthcare and DMTs accessibility. Data covering the following topics was collected via an international survey (Appendix A) completed by experts from different countries around the world between October 2019 and April 2020: diagnostic criteria used, barriers to diagnosis, types of DMTs used and barriers to accessing them, symptomatic therapies, rehabilitation, number of health care professionals in the country, national guidelines and standards for MS diagnosis and treatment. English, Spanish, and French versions of the survey were available to encourage greater response rates and collaboration with all national experts. The survey was piloted prior to launch to test clarity, understanding and ease of completion. All MS experts provided consent to participate in the survey. As no patient data was included, no ethical approval was required.

Country coordinators, typically representatives from MS organizations, neurologists, epidemiologists or researchers with expertise in MS, were identified in each country and asked to complete the survey by making use of all possible sources of information available to them including publications, presentations, registries, government/health system statistics, administrative data sets, electronic medical records, and through collaboration with other experts in the country where possible and/or necessary (expert opinion). Survey responses covered 85%–91% of the population in each World Health Organization (WHO) region (Europe (89%), Americas (89%), South East Asia (90%), Eastern Mediterranean (91%), Western Pacific (85%)), except for Africa with only 42% of the population represented (Multiple Sclerosis International Federation 2023). A glossary of terms (Appendix B) was provided within the survey, to improve uniformity and comparability of the information received.

This is a descriptive, survey-based study in which we extracted data from the Atlas of MS relevant to countries in the MENA region. Only answers for questions 11 to 32 in the full survey, which related to DMTs and barriers to accessibility, were entered into an Excel Spreadsheet and analyzed using frequencies.

We assessed the local regulatory approval of originators versus follow-on DMTs in each MENA country. Originator DMT was defined as the product that was first authorized worldwide for marketing (typically patented) on the basis of documentation of its efficacy, safety, and quality according to requirements at the time of authorization (Morant et al., 2019). Follow-on DMT was defined as a medication similar to a pre-existing DMT - but with some minor modifications, creating slight

changes in drug action or adverse effects - used to treat the same condition which is MS in this case (Moss and Cohen, 2019). We also investigated the use of on-label versus off-label DMTs across the region. On-label DMT is a drug used for a condition for which it has been officially approved. Off-label use is the use of drugs for an unapproved indication. Interferons beta 1a and 1b, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, siponimod, cladribine, natalizumab, ocrelizumab, alemtuzumab and mitoxantrone are US FDA and EMA approved for the treatment of MS (US Food and Drug Administration 2023, European Medicines Agency 2023). Conversely, rituximab, azathioprine, cyclophosphamide, fludarabine, fumadem, leflunomide, methotrexate, and minocycline are used off-label (National Multiple Sclerosis Society 2023). For the purpose of this analysis, DMTs were divided into three categories based on their presumed efficacy: low, moderate or high efficacy. This was based on either head to head trials (Hauser et al., 2020, Cohen et al., 2012, Hauser et al., 2017, Svenningsson et al., 2022) or real world evidence based on propensity score matching comparisons (Granqvist et al., 2013, Kalincik et al., 2015, Kalincik et al., 2017). The different barriers to treatment reported were stratified by Gross National Income (GNI) per capita. GNI is defined and reported by the World Bank and allows classification of countries into high, upper middle, lower middle, and low income. In the MENA region, Kuwait, Oman, Qatar, Bahrain, Saudi Arabia, and UAE are considered high-income countries. Iraq, Lebanon and Libya are upper-middle income. Algeria, Egypt, Morocco, Palestine, and Tunisia are lower-middle income and Sudan, Syria, and Yemen are low-income countries (The World Bank, 2023).

## 3. Results

### 3.1. Participating countries

16 countries in the MENA region that contributed data to the Atlas of MS were included in this study: Algeria, Egypt, Iraq, Lebanon, Libya, Morocco, Palestine, Sudan, Syria, Tunisia, Yemen, Kuwait, Oman, Qatar, Saudi Arabia, and UAE. Although very limited data was provided by Yemen, such data were included where available. The Gulf countries in this study refer to Kuwait, Oman, Qatar, Saudi Arabia, and UAE.

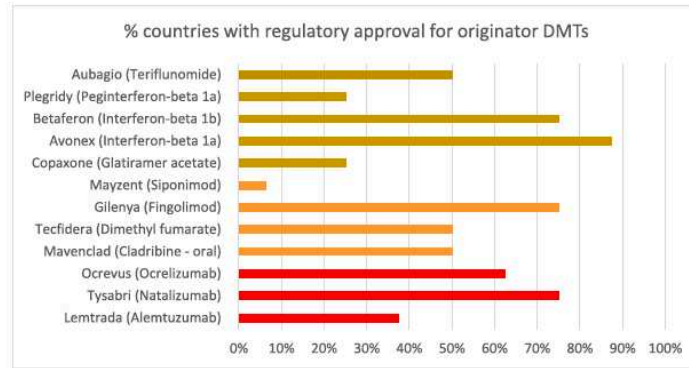
### 3.2. Regulatory approval of DMTs in the MENA region

Two countries did not have any originator DMTs approved (Sudan and Syria). Among low efficacy originator DMTs, interferons were the most widely approved DMTs (14/16 or 88% of countries) followed by glatiramer acetate (50%) and pegylated interferon (25%) (Fig. 1). As for the moderate-efficacy DMTs, fingolimod was approved in 12 out of 16 countries (75%) followed by dimethyl-fumarate and cladribine, each approved in 8/16 countries (50%). Siponimod was only approved in Kuwait at the time of this analysis. Three countries (19%) did not have any high efficacy DMTs (natalizumab, ocrelizumab and alemtuzumab) approved. Natalizumab and ocrelizumab were approved in 12/16 (75%) and 10/16 (63%) of countries, respectively and alemtuzumab in 6/16 (38%)

On the other hand, follow-on DMTs (generic or copy) were approved in half (50%) of the MENA countries (Fig. 2). Follow-on fingolimod received approval in 5 countries (36%); Libya, Syria, Tunisia, Saudi Arabia and United Arab Emirates. Follow-on dimethyl fumarate and intramuscular interferon beta 1a were each approved in 3 countries (21%). Follow-on glatiramer acetate was only approved in Tunisia and follow-on interferon beta 1b and teriflunomide were both approved in Syria.

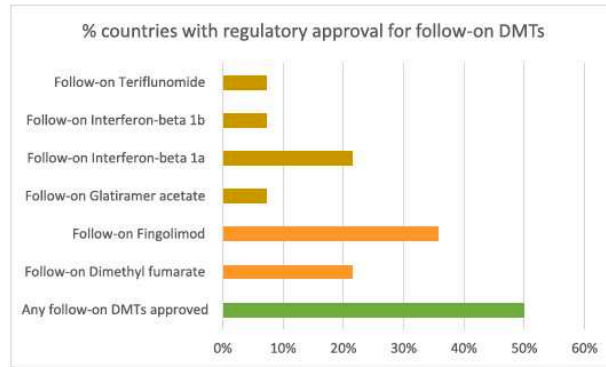
### 3.3. Use of on- and off-label DMTs in the MENA region

Thirteen countries in the MENA region reported the use of off-label DMTs (Fig. 3), including: rituximab, azathioprine, cyclophosphamide,



MENA = Middle East and North Africa; DMTs= Disease-Modifying Therapies

Fig. 1. Percentage of MENA countries with regulatory approval for originator DMTs. Green = High efficacy; Yellow = Moderate efficacy; Red = Low efficacy.



MENA = Middle East and North Africa; DMTs= Disease-Modifying Therapies

Fig. 2. Proportion of MENA countries with regulatory approval for generic and follow-on DMTs Yellow = Moderate efficacy; Red = Low efficacy.

fludarabine, fumadern, leflunomide, methotrexate, and minocycline.

Sudan reported lack of access to any approved DMT, but did report access to off-label DMTs; however, no high efficacy DMTs, either on- or off-label, were available. Sudan is the only country in the MENA region lacking access to any high efficacy DMT.

In Syria, none of the on-label high efficacy DMTs were available, but report access to rituximab, an off-label high efficacy DMT widely used in MS worldwide. Overall, rituximab was used in 11/15 (73%) countries.

The most commonly used on-label DMTs in the MENA region countries were natalizumab (87%) as high efficacy DMT, fingolimod (87%) as moderate efficacy DMT and interferons (beta 1a and 1b, 93% and 87% respectively) as low efficacy DMTs. Among off-label DMTs, azathioprine (low efficacy) and rituximab (high efficacy) were the two most widely used (73% of both) (Fig. 3).

3.4. Barriers to treatment

The major barriers for PwMS to access DMTs sorted by country and GNI per capita are shown in Fig. 4. Overall, 9 countries (56%) reported some barriers to treatment access.

Cost of treatment, which refers to cost for governments, healthcare providers, or insurance providers, was the most important barrier, reported by nearly half (47%) of the countries.

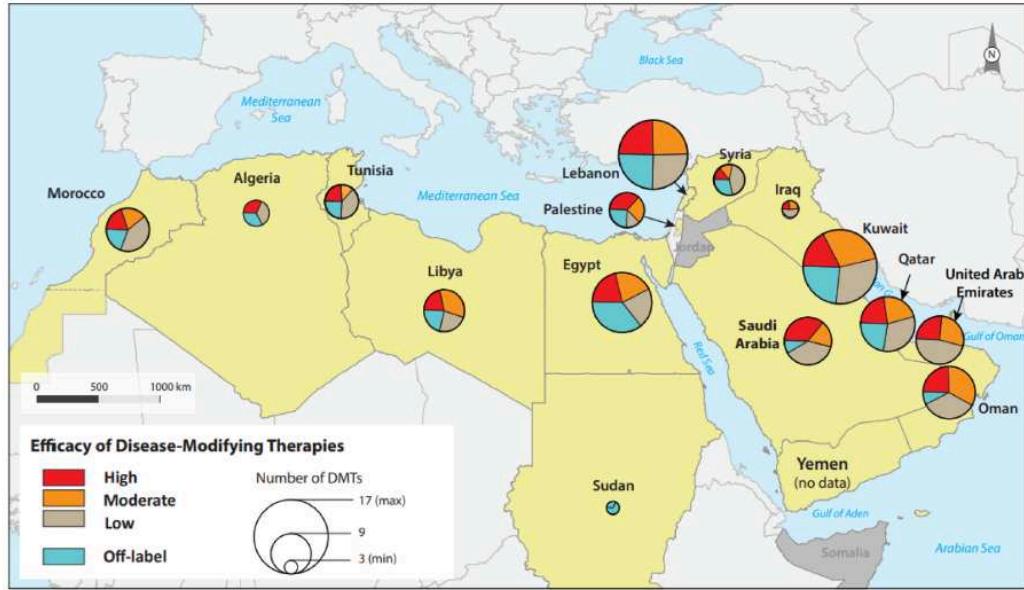
Access to specialized medical equipment or tests to monitor treatment were readily available in all Gulf countries, but 40% (6/16) of MENA countries reported lack of specialized medical equipment and tests.

Around a third of the countries (5/16) reported poor adherence to prescribed DMTs, primarily due to high out of pocket cost, inability to travel, or fear of adverse effects.

Other reasons for non-accessibility to DMTs included: availability of DMTs only in some areas of the country or in few hospitals (4/16), non-availability of the complete range of DMTs (4/16), lack of neurologists specialized in MS (4/16), and lack of awareness among health care professionals regarding the safety, efficacy and administration of DMTs (3/16).

Based on the reports given, the number of barriers to treatment access appears to be linked with GNI per capita. High income countries (Gulf countries) report the fewest barriers, while low income countries report the highest number of barriers.





Treatment availability	DMTs																						
Countries	Alemtuzumab	Mitoxantrone	Natalizumab	Ocrelizumab	Cladribine (IV)	Cladribine (oral)	Dimethyl fumarate	Fingolimod	Siponimod	Glatiramer acetate	Interferon-beta 1a	Interferon-beta 1b	Peginterferon-beta 1a	Teriflunomide	Azathioprine	Cyclophosphamide	Fludrabine	Fumaderm	Leflunomide	Methotrexate	Minocycline	Rituximab	
Algeria																							
Egypt																							
Iraq																							
Lebanon																							
Libya																							
Morocco																							
Palestine																							
Sudan																							
Syria																							
Tunisia																							
Kuwait																							
Oman																							
Qatar																							
Saudi Arabia																							
United Arab Emirates																							

Fig. 3. DMTs in use in MENA by country. Fig. 3A: Number of DMTs available in each country with proportions of on-label DMT efficacy and off-label DMT use indicated. Fig. 3B: List of DMTs in use by country.

3.5. Cost of DMTs

The most commonly reported barrier to treatment access in the MENA region was treatment cost for governments, healthcare providers and insurance providers. On the other hand, in 67% (10/15) of countries, PwMS are required to pay for a proportion of their treatment. In 4

of these countries (Morocco, Sudan, Qatar and Palestine), over half of them have to contribute towards the cost of DMTs, while in the remaining 6 countries the proportion is ≤ 25%. In most MENA countries however, MS patients who do contribute to DMT payment, typically pay less than 25% of the total cost except for Sudan where it can reach 75% and Egypt and the UAE where it can go up to 50%.

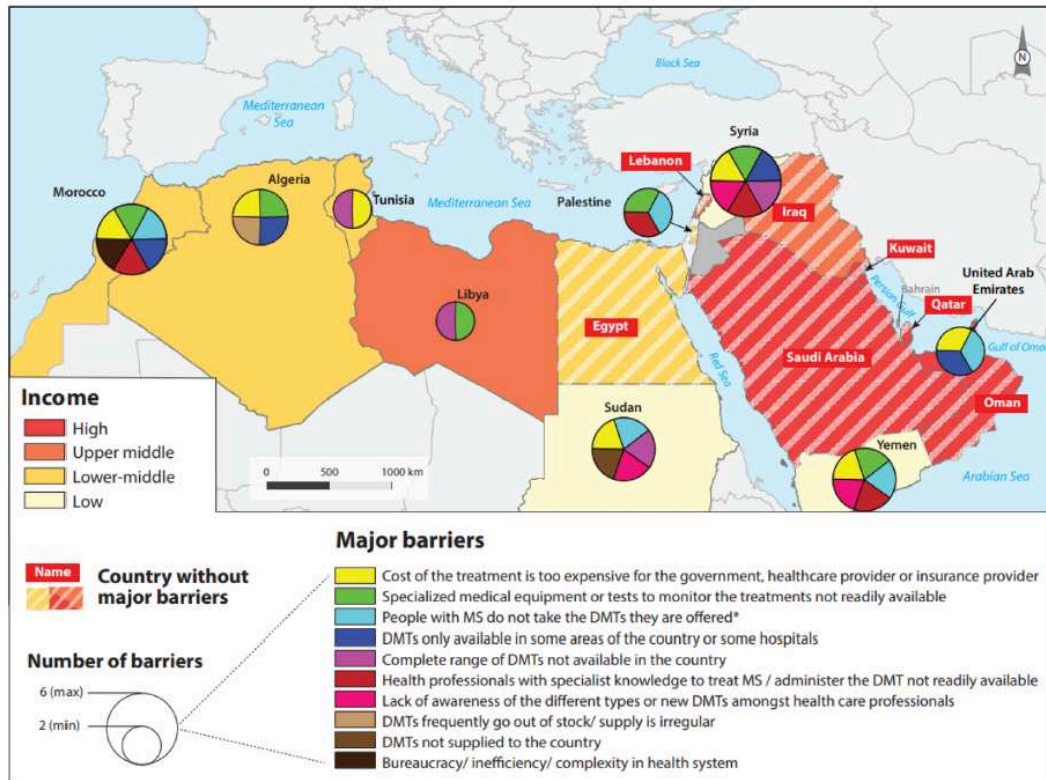


Fig. 4. Major barriers to treatment by country, sorted by GNI per capita.

There are different reasons why PwMS pay towards the cost of DMTs. It is either due to lack of health insurance (Morocco, Oman and UAE), or lack of coverage of DMTs by their health insurance (Sudan and UAE). In other cases, health insurance covers DMTs, but the recommended DMT is not on the approved list of therapies or they do not meet the eligibility criteria (Egypt, Morocco, Palestine, and UAE).

### 3.6. Continuous access to DMTs after treatment initiation

More than half (56%) of the MENA region countries reported issues with continuing treatment due to irregular supply (9/16), lack of monitoring tests required to prove continued eligibility for treatment continuation (3/16), need for regular renewal of reimbursement (2/16) or time-limited supply of DMTs (1/16) (Fig. 5). The most common barrier to treatment continuation was irregular supply of DMTs, reported by 56% of countries. Algeria, Sudan, and Yemen require proof of eligibility to continue treatment. Morocco is the only country reporting a time-limited supply of DMTs. Lebanon, Tunisia and the Gulf countries are the only countries with continuous access to MS treatments after treatment initiation.

## 4. Discussion

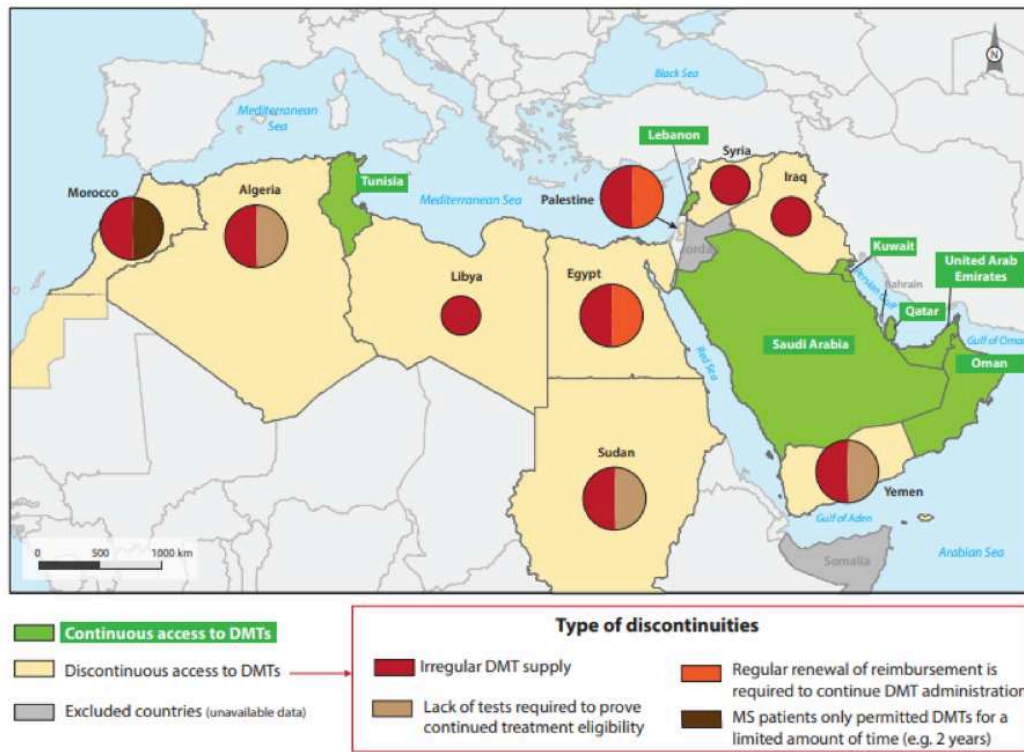
The treatment of MS has evolved exponentially over the last three decades with the introduction of high efficacy DMTs targeting different immunological pathways. This is the first study evaluating access to MS

therapies in the region.

This study showed that DMTs, including high-efficacy DMTs, are used in most MENA countries. However, there were significant disparities across the region with some countries having access to most DMTs such as Kuwait, Oman, Saudi Arabia, UAE and Qatar, while for others such as Tunisia, Algeria, Syria, Iraq and Sudan, the therapeutic options were limited, especially for high efficacy DMTs. This disparity is likely due to the considerable disparities in socioeconomic status across countries of the MENA region. According to a 2018 study by the World Inequality Lab (Moshrif, November 2022), the Middle East is the most unequal region in the world with a regional economic inequality as high as that measured within some of the most unequal countries, such as Brazil and South Africa. Other potential factors contributing to this disparity are political instability and wars in countries like Syria, Sudan, Palestine, Libya and Yemen. Inequity to accessing DMTs within countries is also an important factor to consider; availability and affordability of DMTs can vary greatly depending on which DMTs are covered by a particular health system scheme or insurance.

Compared to other parts of the world, 88% of MENA countries reported having access to approved originator DMTs which is similar to Southeast Asia (83%) and Western Pacific (89%) but lower than Europe (98%) and the United States of America (USA) (94%) according to the latest Atlas of MS (Multiple Sclerosis International Federation 2023). Follow-on DMTs are also available in half of the MENA countries, which is slightly lower than the global average of 64% as per global MSIF data (Multiple Sclerosis International Federation 2023). Follow-on DMTs are





DMTs= Disease-Modifying Therapies; MS=Multiple Sclerosis

Fig. 5. Continuous access to DMTs after treatment initiation.

important, especially in low income countries, due to their lower price and local production in some cases. In that respect, they might fill an important gap in treatment access for PwMS.

The high accessibility to DMTs across the MENA region is due to multiple factors including increased number of specialized MS neurologists, emergence of multidisciplinary MS Centers which are now participating in global multicenter clinical trials, the foundation of MENACTRIMS which created a regional organization that has gradually become the most significant stimulus for clinical education, research and awareness about MS among health care professionals and patients' societies, the publication of regional treatment guidelines (Yamout et al., 2020), and the establishment of the MENACTRIMS registry (Middle East and North Africa Committee for Treatment and Research in Multiple Sclerosis 2023).

The proportion of countries that reported using off-label DMTs in the MENA region was similar to the global average (87%). Among off-label DMTs, azathioprine and rituximab were the most commonly used. The main reasons for the use of off-label DMTs were lack of availability of similar approved DMTs in countries such as Syria where rituximab was the only available high-efficacy DMT, or the unaffordability of originator DMTs. An example highlighting the use of off-label DMTs in the MENA region is the Lebanese experience in treating refugees (Zeineddine and Yamout, 2020). Zeineddine et al. (Zeineddine and Yamout, 2020) reported the use of rituximab and off-label immunosuppressive medications, such as mycophenolate mofetil, cyclophosphamide,

azathioprine, and methotrexate, in Syrian and Palestinian refugees who had no insurance coverage for their chronic medications and could not afford expensive DMTs. In fact, rituximab was the most cost-effective therapy for refugees. The use of off-label DMTs was further encouraged by the recent publication of the MSIF guidelines for the use of off-label azathioprine and rituximab for the treatment of MS in low-resource settings (Multiple Sclerosis International Federation 2023).

The most important barrier to MS treatment reported in the MENA region as well as worldwide (Ch et al., 2017, Contentti et al., 2021) was treatment cost to governments, healthcare system and insurance providers, cited by experts in around half of all reporting countries. In addition, it was not uncommon for PwMS to pay part of the cost of their DMTs. This was reported in 63% of the MENA countries which is slightly higher than the global rate of 57%. Although in most MENA countries contribution to DMT payment was less than 50% of the total cost, this co-payment could be considerable given the high price of most DMTs, making treatment unaffordable for many PwMS. In fact, the prices of DMTs have risen dramatically over the last 15 years, far outpacing inflation, with a current mean price of more than \$86,000 per year to treat one person (Hartung and Bourdette, 2019). Similar to our findings, a study from the USA (Simacek et al., 2018) showed that half of the PwMS reported difficulty accessing DMTs due to high out-of-pocket costs and approval requirements by insurance. The second most common barrier to MS treatment was access to specialized medical



equipment or tests to monitor treatment, reported by 40% of MENA countries, which was higher than the global rate (27%) (Multiple Sclerosis International Federation 2023).

Our study showed that the number of barriers to treatment appeared to be linked to the GNI per capita. High income countries (Gulf countries) reported the fewest, while low income countries reported the most barriers to access to DMTs. This can be explained by the fact that MS is a chronic disease with huge economic burden on healthcare systems and societies, with direct costs of prescription drugs and indirect productivity loss being important cost drivers (Naci et al., 2010). A recent study from Lebanon (Matni et al., 2022) reported an average per-person annual medical cost of \$25,645 with DMTs accounting for the largest proportion of this cost.

Furthermore, more than half (56%) of the MENA region countries reported problems with continuous provision of DMTs, which was higher than the global average of 48% (Multiple Sclerosis International Federation 2023). The most common barrier to continuous access to treatment was irregular supply of DMTs, reported by 56% of countries, which is much higher compared to the global average, where only 27% of countries reported such issue (Multiple Sclerosis International Federation 2023).

There are several limitations to our study which used data collected via the Atlas of MS international survey. Although the Atlas of MS is one of the most comprehensive global data sources on clinical management of MS, the initially collected data relied on expert opinions of clinicians or specialists in each country since few peer-reviewed publications exist on the availability and access to DMTs in the MENA region. However, we improved confidence in the data collected by asking country coordinators to collaborate with other local experts when submitting answers to the survey and to report data sources if available. Moreover, for relevant questions in the survey, country coordinators were asked to indicate the source of their information. Crucially, for the data presented in this article, most countries referenced independent evidence such as data from academic papers or patient data (surveys or registries). Another limitation is the fact that data collected is at a national level and might not reflect disparities and barriers to treatment access within the country.

In conclusion, our study shows that although most MENA countries have access to some DMTs, whether originator, follow-on, or off-label, more than half of them report problems with treatment access and continuation, especially in low and middle income countries. Recognizing and addressing barriers to treatment access encountered by PwMS is essential to improve their quality of life and disease outcomes. Our study can support the development of a comprehensive strategy for MS care in MENA countries which is a fundamental step to improve person-centered management and promote the health of PwMS. Such targeted regional strategy needs to address the variations in access to treatment for PwMS. A greater investment in healthcare infrastructure devoted to MS is required in many MENA countries. Since affordability was a key barrier to accessing DMTs, local reimbursement decisions should be based on policies that improve affordability of a range of DMTs and continuity of treatment. Given the widespread use of off-label DMTs, evidence-based guidance on the use of off-label DMTs should be made available to support clinical decision-making and reimbursement decisions.

In addition, local MS registries and databases need to be further developed in order to provide epidemiological and clinical data to help assess, compare and enhance the status of PwMS across the MENA region. Finally, local MS patients' societies should be supported, and their role enhanced, as they can provide key services such as programs or resources to help PwMS navigate the complexity of accessing DMTs. Such strategies will allow better access to DMTs in our MENA region, leading to significant benefits to PwMS and the whole healthcare system.

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## Declaration of Competing Interest

Maya Zeineddine has received honoraria for lectures from Biologix, Biogen, Janssen, Hikma Pharmaceuticals, Novartis, Merck, Roche and Sanofi-Genzyme. She received travel grants from Novartis, Merck and Roche and a research grant from Biogen. She has no conflict of interest related to this study.

Amal Al-Hajje declares that there is no conflict of interest.

Pascale Salameh declares that there is no conflict of interest.

Anne Helme and Michael Gunnar Thor declare the following: Multiple Sclerosis International Federation (MSIF) is an alliance of national multiple sclerosis (MS) organizations. MSIF receives income from a wide range of sources, including healthcare and other companies, individuals, member organizations, campaigns, foundations and trusts. Over the last 5 years, MSIF received funding from the following companies: Biogen, BristolMyersSquibb, Coloplast, Janssen, Merck, Mylan, Novartis, Roche and Sanofi – all of which is publicly disclosed. MSIF has not received any funding from industry for its access to medicines work in 2019, 2020, 2021 or 2022.

Farid Boumediene declares that there is no conflict of interest.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.msard.2023.104959](https://doi.org/10.1016/j.msard.2023.104959).

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## Appendix 5. Editorial of Study 1

Multiple Sclerosis and Related Disorders 79 (2023) 105086



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### Multiple Sclerosis and Related Disorders

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#### Editorial

#### Can we improve outcomes in MS around the world? Access and global considerations across income strata



The past decade has seen impressive success in therapies for MS. Over the span of only a few decades, we have moved from a world with no approved MS therapies to breakthroughs leading to low-moderate efficacy therapies, to high efficacy therapies and a multiplicity of therapeutic choices. Moreover, our diagnostic criteria have led us to earlier and hopefully more precise MS diagnosis. This has resulted in earlier intervention and a marked reduction in clinical relapses and focal MRI activity in treated people with MS (PwMS). Due to this remarkable change in practice, we now expect “no evidence of inflammatory disease activity” in treated PwMS. Sadly, however, this state exists only in situations where MS therapies are readily accessed.

The issue of MS therapy access is of global significance: according to a survey of the Multiple Sclerosis International Federation’s Atlas of MS (2019–2020) (*MS International Federation 2023*), 60 % of African countries and 70 % of low-income countries lack or have no licensed MS therapies. Moreover, 50 % of middle-income and 100 % of low-income countries lack access to high-efficacy therapies. Such availability relates not only to whether one resides in a high-vs. low-income country – access in even the richest countries may be limited. One survey of PwMS conducted by the US-based National MS Society found that 40 % of respondents altered their use of disease-modifying therapies, and over half reported concerns about being able to afford therapies in the future (*National MS Society 2023*). Identifying barriers to treatment access is therefore paramount to improve MS outcomes worldwide.

In this issue of *MSARD*, Zeineddine et al. (2023) address this question. They highlight the 2019–2020 results from the Atlas of MS concerning access to therapy in Middle Eastern and North African (MENA) countries. Of the 19 countries in the MENA region, 16 were included. Of these countries, 3 had no access to high-efficacy therapies, and 2 had no therapies approved. Almost half of the countries surveyed reported cost as the most critical barrier to availability. Importantly, when divided into World Bank income classifications of low, lower-middle, upper-middle and high-income economies, countries classified as high-income economies did not identify barriers to DMT access, while most countries in lower-middle and middle-income economies identified multiple barriers to access. These included cost, lack of monitoring/testing capability, limited DMT availability, lack of specialist knowledge. Reduced uptake by PwMS was also identified in several countries. Notably, those in lower-middle and low-income countries identified the highest number of barriers to therapy access. Continuous access to DMTs was reported only in high-income countries of the region.

Limitations of the report relate to availability of information and reporting sources. Descriptions of access in each country relied upon single representatives/reporters, potentially leading to bias in nations

where access is uneven across the country. Further details regarding insurance coverage and disparities within countries are unavailable from this report but these are important areas for future investigation. Despite these limitations, this report identifies stark differences between access in countries across two regions, distinctions that cleave by income level.

How can we overcome these barriers and achieve equity in therapy access worldwide? A first step has been taken. In December 2022, the MSIF and multiple international partner organizations put forward an application to include MS therapies on the WHO Model List of Essential Medicines. In July 2023, this was approved. Three therapies were chosen for this list based on cost/feasibility, balance of risk and harms, known efficacy, and needs of special populations, namely rituximab, cladribine, and glatiramer acetate. Notably, the list includes both high and lower-efficacy therapies, all of which are relatively inexpensive.

Will this change the trajectory of MS for individuals living in lower-income countries? It is a first step. As identified in the Atlas of MS, access to the technology and medical expertise to make early and accurate diagnosis is fragmented in many parts of the world. It remains to be seen whether advances in the delivery of services will fill this gap.

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## Appendix 6. Glossary

- biosimilar drug - biological medicine highly similar to another already approved biological medicine
- DMT – disease-modifying therapy, may reduce relapses; or prevent relapses, new brain, and spinal cord lesions, and worsening neurological disability
- follow-on drug- medication similar to a pre-existing drug - but with some minor modifications, creating slight changes in drug action or its adverse effects - used to treat conditions for which drugs already exist
- generic - a drug created to be the same as an existing approved brand-name drug in dosage form, safety, strength, route of administration, quality, and performance characteristics.
- GNI per capita - gross national income per capita, as defined by the World Bank. Allows classification of countries into high income, upper middle income, lower middle income, and low income country.
- off-label - Off-label use is the use of drugs for an unapproved indication or in an unapproved age group, dosage, or route of administration
- on-label - A drug used for a condition for which it has been officially approved
- originator DMT - the product that was first authorized worldwide for marketing (typically patented) on the basis of the documentation of its efficacy, safety, and quality according to requirements at the time of authorization
- registry –a database collecting and organising healthcare information, to evaluate and improve outcomes for a population defined by a particular condition, disease, or exposure
- survey - a list of questions aimed for extracting specific data from a particular group of people



بسبب إصابتك بمرض التصلب العصبي المتعدد وخلال الأربعة أسابيع الماضية، هل...

اختر/اخترى الإجابة الأقرب إلى ما تشعر/تشعرين به، لكل سؤال	أبدًا لا على الإطلاق	نادرًا قليلاً	أحيانًا إلى حد ما	معظم الوقت كثيرًا	دائمًا إلى أقصى درجة
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14 شعرت بصعوبة في التركيز: أثناء القراءة، مشاهدة فيلم، أو متابعة مناقشة...؟	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
15 أزعجك بصرك: أصبح أسوأ أو غير مريح؟	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
16 شعرت بأحاسيس غير مريحة مثل الخز أو البرد...؟	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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بسبب إصابتك بمرض التصلب العصبي المتعدد وخلال الأربعة أسابيع الماضية، هل...

اختر/اخترى الإجابة الأقرب إلى ما تشعر/تشعرين به، لكل سؤال	أبدًا لا على الإطلاق	نادرًا قليلاً	أحيانًا إلى حد ما	معظم الوقت كثيرًا	دائمًا إلى أقصى درجة
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27 شعرت بالضيق من تحديق الآخرين فيك؟	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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29 أنت راضٍ عن المعلومات حول مرضك أو العلاج الذي يقدمه لك الأطباء والممرضون وأخصائيو علم النفس الذين يهتمون بمرضك؟	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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31 شعرت بأنك راضي/راضية عن علاجك؟	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

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## Appendix 8. Publication : Disease-modifying therapies, outcomes, risk factors and severity of COVID-19 in multiple sclerosis: A MENACTRIMS registry based study

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### Disease-modifying therapies, outcomes, risk factors and severity of COVID-19 in multiple sclerosis: A MENACTRIMS registry based study

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Severity  
COVID-19  
Multiple sclerosis  
Disease-modifying therapies

**ABSTRACT**

**Background:** There is a lack information regarding risk factors associated with worse COVID-19 outcomes in patients with multiple sclerosis (MS) in the MENA region.

**Methods:** This is a multicenter, retrospective cohort study that included all MS patients with a suspected or confirmed COVID-19 infection using the MENACTRIMS registry. The association of demographics, disease characteristics, and use of disease-modifying therapies (DMTs) with outcomes and severity of COVID-19 were evaluated by multivariate logistic model.

**Results:** A total of 600 MS patients with confirmed ( $n = 542$ ) or highly suspected ( $n = 58$ ) COVID-19 were analyzed. Seventy-three patients (12.2 %) had a COVID-19 severity score of  $\geq 3$  on a 7-point ordinal scale (ranging from 1 [not hospitalized with no limitations on activities] to 7 [death] with a cutoff at 3 [hospitalized and not requiring supplemental oxygen]), and 15 patients (2.5 %) died. Out of 73 patients with a severity score  $\geq 3$ , 90.4 % were on DMTs; 50.6 % of them were on anti-CD20, including ocrelizumab and rituximab. Multivariate logistic regression showed that older age (odds ratio per 10 years, 1.4 [95 %CI, 1.0–1.8]), disability (OR for EDSS 3.0–5.5, 2.9 [95 %CI, 1.5–5.7]), OR for EDSS  $\geq 6.0$ , 2.3 [95 %CI, 1.0–5.1]), obesity (OR, 3.0 [95 %CI, 1.5–6.0]), and treatment with rituximab (OR, 9.0 [95 %CI, 3.1–25.3]) or off-label immunosuppressive medications (OR, 5.6 [95 %CI, 1.1–27.8]) were risk factors for moderate or severe COVID-19.

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**Conclusion:** In this registry-based study of MS patients, age, sex, EDSS, obesity, progressive MS were risk factors for severe COVID-19. Moreover, there was an association found between exposure to anti-CD20 DMTs and COVID-19 severity.

## 1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has raised concerns regarding the risk of infection and its effects on patient populations, particularly people with multiple sclerosis (PwMS) as they may be more vulnerable to infections due to disability and/or treatment with disease-modifying therapies (DMTs) that alter the immune response (Winkelmann et al., 2016). In the general population, risk factors for poorer outcomes with COVID-19 include older age, male sex, and comorbidities such as obesity, diabetes, hypertension, coronary heart disease, chronic pulmonary or kidney disease, and cancer (GDCa, 2020; ISARIC ISARaEIC 2023; Williamson et al., 2020). The current evidence suggests that multiple sclerosis (MS) does not increase the risk of COVID-19 infection nor does it worsen clinical outcomes compared to people without MS (Evangelou et al., 2020; Parrotta et al., 2020). Several studies evaluating the epidemiology of COVID-19 severity have been published and generally reported mixed results (Louapre et al., 2020; Sormani et al., 2021; Simpson-Yap et al., 2021; Salter et al., 2021). The COVSEP, a French clinical registry-based study which included 347 PwMS with confirmed or highly suspected COVID-19, found that age, disability and obesity were risk factors for severe infection, but not exposure to DMTs (Louapre et al., 2020). In contrast, Sormani et al. reported the results of the national Musc-19 Italian registry study on 593 suspected and 191 confirmed COVID-19 infection (Sormani et al., 2021). This study showed that progressive MS course, recent corticosteroids use, and anti-CD20 DMTs (ocrelizumab and rituximab) were significantly associated with an increased risk of severe COVID-19 course. These results were replicated in the pooled analysis of the MS Global Data-Sharing Initiative comprising 5648 PwMS with suspected or confirmed COVID-19 diagnosis, concluding that anti-CD20 DMTs, ocrelizumab and rituximab, were associated with greater frequency of hospital admission, Intensive Care Unit (ICU) admission, need for artificial ventilation and death compared to glatiramer acetate and other DMTs (Simpson-Yap et al., 2021). Moreover, in the United States/Canada, Salter and colleagues conducted a large, multicenter, registry-based cross-sectional study which included 1626 patients (Salter et al., 2021). They identified increased disability, older age, black race, cardiovascular comorbidities and recent use of corticosteroids as risk factors for worse COVID-19 outcomes. The authors also found that compared with untreated PwMS, ocrelizumab and rituximab were associated with a higher risk of hospitalization; however, only rituximab showed positive trends for ICU admission, artificial ventilation and death (Salter et al., 2021).

In the Middle East and North Africa (MENA) region, studies identifying clinical characteristics of MS associated with worse COVID-19 outcomes are lacking. Accordingly, we conducted a large, Middle East and North Africa Committee for Treatment and Research in Multiple Sclerosis (MENACTRIMS) registry-based study to determine whether the outcomes of these global studies were applicable to our MS population in the MENA region. The purpose of this study was to identify clinical and DMTs-related risk factors for severe COVID-19 in PwMS in the MENA region.

## 2. Methods

### 2.1. Data collection

This was a multicenter, retrospective, observational cohort study of patients with confirmed or highly suspected COVID-19 infection. Data were collected from the MENACTRIMS registry, local COVID-19

registries and cohorts from nine Middle Eastern countries, including Algeria, Egypt, Iraq, Iran, Kuwait, Lebanon, Oman, Tunis and United Arab of Emirates (UAE). The MENACTRIMS registry, the largest MS patients' registry in the MENA region (MENACTRIMS., 2023), received approval from the Institutional review board (IRB) of the American University of Beirut (AUB) for collection and use of confidential electronically processed patient data. Study data were collected for patients diagnosed with COVID-19 between March 01,2020 and February 01, 2021, before the introduction of any COVID-19 vaccine in the MENA region.

### 2.2. Inclusion criteria

A confirmed diagnosis of MS with at least one of the following 4 criteria: (1) a confirmed COVID-19 diagnosis based on a positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test, (2) Typical abnormalities on thoracic computed tomography (CT) scan manifested as ground-glass opacities, (3) sudden onset of anosmia or ageusia in the absence of rhinitis or nasal obstruction, and (4) typical COVID-19 symptoms (triad of cough, fever, and asthenia) in an epidemic area of COVID-19.

### 2.3. Study variables

Demographic variables collected were sex, age, country at time of infection, smoking status, alcohol consumption, and employment status. Comorbidities were queried, including obesity, hypertension (HTN), cardiovascular disease (CVD), diabetes mellitus (DM), thyroid disease, chronic lung disease, chronic kidney disease, chronic liver disease and cancer. Obesity was defined as a body mass index (BMI)  $\geq 30$  (WHO WHO, 2024).

Disease characteristics captured included MS phenotype (Clinically Isolated Syndrome (CIS), Relapsing-Remitting MS (RRMS), Secondary Progressive MS (SPMS) or Primary Progressive MS (PPMS) (Lublin et al., 2014), and disease duration. Disability was assessed by the Expanded Disability Status Scale (EDSS) which was dichotomized into 3 categories:  $<3.0$ ,  $3.0-5.5$ ,  $\geq 6.0$ , and by the ambulation milestones (fully ambulatory, walks with assistance, non-ambulatory) (D'Souza et al., 2017; Kurtzke, 1983). DMT use at the time of COVID-19 infection was recorded as one of the following: alemtuzumab, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate (GA), interferons, natalizumab, ocrelizumab, ofatumumab, rituximab, siponimod, teriflunomide, other DMTs (off-label use of azathioprine, mycophenolate mofetil or methotrexate), or none. Data on DMT dose and duration were not documented. Additionally, the use of glucocorticoids during the prior 1-month was recorded.

Regarding COVID-19, we collected symptoms and diagnostic data (PCR for SARS-CoV-2, serological tests and CT chest findings).

### 2.4. Definition of study endpoints

The primary endpoint was the patient's clinical status at the most severe point of their COVID-19 course, referred to as the COVID-19 severity score (Cao et al., 2020). This is a 7-point ordinal scale where 1 indicates the patient was not hospitalized and had no limitations on activities; 2, the patient was not hospitalized but had limitations on activities; 3, the patient was hospitalized but did not require supplemental oxygen; 4, the patient was hospitalized and required supplemental oxygen; 5, the patient was hospitalized and received noninvasive ventilation or high flow oxygen; 6, the patient was hospitalized and

received invasive mechanical ventilation or extracorporeal membrane oxygenation; and 7, death.

2.5. Statistical analysis

Patients' demographic and clinical characteristics were summarized using count and percentage for categorical variables and median and range for numerical data such as duration of hospitalization. Severity score by DMT type was reported using frequency and percent and statistical significance was tested using Pearson chi-square. Difference in age and EDSS according to hospitalization, ICU and living status, were reported based on median and tested using the Mann Whitney U test, where differences in distribution of phenotypes for same outcomes were tested using Pearson's chi-square. Any 2-sided p-value < 0.05 was considered statistically significant.

Logistic regressions were performed at the univariate and multivariate level predicting severity score (≥ 3). Coefficients produced by the logistic regression were exponentiated to produce odds ratios (ORs) and 95 % confidence interval (CI). In the multivariate analysis, Receiver Operating Characteristic (ROC) curves and Concordance (C) statistics were done to show the model discrimination capacity in predicting the severity of COVID-19 infection (Logan, 2013). Predicted probabilities were used to draw a calibration line. The produced model was repeated using severity score ≥ 4 as a sensitivity analysis. Statistical analyses were conducted using SPSS software version 27.

3. Results

3.1. Study population

As of February 2021, 600 PwMS were included in the study. Five-hundred forty-two (542) patients had a positive SARS-CoV-2 PCR result. One patient had a negative SARS-CoV-2 PCR result but a chest CT showing typical lesions of COVID-19. For the remaining 57 patients with unavailable SARS-CoV-2 PCR results, 27 had positive SARS-CoV-2 serology, 7 had ground-glass opacity on thoracic CT scan, and 23 presented with typical COVID-19 symptoms.

3.2. Demographics and clinical characteristics

The mean (Standard Deviation [SD]) age was 36.4 (10.2) years, 414 (69.0 %) were women, and the mean (SD) disease duration was 8.3 (6.6) years. Obesity (n = 77, 12.8 %), HTN (n = 41, 6.8 %), and CVD (n = 41, 6.8 %) were the most frequently reported comorbidities. The majority of patients had RRMS (n = 495, 82.5 %) and were full ambulatory (n = 494, 82.3 %). The median EDSS was 2.0 (range, 0.0 – 9.0), and 559 patients (93.2 %) were receiving DMT but 107 (19.4 %) withheld their MS treatment at onset of the infection (Table 1).

Seventy-three patients (12.2 %) had a COVID-19 severity score ≥3 (needed hospitalization), and 15 patients (2.5 %) died of COVID-19. Among hospitalized patients, 26 (4.3 %) required ICU, 52 (8.7 %) required oxygen, and 18 (3.0 %) required mechanical ventilation. The most frequently recorded symptoms for COVID-19 were fever (n = 318, 53.0 %), cough (n = 226, 37.7 %), anosmia/ageusia (n = 203, 33.8 %), and fatigue (n = 179, 29.8 %).

3.3. Factors associated with COVID-19 severity

Comparing patients that required hospitalization to those that did not, patients requiring hospitalization were older (median [range] age, 41.4 [21–61] years vs 35.0 [15–73] years; p < 0.001), had a higher EDSS (median [range], 3.0 (0.0–9.0) vs 2.0(0.0–8.0); p < 0.001), and were more likely to have a progressive course (17/66 [25.8 %] SPMS and 7/26 [26.9 %] PPMS vs 49/495 [9.9 %] RRMS; p < 0.001) (Fig. 1). There was no statistically significant difference between males and females. Although, ICU admission was not associated with older age (median

Table 1 Demographic and clinical characteristics of patients with multiple sclerosis diagnosed with Coronavirus disease 2019.

Characteristics	N.	%
Number. of patients with MS	600	
Demographics		
Age, mean (SD) in years	36.4 (10.1)	
Gender		
Male	196	31.0
Female	414	69.0
Current Smoker	121	20.2
Former Smoker	27	4.5
Alcohol Consumer	92	15.3
Disease Course		
Clinically isolated syndrome (CIS)	13	2.2
Remitting-relapsing MS (RRMS)	495	82.5
Secondary progressive MS (SPMS)	66	11.0
Primary progressive MS (PPMS)	26	4.3
Disease Duration in years, mean (SD)	8.3 (6.6)	
Expanded Disability Severity Scale Score, median (range)	2.0 (0.0-9.0)	
Ambulatory Status		
Non-Ambulatory	37	6.2
Walk with Assistance	64	10.7
Full Ambulatory	494	82.3
Used Steroids in the Last Month	16	2.7
Disease-modifying therapies		
None	41	6.8
Interferon beta	159	26.5
Teriflunomide	17	2.8
Dimethyl Fumarate	46	7.7
Cladribine	4	0.7
Fingolimod/Siponimod	112	18.7
Natalizumab	50	8.3
Ocrelizumab	47	7.8
Rituximab	96	16.0
Ofatumumab	1	0.2
Alemtuzumab	6	1.0
Glatiramer Acetate (GA)	6	1.0
Others*	15	2.5
DMT withheld at COVID-19 onset	107	19.4
Comorbid Conditions		
Obesity (BMI ≥ 30)	77	12.8
Hypertension	41	6.8
Cardiovascular Disease	41	6.8
Diabetes Mellitus	17	2.8
Thyroid Disease	12	2.0
Chronic Lung Disease	5	0.8
Anemia	4	0.7
Active Malignancy	3	0.5
Malignancy Remission	2	0.3
Renal Disease	1	0.2
Liver Disease	1	0.2
COVID-19 Diagnosis		
SARS-CoV-2 PCR	543	90.5
Serological Test, without fulfilling the criteria	148	24.7
Thoracic CT, without fulfilling the criteria	184	30.7
COVID-19 Symptoms		
Fever	318	53.0
Cough	226	37.7
Anosmia/ageusia	203	33.8
Fatigue	179	29.8
Sore Throat	136	22.7
Pain	124	20.7
Dyspnea	85	14.2
Runny Nose	78	13.0
Headache	66	11.0
Diarrhea	31	5.2
Nausea/Vomiting	6	1.0
Others	11	1.8
Inclusion Criteria for COVID19cases		
Positive SARS-CoV-2 PCR	542	90.3
Positive Serological Test, without fulfilling the criteria	27	4.5
Ground-glass opacity on thoracic CT, without fulfilling the criteria	8	1.3
Typical COVID-19 symptoms without fulfilling the criteria	23	3.8

(continued on next page)

Table 1 (continued)

Characteristics	N.	%
Abbreviations: MS, multiple sclerosis; SD, Standard Deviation; BMI, body mass index; SARS-CoV2: severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction; CT, Computerized tomography; COVID-19, coronavirus disease 2019.		
*Other treatments for patients with multiple sclerosis: mycophenolate mofetil, azathioprine and methotrexate.		

[range], 39.0 [21–61] vs 41.5 [22–63];  $p = 0.818$ ), ICU patients had a higher EDSS (median [range], 5.0 [1.0–8.0] vs 3.0 [0.0–9.0];  $p = 0.005$ ) and a higher likelihood of a progressive clinical course (10/17 (58.8 %) SPMS and 5/7 (71.4 %) PPMS vs 11/49 (22.4 %) RRMS;  $p < 0.003$ ). Similarly, older age (median [range], 45.0 [32–61] vs 35.0 [15–73];  $p = 0.002$ ), higher EDSS (median [range] 6.0 [2.0–8.0] vs 2.0 [0.0–9.0];  $p < 0.001$ ), and progressive course (7/66 [10.6 %] SPMS and 2/26 [7.7 %] PPMS vs 6/495 [1.2 %] RRMS) were associated with death due to COVID-19.

Having at least one comorbidity was significantly associated with increased risk of severe COVID-19. The proportion of patients with at

least one comorbidity was lower in non-hospitalized patients (61 of 527 [11.6 %] vs 17 of 73 [23.3 %];  $p = 0.005$ ). Hypertension and cardiovascular comorbidities were significantly associated with more severe COVID-19 (11 of 73 [15.1 %] vs 30 of 527 [5.7 %];  $p = 0.003$ ).

Sixty-six out of the 73 (90.4 %) hospitalized patients were maintained on DMTs. The majority ( $n = 37$ ; 56.6 %) were on anti-CD20s (ocrelizumab, rituximab or ofatumumab) compared to 20.1 % ( $n = 107$ ) of the non-hospitalized patients receiving treatment ( $p < 0.001$ ). The distribution of clinical severity for COVID-19 according to the different DMTs is presented in Fig. 2.

3.4. Multivariate logistic regression models of severe COVID-19

A multivariate logistic regression analysis was performed to assess variables independently associated with severe COVID-19 (severity score  $\geq 3$ ) (Table 2).

Results showed that older age (OR per 10 years, 1.4 [95 %CI, 1.0–1.8]), disability (OR for EDSS 3.0–5.5, 2.9 [95 %CI, 1.5–5.7], OR for EDSS  $\geq 6.0$ , 2.3 [95 %CI, 1.0–5.1]), obesity (OR, 3.0 [95 %CI, 1.5–6.0]), and treatment with rituximab (OR, 9.0 [95 %CI, 3.1–25.3]) or off-label

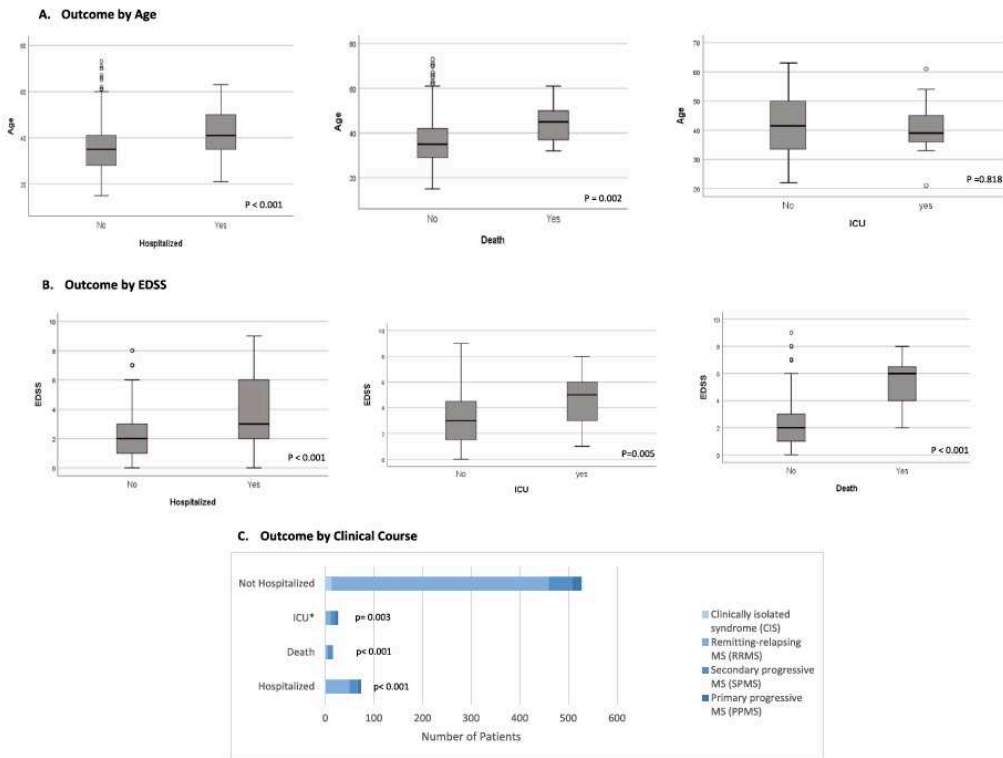


Fig. 1. Characteristics of COVID-19 and MS patients stratified by not hospitalized, hospitalized, admitted to the intensive care unit (ICU) or Died

Abbreviations: EDSS, Expanded Disability Severity Scale (EDSS); ICU, Intensive Care Unit

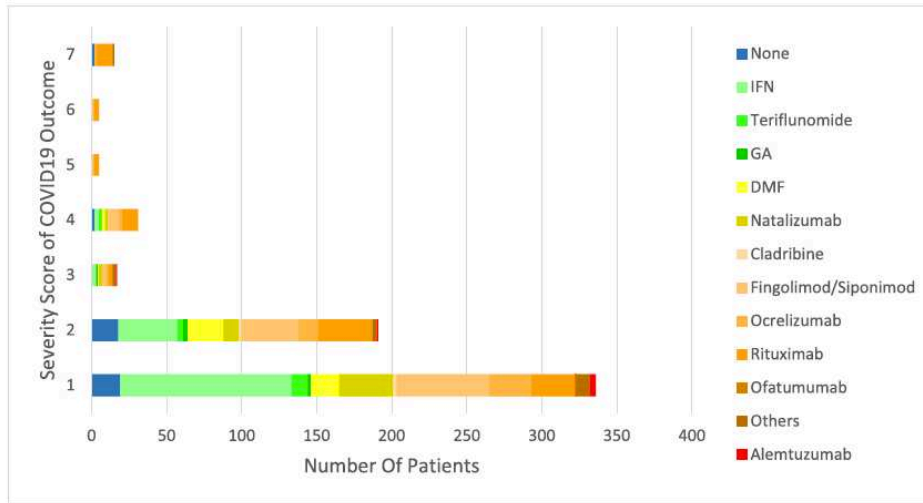
- A. Outcome by Age
- B. Outcome by EDSS
- C. Outcome by Clinical Course

\*Among hospitalized patients

The p-values were obtained from Mann-Whitney U tests for age and EDSS group differences (Figs. 1A and 1B) and Pearson Chi-square tests for clinical course distribution differences (Fig. 1C).



**A. Patients grouped by severity of COVID-19 outcome**



**B. Patients grouped by disease-modifying therapy**

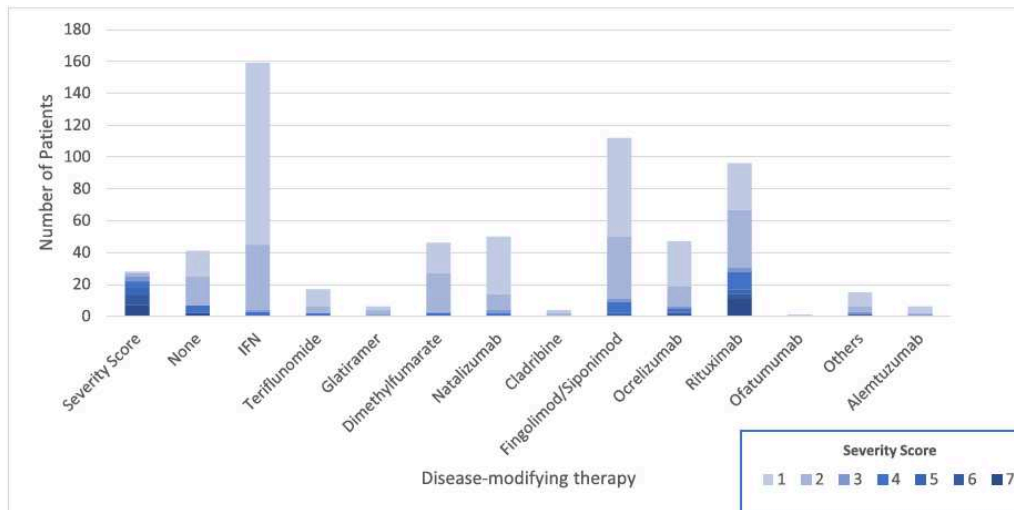


Fig. 2. Clinical severity of Coronavirus Disease 2019 (COVID-19) and disease-modifying therapies in patients with multiple sclerosis

A. Patients grouped by severity of COVID-19 outcome

1: Not hospitalized, no limitations on activities; 2: Not hospitalized, limitation on activities; 3: Hospitalized, not requiring supplemental oxygen; 4: Hospitalized, requiring supplemental oxygen; 5: Hospitalized, or noninvasive ventilation or high-flow oxygen devices; 6: Hospitalized, on invasive mechanical ventilation or ECMO; 7: Death

B. Patients grouped by disease-modifying therapy

Abbreviations: COVID-19: Coronavirus Disease 2019; IFN, Interferon beta; GA: Glatiramer acetate; DMF: Dimethyl Fumarate

<sup>†</sup>Other treatments for patients with multiple sclerosis: mycophenolate mofetil, azathioprine and methotrexate.

<sup>\*</sup>*p* < 0.001 using the Pearson Chi-square  $\chi^2=143.86$  *df*=72.



**Table 2**  
Associated risk factors of severe Coronavirus Disease 2019 (COVID-19) among multiple sclerosis (MS) patients.

	Severe COVID-19 (Severity Score ≥ 3)			
	OR <sub>c</sub> (95 % CI)	P-value	OR <sub>a</sub> (95 % CI)	P-value
Age per 10 years	1.67 (1.33-2.10)	<0.001	1.38 (1.04-1.83)	0.025
Male	1.77 (1.07-2.92)	0.025	-	NS
Obesity	2.60 (1.43-4.72)	0.002	3.02 (1.52-6.01)	<0.001
Cardiovascular comorbidity	2.94 (1.40-6.16)	0.004	-	NS
Hypertension	2.94 (1.40-6.16)	0.004	-	NS
Diabetes Mellitus	2.29 (0.73-7.23)	0.157	-	NS
Smoking	0.99 (0.53-1.84)	0.962	-	NS
Progressive Course				
- SPMS	3.16 (1.69-5.90)	<0.001	-	NS
- PPMS	3.35 (1.34-8.38)	0.010	-	NS
Disease Duration per 10 years	1.66 (1.20-2.29)	0.002	-	NS
EDSS score < 3 (reference)				
EDSS score 3-5.5	3.73 (2.05-6.79)	<0.001	2.93 (1.50-5.74)	0.002
EDSS score ≥ 6	5.67 (2.92-10.99)	<0.001	2.31 (1.04-5.15)	0.040
DMT (IFN/GA reference)				
Teriflunomide	4.27 (0.76-23.9)	0.099	3.17 (0.53-18.93)	0.206
Dimethyl Fumarate (DMF)	2.23 (0.51-9.71)	0.264	1.91 (0.42-8.65)	0.399
Fingolimod/Siponimod	3.49 (1.18-10.33)	0.024	2.28 (0.74-7.04)	0.153
Natalizumab	2.78 (0.72-10.79)	0.139	1.69 (0.41 -6.90)	0.466
Ocrelizumab	4.68 (1.36-16.11)	0.014	2.04 (0.55 -7.67)	0.289
Rituximab	15.26 (5.69-40.97)	<0.001	9.0 (3.12 -25.36)	<0.001
Others	8.00 (1.70-37.58)	0.008	5.58 (1.12-27.94)	0.036
None	6.59 (1.97-22)	0.002	1.85 (0.42-8.20)	0.419
Full Ambulatory (reference)	NA			
Non-Ambulatory	5.40 (2.58-11.34)	<0.001	-	NS
Walk With Assistance	2.79 (1.43-5.44)	0.003	-	NS
DMT Withheld at COVID-19 onset	2.40 (1.35-4.23)	0.003	-	NS

Abbreviations: COVID-19, Coronavirus Disease 2019; OR<sub>c</sub>, Crude Odds Ratio; OR<sub>a</sub> Adjusted Odds Ratio; CI, Confidence Interval; SPMS, Secondary Progressive; Multiple Sclerosis; PPMS, Primary Progressive MS; EDSS, Expanded Disability Severity Status; NA, Not Applicable; DMT, Disease-Modifying Therapy.

immunosuppressive medications such as azathioprine, mycophenolate mofetil or methotrexate (OR, 5.6 [95 %CI. 1.1-27.8]) were risk factors for severe COVID-19 requiring hospitalization.

To validate our results, a post hoc analysis with a threshold of 4 for COVID-19 severity score was performed. Results were similar in both cases indicating that the model used showed sensitivity. In the sensitivity analysis, obesity (OR, 3.7 [95 % CI, 1.7-7.8],  $p = 0.001$ ), higher EDSS (EDSS score 3.0-5.5 OR, 3.62 [95 % CI, 1.7-7.7],  $p = 0.001$ ; EDSS score ≥ 6.0 OR, 2.8 [95 % CI, 1.2-6.7],  $p = 0.021$ ), and treatment with rituximab (rituximab, 12.5 [95 % CI, 3.5 - 44.6],  $p < 0.001$ ) were retained as independent variables associated with severe COVID-19.

Unlike the first model, off-label immunosuppressive medications such as azathioprine, mycophenolate mofetil or methotrexate and older age were not significantly associated with higher COVID-19 severity score although higher age showed a trend toward significance (OR, 1.3 [95 % CI, 1.0-1.8],  $p = 0.061$ ).

The model was checked for calibration in for its predictive capacity. The predicted probability of severity was regressed against the observed probability, and a linear model was produced with a coefficient of 0.97 and an R2 of 94.6 % indicating a good calibrated model. C statistics was 0.81 [95 % CI, 0.8-0.9], indicating a good discrimination capacity of the model in predicting high and low severity (Fig. 3. Including only PCR+ cases in the logistic regression model (543/600) led to identical results.

### 3.5. Death rate in patients with multiple sclerosis hospitalized for COVID-19

Fifteen patients (2.5 %) in this study died due to COVID-19. Compared to surviving patients, they were older (OR, 1.9 [95 % CI, 1.2-2.9],  $p < 0.004$ ), non-ambulatory (OR, 13.5 [95 % CI, 4.3-42.5],  $p < 0.001$ ) with at least one comorbidity (OR, 8.4 [95 % CI, 2.9-23.9],  $p < 0.001$ ), a progressive course (ORs, SPMS, 9.7 [95 % CI, 3.1-29.7],  $p < 0.001$ ; PPMS, 6.8 [95 % CI, 1.3-35.4],  $p = 0.023$ ), higher EDSS (ORs, EDSS 3.0-5.5, 8.9 [95 % CI, 1.7-46.7],  $p = 0.009$ ; EDSS ≥ 6.0, 26.9 [95 % CI, 5.6-129.8],  $p < 0.001$ ) and longer disease duration (OR per 10 years, 2.0 [95 % CI, 1.1-3.5],  $p = 0.013$ ).

## 4. Discussion

Our study showed that COVID-19 symptoms in PwMS were similar to what has been described in the general population. In our cohort, fever, cough, anosmia/ageusia and fatigue were the most frequently recorded symptoms. Similarly, a cross-sectional study of the general population conducted in seven MENA region countries (Algeria, Egypt, Iraq, Lebanon, Libya, Tunisia, and the United Arab of Emirate) showed that more than half of the participants reported fever, cough, and fatigue as the most frequent symptoms during the course of infection (Jirjees et al., 2022).

Univariate logistic regression models showed that older age, male sex, comorbidities, progressive MS, longer disease duration, higher EDSS, deteriorated ambulation, and withholding DMT were associated with COVID-19 severity scores of 3 or more. Our results were similar to other international COVID-19 registries, mainly the COVISEP French registry (Louapre et al., 2020), and the MS Global Data Sharing Initiative study (Simpson-Yap et al., 2021) that showed that older age, higher EDSS, progressive MS course and male sex were associated with more severe COVID-19 infection. It is of note that male sex was not a risk factor in our cohort.

Similar to the North American Registry-based cohort (Salter et al., 2021), our study demonstrated a significant association between hypertension and cardiovascular comorbidities with worse COVID-19 infection. A retrospective case study conducted throughout China involving 11,791 MS patients with confirmed COVID-19 also showed that hypertension and cardiac disease were among the most common comorbidities associated with poorer prognosis (Guan et al., 2020).

Given the possible interaction between the independent variables, we carried out a multivariate logistic regression analysis. Only older age, higher EDSS, obesity and off-label use of immunosuppressive medications such as azathioprine, mycophenolate mofetil or methotrexate remained as risk factors for severe COVID-19 infection.

The increased severity of COVID-19 among MS patients with higher EDSS can be linked to the fact that respiratory dysfunction is common in such patients and is linked to expiratory muscles weakness and cough impairment (Levy et al., 2017). These findings should lead to improving preventive measures to limit the risk of COVID-19 infection in older patients and in patients with advanced disability.

Obesity was associated with 3-fold increased odds of severe COVID-

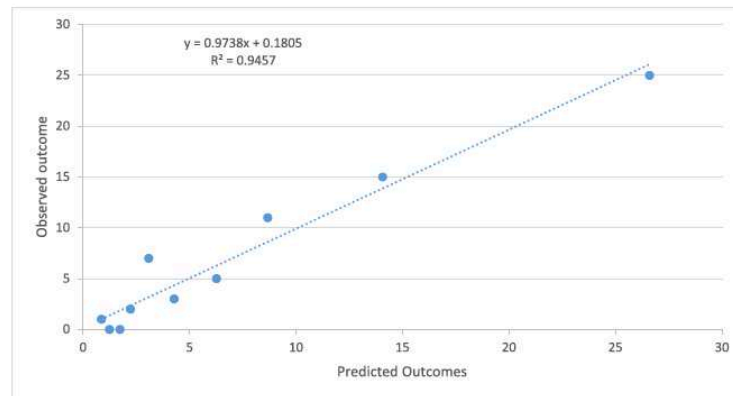


Fig. 3. Calibration plot for the logistic regression.

19 infection. This is compatible with the results of a meta-analysis from China that showed that patients with obesity have a greater risk of infection, hospitalization, severe disease, mechanical ventilation, ICU admission, and mortality due to COVID-19 (Cai et al., 2021). Petrilli et al. (Petrilli et al., 2020), in a large prospective analysis of 5279 COVID-19 patients in the United States demonstrated as well that obese patients have greater tendency to develop adverse events, including respiratory failure, admission to ICU, and invasive mechanical ventilation. Obesity-related respiratory dysfunction is probably the main cause of severe COVID-19 infection in those patients (Yan et al., 2021).

Surprisingly, diabetes mellitus was not associated with increased COVID-19 severity in our study. However, several published studies indicated that type 2 diabetes mellitus is a significant risk factor for COVID-19 severity, and mortality. A large meta-analysis involving 78,874 confirmed COVID-19 hospitalized patients showed that pre-existing diabetes is significantly associated with a greater risk of severe/critical illness and in-hospital mortality in patients admitted to hospital with COVID-19 (Mantovani et al., 2020).

Multiple studies evaluated the impact of DMT use on COVID-19 infection in PwMS. Given their anti-viral effect, patients treated with interferon beta and teriflunomide were at a lower risk of COVID-19 infection and disease severity (Thakolwiboon et al., 2020). The French (Louapre et al., 2020) and Italian (Sormani et al., 2021) cohorts showed no association between interferon beta, glatiramer acetate and dimethyl fumarate use and COVID-19 severity. In other studies, fingolimod (Louapre et al., 2020; Sormani et al., 2021), natalizumab (Laroni et al., 2021), alemtuzumab (Carandini et al., 2020; Guevara et al., 2020), cladribine (De Angelis et al., 2020), and corticosteroids (Naser Moghadas et al., 2021) were not associated with COVID-19 severity. Our results were similar, showing no impact of interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, cladribine, sphingosine-1-phosphate (S1P) receptor modulators, natalizumab and alemtuzumab on COVID-19 severity.

The MENA cohort, however, showed that exposure to rituximab and immunosuppressive medications such as azathioprine, mycophenolate mofetil and methotrexate increased the risk of severe COVID-19. Rituximab use was associated with a 9-folds increase in risk of severe COVID-19 infection. This was consistent with the findings of Simpson-Yap et al. (2021) who reported on 2340 MS patients with COVID-19 infection from 28 countries and showed a significant association between rituximab and increased risk of hospitalization, ICU admission, and need for artificial ventilation. The same outcomes were replicated in the pooled analysis studies from Italy and France (Louapre et al., 2020; Sormani et al., 2021).

We found no association between ocrelizumab and COVID-19 increased severity, despite a trend towards higher severity of infection. Although both rituximab and ocrelizumab are anti-CD20 therapies, this discrepancy might be due to different molecular structure or mechanism of cytotoxicity. Another possible explanation is that ocrelizumab was only recently introduced in the MENA region, and therefore the duration of treatment with rituximab was probably longer, knowing that hypogammaglobulinemia and infections increase with the treatment duration of anti-CD20 drugs. Socioeconomic factors might have also played a role, since rituximab is usually prescribed to patients without health insurance, especially refugees in the Middle East. Although this result is compatible with the interim report published by Roche-the pharmaceutical company producing ocrelizumab-, it does not harmonize with some other cohort studies (Laroni et al., 2021).The Italian cohort study showed an increased risk in severe forms of COVID-19 in MS patients treated with ocrelizumab (Sormani et al., 2021). The French cohort did not show any association between the use of DMTs and COVID-19 severity, but reported acute respiratory distress syndrome in two patients treated with ocrelizumab (Louapre et al., 2020). This discrepancy might be due to the small number of ocrelizumab-treated patients in our cohort.

The overall mortality rate of COVID-19 in our MS cohort was 2.5 %, similar to the fatality rate of 3.5% reported by Louapre et al. in the COVISEP registry-based study (Louapre et al., 2020). Older age, having at least one co-morbidity, progressive MS, higher disability and a longer disease duration were risk factors for mortality in patients with COVID-19 infection. The global average mortality rate of COVID-19 infection in the general population is 2.7 %, which is similar to the mortality rate detected in our MS population (Edouard Mathieu et al., 2024). This suggests no increased risk of death in patients with MS compared to the general population, but still needs to be confirmed with further epidemiological studies. Two Regional studies from Iran showed similar risk factors for mortality due to COVID-19 infection in the general population, namely older age, obesity and comorbidities (Alamdari et al., 2020; Alizadehsani et al., 2021).

Limitations of this analysis include a potential selection bias as reporting was voluntary by health care professionals, which may have led to selection of more severe cases. Since this study was based on data collected retrospectively from the MENACTRIMS registry and other local registries, we were not able to collect some potentially relevant information like DMT dosage, frequency and duration, and other risk factors beyond those investigated. Some immunosuppressive treatments like ofatumumab, cladribine and alemtuzumab, were not commonly used in our region, limiting the possibility of detecting any association



between their use and COVID-19 severity. Our study strengths include its large sample size and the sensitivity analysis that confirmed the results.

## 5. Conclusion

COVID-19 has significantly impacted the medical practice, and it is likely to remain an issue for several years to come with annual waves. It is therefore crucial to identify the risk factors for more severe infection in Middle-Eastern PwMS who may have different genetic predisposition compared to other populations leading to improvement in the clinical management of MS patients with COVID-19 infection in our region. This is the largest registry-based cohort study in our region and its outcomes were consistent with those described in other international studies. In patients with MS, we identified age, sex, disability, obesity progressive MS and rituximab exposure as independent risk factors for severe COVID-19. We found no association between all other DMTs and severe COVID-19 which should reinforce the recommendation of keeping PwMS and COVID-19 on their DMT and avoid delaying treatment initiation.

## CRedit authorship contribution statement

Maya Zeineddine: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Conceptualization. Amal Al-Hajje: Writing – review & editing, Supervision, Methodology. Pascale Salameh: Writing – review & editing, Supervision, Methodology. Joelle Massouh: Investigation, Data curation. Georges Saab: Investigation. Raed Al-Roughani: Writing – original draft, Investigation. Samar Farouk Ahmed: Investigation, Data curation. Akram Al-Mahdawi: Investigation, Data curation. Nevin Shalaby: Investigation, Data curation. Jihad Inshasi: Writing – original draft, Investigation, Data curation. Mohamad Ali Sahraian: Investigation, Data curation. Riadh Gouider: Investigation, Data curation. Saloua Mrabet: Investigation, Data curation. Jaber Al-Khabouri: Investigation, Data curation. Vahid Shaygannej: Investigation, Data curation. Amina Chentouf: Investigation, Data curation. Farid Boumediene: Writing – review & editing, Supervision, Methodology. Bassem Yamout: Writing – review & editing, Supervision, Project administration, Conceptualization.

## Declaration of competing interest

No conflict of interest.

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## Appendix 9. Publication : Safety and effectiveness of disease-modifying therapies after switching from natalizumab

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Original Research Paper

### Safety and effectiveness of disease-modifying therapies after switching from natalizumab

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**Abstract**  
**Introduction:** One strategy to mitigate progressive multifocal leukoencephalopathy (PML) risk is to switch to other highly effective disease-modifying therapies (DMTs). However, the optimal switch DMT following natalizumab (NTZ) discontinuation is yet to be determined.  
**Objective:** The objective of the study is to determine the most effective and tolerable DMTs to switch to following NTZ discontinuation due to John Cunningham virus (JCV) antibody positivity.  
**Methods:** This is a multicenter observational cohort study that included all stable relapsing-remitting multiple sclerosis (MS) patients who were treated with NTZ for at least 6 months before switching therapy due to JCV antibody positivity.  
**Results:** Of 321 patients, 255 switched from NTZ to rituximab/ocrelizumab, 52 to fingolimod, and 14 to alemtuzumab, with higher annualized relapse rate (ARR) in fingolimod switchers (0.193) compared with rituximab/ocrelizumab or alemtuzumab (0.028 and 0.032, respectively). Fingolimod switchers also had increased disability progression ( $p=0.014$ ) and a higher proportion developed magnetic resonance imaging (MRI) lesions compared with rituximab/ocrelizumab (62.9% vs. 13.0%,  $p<0.001$ , and 66.6% vs. 24.0%,  $p<0.001$ , respectively). Mean drug survival favored rituximab/ocrelizumab or alemtuzumab over fingolimod ( $p<0.001$ ).  
**Conclusion:** Our study shows superior effectiveness of rituximab/ocrelizumab and alemtuzumab compared with fingolimod in stable patients switching from NTZ due to JC virus antibody positivity.

**Keywords:** Natalizumab, switching, PML, multiple sclerosis, fingolimod, effectiveness, rituximab

Date received: 12 March 2024; revised: 18 May 2024; accepted: 27 May 2024

**Introduction**  
Natalizumab (NTZ) is a monoclonal antibody approved for treating relapsing-remitting multiple sclerosis (RRMS). It blocks  $\alpha4\beta1$  integrin on leukocytes, preventing mononuclear cell trafficking across the blood–brain barrier (BBB).<sup>1</sup> Phase III clinical trials<sup>2,3</sup> and observational studies<sup>4–6</sup> have confirmed its long-term efficacy and safety in RRMS.

The most significant risk with NTZ is progressive multifocal leukoencephalopathy (PML), especially in patients treated for over 2 years, those with prior immunosuppressive therapy exposure, or those who are John Cunningham virus (JCV) antibody–positive with a high index.<sup>7,8</sup>

With the availability of high-efficacy disease-modifying therapies (DMTs), the risk of PML in NTZ-treated patients can be mitigated by switching treatments. However, NTZ is associated with a rebound phenomenon and severe disease reactivation risk.<sup>9</sup> The RESTORE trial showed that switching from NTZ to less efficacious DMTs, such as interferons, glatiramer acetate, or methylprednisolone, led to clinical relapses in 15%–29% of patients, with magnetic resonance imaging (MRI) activity detected as early as 12 weeks post-treatment cessation.<sup>10</sup> Similarly, real-world studies found breakthrough disease in patients switched from NTZ to dimethyl fumarate<sup>11</sup> or teriflunomide.<sup>12</sup>

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Only few small observational studies<sup>13–16</sup> looked at efficacy and safety of fingolimod, ocrelizumab (OCR), rituximab (RTX), or cladribine after NTZ cessation.

The aim of this study was to compare the effectiveness, safety, and drug survival of switching from NTZ to other high-efficacy DMTs due to JCV Ab positivity.

## Methods

### Study setting and population

We conducted a multicenter retrospective observational study of patients with RRMS treated with NTZ for at least 6 months before switching to high-efficacy DMTs due to JCV Ab positivity. Patient data were obtained from the MENACTRIMS registry, the largest regional MS registry,<sup>17</sup> and local national registries from different countries in the MENA region, including Kuwait, Lebanon, United Arab of Emirates (UAE), Iraq, Oman, Algeria, and Tunisia. Data were extracted and analyzed between October 2022 and March 2023. All patients diagnosed with RRMS according to the 2010<sup>18</sup> or 2017<sup>19</sup> McDonald criteria and fulfilling the following inclusion criteria were included in the study: age between 18 and 65 years, Expanded Disability Status Score (EDSS) between 0 and 6, treated with NTZ for at least 6 months before switching to another DMT due to positive serum JCV Ab or high antibody index (AI), and a follow-up period on the new DMT of at least 1 year or until drug discontinuation whichever comes first. Patients who discontinued NTZ treatment for other reasons than a positive JCV Ab or shifted to other DMTs after a wash out period longer than 3 months were excluded.

### Outcomes

The study outcomes were annualized relapse rate (ARR), time to first relapse, confirmed disability progression (CDP), new MRI activity after switching to the new DMT, no evidence of disease activity (NEDA-3) defined as absence of relapses, new MRI lesions or disability progression, drug survival, and adverse events. The study baseline was defined as the date of initiation of the new DMT.

Relapse was defined as new or recurrent neurological symptoms lasting for more than 24 hours without fever or infection.<sup>20</sup> ARR was calculated by dividing the total number of relapses by the total number of person-years at risk.<sup>21</sup>

The Expanded Disability Status Scale (EDSS) obtained within 6 months before or 3 months after switching to the new DMT was chosen as baseline. Disability progression was defined as 3 or 6 months sustained EDSS increase by  $\geq 1$  point for a baseline EDSS between 2 and 5.5, or 0.5 points for an EDSS above 5.5, or 1.5 points for an EDSS between 0 and 1.5.<sup>22</sup>

Baseline MRI was defined as the MRI scan performed at least 3 months after initiating the new DMT. Enhancing lesions and new T2 lesions on MRIs were calculated as proportion of patients with positive scans among patients with valid baseline and follow-up MRIs.

Registered adverse events were severe infections requiring medications, persistent lymphopenia for  $>3$  months, increased liver enzymes  $\geq 3$  times upper limit of normal, bradycardia, autoimmune disorders, hypersensitivity reactions, PML, and malignancies. The date of discontinuation of the new DMT was recorded as the date of last administration. Drug survival was defined as persistence on the new DMT during the observational period. Alemtuzumab treatment discontinuation was defined as beginning of an alternative DMT within the first year or when the decision against administration of the second treatment course was made.<sup>23</sup>

### Data collection

Patient data were recorded during routine clinic visits at participating centers via the locally installed iMed or MDS software programs. Data were collected from the MENACTRIMS and local MS registries using a standardized data collection sheet.

### Standard protocol approvals

Ethical approval for the MENACTRIMS registry was granted by the American University of Beirut Ethics Committee. Approvals from local ethical committees in participating centers were also obtained.

### Statistical analyses

Patient data were coded and entered for analysis in SPSS V28. Sample characteristics were summarized using frequency, proportion for categorical variable, mean and standard deviation or median and interquartile range for numerical data.

Number of relapses were counted and normalized per year duration to produce ARR, followed by



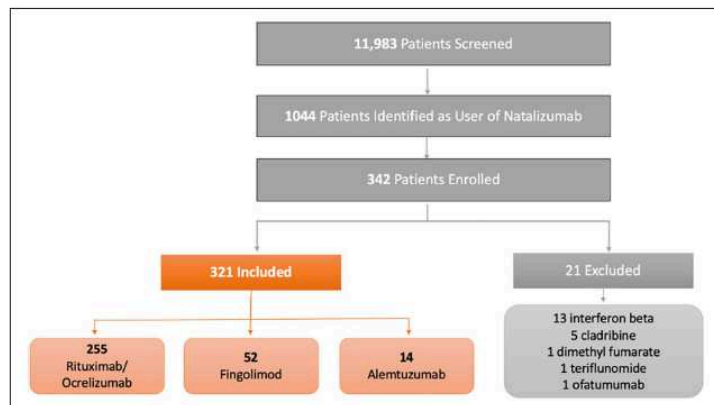


Figure 1. Flow chart of the included/excluded patients.

multivariable modeling using the Poisson distribution to produce relative risk (RR), 95% confidence intervals (CIs), and  $p$  value.

Kaplan–Meier survival analysis was utilized to look at time for first relapse after switching to the new DMT. Log rank test produced  $p$  value comparing the different DMT.

CDP at 3 and 6 months was computed. Crude and adjusted odds ratio (OR) were computed using univariate and multivariable regression models adjusting for other statistically significant covariates.

MRI activity outcomes, new T2 lesions, and gadolinium-enhancing lesions were also counted and compared between the different DMT using the Pearson chi-square, and subsequently followed by the multivariable logistic regression to compute OR, 95% CI adjusted for the following confounding variables: age, sex, disease duration, washout period, baseline EDSS, EDSS upon initiating NTZ, ARR in the year preceding NTZ treatment, and duration of follow-up on the new DMT. All analyses were carried out at the 0.05 significance level.

## Results

### Study population

In total, 342 patients switched from NTZ due to JCV Ab positivity. We excluded 15 patients switching to low-efficacy DMTs (13 to interferon beta and 2 to teriflunomide and dimethyl fumarate). Six patients

switching to cladribine and one to ofatumumab were also excluded due to small numbers. A total of 321 patients were included in the final analysis: 255 on RTX/OCR, 52 on fingolimod, and 14 on alemtuzumab (Figure 1).

Baseline characteristics of the study population are shown in Table 1. The mean duration of follow-up on the new DMT was 2.4, 4.3, and 4.0 years on RTX/OCR, fingolimod, and alemtuzumab, respectively.

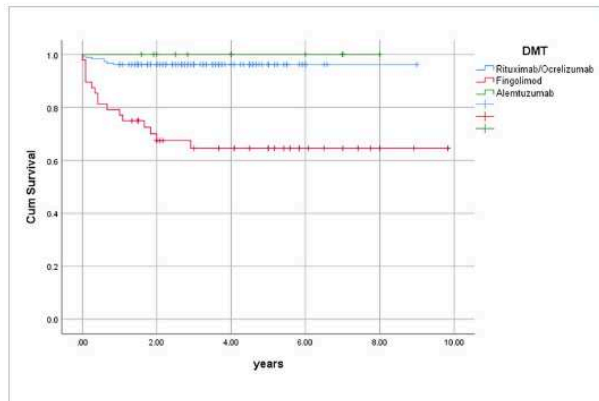
### Effectiveness

**Clinical relapses.** Switching to RTX/OCR was associated with a statistically significant reduction in ARR compared with fingolimod (0.028 vs. 0.193;  $p$  value < 0.001). No significant difference in ARR was found between patients shifting to RTX/OCR versus alemtuzumab (0.028 vs. 0.032;  $p$  value = 0.987). Similar results were obtained when adjusting for the following confounding variables: age, sex, disease duration, washout period, baseline EDSS, EDSS upon initiating NTZ, ARR in the year preceding NTZ treatment, and duration of follow-up on the new DMT. The time to first relapse was significantly shorter in patients switching to fingolimod as compared with RTX/OCR, with a mean time of  $6.7 \pm 0.6$  and  $8.7 \pm 0.1$  years ( $p$  value < 0.001), respectively (Figure 2). There was no significant difference in time to first relapse between patients switching to RTX/OCR versus alemtuzumab. Only one patient had a relapse on the latter. The results were similar after adjusting for the selected confounding variables.

**Table 1.** Baseline characteristics of the study population.

	Rituximab/ocrelizumab (n=255)	Fingolimod (n=52)	Alemtuzumab (n=14)
Sex	N (%)	N (%)	N (%)
Male	79 (31)	20 (38.5)	4 (28.5)
Female	176 (69)	32 (61.5)	10 (71.4)
Age (years)	Mean ± SD	Mean ± SD	Mean ± SD
	38.3 ± 8.5	40.1 ± 9.2	38.6 ± 6.1
Age of diagnosis (years)	26.4 ± 7.9	26.3 ± 7.4	25.6 ± 6.5
Age at initiation of NTZ (years)	32.1 ± 8.6	30.6 ± 8.8	30.8 ± 5.6
Total disease duration (years)	11.9 ± 5.5	13.8 ± 5.6	12.9 ± 5.4
Number of relapses in the year prior starting NTZ	1.5 ± 0.8	1.3 ± 0.6	1.4 ± 0.6
	Median (IQR)	Median (IQR)	Median (IQR)
Washout period (weeks)	4.0 (2–6)	6.0 (4–11)	4.5 (4–9)
EDSS upon initiating NTZ	2.0 (1–4)	2.0 (1–3)	2.0 (1–5.6)
EDSS upon initiating the new DMT	2.0 (1–4)	2.0 (1–4.4)	2.3 (1–6)
Duration of follow-up on DMT (years)	2.4 (1.5–4)	4.3 (2–6.4)	4 (2.4–7)

SD: standard deviation; IQR: interquartile range; NTZ: natalizumab; EDSS: Expanded Disability Status Score; DMT: disease-modifying therapy.



**Figure 2.** Time to first relapse on the new disease-modifying therapy.

*P* value from KM: Log Rank *p* value < 0.001.  
 Alemtuzumab versus rituximab/ocrelizumab *p* value = 0.476.  
 Fingolimod versus rituximab/ocrelizumab *p* value < 0.001.  
 Fingolimod versus alemtuzumab *p* value = 0.019.

	Mean time to first relapse (years)	Standard deviation
Rituximab/ocrelizumab	8.7	0.1
Fingolimod	6.7	0.6
Alemtuzumab <sup>a</sup>	–	–

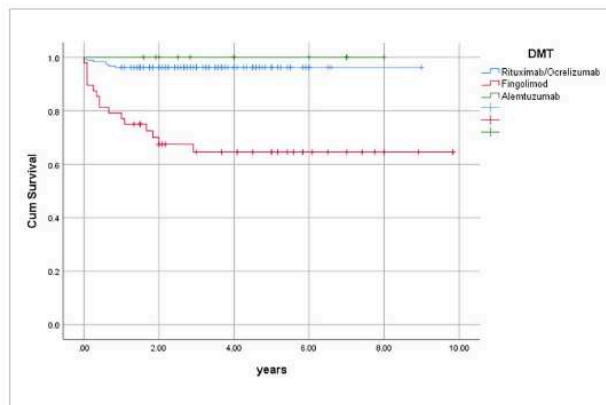
<sup>a</sup>Only one patient had a relapse on alemtuzumab.



**Table 1.** Baseline characteristics of the study population.

	Rituximab/ocrelizumab (n=255)	Fingolimod (n=52)	Alemtuzumab (n=14)
Sex	N (%)	N (%)	N (%)
Male	79 (31)	20 (38.5)	4 (28.5)
Female	176 (69)	32 (61.5)	10 (71.4)
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	38.3 ± 8.5	40.1 ± 9.2	38.6 ± 6.1
Age of diagnosis (years)	26.4 ± 7.9	26.3 ± 7.4	25.6 ± 6.5
Age at initiation of NTZ (years)	32.1 ± 8.6	30.6 ± 8.8	30.8 ± 5.6
Total disease duration (years)	11.9 ± 5.5	13.8 ± 5.6	12.9 ± 5.4
Number of relapses in the year prior starting NTZ	1.5 ± 0.8	1.3 ± 0.6	1.4 ± 0.6
	Median (IQR)	Median (IQR)	Median (IQR)
Washout period (weeks)	4.0 (2–6)	6.0 (4–11)	4.5 (4–9)
EDSS upon initiating NTZ	2.0 (1–4)	2.0 (1–3)	2.0 (1–5.6)
EDSS upon initiating the new DMT	2.0 (1–4)	2.0 (1–4.4)	2.3 (1–6)
Duration of follow-up on DMT (years)	2.4 (1.5–4)	4.3 (2–6.4)	4 (2.4–7)

SD: standard deviation; IQR: interquartile range; NTZ: natalizumab; EDSS: Expanded Disability Status Score; DMT: disease-modifying therapy.



**Figure 2.** Time to first relapse on the new disease-modifying therapy.

*P* value from KM: Log Rank *p* value < 0.001.  
 Alemtuzumab versus rituximab/ocrelizumab *p* value = 0.476.  
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 Fingolimod versus alemtuzumab *p* value = 0.019.

	Mean time to first relapse (years)	Standard deviation
Rituximab/ocrelizumab	8.7	0.1
Fingolimod	6.7	0.6
Alemtuzumab <sup>a</sup>	–	–

<sup>a</sup>Only one patient had a relapse on alemtuzumab.

**Table 2.** Confirmed 3- and 6-month disability progression on the new DMT.

Odds ratio of 3-month and 6-month CDP by DMT type						
3-month CDP	Unadjusted			Adjusted <sup>a</sup>		
	OR	95% CI	<i>p</i> value	OR	95% CI	<i>p</i> value
Rituximab/ocrelizumab	1.00 ( <i>ref</i> )					
Fingolimod	3.29	1.27–8.51	0.014	3.28	1.06–10.09	0.039
<b>6-month CDP</b>						
Rituximab/ocrelizumab	1.00 ( <i>ref</i> )					
Fingolimod	2.29	1.03–5.06	0.041	2.89	1.06–7.87	0.038

CDP: confirmed disability progression; OR: odds ratio; CI: confidence interval; DMT: disease-modifying therapy; EDSS: Expanded Disability Status Score; ARR: annualized relapse rate; NTZ: natalizumab.  
 Alemtuzumab was removed from the analysis because the number of patients was too low.  
<sup>a</sup>Adjusted for age, sex, disease duration, washout period, EDSS baseline, EDSS upon initiating NTZ, ARR before NTZ treatment.

**Disability progression.** Compared with RTX/OCR, switching to fingolimod was associated with a significant increase in risk of 3- and 6-month CDP, even after adjusting for confounding variables (adjusted OR = 3.28; 95% CI = 1.06–10.09% and 2.89; 95% CI = 1.06–7.87, respectively). Patients switching to alemtuzumab were not included in the disability progression analysis due to the small sample size (Table 2).

**MRI activity.** Due to the small number of patients with valid MRI scans in the alemtuzumab group ( $n=3$ ), alemtuzumab was not included in the MRI analysis. A higher proportion of new T2 lesions were detected in patients shifting to fingolimod compared with RTX/OCR (66.6% vs. 24.0%;  $p$  value < 0.001) (Table 3). Similar results were obtained for Gd+ lesions with a higher proportion of patients with Gd+ lesions on fingolimod compared with RTX/OCR (62.9% vs. 13.0%,  $p$  value < 0.001). Figure 3 shows that after adjusting for confounding variables, the proportion of patients with new T2 or Gd+ lesions was still lower on RTX/OCR compared with fingolimod (OR = 0.58; 95% CI = 0.35%–0.80% and 0.54; 95% CI = 0.33–0.76, respectively).

The alemtuzumab group was not included in the NEDA-3 analysis due to the small number of patients with MRI. A higher proportion of patients on RTX/OCR achieved NEDA-3 compared with fingolimod: 74.9% (191/255) versus 40.4% (21/52);  $p$  value < 0.001.

#### Safety

Patients on alemtuzumab experienced the highest frequency of adverse events (4/14 patients with

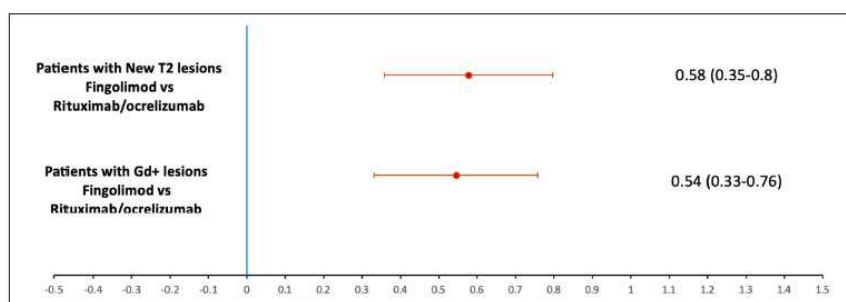
autoimmune thyroiditis) compared with fingolimod and RTX/OCR (28.6%, 21.2%, and 8.6%, respectively). Lymphopenia, increased liver enzymes, and bradycardia were more commonly seen in patients on fingolimod. There was one case of PML (considered a carry-over from NTZ) and one case of breast cancer on RTX and OCR, respectively (Table 4).

#### Drug survival

A total of 31/52 patients (59.6%) on fingolimod discontinued treatment compared with 8/255 (3.1%) on RTX/OCR. The mean drug survival was 8.5 years on RTX/OCR compared with 5.6 years on fingolimod ( $p$  value < 0.001) (Figure 4). The reasons for discontinuation of fingolimod were treatment failure (20/31 (64.5%)), adverse events (7/31 (22.6%)), and pregnancy (4/31 (12.9%)), and for RTX/OCR, patient preference (3/8 (37.5%)), treatment failure (2/8 (25%)), adverse events (2/8 (25%)), and pregnancy (1/8 (12.5%)). None of the patients on alemtuzumab fulfilled the criteria for treatment discontinuation, but three patients received a third cycle due to breakthrough disease.

#### Discussion

In this observational retrospective cohort study, we compared the effectiveness, safety, and drug survival of RTX/OCR, fingolimod, and alemtuzumab after switching from NTZ due to JCV Ab positivity. Compared with fingolimod, RTX/OCR and alemtuzumab were associated with significant reduction in ARR and time to first relapse and had a longer drug survival. Patients switching to RTX/OCR had less



**Figure 3.** Forest plot for MRI activity after adjusting for confounding factors<sup>a</sup>. MRI: magnetic resonance imaging; Gd+: gadolinium-enhancing lesions; EDSS: Expanded Disability Status Scale; NTZ: natalizumab; DMT: disease-modifying therapy. Alemtuzumab was removed from the multivariate regression analysis due to the low number of patients with valid scans. <sup>a</sup>Adjusted for sex, age, washout period, baseline EDSS, and EDSS scores at initiation of NTZ, number of relapses in year prior to NTZ, disease duration, and DMT duration.NEDA-3.

**Table 3.** MRI outcomes on the new DMT.

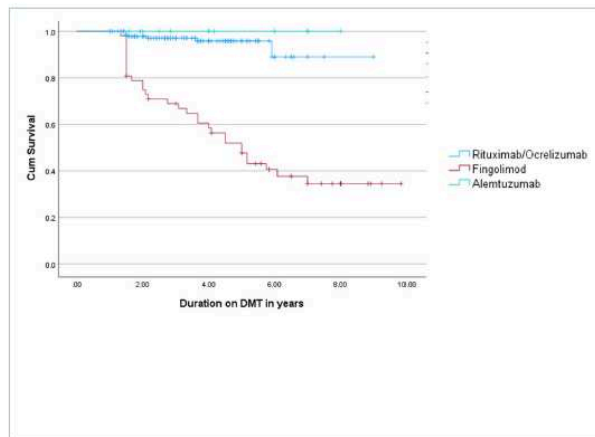
	Rituximab/ocrelizumab (n=100)		Fingolimod (n=27)		p value
	N	%	N	%	
<b>Number of patients with new T2 lesions</b>	24	24.0	18	66.6	<0.001
<b>Number of new T2 lesions</b>					
0	76	76.0	9	33.3	<0.001
1	22	22.0	5	18.5	
2	2	2.0	5	18.5	
3	0	0.0	6	22.2	
4+	0	0.0	2	7.4	
<b>Number of patients with Gd+ lesions</b>	13	13.0	17	62.9	<0.001
<b>Number of Gd+ lesions</b>					
0	87	87.0	10	37.0	<0.001
1	12	12.0	6	22.2	
2	1	1.0	6	22.2	
3	0	0.0	5	18.5	

DMT: disease-modifying therapy; Gd+: gadolinium enhancing. Alemtuzumab was removed from the analysis because the number of MRI scans in this group was too low.

disability progression, fewer new T2 and Gd+ lesions, and higher rates of NEDA-3 compared with fingolimod. The results were similar after adjusting for the selected confounding variables. Due to the low number of patients switching to alemtuzumab, the latter was not included in the disability progression, NEDA-3, and MRI activity analyses. The safety profile also favored RTX/OCR versus both fingolimod and alemtuzumab with higher rate of infections, liver toxicity, and lymphopenia on fingolimod and autoimmune thyroiditis on alemtuzumab. It is of note,

however, that there was one case of PML and one case of breast cancer on RTX and OCR, respectively. The better drug survival of RTX/OCR and alemtuzumab compared with fingolimod was mainly due to a higher rate of treatment failure on fingolimod.

To our knowledge, this is the first study comparing the effectiveness, safety, and drug survival of RTX/OCR, alemtuzumab, and fingolimod after switching from NTZ. It is of note that to date, no randomized controlled trial comparing the efficacy and safety of



**Figure 4.** DMT survival.  
 KM Log-rank  $p$  value < 0.001.  
 Alemtuzumab versus rituximab/ocrelizumab  $p$  value = 0.458.  
 Fingolimod versus rituximab/ocrelizumab  $p$  value < 0.001.  
 Fingolimod versus alemtuzumab  $p$  value = 0.004.

**Table 4.** Adverse events.

Adverse events	Rituximab/ocrelizumab ( $n=255$ )		Fingolimod ( $n=52$ )		Alemtuzumab ( $n=14$ )	
	$N$	%	$N$	%	$N$	%
Yes	22	8.6	11	21.2	4	28.6
Infections	9	3.5	5	9.6	0	0.0
Hypersensitivity reactions	7	2.7	0	0.0	0	0.0
Asymptomatic bradycardia	0	0.0	1	1.9	0	0.0
Persistent lymphopenia	0	0.0	3	5.8	0	0.0
Increase in liver enzymes $\geq 3 \times$ ULN	1	0.4	2	3.8	0	0.0
Autoimmune thyroiditis	0	0.0	0	0.0	4	28.6
PML	1	0.4	0	0.0	0	0.0
Breast cancer	1	0.4	0	0.0	0	0.0

UTI: urinary tract infection; ULN: upper limit of normal; PML: progressive multifocal leukoencephalopathy; DMT: disease-modifying therapy.

switching from NTZ to high-efficacy DMTs due to JCV Ab positivity has been performed.

In a Swedish multicenter study of 256 patients switching from NTZ to RTX or fingolimod due to JCV Ab positivity, RTX was associated with significantly lower relapse rates (1.8% vs. 17.6%), Gd+ lesions (1.4% vs. 24.2%), and treatment discontinuation rates (1.8% vs. 28.2%) during 1.5 years of follow-up.<sup>24</sup> Our study showed similar results when comparing RTX/OCR

with fingolimod over a longer follow-up period (2.4–4.3 years).<sup>25</sup> Similar outcomes were reported in a large retrospective observational MSBase registry study<sup>25</sup> comparing the effectiveness and treatment discontinuation rates in patients switching from NTZ to dimethyl fumarate, fingolimod, or OCR. Patients on fingolimod had higher ARRs (OR=4.33; 95% CI = 3.12–6.01), increased risk of disability progression (49%), and higher treatment discontinuation rates (OR=2.57; 95% CI = 1.74–3.80) compared with OCR.



In a retrospective French study,<sup>26</sup> 48 patients on OCR were compared with 54 on fingolimod after NTZ cessation. Patients on OCR had a significantly lower ARR after 1 year (0.12 vs. 0.41,  $p=0.026$ ), similar to our findings.

In a retrospective multicenter German study,<sup>27</sup> 101 patients receiving fingolimod were compared with 42 patients receiving alemtuzumab after NTZ cessation. Similar to our study, patients on fingolimod had higher relapse rate (OR=2.24; 95% CI = 1.12–4.50), disability progression (OR = 4.84; 95% CI = 1.74–13.47), and MRI progression (OR=2.41; 95% CI = 1.26–4.60). Unlike our study, adverse events were much more common in patients receiving fingolimod compared with patients receiving alemtuzumab (OR=7.78; 95% CI = 1.04–57.95). Patients, however, were only followed for 1 year, knowing that the most common adverse events of alemtuzumab, namely, autoimmune disorders, peak in the third year of treatment.

In a recent study, Santiago-Setien et al. assessed clinical outcomes in 30 patients maintained on NTZ extended interval dosing or shifted to OCR. There were no significant differences in ARR, radiological activity, or disability progression between the two groups.<sup>28</sup>

Our study has several limitations. The retrospective observational design could have introduced a selection bias. However, adjusting for multiple confounding variables did not alter the outcomes. Combining both B-cell-depleting therapies (OCR and RTX) into a single group might have obscured any differential effects between them, but most studies have shown similar effectiveness and safety profiles for both DMTs. For instance, a retrospective multicenter Italian study found that OCR and RTX had similar reductions in ARR and MRI activity in patients switching from NTZ.<sup>29</sup> In addition, we could not determine the JCV Ab index due to inconsistent reporting in the registries. We also lacked detailed information on the dosage and interval dosing of NTZ and the B-cell-depleting therapies. Some patients on RTX received doses ranging from 500 to 1000 mg at intervals of 6 to 12 months, a common practice in the MENA region. However, previous studies have indicated that such variations in dosing or treatment interval did not affect the effectiveness of RTX.<sup>30–32</sup>

The strengths of this study include the large number of patients and long follow-up duration compared with most previous studies. It is also, to our knowledge, the first study to compare RTX/OCR, fingolimod, and alemtuzumab as potential exit strategies in patients on NTZ and JCV Ab positivity.

## Conclusion

Our study showed that in patients switching from NTZ due to JCV Ab positivity, RTX/OCR showed higher effectiveness and better safety profile compared with fingolimod. Compared with alemtuzumab, RTX/OCR had similar effectiveness but better safety profile.

## Declaration of Conflicting Interests


The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: M.Z. has received honoraria for lectures from Biologix, Biogen, Janssen, Hikma Pharmaceuticals, Novartis, Merck, Roche, and Sanofi-Genzyme. She received travel grants from Novartis, Merck, and Roche and a research grant from Biogen. She received two research grants from Biogen, one research grant from Merck, and two research grants from MENACTRIMS. She has no conflict of interest related to this study. B.Y. has received speaker honoraria from Bayer, Biogen, Merck, Novartis, Roche, and Sanofi; research grants from Bayer, Biogen, Merck, Novartis, and Pfizer; and advisory board honoraria from Bayer, Biogen, Merck, Novartis, Roche, and Sanofi. He has no conflict of interest related to this study. A.A.-A. has received honoraria from Novartis, Sanofi, Biologix, Merck, Roche, Biogen, and Bayer. He serves on the scientific advisory boards of Novartis, Merck, and Roche. He has no conflict of interest related to this study. R.G. has received research grant from Roche and advisory board honoraria from Biogen, Hikma, Merck, Roche, and Sanofi. He has no conflict of interest related to this study. S.M. received a MENACTRIMS clinical research grant (2020) but has no conflict of interest related to this study. R.A.-R., S.F.A., S.K., N.E.-A., A.A.-M., J.A.-K., A.C., J.I., N.S., J.M., F.M.R.H.M., A.A.-H., P.S., H.D., and F.B. declare that there is no conflict of interest.

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## Appendix 10. Acceptance of the 5th Study as an Oral presentation in ECTRIMS 2024

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to me ▾

Dear Dr. Maya Zeineddine

Thank you very much for submitting the following abstract to **ECTRIMS 2024 - 40th Congress of ECTRIMS | Copenhagen, Denmark**.

On behalf of the Scientific Committee, we are pleased to inform you that the following abstract has been accepted for **Oral presentation**

Abstract Number	1296
Abstract Title	The Comparative Effectiveness of Natalizumab and Anti-CD20 Monoclonal Antibodies in Relapsing-Remitting Multiple Sclerosis: A Real-World based Study

Your presentation is scheduled for the following session

Session Title	Free Communications 6: Treatment 2
Session Date	19/09/2024
Presenting Time	15:30 - 15:40

We kindly ask you to check that the abstract title has been written correctly and advise us latest by **Tuesday, 26 June 2024** should there be any discrepancies.

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Please note that the programme is subject to change. We recommend visiting the congress website regularly for any updates or changes to the scientific programme. Click [HERE](#) to access.

#### Format

You will have a maximum of **7 minutes** for your oral presentation, followed by 3 min for Q&A right after your presentation. Your strict adherence to the time limit mentioned above is requested.

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A pre-upload of your presentation will be available via an online system and detailed information on this will be sent a few weeks before the congress.

#### Confirmation of your attendance

The presenting author has to confirm his/her attendance by registering to ECTRIMS 2024 by **Tuesday, 26 June 2024, 23:59 CEST at the latest to ensure publication** of the abstract in the programme and abstract book.

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We look forward to welcoming you to **ECTRIMS 2024 - 40th Congress of ECTRIMS | Copenhagen, Denmark** in September.

Best regards  
The ECTRIMS 2024 Abstract Team

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## **Sécurité et Efficacité à Long Terme des Thérapies Modificatrices de la Maladie à Haute Efficacité chez les Patients Atteints de Sclérose en Plaques**

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La sclérose en plaques (SEP) est une maladie inflammatoire chronique du système nerveux central, entraînant une invalidité significative chez les personnes atteintes. Le paysage thérapeutique de la SEP a évolué au cours des dernières décennies, avec l'introduction de diverses thérapies modificatrices de la maladie (TMM) à haute efficacité. Cette thèse examine la sécurité et l'efficacité à long terme de ces thérapies, en particulier dans le contexte de la région du Moyen-Orient et de l'Afrique du Nord (MENA). La recherche comprend une analyse approfondie de l'accessibilité aux traitements, des obstacles à la thérapie, et des résultats cliniques des patients atteints de SEP dans cette région. Elle inclut cinq études explorant la disponibilité et l'accessibilité des TMM, l'impact de la pandémie de COVID-19 sur la gestion de la SEP, et la comparaison du natalizumab avec les anticorps monoclonaux anti-CD20. Les résultats soulignent des disparités significatives dans l'accès aux traitements et la nécessité de stratégies régionales ciblées pour améliorer la prise en charge de la SEP. De plus, la recherche contribue à la compréhension mondiale de la SEP en fournissant des informations sur les résultats à long terme des TMM à haute efficacité dans un contexte réel.

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Mots-clés : sclérose en plaques, thérapies modificatrices de la maladie, Moyen-Orient et de l'Afrique du Nord, la sécurité à long terme, l'efficacité à long terme

## **Long-term Safety and Efficacy of High Efficacy Disease-Modifying Therapies in Multiple Sclerosis Patients**

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Multiple Sclerosis (MS) is a chronic inflammatory disease of the central nervous system, leading to significant disability among affected individuals. The treatment landscape for MS has evolved over the past decades, with the introduction of various high-efficacy disease modifying therapies (DMTs). This thesis investigates the long-term safety and efficacy of these therapies, particularly in the context of the Middle East and North Africa (MENA) region. The research involves a comprehensive analysis of treatment accessibility, barriers to therapy, and the clinical outcomes of MS patients in this region. It includes five studies that explore the availability and accessibility of DMTs, the impact of the COVID-19 pandemic on MS management, and the comparison of natalizumab with anti-CD20 monoclonal antibodies. The findings underscore significant disparities in treatment access and the need for targeted regional strategies to improve MS management. Furthermore, the research contributes to the global understanding of MS by providing insights into the long-term outcomes of high-efficacy DMTs in a real-world setting.

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Keywords: multiple sclerosis, disease-modifying therapies, middle east and north africa, longterm safety, long-term efficacy

