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# Morbimortality in giant cell arteritis and the impact of therapeutics

Sabine Jardel Mainbourg

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**Morbi-mortalité de l'artérite à cellules géantes et impact des thérapeutiques**

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## Résumés

### **Morbimortalité de l'artérite à cellules géantes et impact des thérapeutiques**

L'artérite à cellules géantes (ACG) est une inflammation des parois des gros et moyens vaisseaux, particulièrement ceux à destination céphalique. Cette pathologie concerne les adultes de plus de 50 ans, avec une incidence estimée entre 1 and 30/10<sup>5</sup> et se manifeste classiquement par des céphalées, une altération de l'état général et un syndrome inflammatoire biologique. Des complications sévères peuvent survenir, comme cécité, accident vasculaire cérébral, ou accident ischémique distal. La corticothérapie est la pierre angulaire du traitement, mais entraîne de nombreuses complications lors d'une prise prolongée (diabète, ostéoporose, infection, ...). Les essais randomisés réalisés avec des traitements d'épargne cortisoniques (immunosuppresseurs) ont pour l'instant démontré l'efficacité d'un anti-IL6, le tocilizumab, et du methotrexate. L'objectif de ce travail était (i) de faire l'état des lieux de la morbi-mortalité de la pathologie, à partir des données publiées, et des données de mortalité disponibles via EUROSTAT ; (ii) d'évaluer l'intérêt relatif en terme d'efficacité et de tolérance des molécules à visée d'épargne cortisonique actuellement disponibles.

Dans un premier temps, une revue de la littérature de l'ACG a été réalisée : épidémiologie, diagnostic, et prise en charge thérapeutique.

Dans un deuxième temps, la prévalence des rechutes a été estimée par des techniques méta-analytiques, en utilisant un modèle à effet aléatoire. La recherche a été conduite sur Medline jusqu'à décembre 2017 et 34 études ont été incluses totalisant 2 505 patients. La prévalence globale était estimée à 47,2% (intervalle de confiance (IC) à 95% 40,0 – 54,3), avec une forte hétérogénéité ( $I^2=93\%$ ). La prévalence des rechutes était significativement plus haute dans les essais randomisés par rapport aux études observationnelles (65,8% versus 41,7%,  $p<0.0001$ ). La prévalence des rechutes était également associée à l'année de publication (34 études, augmentation de 8.3% par décennie;  $p<0.0001$ ) et à la durée de la corticothérapie (17 études, diminution de 1.7% pour chaque mois supplémentaire;  $p<0.001$ ), la durée de la corticothérapie étant plus courte dans les essais randomisés (12,8 mois) comparés aux études observationnelles (28,8 mois). De la même façon, la prévalence et l'incidence des rechutes sévères a été estimée par une méta-analyse avec des modèles à effets aléatoires. La recherche a été conduite sur MedLine jusqu'à mars 2020, et 26 études ont été incluses, totalisant 2 754 patients. La prévalence des rechutes majeures était estimée à 3,3% (IC 95% 1,7 – 5,6;  $I^2=86\%$ ) et l'incidence à 14,5/100 patient-année (IC 95% 5,2 – 27,2;  $I^2=90\%$ ). Les manifestations cliniques étaient les claudications de la mâchoire (44,3%), les atteintes

ophtalmologiques (32,7%), l'ischémie des membres inférieurs (12,5%), les atteintes aortiques (7,7%), et les atteintes neurologiques (4,8%). Lors de la méta-régression, la durée de suivi était inversement corrélée à l'incidence des rechutes majeures (Beta = -0.015, IC 95% -0,026 – -0,0042; p=0,0063). L'incidence des rechutes majeures était significativement plus forte dans les études prospectives (55,2/100 patient-année, IC 95% 15,3 – 114,3) que dans les études rétrospectives (4,1/100 patient-année, IC 95% 1,1 – 8,4 ;  $p_{interaction}=0,0002$ ).

Dans un troisième temps, une analyse a été conduite sur les données de mortalité liée à l'ACG en Europe (Eurostat). Les données de mortalité concernant l'ACG ont été extraites entre 1994 et 2016 à l'aide des codes International Classification of Disease (ICD)-10 M31.5 (artérite à cellules géantes et pseudopolyarthrite rhizomélique) et M31.6 (autre artérite à cellules géantes) et ICD-9 446.5 (artérite à cellules géantes). La cause sous-jacente de décès a été utilisée (UCD : underlying cause of death), correspondant à la maladie qui a déclenché la série d'événements morbides conduisant directement au décès. Les données ont été extraites pour 31 pays européens : les 27 membres de l'Union Européenne (Autriche, Belgique, Bulgarie, Croatie, Chypre, République Tchèque, Danemark, Estonie, Allemagne, Grèce, Espagne, Finlande, France, Hongrie, Irlande, Italie, Lituanie, Luxembourg, Lettonie, Malte, Pays-Bas, Pologne, Portugal, Roumanie, Suède, Slovénie, Slovaquie), 3 pays membres de l'association européenne de libre-échange (Norvège, Suisse et Islande), et le Royaume-Uni. Les populations ont été agrégées par tranche de 5 ans, entre 50 ans et plus de 85 ans. Les taux bruts et les taux de mortalité normalisés selon l'âge (ASMR) ont été calculés. Entre 1994 et 2016, 5650 décès ont été rapportés à l'ACG. L'ASMR européen variait de 0,436/100 000 population (IC 95% 0,384 – 0,494) en 1994 à 0,146/100 000 population (IC 95% 0,130 – 0,163) en 2016 et diminuait significativement au cours du temps (-0,017 par an,  $p<0,001$ ). Il existait une grande hétérogénéité entre les pays, liée au moins en partie à des différences de codage des certificats de décès.

Enfin, les différents traitements proposés dans l'ACG ont été comparés au sein d'une méta-analyse en réseau. Cette dernière incluait les essais randomisés contrôlés dans l'ACG. La recherche a été effectuée sur MedLine et la base de données internationale ClinicalTrial.gov jusqu'à janvier 2020. Le critère de jugement principal était le taux de rechute. Huit essais ont été inclus, totalisant 572 patients. Tous les essais comparaient un traitement d'épargne cortisonique avec une corticothérapie. La certitude de la preuve a été établie en utilisant la méthode GRADE. Le niveau de preuve était faible ou très faible pour les comparaisons d'intérêt. Le risque de rechute était significativement plus faible avec le tocilizumab comparé au méthotrexate (RR=0,41; IC 95% 0,17 – 0,97), à la corticothérapie prolongée (RR=0,41, IC 95% 0,20 – 0,83), et à la corticothérapie courte (RR=0,32; IC 95% 0,16 – 0,66). Les fréquences d'effets indésirables sévères et d'infections sévères étaient comparables entre les différents traitements. Ces résultats suggèrent que parmi les traitements

d'épargne cortisonique, le tocilizumab est actuellement la meilleure option thérapeutique pour prévenir la rechute de l'ACG avec un faible degré de certitude.

L'ensemble des travaux réalisés ici propose un modèle de connaissance de l'ACG, qui permettra de construire un modèle computationnel, lui-même étant le point de départ de la construction d'une population virtuelle réaliste.

**Mots clefs :** artérite à cellules géantes, méta-analyse, mortalité, rechute, rechute sévère, traitement d'épargne cortisonique, méthotrexate, tocilizumab



# Abstract

## **Morbimortality in giant cell arteritis and the impact of therapeutics**

Giant cell arteritis (GCA) is a type of inflammation affecting the walls of the large and medium vessels, in particular those that supply blood to the head. This condition affects adults over the age of 50, with an incidence estimated between 1 and 30/10<sup>5</sup>. Headaches, weight loss or anorexia, fatigue, fever and biological inflammatory syndrome are the usual manifestations. Severe complications can occur such as blindness, strokes, or distal ischemic strokes. Glucocorticoids therapy constitutes the cornerstone of treatment, but can lead to many complications in case of prolonged usage (diabetes, osteoporosis, infection, etc.). Randomized trials assessing steroid-sparing therapies (immunosuppressive therapies) have demonstrated the efficacy of tocilizumab, an anti-IL6, and methotrexate. The aim of this work was (i) to make an assessment of the individual risk of morbidity related to GCA drawing on published data, described evolution of mortality via EUROSTAT registry and (ii) to evaluate the relative interest in terms of efficacy and tolerance of the steroid-sparing molecules currently available.

Firstly, a review of the literature regarding CGA was performed concerning its epidemiology, diagnosis, and therapeutic management.

Secondly, the prevalence of relapses was estimated using meta-analytic techniques with a random-effects model. Research was performed on Medline until December 2017 and 34 studies were included with a total of 2,505 patients. Global prevalence was estimated to be 47.2% (95% confidence interval [CI] 40.0 – 54.3), with strong heterogeneity ( $I^2=93\%$ ). The prevalence of relapses was significantly higher in the randomized trials compared to the observational studies (65.8% versus 41.7%,  $p<0.0001$ ). The prevalence of relapses was also associated with the year of publication (34 studies, with an increase of 8.3% per decade;  $p<0.0001$ ) and the duration of glucocorticoids therapy (17 studies, with a decrease of 1.7% per each additional month;  $p<0.001$ ), the duration of glucocorticoids therapy being shorter in randomized trials (12.8 months) compared to observational studies (28.8 months). Similarly, the prevalence and the incidence of severe relapses were estimated using a meta-analysis with random-effects models. Research was performed on Medline until March 2020, and 26 studies were included with a total of 2,754 patients. The prevalence of major relapses was estimated to be 3.3% (95% CI 1.7 – 5.6;  $I^2=86\%$ ) and the incidence as 14.5/100 patient-year (95% CI 5.2 – 27.2;  $I^2=90\%$ ). Clinical manifestations included jaw claudication (44.3%), ophtalmological involvement (32.7%), lower limb ischemia (12.5%), aortic involvement (7.7%) and neurological involvement (4.8%). The meta-regression analysis showed that the follow-up duration was inversely

correlated with the incidence of major relapses (Beta = -0.015, 95% CI -0.026 – -0.0042; p=0.0063). The incidence of major relapse was significantly higher in the prospective studies (55.2/100 patient-year, 95% CI 15.3 – 114.3) than in the retrospective studies (4.1/100 patient-year, 95% CI 1.1 – 8.4;  $p_{\text{interaction}}=0.0002$ ).

Thirdly, an analysis was carried out regarding the mortality data related to CGA in Europe (Eurostat registry). Mortality data on CGA were extracted between 1994 and 2016 using the codes of the International Classification of Disease: (ICD)-10 M31.5 (giant cell arteritis with polymyalgia rheumatica) and M31.6 (other giant cell arteritis), and ICD-9 446.5 (giant cell arteritis). The underlying cause of death was used, corresponding to the disease that triggered the series of morbid events leading to direct death. Data were extracted for 31 European countries: the 27 European Union members (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Germany, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Luxemburg, Latvia, Malta, The Netherlands, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia), 3 European Free Trade Association members (Norway, Switzerland and Iceland) and the United Kingdom. Populations were incorporated by 5-year category, between 50 and over 85 years old. Crude rates and age-standardized mortality rates (ASMR) were calculated. Between 1994 and 2016, 5,650 deaths were reported to be CGA-related. The European ASMR varied from 0.436/100,000 population (95% CI 0.384 – 0.494) in 1994 to 0.146/100,000 population (95% CI 0.130 – 0.163) in 2016 and significantly decreased over time (-0.017 per year,  $p<0.001$ ). There was considerable heterogeneity between countries, linked at least in part to differences in the coding of death certificates.

Fourthly, the different treatments proposed to treat CGA were compared using a network meta-analysis. The latter included randomized controlled trials assessing CGA. Research was carried out on Medline and the international database ClinicalTrial.gov until January 2020. The main endpoint was the relapse rate. Eight trials were included, with a total of 572 patients. All the trials compared a steroid-sparing therapy to a glucocorticoid therapy. The certainty of the evidence was established using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) method. The level of evidence was low or very low for the comparisons of interest. The risk of relapse was significantly weaker with tocilizumab compared to methotrexate (RR=0.41; 95% CI 0.17 – 0.97), to prolonged corticotherapy (RR=0.41, 95% CI 0.20 – 0.83), and to short corticotherapy (RR=0.32; 95% CI 0.16 – 0.66). The frequency of severe adverse effects and severe infections were comparable between the different treatments. These results suggest that among the steroid-sparing therapies, tocilizumab is currently the best therapeutic option to prevent CGA relapse with low-certainty evidence.

All the work performed here has built a CGA knowledge model, which will allow a computational model to be built, being itself the starting point of the construction of a realistic virtual population.

**Key words:** giant cell arteritis, meta-analysis, mortality, relapse, severe relapse, glucocorticoid sparing agent, methotrexate, tocilizumab

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## Publications et travaux liés à la thèse

### Publications en premier ou dernier auteur

- **Mainbourg S**, Addario A, Samson M, Puéchal X, François M, Durupt S, Gueyffier F, Cucherat M, Durieu I, Reynaud Q, Lega JC. Prevalence of Giant Cell Arteritis Relapse in Patients Treated With Glucocorticoids: A Meta-Analysis. *Arthritis Care Res (Hoboken)*. 2020 Jun;72(6):838-849. doi: 10.1002/acr.23901. Epub 2020 May 19. PMID: 30951256.
- Aussedat M, Lobbes H, Samson M, Euvrard R, Lega JC, **Mainbourg S**. Epidemiology of major relapse in giant cell arteritis: A study-level meta-analysis. *Autoimmun Rev*. 2021 Sep 2:102930. doi: 10.1016/j.autrev.2021.102930. Epub ahead of print. PMID: 34481940.
- **Mainbourg S**, Tabary A, Cucherat M, Gueyffier F, Lobbes H, Aussedat M, Grenet G, Durieu I, Samson M, Lega JC. Indirect comparison of glucocorticoid sparing agents for the remission maintenance in giant cell arteritis: a network meta-analysis. (*Soumis à Mayo Clinic Proceedings le 2 septembre 2021*)

### Communications orales

- S Mainbourg, A Addario, I Durieu, JC Lega. Corticosteroid exposure in trials testing immunosuppressive drugs for giant cell arteritis: the effect of undertreatment. CO-063. Annual Meeting of French Society of Pharmacology and Therapeutics, and INSERM Clinical Research Centers (CIC) Meeting (Lyon, France 2019)
- S. Jardel, A. Addario, M. Samson, M. François, S. Durupt, F. Gueyffier, M. Cucherat, I. Durieu, Q. Reynaud, J.-C. Lega. Prévalence des rechutes dans l'artérite à cellules géantes : une méta-analyse - 76ème congrès de médecine interne (Paris, 2017)

### Communications affichées

- "Prevalence of Relapses of Giant Cell Arteritis in Patients Treated with Corticosteroids: A Meta-Analysis". 2017 ACR/ARHP Annual Meeting (San Diego, CA, USA 2017)

### Projets en cours

- Mainbourg S, Lega JC. Mortality trends in giant cell arteritis in European countries: Eurostat data analysis from 1994 to 2016
- Rubinsztajn A, Mainbourg S. Characteristics of patients presenting major relapse of giant cell arteritis: a French case-control study

## Abréviations

ACG : Artérite à cellules géantes

AVC : Accident vasculaire cérébral

BAT : biopsie de l'artère temporale

CRP : *C-reactive protein*

DC : *Dendritic cell*

HLA : Human leukocyte antigen

HR : hazard ratio

IC : intervalle de confiance

IL-x : Interleukine-x

IL-6R : Récepteur de l'interleukine 6

LT : Lymphocyte T

LV-GCA : Large vessel giant cell arteritis

PET-scanner : Tomographie par émission de positons

PDGF : *platelet-derived growth factor*

PPR : Pseudo polyarthrite rhizomélique

PVR : population virtuelle réaliste

RR : risque relative

SMOR : standardized mortality rate odd ratio

SMR : standardized mortality rate

TDM : tomodensitométrie

TNF : *Tumor necrosis factor*

Treg : T régulateur

VEGF : *Vascular endothelial growth factor*

VS : Vitesse de sédimentation

# 1 Introduction

## 1.1 Généralités



*“Two patients, a woman aged 55 and a man aged 68, were observed at The Mayo Clinic in the spring of 1931 because of fever, weakness, anorexia, loss of weight, anemia, mild leukocytosis and painful, tender areas over the scalp and along the temporal vessels. The symptoms had been present for 4-6 weeks”*

*Horton BT, Magath TB, Brown GE. An undescribed form of arteritis of the temporal vessels. Proc Staff Meet Mayo Clinic 1932;7:700-1*

L'artérite à cellules géantes (ACG), anciennement maladie de Horton, est une vascularite granulomateuse de cause inconnue affectant préférentiellement les artères de gros calibre, notamment l'aorte et les branches de la carotide externe.<sup>1</sup> La première description histologique date de 1932 par Bayard Taylor Horton et Thomas B. Magath. Il s'agit de la plus fréquente des vascularites de l'adulte, et touche exclusivement les personnes âgées de plus de 50 ans.

## 1.2 Épidémiologie

### 1.2.1 Incidence

L'incidence est estimée entre 1 et 32,8/100 000 habitants, et suit un gradient Nord Sud assez marqué,<sup>2</sup> les incidences rapportées dans les pays scandinaves et en Islande étant 2 à 3 fois supérieures à celles observées en France et dans le reste de l'Europe du Sud. Une étude portant sur les cas incidents d'ACG dans la base de données « Echantillon Généraliste de Bénéficiaires », échantillon représentatif de 1% de la base de données nationale de l'Assurance Maladie française, estime l'incidence en France entre 7 et 10/100 000 habitants de plus de 50 ans.<sup>3</sup>

Les différentes incidences mentionnées dans la littérature sont rapportées dans le tableau suivant :

Pays	Définition de l'ACG	N	Incidence /100 000 hab > 50 ans (IC 95% )	Période	Référence
Islande	ACR 1990	133	27 (22,7-32,1)	1984-1990	Baldursson, 1994 <sup>4</sup>
Danemark	Diagnostic ICD10 + au moins 3 prescriptions de corticoïde	15 548	22,2 (21,8-22,7)	1996-2018	Therkildsen, 2021 <sup>5</sup>

<sup>1</sup> Salvarani, Cantini, et Hunder, « Polymyalgia Rheumatica and Giant-Cell Arteritis ».

<sup>2</sup> Mahr et al., « Épidémiologie et histoire naturelle de l'artérite à cellules géantes (Horton) ».

<sup>3</sup> Mahr et al., « Characteristics and Management of Giant Cell Arteritis in France ».

<sup>4</sup> Baldursson et al., « Giant Cell Arteritis in Iceland. »

<sup>5</sup> Therkildsen et al., « Giant Cell Arteritis ».

Pays	Définition de l'ACG	N	Incidence /100 000 hab > 50 ans (IC 95% )	Période	Référence
Danemark	?	10 818 2651 BAT+	20,4 (19-23) BAT+ : 15,1 (11-20)	1982-1994	Elling, 1996 <sup>6</sup>
Norvège Sud	ACR 1990, ou BAT+, ou artérite des gros et moyens vaisseaux confirmés à l'imagerie	206 152 BAT+	16,8 (14,6-19,2) BAT+ : 12,8 (10,5-14,5)	2000-2013	Andersen, 2021 <sup>7</sup>
Norvège Sud	BAT+	66	29,0	1987-1994	Gran 1997 <sup>8</sup>
Norvège Sud	ACR 1990, 94% BAT+	53	32,8 BAT+ : 29.1	1992-1996	Haugeberg 2000 <sup>9</sup>
Suède	BAT+	664	22,2	1976-1995	Nordborg, 2003 <sup>10</sup>
Suède Sud	BAT+	840	14,1 (13,1-15,0)	1997-2010	Mohammad, 2015 <sup>11</sup>
Suède Sud	BAT+	1360	13,3 (12,6-14,0)	1997-2019	Stamatis, 2021 <sup>12</sup>
Finlande	?	66	4,5 (1970-1979) 9,2 (1980-1989)	1969-1989	Rajala, 1993 <sup>13</sup>
Finlande (Northern Savo)	ACR 1990	8	7,4 (6,3-8,7)	2010	Elfving, 2016 <sup>14</sup>
Grande Bretagne	Codes ACG de la base CPRD, âge>50 ans, et prescription de corticoïdes dans les 6 mois	4671	10	2000-2011	Petri, 2015 <sup>15</sup>
Grande Bretagne	Codes ACG de la base GPRD, et au moins 2 prescriptions de corticoïdes	3928	22 (21-23)	1990-2001	Smeeth, 2006 <sup>16</sup>
Ile de la Réunion (France)	ACR 1990	60	2,72 (2,04-3,39) BAT+ : 1,53 (1,03-2,04)	2005-2018	Richier, 2020 <sup>17</sup>
France	ICD10 + au moins 4 dispensations de GC au cours des 6 mois suivant le diagnostic	117	7-10	2007-2015	Mahr, 2020 <sup>18</sup>
France	BAT+ ou tableau clinique compatible	110	9,4	1970-1979	Barrier, 1982 <sup>19</sup>
Espagne du Nord	BAT+	255	10,1 (8,9-11,5)	1981-2005	Gonzalez-Gay, 2007 <sup>20</sup>
Italie du nord	BAT+	285	5,8 (5,1-6,5)	1986-2012	Catanoso, 2017 <sup>21</sup>

<sup>6</sup> Elling, Olsson, et Elling, « Synchronous Variations of the Incidence of Temporal Arteritis and Polymyalgia Rheumatica in Different Regions of Denmark; Association with Epidemics of Mycoplasma Pneumoniae Infection ».

<sup>7</sup> Andersen et al., « Incidence Trends and Mortality of Giant Cell Arteritis in Southern Norway ».

<sup>8</sup> Gran et Myklebust, « The Incidence of Polymyalgia Rheumatica and Temporal Arteritis in the County of Aust Agder, South Norway ».

<sup>9</sup> Haugeberg, Paulsen, et Bie, « Temporal Arteritis in Vest Agder County in Southern Norway ».

<sup>10</sup> Nordborg, « The Epidemiology of Biopsy-Positive Giant Cell Arteritis ».

<sup>11</sup> Mohammad et al., « Incidence and Mortality Rates of Biopsy-Proven Giant Cell Arteritis in Southern Sweden ».

<sup>12</sup> Stamatis et al., « Epidemiology of Biopsy-Confirmed Giant Cell Arteritis in Southern Sweden—an Update on Incidence and First Prevalence Estimate ».

<sup>13</sup> Rajala et al., « Incidence and Survival Rate in Cases of Biopsy-Proven Temporal Arteritis ».

<sup>14</sup> Elfving et al., « Estimating the Incidence of Connective Tissue Diseases and Vasculitides in a Defined Population in Northern Savo Area in 2010 ».

<sup>15</sup> Petri et al., « Incidence of Giant Cell Arteritis and Characteristics of Patients ».

<sup>16</sup> Smeeth, « Incidence of Diagnosed Polymyalgia Rheumatica and Temporal Arteritis in the United Kingdom, 1990-2001 ».

<sup>17</sup> Richier et al., « Giant Cell Arteritis Incidence in La Reunion Island, a Particularly Cosmopolite Region of South Hemisphere ».

<sup>18</sup> Mahr et al., « Characteristics and Management of Giant Cell Arteritis in France ».

<sup>19</sup> Barrier et al., « [Epidemiologic approach to Horton's disease in the department of Loire-Atlantique. 110 cases in 10 years (1970-1979)] ».

<sup>20</sup> Gonzalez-Gay et al., « Giant Cell Arteritis in Northwestern Spain ».



Pays	Définition de l'ACG	N	Incidence /100 000 hab > 50 ans (IC 95% )	Période	Référence
Italie du Nord	Critères GiaCTA	207	8,3 (7,1-9,4)	2005-2016	Muratore, 2021 <sup>22</sup>
Etats-Unis (Minnesota)	ACR 1990	125	17,8 (14,7-21,0)	1950-1991	Salvarani, 1995 <sup>23</sup>
Etats-Unis (Minnesota)	ACR 1990	173	18,8 (15,9 –21,6)	1950-1999	Salvarani, 2004 <sup>24</sup>
Etats-Unis (Minnesota)	ACR 1990	74	19,8 (15,2-24,3)	2000-2009	Chandran, 2015 <sup>25</sup>
Etats-Unis (Tennessee)	BAT+ ou tableau clinique compatible	26	1,58	1971-1980	Smith, 1983 <sup>26</sup>
Etats-Unis (Alaska)	BAT+	3	1	1983-2003	Mader, 2009 <sup>27</sup>
Canada (Saskatoon)	BAT+	36	9,4	1998-2003	Ramstead, 2007 <sup>28</sup>
Israël (Jerusalem)	ACR 1990 ou BAT+	206 170 BAT+	11,3 BAT+ : 9,5	1980-2004	Bas-Lando, 2007 <sup>29</sup>
Israël (Jérusalem)	ACR 1990	140	8,1 (5,7-10,6)	1990-2009	Nesher, 2016 <sup>30</sup>
Turquie	ACR 1990	19	1,13	2002-2008	Pamuk, 2009 <sup>31</sup>
Australie du Sud	BAT+	314	3,2 (2,8-3,6)	1992-2011	Dunstan, 2014 <sup>32</sup>
Nouvelle Zélande	BAT+	70	12,7 (11,7-14,3)	1996-2005	Abdul-Rahman, 2011 <sup>33</sup>

ACG : Artérite à cellules géantes, ACR : American College of Rheumatology, BAT : biopsie de l'artère temporale, CPRD : UK-based Clinical Practice Research Datalink , GPRD : UK General Practice Research Database, hab : habitant, IC : intervalle de confiance

<sup>21</sup> Catanoso et al., « Incidence, Prevalence, and Survival of Biopsy-Proven Giant Cell Arteritis in Northern Italy During a 26-Year Period ».

<sup>22</sup> Muratore et al., « Incidence and Prevalence of Large Vessel Vasculitis (Giant Cell Arteritis and Takayasu Arteritis) in Northern Italy ».

<sup>23</sup> Salvarani et al., « The Incidence of Giant Cell Arteritis in Olmsted County, Minnesota ».

<sup>24</sup> Salvarani et al., « Reappraisal of the Epidemiology of Giant Cell Arteritis in Olmsted County, Minnesota, over a Fifty-Year Period ».

<sup>25</sup> Chandran et al., « The Incidence of Giant Cell Arteritis in Olmsted County, Minnesota, over a 60-Year Period 1950–2009 ».

<sup>26</sup> Smith, Fidler, et Pinals, « The Epidemiology of Giant Cell Arteritis. Report of a Ten-Year Study in Shelby County, Tennessee ».

<sup>27</sup> Mader et al., « Giant Cell Arteritis in Alaska Natives ».

<sup>28</sup> Ramstead et Patel, « Giant Cell Arteritis in a Neuro-Ophthalmology Clinic in Saskatoon, 1998–2003 ».

<sup>29</sup> Bas-Lando et al., « The Incidence of Giant Cell Arteritis in Jerusalem over a 25-Year Period ».

<sup>30</sup> Nesher et al., « The Incidence of Primary Systemic Vasculitis in Jerusalem ».

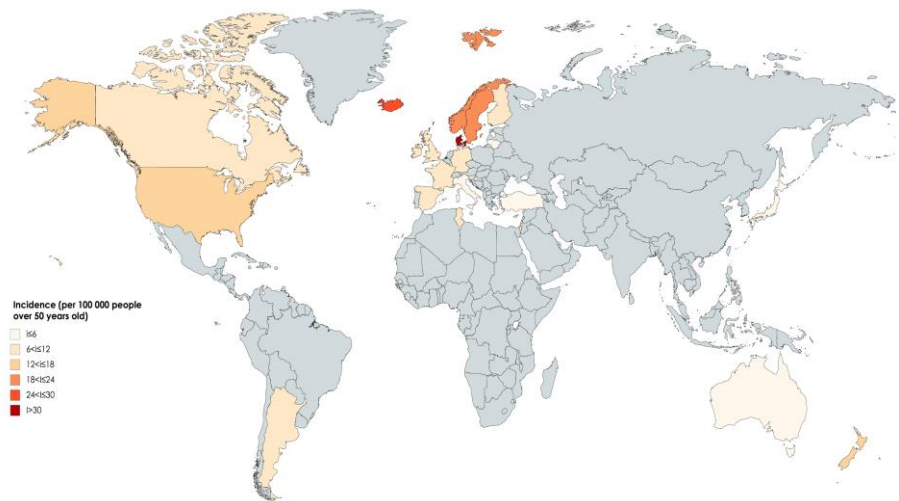
<sup>31</sup> Pamuk et al., « Giant Cell Arteritis and Polymyalgia Rheumatica in Northwestern Turkey ».

<sup>32</sup> Dunstan et al., « Epidemiology of Biopsy-Proven Giant Cell Arteritis in South Australia ».

<sup>33</sup> Abdul-Rahman, Molteno, et Bevin, « The Epidemiology of Giant Cell Arteritis in Otago, New Zealand ».

Une récente méta-analyse résume l'épidémiologie de l'ACG dans le temps et dans l'espace, permettant de représenter graphiquement les résultats sur la carte du monde :<sup>34</sup>

*Li et al, 2021 : Global Incidence of Giant Cell Arteritis on the World Map (grey = no data)*



L'évolution dans le temps de l'incidence laisse entrevoir une augmentation jusqu'aux années 2000, puis une diminution depuis. En effet, une étude suédoise entre 1997 et 2010, sur 4 216 patients présentant une ACG histologiquement prouvée, a retrouvé une incidence à 15,9/100 000 habitants de plus de 50 ans (intervalle de confiance (IC) 95% 14,2 – 17,7) entre 1997 et 2001, significativement supérieure à l'incidence des périodes suivantes 2002-2006 et 2007-2010, respectivement 13,4 (IC 95% 11,8 – 15,0) et 13,3 (IC 95% 11,7 – 14,9).<sup>35</sup> Ces résultats sont confortés par une étude sur 285 cas d'ACG histologiquement prouvée entre 1986 et 2012 en Italie du Nord, mettant en évidence une augmentation des taux d'incidence annuelle (ajustés sur l'âge et le sexe) de 15,9% par 3 ans entre 1986 et 2000, puis une diminution de -4,8% par 3 ans entre 2001 et 2012.<sup>36</sup> Une autre étude épidémiologique italienne n'a pas mis en évidence de variation significative entre 2005 et 2016.<sup>37</sup> Une variation saisonnière a également été évoquée, conduisant à suspecter un pathogène viral ou bactérien comme facteur déclenchant de la maladie.<sup>38</sup>

Plus récemment, plusieurs études ont décrit une augmentation de l'incidence du diagnostic d'ACG au cours de la pandémie liée à la Covid 19<sup>39</sup>. La recherche du virus SARS-CoV-2 par PCR a été réalisée sur des échantillons de biopsie de l'artère temporale (BAT), mais aucune n'est revenue positive, ne

<sup>34</sup> Li et al., « A Meta-Analysis of the Epidemiology of Giant Cell Arteritis across Time and Space ».

<sup>35</sup> Mohammad et al., « Incidence and Mortality Rates of Biopsy-Proven Giant Cell Arteritis in Southern Sweden ».

<sup>36</sup> Catanoso et al., « Incidence, Prevalence, and Survival of Biopsy-Proven Giant Cell Arteritis in Northern Italy During a 26-Year Period ».

<sup>37</sup> Muratore et al., « Incidence and Prevalence of Large Vessel Vasculitis (Giant Cell Arteritis and Takayasu Arteritis) in Northern Italy ».

<sup>38</sup> Salvarani et al., « The Incidence of Giant Cell Arteritis in Olmsted County, Minnesota »; Bas-Lando et al., « The Incidence of Giant Cell Arteritis in Jerusalem over a 25-Year Period ».

<sup>39</sup> Luther et al., « Increased Number of Cases of Giant Cell Arteritis and Higher Rates of Ophthalmic Involvement during the Era of COVID-19 »; Monti et al., « Impact of Delayed Diagnoses at the Time of COVID-19 »; Parreau et al., « High Incidence of Giant Cell Arteritis during the COVID-19 Pandemic »; Lecler et al., « Increased Rather than Decreased Incidence of Giant-Cell Arteritis during the COVID-19 Pandemic ».

permettant pas d'étayer l'hypothèse d'un facteur déclenchant infectieux. L'hypothèse d'un rôle favorisant du stress dans l'émergence de l'ACG a été évoquée.<sup>40</sup>

## 1.2.2 Caractéristiques démographiques

L'ACG survient tardivement au cours de la vie, toujours à partir de l'âge de 50 ans, et plus communément à partir de 70 ans. L'incidence est maximale entre 70 et 80 ans.<sup>41</sup> Il s'agit de la vascularite la plus fréquente en Europe et en Amérique du Nord. Par ailleurs, la maladie touche préférentiellement les femmes, avec un ratio à 3:1, et semble concerner plutôt les populations d'origine européennes,<sup>42</sup> comme en témoigne une étude menée en 1982 sur 26 patients du Tennessee diagnostiqués entre 1971 et 1980, retrouvant une incidence de 0,36/100 000 habitants de plus de 50 ans chez les sujets noirs, versus 2,24 pour les sujets blancs.<sup>43</sup> Ces variations ethniques laissent entrevoir un facteur de susceptibilité génétique à l'origine de la maladie. En effet, une association avec certains allèles du système HLA de classe II, en particulier HLA-DRB1\*04 a été mise en évidence.<sup>44</sup>

## 1.2.3 Mortalité

Les données sur la mortalité associée à l'ACG sont équivoques. En effet, la plupart des études sur la mortalité dans l'ACG rapportent une mortalité similaire à celle de la population générale ou à peine augmentée. Néanmoins, certaines études suggèrent un excès de mortalité, particulièrement dans les premières années suivant le diagnostic.<sup>45</sup>

Une étude sur 285 patients présentant une ACG histologiquement prouvée en Italie du Nord n'a pas trouvé de surmortalité par rapport à la population témoin sans ACG, issue de la même aire géographique et appariée sur l'âge et le sexe (ratio du taux de mortalité=0,87 ; IC 95% 0,67 – 1,13).<sup>46</sup>

Une étude danoise entre 1993 et 2011, sur 1 787 patients présentant une ACG prouvée histologiquement, et comparés à une cohorte de 33 953 personnes appariées sur l'âge et le sexe, a mis en évidence un sur-risque de mortalité dans les deux premières années suivant le diagnostic avec un risque relatif (RR)=1,17 (IC 95% 1,01 – 1,36), ces événements étant majoritairement liés à

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<sup>40</sup> Parreau et al., « High Incidence of Giant Cell Arteritis during the COVID-19 Pandemic ».

<sup>41</sup> Muratore et al., « Incidence and Prevalence of Large Vessel Vasculitis (Giant Cell Arteritis and Takayasu Arteritis) in Northern Italy ».

<sup>42</sup> Gonzalez-Gay et al., « Epidemiology of Giant Cell Arteritis and Polymyalgia Rheumatica ».

<sup>43</sup> Smith, Fidler, et Pinals, « The Epidemiology of Giant Cell Arteritis. Report of a Ten-Year Study in Shelby County, Tennessee ».

<sup>44</sup> Weyand et al., « The HLA-DRB1 Locus as a Genetic Component in Giant Cell Arteritis. Mapping of a Disease-Linked Sequence Motif to the Antigen Binding Site of the HLA-DR Molecule »; Combe et al., « Distribution of HLA-DRB1 Alleles of Patients with Polymyalgia Rheumatica and Giant Cell Arteritis in a Mediterranean Population ».

<sup>45</sup> Hill et al., « Risk of Mortality in Patients with Giant Cell Arteritis ».

<sup>46</sup> Catanoso et al., « Incidence, Prevalence, and Survival of Biopsy-Proven Giant Cell Arteritis in Northern Italy During a 26-Year Period ».

des pathologies cardiovasculaires incluant les anévrismes aortiques. Cette augmentation du risque n'était pas retrouvée entre 2 et 10 ans d'évolution (RR=0,96 ; IC 95% 0,88 – 1,05), mais était de nouveau mise en évidence au-delà de 10 ans du diagnostic (RR=1,22 ; IC 95% 1,05 – 1,41).<sup>47</sup> De même, une étude suédoise entre 1997 et 2010, sur 840 patients présentant une ACG histologiquement prouvée a mis en évidence une mortalité globale superposable à la population générale (ratio de mortalité standardisé (SMR)=0,91 ; IC 95% 0,80 – 1,02), avec cependant une surmortalité les deux années suivant le diagnostic (SMR à 1 an=2,17 ; IC 95% 1,48 – 2,86 ; SMR à 2 ans=1,52 ; IC 95% 1,20 – 1,85).

Une étude de cohorte danoise de plus grande ampleur, sur registres médicaux et administratifs, a inclus 9 908 patients avec un diagnostic d'ACG et au moins 3 prescriptions comportant une corticothérapie dans les 6 mois suivant le diagnostic entre 1996 et 2018, appariés sur l'âge et le sexe à 98 204 patients de la population générale sans ACG. Le risque relatif de mortalité globale était estimé à 1,49 (IC 95% 1,36 – 1,64) à 1 an, et 1,03 (IC 95% 1,00 – 1,05) à 10 ans. Les résultats différaient selon le statut de la BAT, le risque le plus faible étant retrouvé pour les patients dont la BAT était positive :<sup>48</sup>

<b>RR de mortalité</b> IC 95%	<b>BAT positive</b>	<b>BAT négative</b>	<b>Pas de BAT</b>
A 1 an	<b>1,19</b> 1,00 – 1,43	<b>1,49</b> 1,27 – 1,74	<b>1,78</b> 1,54 – 2,06
A 10 ans	<b>1,00</b> 0,97 – 1,04	<b>1,00</b> 0,96 – 1,05	<b>1,08</b> 1,04 – 1,13

Les principales causes de décès à 1 an dans cette étude étaient infectieuses (RR=2,58 ; IC 95% 1,45 – 4,60), endocriniennes, essentiellement liées au diabète (85% ; RR=2,67 ; IC 95% 1,53 – 4,64), cardiovasculaires (RR=1,48 ; IC 95% 1,25 – 1,77) et gastro-intestinales (RR=2,73 ; IC 95% 1,89 – 3,94) comprenant 18% d'ulcères, 15% d'ischémies mésentériques et 13% de diverticulites. A 10 ans, le risque de décès par cancer était diminué par rapport à la population générale (RR=0,89 ; IC 95% 0,82 – 0,96).<sup>49</sup> Ces résultats rejoignent ceux de deux études sur les certificats de décès en France mentionnant l'ACG comme cause du décès ou ayant contribué au décès :<sup>50</sup> les principales causes associées étaient cardiovasculaires (79%), et infectieuses (35%), avec un sur-risque observé par rapport à la population générale concernant, entre autre, les anévrismes aortiques et les dissections

<sup>47</sup> Baslund et al., « Mortality in Patients with Giant Cell Arteritis ».

<sup>48</sup> Therkildsen et al., « All-Cause and Cause-Specific Mortality in Patients with Giant Cell Arteritis ».

<sup>49</sup> Therkildsen et al.

<sup>50</sup> Aouba et al., « Mortality Causes and Trends Associated with Giant Cell Arteritis »; Chazal et al., « Giant-Cell Arteritis-Related Mortality in France ».

(odds ratio de mortalité standardisée [SMOR]=3,09 ; IC 95% 2,48 – 3,82), l'hypertension artérielle (SMOR=2,22 ; IC 95% 1,97 – 2,50), le diabète (SMOR=1,96 ; IC 95% 1,72 – 2,23), et les pathologies infectieuses (SMOR=1,76 ; IC 95% 1,55 – 2,00).<sup>51</sup> Comme précédemment, le risque de cancer apparaît, au contraire, plus faible que dans la population générale (SMOR=0,52 ; IC 95% 0,45 – 0,59). Une étude sur une cohorte rétrospective de 204 patients présentant des manifestations de type aorto-artérite, met en évidence une surmortalité chez les patients présentant un anévrisme aortique ou une dissection (SMR=2,63 ; IC 95% 1,78 – 2,73), mais non retrouvée chez les patients présentant une sténose des gros vaisseaux (SMR=1,44 ; IC 95% 0,87 – 2,25).<sup>52</sup>

L'évolution du taux de décès dans le temps a été étudiée dans cette étude analysant les certificats de décès en France établis entre 1980 et 2011 et mentionnant l'ACG et met en évidence une augmentation significative du taux de décès jusqu'à un pic atteint en 1997 (4,37/100 000 habitants de plus de 55 ans), puis une diminution significative jusqu'à 2011.<sup>53</sup> La deuxième étude sur l'analyse des certificats de décès français a été réalisée entre 2005 et 2014, et retrouvait une globale stabilité du taux standardisé sur l'âge de mortalité liée à l'ACG (7,2/100 000), mais une diminution de la mortalité chez les hommes.<sup>54</sup>

### 1.3 Physiopathologie

Bien que d'importants progrès aient été réalisés sur la connaissance de la physiopathologie de l'ACG ces dernières années, les mécanismes conduisant à l'apparition de la maladie restent non complètement élucidés.

Cette vascularite est caractérisée par une importante inflammation de la paroi des gros vaisseaux, associée à une réaction inflammatoire systémique.<sup>55</sup> Le modèle physiopathologique de l'ACG peut être divisé en quatre phases :<sup>56</sup>

#### - **Phase 1 : rupture de tolérance et activation des cellules dendritiques (DC)**

Les DC, physiologiquement situées dans l'adventice des artères, jouent un rôle de surveillance immunitaire. En présence d'un signal de danger, elles sont activées via leurs récepteurs, les *toll-like receptor*, et vont alors produire des chémokines responsables du recrutement des lymphocytes T (LT) CD4+ dans la paroi artérielle.

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<sup>51</sup> Aouba et al., « Mortality Causes and Trends Associated with Giant Cell Arteritis ».

<sup>52</sup> Kermani et al., « Large-Vessel Involvement in Giant Cell Arteritis ».

<sup>53</sup> Aouba et al., « Mortality Causes and Trends Associated with Giant Cell Arteritis ».

<sup>54</sup> Chazal et al., « Giant-Cell Arteritis-Related Mortality in France ».

<sup>55</sup> Samson et Bonnotte, « [Pathogenesis of large vessel vasculitis] ».

<sup>56</sup> Samson et al., « Recent Advances in Our Understanding of Giant Cell Arteritis Pathogenesis ».

## - Phase 2 : recrutement, activation et polarisation des LT

Les LT, alors recrutés dans la paroi artérielle vont être activés in situ par les DC qui leur présentent un ou plusieurs antigènes encore non identifiés. Les LT prolifèrent et se polarisent en lymphocytes Th1 et Th17 selon les cytokines pro-inflammatoires (IL-12, IL-18, IL-23, IL-6, IL-1 $\beta$ ) présentes dans le micro-environnement. Les cellules Th1 sont générées en présence d'IL-12 et IL-18, et produisent de l'interféron  $\gamma$  (IFN- $\gamma$ ), tandis que les cellules Th17 sont générées en présence d'IL-6, IL-1 $\beta$  et IL-23 et produisent de l'IL-17. Deux voies pathogéniques sont alors suggérées :<sup>57</sup> la première impliquant les cellules Th17, sensibles aux corticoïdes, et la seconde via les cellules Th1, expliquant la persistance de phénomènes inflammatoires malgré la corticothérapie. Une autre hypothèse serait celle d'une plasticité entre les voies Th1 et Th17, modulées par l'histoire naturelle de la maladie et les traitements. La présence d'un infiltrat massif de LT CD4+/CD161+ dans les biopsies d'artère temporale, connus pour leur plasticité entre la voie Th1 et Th17 corrobore cette hypothèse<sup>58</sup>.

En parallèle, le taux de lymphocytes T régulateurs (Treg) est inférieur à celui des témoins chez les patients atteints d'ACG, suggérant un déséquilibre de la balance Th17/Treg. Cette hypothèse est soutenue par la présence dans le sérum des patients atteints d'ACG d'un fort taux d'IL-6, cytokine contrôlant la balance Th17/Treg.

## - Phase 3 : recrutement des monocytes et des LT CD8+

La forte infiltration de la paroi artérielle par les cellules Th1 et Th17 entraîne respectivement une forte production d'IFN- $\gamma$  et d'IL-17. L'IFN- $\gamma$  induit alors la production de plusieurs chémokines (CCL2, CXCL9, CXCL10 et CXCL1) par les cellules musculaires lisses vasculaires. CCL2 entraîne le recrutement des monocytes en macrophages fusionnant pour former des cellules géantes multinucléées, caractéristiques de l'ACG. Dans l'adventice, ces dernières sécrètent de l'IL-1 $\beta$  et d'IL-6, qui sont à l'origine du syndrome inflammatoire et des signes généraux de l'ACG.

D'autre part, CXCL9, CXCL10 et CXCL 1 permettent le recrutement des LT Th1 et CD8+, entraînant ainsi une augmentation de la production d'IFN- $\gamma$ , probablement à l'origine d'une boucle positive à l'origine de la chronicisation de la réponse inflammatoire Th1 observée dans l'ACG.

## - Phase 4 : remodelage vasculaire

Dans la media, les macrophages et les cellules géantes sont à l'origine d'une production de radicaux libres dérivés de l'oxygène, entraînant in fine la destruction de la matrice extra cellulaire et la

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<sup>57</sup> Deng et al., « Th17 and Th1 T-cell responses in Giant Cell Arteritis ».

<sup>58</sup> Samson et al., « Th1 and Th17 Lymphocytes Expressing CD161 Are Implicated in Giant Cell Arteritis and Polymyalgia Rheumatica Pathogenesis ».

fragmentation de la limitante élastique interne. Les macrophages produisent également les facteurs de croissance *platelet-derived growth factor* (PDGF), induisant une prolifération intimale, et *vascular endothelial growth factor* (VEGF), responsable d'une néoangiogenèse augmentant le recrutement de nouvelles cellules immunes dans la paroi artérielle. Ces différents éléments de remodelage de la paroi artérielle conduisent au rétrécissement progressif des artères et à l'occlusion progressive de la lumière vasculaire, et expliquent les manifestations ischémiques de l'ACG.

## 2 Diagnostic

### 2.1 Description clinique

La présentation clinique de l'ACG se décline en trois phénotypes distincts mais pouvant coexister.<sup>59</sup> le phénotype « céphalique », l'aorto-artérite, et la pseudopolyarthrite rhizomélique (PPR).

- **Le phénotype céphalique** correspond à la définition historique de l'ACG, et se manifeste par des céphalées, une hyperesthésie du cuir chevelu, une claudication de la mâchoire. L'atteinte des troncs supra-aortiques explique ces manifestations. Des manifestations visuelles sont décrites et font la gravité de la maladie car peuvent conduire à la cécité. Elles sont classiquement secondaires à une neuropathie ischémique antérieure aiguë, mais une occlusion des artères centrales de la rétine ou une névrite optique rétrobulbaire sont possibles. Des accidents vasculaires cérébraux (AVC), essentiellement vertébro-basilaires font également partis du spectre de la pathologie, mais restent rares : une série de 287 patients mettait en évidence un taux d'AVC au diagnostic ou dans les quatre premières semaines suivant l'introduction de la corticothérapie de 2,8%.<sup>60</sup> Chez les patients présentant une ACG, le risque relatif d'AVC est estimé à 1,40 (IC 95% 1,27 – 1,56) par rapport aux patients non atteints.
- **L'aorto-artérite** a été définie plus récemment comme appartenant au spectre de l'ACG. Elle regroupe l'atteinte de l'aorte et de ses branches, et comprend l'aorto-artérite idiopathique du sujet de plus de 50 ans. L'aortite peut se révéler par des signes non spécifiques d'anévrisme abdominal, un tableau de dissection ou de rupture de l'aorte. La claudication des extrémités, l'asymétrie tensionnelle, un souffle sur les axes vasculaires ou l'abolition d'un pouls peuvent également conduire au diagnostic. L'aortite peut se manifester également par une fièvre nue et une altération de l'état général, un syndrome inflammatoire isolé, une

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<sup>59</sup> Mahr et al., « Épidémiologie et histoire naturelle de l'artérite à cellules géantes (Horton) ».

<sup>60</sup> Gonzalez-Gay et al., « Strokes at Time of Disease Diagnosis in a Series of 287 Patients With Biopsy-Proven Giant Cell Arteritis ».

dyspnée ou des douleurs abdominales.<sup>61</sup> Le plus souvent, l'atteinte aortique est asymptomatique et mise en évidence à l'imagerie.<sup>62</sup>

- **La PPR** est la manifestation rhumatologique la plus classique. Elle entraîne des douleurs inflammatoires des ceintures pelviennes et scapulaires.<sup>63</sup>

## 2.2 Diagnostic

Le diagnostic est posé par un faisceau d'arguments cliniques, biologiques et histologiques.

Le test diagnostique de référence est la BAT, dont la sensibilité est estimée à 61% (IC 95% 38 – 79) et la spécificité à 98% (IC 95% 95 – 99) dans une récente méta-analyse.<sup>64</sup> Le prélèvement doit mesurer au moins 1cm. L'analyse histologique met en évidence un infiltrat inflammatoire mononucléé de la media et/ou de l'intima. Une fragmentation de la limitante élastique interne et la présence de cellules géantes sont des signes pathognomoniques, mais inconstants.

En 1990, l'American College of Rheumatology a publié des critères diagnostiques.<sup>65</sup> Le diagnostic est probable si 3 critères ou plus sont présents avec une sensibilité de 94% et une spécificité de 91%. Plus récemment, les critères d'inclusion de l'essai GiACTA<sup>66</sup> ont été admis par la communauté internationale.

ACR 1990 Au moins 3 critères	GiACTA
<ul style="list-style-type: none"> <li>- Age supérieur à 50 ans au début des symptômes</li> <li>- Céphalées inhabituelles</li> <li>- Anomalies cliniques des artères temporales à type de douleurs provoquées par la palpation ou diminution du pouls temporal ou claudication de la mâchoire</li> <li>- Vitesse de sédimentation (VS) &gt; 50 mm/h</li> </ul>	<ul style="list-style-type: none"> <li>- Age supérieur à 50 ans</li> <li>- Symptômes céphaliques ou systémiques de GCA, ou PPR</li> <li>- VS&gt;50 mm/h ou CRP&gt;10 mg/L</li> </ul> <p style="text-align: center;"><b>ET</b></p> <ul style="list-style-type: none"> <li>- BAT mettant en évidence une infiltration transmurale de cellule mononucléées dans le mur artériel, avec ou sans cellules géantes (<i>cranial-GCA</i>)</li> <li>- <b>Ou</b> évidence d'une atteinte des gros vaisseaux attribuables à l'ACG par des imageries en coupe</li> </ul>

<sup>61</sup> Espitia et Agard, « Aortite et complications aortiques de l'artérite à cellules géantes (maladie de Horton) ».

<sup>62</sup> Marie et al., « Long-Term Follow-Up of Aortic Involvement in Giant Cell Arteritis ».

<sup>63</sup> Weyand, « Giant-Cell Arteritis and Polymyalgia Rheumatica ».

<sup>64</sup> Dua et al., « Giant Cell Arteritis ».

<sup>65</sup> Hunder et al., « The American College of Rheumatology 1990 Criteria for the Classification of Giant Cell Arteritis ».

<sup>66</sup> Stone et al., « Trial of Tocilizumab in Giant-Cell Arteritis ».



Plusieurs techniques d'imagerie permettent d'étayer le diagnostic :

- La tomодensitométrie (TDM) avec émission de positron (TEP) au <sup>18</sup>F<sup>18</sup>FDG est largement utilisée lors de la phase diagnostic, avec une sensibilité estimée entre 73% et 92% et une spécificité estimée entre 83% et 85%<sup>67</sup>. Elle met en évidence une absorption importante du traceur au niveau des parois artérielles de manière diffuse, au niveau de l'aorte ou des troncs supra-aortiques<sup>68</sup>. Sa place au cours du suivi est encore discutée. Une méta-analyse a rapporté des caractéristiques médiocres, avec une sensibilité de 77,3% (IC 95% 56,5 – 89,9) et une spécificité de 70,9% (IC 95% 47,3 – 86,8) pour discriminer une pathologie active versus en rémission au cours du suivi.<sup>69</sup>
- L'échographie doppler de l'artère temporale peut guider la biopsie de l'artère temporale, en repérant des zones inflammatoires (signe du halo).<sup>70</sup> La sensibilité est estimée entre 40% et 67% et la spécificité entre 81% et 93%.<sup>71</sup> La technique nécessite un opérateur entraîné, et peine à trouver sa place dans la démarche diagnostique en France.
- L'angio-TDM peut également mettre en évidence une atteinte inflammatoire aortique, par un épaissement circonférentiel de la paroi artérielle, de même que l'angio-IRM, mais cette dernière est onéreuse et d'accès limité.

Dans le contexte de l'urgence thérapeutique que représente l'ACG, des filières de prise en charge rapide, des « GCA fast-track clinic » (FTC), ont été mises en place associant une évaluation clinique rapide, un dosage des paramètres inflammatoires, et un examen échographique de l'artère temporale.<sup>72</sup> Ces filières semblent associées à une amélioration du pronostic visuel des patients, en réduisant le délai d'initiation du traitement. Dans ce contexte, un score a été proposé pour optimiser l'orientation des patients : le GCAPS (Giant Cell Arteritis Probability Score), généré par deux experts sur la base de leur expérience clinique. Ce score a ensuite été validé par une cohorte rétrospective de 122 patients consécutifs, le diagnostic étant confirmé par

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<sup>67</sup> Dua et al., « Giant Cell Arteritis ».

<sup>68</sup> Sammel et al., « Diagnostic Accuracy of Positron Emission Tomography/Computed Tomography of the Head, Neck, and Chest for Giant Cell Arteritis ».

<sup>69</sup> van der Geest et al., « Diagnostic Value of [18F]FDG-PET/CT for Treatment Monitoring in Large Vessel Vasculitis ».

<sup>70</sup> Arida et al., « The diagnostic value of ultrasonography-derived edema of the temporal artery wall in giant cell arteritis ».

<sup>71</sup> Dua et al., « Giant Cell Arteritis ».

<sup>72</sup> Diamantopoulos et al., « The Fast-Track Ultrasound Clinic for Early Diagnosis of Giant Cell Arteritis Significantly Reduces Permanent Visual Impairment »; Andel et al., « Diagnosing Giant Cell Arteritis »; Monti et al., « Fast-Track Ultrasound Clinic for the Diagnosis of Giant Cell Arteritis Changes the Prognosis of the Disease but Not the Risk of Future Relapse »; Patil et al., « Fast Track Pathway Reduces Sight Loss in Giant Cell Arteritis: Results of a Longitudinal Observational Cohort Study »; Sebastian et al., « Probability-Based Algorithm Using Ultrasound and Additional Tests for Suspected GCA in a Fast-Track Clinic »; Sené et al., « Délais de prise en charge des complications visuelles d'artérite à cellules géantes »; Luther et al., « Increased Number of Cases of Giant Cell Arteritis and Higher Rates of Ophthalmic Involvement during the Era of COVID-19 ».

des critères cliniques, une BAT, une échographie doppler de l'artère temporale, et/ou un TEP au <sup>18</sup>FDG. Les performances diagnostiques de ce score étaient une sensibilité à 95,7% et une spécificité à 86,7% pour un seuil optimal à 9,5 (aire sous la courbe 0,95, 95%IC 0,91 – 0,99).<sup>73</sup>

#### Score GCAPS (Laskou *et al.* 2019)

Pondération	-3	0	+1	+2	+3
<b>Caractéristiques démographiques</b>					
Age (années)		≤49	50-60	61-65	≥66
Sexe			M	F	
<b>Evolution des symptômes (semaines)</b>					
		> 24	12-24	6-12	<6
<b>CRP (mg/L)</b>					
		0-5	6-10	11-25	≥25
<b>Symptômes</b>					
Céphalées		NON	OUI		
Polymyalgies		NON		OUI	
Signes systémiques		NON	Unique		Plusieurs
Signes ischémiques		NON			OUI
<b>Examen clinique</b>					
Atteinte visuelle*		NON			
Anomalie de l'artère temporale		NON	Induration	Epaississement	Abolition du pouls
Anomalie des artères extra-crânielles		NON	Epaississement	Souffle	Abolition du pouls
Paralysie d'un nerf crânien		NON			OUI
<b>Diagnostic alternatif</b>					
Infection	OUI				
Cancer	OUI				
Rhumatisme inflammatoire	OUI				
Pathologie de la tête et du cou	OUI				
Autre	OUI				

\*neuropathie ischémique antérieure aigue, occlusion des artères centrales de la rétine, amputation du champ visuel

## 2.3 Rechute

Les rechutes sont fréquentes et semblent concerner la moitié des patients.<sup>74</sup> Classiquement, la rechute est définie par la résurgence de symptômes ou la réapparition d'un syndrome inflammatoire.

<sup>73</sup> Laskou *et al.*, « A Probability Score to Aid the Diagnosis of Suspected Giant Cell Arteritis ».

<sup>74</sup> Salvarani, Cantini, *et Hunder*, « Polymyalgia Rheumatica and Giant-Cell Arteritis ».

### 2.3.1 Définition

Une définition consensuelle de la rechute a été récemment établie par l'European League Against Rheumatism (EULAR),<sup>75</sup> qui propose l'utilisation des termes « rechute mineure » ou « rechute majeure » :

- Rechute mineure : récurrence d'une maladie active, ne remplissant pas les critères de la rechute majeure
- Rechute majeure : récurrence de la maladie active avec l'une des caractéristiques suivantes :
  - o Eléments cliniques ischémiques (incluant claudication de la mâchoire, symptômes visuels, perte de vision attribuable à l'ACG, nécrose du cuir chevelu, accident vasculaire cérébral, claudication des membres).
  - o Preuve d'une inflammation aortique active entraînant une dilatation, une sténose ou une dissection progressive de l'aorte ou des gros vaisseaux.

La maladie active est définie par la présence de signes ou symptômes typiques de vascularite active, et au moins un critère parmi activité persistante sur l'imagerie ou l'histologie, complications ischémiques attribuées à la vascularite, et persistance de marqueurs de l'inflammation augmentés (les autres causes ayant été exclues).

### 2.3.2 Facteurs de risque de rechute

Les facteurs de risque de rechute sont mal connus. Néanmoins, plusieurs facteurs ont été décrits comme prédictifs :

Facteur étudié	Risque relatif	IC 95%	Référence
Genre féminin	HR=1,04	1,20 – 3,33	de Mornac <i>et al.</i> <sup>76</sup>
	HR=1,37	0,99 – 1,91	Labarca <i>et al.</i> <sup>77</sup>
Anémie <120 g/L	OR=2,17	1,02 – 4,62	Martinez-Lado <i>et al.</i> <sup>78</sup>
Hypertension artérielle	HR=1,30	0,99 – 1,71	Labarca <i>et al.</i> <sup>79</sup>
Antécédent de thrombose veineuse	HR=2,27	1,12 – 4,62	Labarca <i>et al.</i>
Claudication des jambes	HR=2,53	1,03 – 6,20	Labarca <i>et al.</i>

<sup>75</sup> Hellmich *et al.*, « 2018 Update of the EULAR Recommendations for the Management of Large Vessel Vasculitis ».

<sup>76</sup> de Mornac *et al.*, « Risk Factors for Symptomatic Vascular Events in Giant Cell Arteritis ».

<sup>77</sup> Labarca *et al.*, « Predictors of Relapse and Treatment Outcomes in Biopsy-Proven Giant Cell Arteritis ».

<sup>78</sup> Martinez-Lado *et al.*, « Relapses and Recurrences in Giant Cell Arteritis ».

<sup>79</sup> Labarca *et al.*, « Predictors of Relapse and Treatment Outcomes in Biopsy-Proven Giant Cell Arteritis ».

Facteur étudié	Risque relatif	IC 95%	Référence
Fièvre > 38°C	HR=2,14	1,06 – 4,32	Restuccia <i>et al.</i> <sup>80</sup>
Sévérité de l'inflammation (modérée/sévère vs légère)	HR=5,41	1,64 – 17,87	Restuccia <i>et al.</i>
Atteinte des gros vaisseaux à l'imagerie	HR=1,49	1,002 – 2,12	Dumont <i>et al.</i> <sup>81</sup>
Pseudo-polyarthrite rhizomélique	RR=1,59*	P=0,042	Alba <i>et al.</i> <sup>82</sup>
Sensibilité du cuir chevelu	RR=1,57*	P=0,001	Alba <i>et al.</i>
Manifestations musculosquelettiques périphériques	HR=2,78	1,23 – 6,28	de Mornac <i>et al.</i>
Biopsie de l'artère temporale négative <sup>§</sup>	HR=2,29	1,18 – 4,45	de Mornac <i>et al.</i>
Ischémie du membre supérieur <sup>§</sup>	HR=8,84	2,48 – 31,56	de Mornac <i>et al.</i>
Inflammation des artères du bras <sup>§</sup>	HR=2,39	1,02 – 5,58	de Mornac <i>et al.</i>

HR : hazard ratio, IC : intervalle de confiance, RR : risque relatif

\*calculé à partir du nombre d'évènements dans l'étude

<sup>§</sup>facteurs prédictifs de rechutes multiples

### 3 Prise en charge thérapeutique

#### 3.1 Corticothérapie

La pierre angulaire du traitement repose sur une corticothérapie, initiée à forte dose (0,7 à 1mg/kg/j).<sup>83</sup> En cas d'atteinte ophtalmologique, l'introduction de la corticothérapie est une urgence et ne doit pas être différée par la réalisation d'examen complémentaires. Des bolus intraveineux de glucocorticoïdes sont également administrés les trois premiers jours en cas d'atteinte ischémique sévère.<sup>84</sup> La méta-analyse des deux essais rétrospectifs évaluant la corticothérapie forte dose intraveineuse versus orale chez les patients présentant une atteinte ischémique crâniale n'a pas mis en évidence d'effet significatif sur le pronostic visuel (27,4% vs 12,3%; OR=2,39 IC 95% 0,75 – 7,62), avec un très faible niveau de preuve.<sup>85</sup> Par ailleurs, deux essais randomisés ont comparé des bolus intraveineux initiaux à un placebo. Le premier n'a pas montré de différence significative sur la dose cumulée de corticoïde à 1 an (p=0,39).<sup>86</sup> Le deuxième a démontré l'intérêt d'un traitement d'attaque par bolus à 15mg/kg pendant 3 jours pour prévenir les rechutes (21 rechutes chez 14 patients dans le

<sup>80</sup> Restuccia *et al.*, « Flares in Biopsy-Proven Giant Cell Arteritis in Northern Italy ».

<sup>81</sup> Dumont *et al.*, « Factors Associated with Relapse and Dependence on Glucocorticoids in Giant Cell Arteritis ».

<sup>82</sup> Alba *et al.*, « Relapses in Patients With Giant Cell Arteritis ».

<sup>83</sup> Hellmich *et al.*, « 2018 Update of the EULAR Recommendations for the Management of Large Vessel Vasculitis »; Dasgupta *et al.*, « BSR and BHPR Guidelines for the Management of Giant Cell Arteritis »; Bienvenu, « Management of Giant Cell Arteritis: Recommendations of the French Study Group for Large Vessel Vasculitis (GEFA) ».

<sup>84</sup> Bienvenu, « Management of Giant Cell Arteritis: Recommendations of the French Study Group for Large Vessel Vasculitis (GEFA) ».

<sup>85</sup> Dua *et al.*, « Giant Cell Arteritis ».

<sup>86</sup> Chevalet *et al.*, « A Randomized, Multicenter, Controlled Trial Using Intravenous Pulses of Methylprednisolone in the Initial Treatment of Simple Forms of Giant Cell Arteritis ».

groupe bolus IV versus 37 rechutes chez 13 patients dans le groupe placebo,  $p=0,028$ ) et diminuer la dose cumulée de la corticothérapie (5 636 mg versus 7 860 mg à la 78<sup>ème</sup> semaine,  $p=0,001$ ).<sup>87</sup> Cet essai présente un effectif limité (27 patients inclus) et un faible niveau de preuve. Du fait du risque d'intolérance des fortes doses chez les personnes âgées, cette approche a été peu adoptée dans la pratique courante et réservée aux situations sévères.

La durée de la corticothérapie n'est pas clairement établie, et aucun essai randomisé contrôlé n'a été réalisé dans ce sens. Néanmoins, les recommandations européennes proposent un traitement prolongé sur 12 à 18 mois avec une décroissance progressive.<sup>88</sup> Les recommandations américaines proposent une décroissance plus rapide.<sup>89</sup> Une récente cohorte allemande a étudié la corticothérapie en vie réelle sur 54 patients atteints d'ACG, et leur adhérence aux recommandations de l'EULAR : 63% des patients avaient une dose initiale supérieure aux recommandations, 72% étaient dans l'intervalle recommandé entre 2 et 3 mois (15-20 mg), et 63% étaient à 5 mg ou moins à 1 an de traitement, comme recommandé.<sup>90</sup> La dose cumulée reçue par ces patients était considérée comme superposable à celle reçue dans l'essai GiACTA malgré une durée beaucoup plus longue (4,9g versus 3,8g ; 70 versus 52 semaines respectivement) : la corticothérapie a été réduite plus rapidement initialement, mais de 1 mg par mois seulement à partir de 10 mg, permettant un taux de rechute inférieur (44% versus 82% respectivement).<sup>91</sup> Une étude récente réalisée sur les centres hospitaliers de Paris et Dijon, étudiant rétrospectivement les effets secondaires de la corticothérapie chez 206 patients, retrouve une dose initiale médiane (écart interquartile) de 0,7 (0,7 – 0,7) mg/kg/jour, une durée médiane de 21 (17 – 29) mois avant l'arrêt de la corticothérapie, et 11 (9 – 16) mois avant la dose de 5 mg/jour.<sup>92</sup> L'analyse sur base de données d'une cohorte américaine de 2 497 patients a retrouvé une dose initiale médiane de 40 mg, une durée médiane de traitement de 33 mois, une médiane de 7 mois avant la dose de 5mg/jour, et une dose cumulée en moyenne (écart-type) à 6 983 (6 520) mg.<sup>93</sup> Un essai randomisé ouvert (CORTODOSE, NCT04012905) propose de comparer une décroissance sur 28 semaines à une décroissance sur 52 semaines chez des patients nouvellement diagnostiqués.

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<sup>87</sup> Mazlumzadeh et al., « Treatment of Giant Cell Arteritis Using Induction Therapy with High-Dose Glucocorticoids ».

<sup>88</sup> Hellmich et al., « 2018 Update of the EULAR Recommendations for the Management of Large Vessel Vasculitis »; Bienvenu, « Management of Giant Cell Arteritis: Recommendations of the French Study Group for Large Vessel Vasculitis (GEFA) »; Mackie et al., « British Society for Rheumatology Guideline on Diagnosis and Treatment of Giant Cell Arteritis ».

<sup>89</sup> Maz et al., « 2021 American College of Rheumatology/Vasculitis Foundation Guideline for the Management of Giant Cell Arteritis and Takayasu Arteritis ».

<sup>90</sup> Felten, Leuchten, et Aringer, « Glucocorticoid Dosing and Relapses in Giant Cell Arteritis-a Single Center Cohort Study ».

<sup>91</sup> Felten, Leuchten, et Aringer; Stone et al., « Trial of Tocilizumab in Giant-Cell Arteritis ».

<sup>92</sup> Perrineau et al., « A French Cohort of Patients with Giant Cell Arteritis: Glucocorticoid Treatment and Its Associated Side Effects ».

<sup>93</sup> Broder et al., « Corticosteroid-Related Adverse Events in Patients with Giant Cell Arteritis ».

Une étude s'est intéressée à l'évolution de l'usage de la corticothérapie dans l'ACG au cours du temps chez 245 patients (61 sur la période 1950 – 1979 et 184 sur la période 1980 – 2009). Alors que la dose initiale est globalement constante au cours du temps (entre 40 et 60 mg/jour), la dose cumulée moyenne (écart-type) a significativement augmenté : 5 600 mg (3 600 mg) pour la période 1950 – 1979 vs 10 700 mg (6 300 mg) pour la période 1980 – 2009,  $p=0,002$ . L'explication vient vraisemblablement du temps d'exposition, puisque le temps médian avant l'arrêt complet était de 1,5 ans dans la cohorte 1950-1979 et de 2,6 ans dans la cohorte 1980-2009. Aucune donnée sur les rechutes n'était disponible dans l'étude. Le risque d'effet secondaire, à 10 ans du diagnostic d'ACG, était considéré comme similaire entre les deux périodes (50% pour la période 1950 – 1979 vs 57% pour la période 1980 – 2009,  $p=0,52$ ).<sup>94</sup>

En effet, la corticothérapie prolongée est grevée de nombreux effets secondaires, particulièrement dans la population âgée de l'ACG, exposée habituellement à des doses de corticoïdes plus importantes et plus longues comparées aux autres maladies inflammatoires systémiques :<sup>95</sup> ostéoporose et fracture, hyperglycémie et diabète de type 2, maladies cardiovasculaires dont hypertension artérielle, troubles de l'humeur, atrophie cutanée, cataracte, ...<sup>96</sup>

En effet, dans la récente cohorte française bicentrique,<sup>97</sup> 64% des patients vont présenter en médiane un effet secondaire lié à la corticothérapie : les principaux sont les fractures (13%), et les infections sévères (13%). La prise de poids (+10% du poids initial) concerne 10% des patients, une hypertension artérielle va se déclarer chez 9% d'entre eux, 2% vont développer un diabète. Il est intéressant de noter que les patients inclus présentent initialement de nombreuses comorbidités : 44% sont hypertendus, 10% diabétiques, 10% ont des antécédents cardiovasculaires, 19% sont ou ont été fumeurs, 11% présentent déjà une ostéoporose.

Une étude de pharmaco-épidémiologie au Royaume-Uni a analysé les incidences de diabète, ostéoporose, fracture et glaucome dans une cohorte de 5 011 patients atteints d'ACG, et les a comparés à une cohorte de 5011 patients témoins, ne présentant pas d'ACG et appariés sur l'âge et le sexe. Les ratios de taux d'incidence mettaient en évidence un sur-risque de l'ensemble des facteurs étudiés :<sup>98</sup>

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<sup>94</sup> Chandran et al., « Glucocorticoid Usage in Giant Cell Arteritis over Six Decades ».

<sup>95</sup> Buttgerit et al., « Prevention of Glucocorticoid Morbidity in Giant Cell Arteritis ».

<sup>96</sup> Rice et al., « Long-Term Systemic Corticosteroid Exposure ».

<sup>97</sup> Perrineau et al., « A French Cohort of Patients with Giant Cell Arteritis: Glucocorticoid Treatment and Its Associated Side Effects ».

<sup>98</sup> Wilson et al., « Incidence of Outcomes Potentially Associated with Corticosteroid Therapy in Patients with Giant Cell Arteritis ».

Facteur étudié	Ratios de taux d'incidence	IC 95%
Diabète	1,4	1,2 – 1,7
Ostéoporose	2,4	2,1 – 2,8
Fracture	1,4	1,2 – 1,6
Glaucome	2,0	1,6 – 2,5
Infection sévère nécessitant une hospitalisation	1,5	1,3 – 1,7

Par ailleurs, le même auteur a analysé les conditions de survenue d'un effet secondaire lié à la corticothérapie dans cette cohorte de 5 011 patients atteints d'ACG, en comparant les cas index (présentant l'effet secondaire) à des cas contrôles (ACG sans l'effet secondaire), appariés sur l'âge et le sexe. Glaucome, diabète et ostéoporose survenaient majoritairement dans les deux premières années de traitement. L'apparition d'un diabète et d'une ostéoporose semblait reliée à la dose cumulée de corticoïdes ; cependant, cela n'a pas été démontré pour les fractures et les infections sévères. En revanche, pour l'ensemble des effets secondaires étudiés le risque de développer un effet secondaire semblait relié à la dose moyenne quotidienne :<sup>99</sup>

Dose quotidienne moyenne	Odds ratio ajusté (intervalle de confiance 95%)					
	Fractures	Ostéoporose	Infection	Décès	Diabète	Glaucome
≤ 5 mg/j	1,00	1,00	1,00	1,00	1,00	1,00
5-10 mg/j	1,1(0,8–1,5)	1,3(1,0–1,8)	1,1(0,8–1,6)	1,1(0,8–1,5)	0,9(0,6–1,4)	1,1(0,7–1,7)
10-20 mg/j	1,9(1,3–2,6)	1,5(1,1–2,2)	1,3(0,9–1,9)	1,4(1,0–2,0)	1,2(0,7–1,8)	1,1(0,7–1,8)
20-30 mg/j	2,0 (1,2–3,2)	1,7(1,1–2,7)	1,7(1,0–2,7)	1,7(1,0–2,8)	2,5 (1,4–4,3)	1,6(0,9–3,0)
> 30 mg/j	2,6 (1,6–4,3)	1,9(1,2–2,9)	3,3 (2,2–5,2)	2,1(1,3–3,5)	4,7 (2,8–7,8)	3,5 (2,0–6,1)

Une autre étude sur base de donnée américaine retrouvait une association significative entre augmentation de l'exposition à la corticothérapie orale et apparition d'un effet secondaire osseux, de diabète (+5% pour chaque 1000 mg de corticoïde,  $p < 0,001$ ), de cataracte, de glaucome et de pneumonie infectieuse.<sup>100</sup>

### 3.2 Antiagrégant plaquettaire

La prescription d'antiagrégant plaquettaire (aspirine 75 à 300 mg/jour) est proposée chez les patients présentant une atteinte ophtalmologique, dans un objectif de prévention d'un nouvel évènement

<sup>99</sup> Wilson et al., « Serious Adverse Effects Associated with Glucocorticoid Therapy in Patients with Giant Cell Arteritis (GCA) ».

<sup>100</sup> Broder et al., « Corticosteroid-Related Adverse Events in Patients with Giant Cell Arteritis ».

ischémique oculaire.<sup>101</sup> Aucun essai randomisé n'a été conduit sur le sujet, et les données sont issues d'études rétrospectives suggérant un bénéfice sur les événements ischémiques.<sup>102</sup> Lorsqu'il n'y a pas d'atteinte ophtalmologique, la prescription systématique ne semble pas légitime et doit se faire au cas par cas selon le risque cardiovasculaire individuel.<sup>103</sup>

### 3.3 Epargne cortisonique

Pour diminuer l'exposition à la corticothérapie, plusieurs traitements à visée d'épargne cortisonique ont été testés. Parmi eux, deux ont démontré leur efficacité pour réduire le taux de rechute : le méthotrexate et le tocilizumab. Les essais ont été réalisés avec une corticothérapie en groupe contrôle, et aucun essai en face-à-face ne permet aujourd'hui de hiérarchiser ces traitements.

Une étude rétrospective a comparé deux stratégies : traitement immunosuppresseur d'emblée (114 patients) versus corticothérapie seule ou immunosuppresseurs plus de 3 mois après le diagnostic (51 patients). Les immunosuppresseurs concernés étaient le méthotrexate (138 patients), le cyclophosphamide (48 patients) et le tocilizumab (27 patients). Le taux de rechute était significativement plus faible dans le groupe immunosuppresseur d'emblée (38,6%) par rapport à l'autre groupe (66,7% ;  $p=0,001$ ), la dose cumulée de corticoïde était aussi significativement plus faible à 1 et 3 mois, avec moins de diabète cortico-induit (7% versus 23,5%,  $p=0,003$ ), sans différence pour le taux d'infection ( $p=0,64$ ).<sup>104</sup> Si un effet bénéfique d'un traitement d'emblée est suggéré par cette étude, les résultats sont à pondérer par des populations non comparables, avec un risque de confusion résiduelle important. En effet, les patients du groupe immunosuppresseur d'emblée étaient globalement plus jeunes (68,9 ans versus 72,3,  $p=0,005$ ), avec une atteinte visuelle moins fréquente même si la différence n'était pas statistiquement significative (19,5% versus 31,4%,  $p=0,094$ ).

#### 3.3.1 Méthotrexate

Le méthotrexate est un anti-métabolite largement utilisé en cancérologie. A des doses beaucoup plus faibles, il a démontré son efficacité dans les pathologies auto-immunes, et notamment dans la polyarthrite rhumatoïde.<sup>105</sup> Plusieurs essais thérapeutiques randomisés<sup>106</sup> ont comparé le

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<sup>101</sup> FAI2R et GEFA, « PNDS Artérite à Cellules Géantes (Horton) ».

<sup>102</sup> Mollan et al., « Aspirin as Adjunctive Treatment for Giant Cell Arteritis ».

<sup>103</sup> FAI2R et GEFA, « PNDS Artérite à Cellules Géantes (Horton) ».

<sup>104</sup> Quartuccio et al., « Treatment Strategy Introducing Immunosuppressive Drugs with Glucocorticoids Ab Initio or Very Early in Giant Cell Arteritis ».

<sup>105</sup> Aletaha et Smolen, « Diagnosis and Management of Rheumatoid Arthritis ».

<sup>106</sup> Spiera et al., « A Prospective, Double-Blind, Randomized, Placebo Controlled Trial of Methotrexate in the Treatment of Giant Cell Arteritis (GCA) »; Hoffman et al., « A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of Adjuvant Methotrexate Treatment for Giant Cell Arteritis »; Jover et al., « Combined Treatment of Giant-Cell Arteritis with Methotrexate and Prednisone ».



méthotrexate en traitement adjuvant à une corticothérapie seule dans l'ACG. Une méta-analyse sur données individuelles<sup>107</sup> a repris l'ensemble de ces essais, confirmant l'efficacité du méthotrexate sur le risque de première rechute avec un hazard ratio (HR)=0,65 (IC 95% 0,44 – 0,98). Néanmoins, ces essais utilisent le méthotrexate par voie orale, à des doses relativement faibles (entre 7,5 et 15mg/semaine). Il est établi que l'efficacité du méthotrexate est meilleure par voie sous cutanée, notamment du fait d'une biodisponibilité accrue<sup>108</sup> et est donc probablement sous-estimée dans ces essais.

Les effets secondaires du méthotrexate sont numériquement nombreux, essentiellement une fatigue les jours suivant la prise, des troubles gastro-intestinaux et une élévation des enzymes hépatiques. Plus rarement, une pancytopenie et une pneumopathie médicamenteuse peuvent survenir<sup>109</sup>. Des études observationnelles suggèrent que 20 à 30% des patients avec une polyarthrite rhumatoïde arrêtent le méthotrexate dans la première année de traitement, plus fréquemment à cause d'effets secondaires que d'un manque d'efficacité.<sup>110</sup>

### 3.3.2 Tocilizumab

La concentration en IL-6, cytokine pro-inflammatoire, est fortement augmentée dans le sérum des patients présentant une ACG, et son taux est corrélé à l'activité de la maladie et au taux de CRP.<sup>111</sup> Le tocilizumab est un anticorps monoclonal humanisé dirigé contre le récepteur de l'IL-6, bloquant la signalisation de l'IL-6, et, entre autre, la production de CRP.

Une récente revue de la Cochrane conclue à un effet bénéfique du tocilizumab sur la rémission, la survie sans rechute, et le traitement de l'ACG réfractaire, avec un niveau de preuve modéré du fait de l'existence de deux essais randomisés seulement.<sup>112</sup> Le premier, incluant 30 patients, retrouvait une survie sans rechute à 52 semaines chez 85% des patients sous tocilizumab hebdomadaire, versus 20% dans le groupe placebo (différence de risque=65%, IC 95% 3% – 94%).<sup>113</sup> Néanmoins, cet essai utilisait la CRP dans le critère de jugement (définition de la rechute), entraînant potentiellement une surestimation de l'efficacité du tocilizumab, ce d'autant que le groupe contrôle recevait une corticothérapie courte (6 mois), remettant en cause la validité externe des résultats.<sup>114</sup> Le deuxième, incluant 250 patients, confirmait l'efficacité du tocilizumab administré en sous cutanée de manière

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<sup>107</sup> Mahr et al., « Adjunctive Methotrexate for Treatment of Giant Cell Arteritis ».

<sup>108</sup> Bianchi et al., « Methotrexate and Rheumatoid Arthritis ».

<sup>109</sup> Albrecht et Müller-Ladner, « Side Effects and Management of Side Effects of Methotrexate in Rheumatoid Arthritis ».

<sup>110</sup> Schnabel et Gross, « Low-Dose Methotrexate in Rheumatic Diseases--Efficacy, Side Effects, and Risk Factors for Side Effects ».

<sup>111</sup> Samson et al., « Biological Treatments in Giant Cell Arteritis & Takayasu Arteritis ».

<sup>112</sup> Antonio, Santos, et Abariga, « Tocilizumab for Giant Cell Arteritis ».

<sup>113</sup> Villiger et al., « Tocilizumab for Induction and Maintenance of Remission in Giant Cell Arteritis ».

<sup>114</sup> Samson et al., « Biological Treatments in Giant Cell Arteritis & Takayasu Arteritis ».

hebdomadaire, permettant une rémission soutenue chez 56% des patients versus 14% des patients sous corticoïdes seuls, avec une décroissance sur 26 semaines (RR=4,00 IC 95% 1,97 – 8,12), sans majoration du risque infectieux (7% vs 4%, RR=1,75 IC 95% 0,38 – 8,12). Le bras recevant du tocilizumab hebdomadaire avec une corticothérapie dégressive sur 26 semaines recevait une dose cumulée médiane à 1 an de 1 862 mg (écart interquartile 630 – 6 602).<sup>115</sup> La durée courte de la corticothérapie pose de nouveau la question de la validité externe des résultats. Une étude rétrospective observationnelle espagnole a inclus 134 patients traités par tocilizumab, intraveineux mensuel ou sous cutané hebdomadaire. A 12 mois, sur les 71 patients encore suivis, 70,4% étaient en rémission soutenue. Dans cette étude, 24% des patients ont présenté un effet indésirable notable, essentiellement de nature infectieuse ou hématologique. Une infection sévère est survenue chez 12% de patients.<sup>116</sup> Une autre étude rétrospective s'est intéressée à l'administration du tocilizumab chez 21 patients de plus de 80 ans : 67% ont arrêté la corticothérapie après l'introduction du tocilizumab dans un délai médian de 8 mois.<sup>117</sup>

Peu de données sont disponibles sur l'arrêt du tocilizumab une fois la rémission obtenue, et les recommandations françaises suggèrent de l'arrêter à 12 mois en l'absence de rechute.<sup>118</sup> Néanmoins, l'efficacité suspensive du tocilizumab est étayée par une étude prospective en ouvert proposant le tocilizumab en traitement additionnel dès le diagnostic d'ACG, avec une injection par mois pendant 3 mois (4 injections au total) et une décroissance progressive de la corticothérapie jusqu'à 0,1 mg/kg à 28 semaines, puis réduction d'1 mg par mois jusqu'à l'arrêt complet. Sur les 20 patients inclus, 10 ont présenté une rechute, avec un délai médian de 28 semaines (écart interquartile 20 – 51) et la dose cumulée de corticoïde médiane à 1 an était de 4 029 mg (3 638 – 5 062).<sup>119</sup> Une étude rétrospective récente rapporte des données sur l'utilisation du tocilizumab chez 43 patients dans trois centres français : 14 (33%) ont été traités de manière continue pendant la durée du suivi (médiane 647 jours, écart interquartile 430 – 845), 15 (35%) ont repris le traitement d'une fait d'une rechute, et 14 (33%) ont pu arrêter le tocilizumab sans reprise évolutive de l'ACG. Le taux de rechute à l'arrêt du tocilizumab était de 62% après l'arrêt du tocilizumab.<sup>120</sup> Dans une autre étude observationnelle sur 32 patients, un seul patient a rechuté après l'arrêt du tocilizumab. Dix-neuf ont été traités par

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<sup>115</sup> Stone et al., « Trial of Tocilizumab in Giant-Cell Arteritis ».

<sup>116</sup> Calderón-Goercke et al., « Tocilizumab in Giant Cell Arteritis. Observational, Open-Label Multicenter Study of 134 Patients in Clinical Practice ».

<sup>117</sup> de Boysson et al., « Assessment of the Efficacy and Safety of Tocilizumab in Patients over 80 Years Old with Giant Cell Arteritis ».

<sup>118</sup> FAI2R et GEFA, « PND S Artérite à Cellules Géantes (Horton) ».

<sup>119</sup> Samson et al., « Tocilizumab as an Add-on Therapy to Glucocorticoids during the First 3 Months of Treatment of Giant Cell Arteritis ».

<sup>120</sup> Clément et al., « Real-World Risk of Relapse of Giant Cell Arteritis Treated With Tocilizumab ».

tocilizumab sur une période supérieure à 1 an ; la dose a été réduite chez 13 d'entre eux, et parmi eux, un seul a présenté une rechute nécessitant la reprise de la dose initiale.

La tolérance du tocilizumab est habituellement bonne, et les effets secondaires sont essentiellement marqués par des évènements infectieux, dont le diagnostic est rendu difficile par la négativité des paramètres de l'inflammation inhérente au mécanisme d'action de la molécule. Parmi les 43 patients de la récente cohorte française, 5 ont arrêtés le tocilizumab du fait d'une toxicité du traitement (deux vascularites cutanées, deux infections sévères, une tumeur rénale d'évolution rapide).<sup>121</sup> Dans l'étude de Regola *et al.*, 10 cas d'infections qui ont nécessité l'arrêt temporaire du tocilizumab, ces infections survenant la plupart du cas dans les six premiers mois de traitement.<sup>122</sup> Chez les 21 patients de plus de 80 ans, des effets indésirables sévères (grade  $\geq 3$  de la classification *common toxicity criteria for adverse events*) ont été observés chez 4 patients (19%), et 3 patients ont présenté des évènements infectieux.<sup>123</sup> Un cas d'encéphalopathie postérieure réversible a été imputé au tocilizumab chez une patiente de 65 ans présentant une ACG, traitée depuis plus d'un an.<sup>124</sup> Un cas de toxidermie sévère type Stevens Johnson a également été décrit, chez une patiente de 82 ans, un mois après l'introduction du tocilizumab pour une ACG.<sup>125</sup> Un cas de sarcoïdose induite par le tocilizumab a été décrit chez une patiente traitée pour une ACG, plusieurs cas ayant été décrits également dans la polyarthrite rhumatoïde.<sup>126</sup>

### 3.3.3 Sirukumab

Le sirukumab est également un anticorps monoclonal humanisé dirigé contre l'IL-6. Une étude randomisée, contrôlée contre double aveugle a été menée, mais interrompue précocement du fait de la décision du sponsor d'arrêter le déploiement du sirukumab dans les pathologies auto-immunes. Sur 204 patients prévus initialement, 161 patients ont été inclus, et seulement 28 ont poursuivi leur suivi jusqu'à 52 semaines. Les analyses réalisées étaient en faveur d'une diminution des rechutes chez les patients traités par sirukumab par rapport au placebo, malgré des durées de traitement plus courtes qu'initialement prévues.<sup>127</sup>

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<sup>121</sup> Clément *et al.*

<sup>122</sup> Regola *et al.*, « Long-Term Treatment with Tocilizumab in Giant Cell Arteritis ».

<sup>123</sup> de Boysson *et al.*, « Assessment of the Efficacy and Safety of Tocilizumab in Patients over 80 Years Old with Giant Cell Arteritis ».

<sup>124</sup> Butryn *et al.*, « Tocilizumab-Associated Posterior Reversible Encephalopathy Syndrome in Giant-Cell Arteritis – Case Report ».

<sup>125</sup> Venkateswaran, Khianey, et Generoso, « Stevens Johnson Syndrome in a Patient with Giant Cell Arteritis During Short Term Tocilizumab Therapy ».

<sup>126</sup> Del Giorgio *et al.*, « New-Onset Cutaneous Sarcoidosis under Tocilizumab Treatment for Giant Cell Arteritis ».

<sup>127</sup> Schmidt *et al.*, « A Multicentre, Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Sirukumab in the Treatment of Giant Cell Arteritis ».

### 3.3.4 Ustekinumab

L'ustekinumab est un anticorps monoclonal humanisé bloquant l'activité des cytokines IL-12 et IL-23. Le rôle possible de ces cytokines dans la physiopathologie de l'ACG en fait une option thérapeutique intéressante. Un registre prospectif a été conduit, incluant 25 patients présentant une ACG réfractaire. Ces patients ont reçu 90 mg d'ustekinumab par voie sous cutanée à S0, S4 puis toutes les 12 semaines, et ont été suivi au moins 12 mois. A 52 semaines, aucun patient n'avait présenté de rechute, 24% étaient sevrés complètement de la corticothérapie. L'intervalle entre les injections a été réduit à 8 semaines chez 6 patients du fait d'une maladie insuffisamment contrôlée, et chez 3 patients, les doses ont été réduites à 45 mg toutes les 12 semaines du fait d'une bonne réponse clinique. Huit patients ont présenté des effets indésirables, essentiellement des infections mineures, et 3 d'entre eux ont arrêté le traitement du fait d'effets secondaires.<sup>128</sup> Une étude récente, ouverte et non contrôlée, a testé l'ustekinumab à la même posologie que dans l'étude citée précédemment, chez 13 patients (39% nouvellement diagnostiqués), combiné à une corticothérapie à posologie décroissante sur 6 mois. Les inclusions ont été stoppées avant la fin de l'étude, 10 patients sur les 13 n'ayant pas atteint le critère de jugement principal (absence de rechute à 52 semaines, normalisation des paramètres biologiques inflammatoires, et adhérence au schéma de décroissance de la corticothérapie).<sup>129</sup> Cette étude souffre de limites méthodologiques importantes, de par son caractère ouvert d'une part, et d'autre part, du schéma de décroissance rapide de la corticothérapie.<sup>130</sup> Un essai de phase II randomisé en ouvert est actuellement en cours de recrutement comparant l'ustekinumab associé à une corticothérapie chez les patients présentant une ACG réfractaire à une corticothérapie seule (NCT03711448).

### 3.3.5 Anakinra

L'anakinra est un antagoniste du récepteur de l'IL-1, une interleukine pro-inflammatoire participant à l'apparition de l'ACG. Son efficacité a été largement démontrée dans les pathologies auto-inflammatoires. Une série de 3 patients atteints d'ACG réfractaire a été rapportée en 2014, montrant une efficacité clinique et biologique de l'anakinra.<sup>131</sup> Une série rétrospective issue du registre français du Groupe d'Etude Français des Artérites des gros vaisseaux (GEFA) analyse l'effet de l'anakinra sur 6 patients, traités en médiane 19 mois (écart interquartile 18 – 32 mois). Une rémission complète clinique et biologique a été obtenue pour l'ensemble des patients. La corticothérapie a été arrêtée complètement chez 4 patients, et poursuivie à 5mg/jour pour les deux autres. Un patient a rechuté

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<sup>128</sup> Conway et al., « Ustekinumab for Refractory Giant Cell Arteritis ».

<sup>129</sup> Matza et al., « Ustekinumab for the Treatment of Giant Cell Arteritis ».

<sup>130</sup> Conway et Molloy, « Ustekinumab in Giant Cell Arteritis »; Samson et Bonnotte, « Ustekinumab For the Treatment of Giant Cell Arteritis ».

<sup>131</sup> Ly et al., « Interleukin-1 Blockade in Refractory Giant Cell Arteritis ».

13 mois après l'initiation de l'anakinra, alors que les injections avaient été espacées à une fois toutes les 48 heures.<sup>132</sup> Une étude française, randomisée contrôlée contre placebo testant l'anakinra 100mg/jour en sous-cutané chez des patients nouvellement diagnostiqués ou en rechute est en cours de recrutement (NCT02902731).

### 3.3.6 Cyclophosphamide

Le cyclophosphamide est un agent alkylant ayant un effet pro-apoptotique sur les cellules. Plusieurs séries rétrospectives ont analysé l'efficacité du cyclophosphamide comme traitement d'induction dans l'ACG. Les principales sont résumées ci-dessous.

Séries	N	Critères diagnostiques	BAT+	Profil des patients	Maintenance	Réponse	Rechute
Loock, 2012 <sup>133</sup>	31	ACR 1990, Chapel Hill ou imagerie et signes cliniques compatibles	13	ACG réfrac	MTX (54%), AZA (59%), Lefl (7%)	90%	43% à 21 mois
Quartuccio, 2012 <sup>134</sup>	19	ACR 1990	9	15 réfrac 4 <i>ab initio</i>	MTX (74%)	79%	27%, 12 mois après arrêt CYC
de Boysson, 2013 <sup>135*</sup>	15	ACR 1990	8	Mauvaise tolérance des GC	MTX (20%)	60%	40% à 7 mois
Carbonella, 2016 <sup>136</sup>	11 CYC 12 MTX	ACR 1990	13	<i>Ab initio</i>	MTX chez les rechuteurs sous GC ou CYC		18% Vs 42% sous GC seul et 8% sous GC et MTX à 23 mois

*Ab initio* : nouvellement diagnostiqué, ACR : American College of Rheumatology; AZA : azathioprine ; BAT : biopsie de l'artère temporale; CYC : cyclophosphamide ; GC : corticoïdes ; Lefl : léflunomide ; MTX : méthotrexate ; réfrac : réfractaire

\*Une revue systématique des cas publiés jusqu'en 2012 est disponible dans cette étude.

Les effets secondaires sous cyclophosphamide sont parfois sévères, rapportés chez 19% des patients dans la revue de la littérature de de Boysson *et al.*<sup>137</sup>, et nécessitant l'arrêt du traitement chez 12,5% principalement à cause de cytopénies.

### 3.3.7 Mycophénolate

Le mycophénolate est un anti-métabolite qui inhibe la synthèse des guanines. A ce titre, il supprime la prolifération cellulaire, dont celle des lymphocytes T et B. L'hypothèse d'un rôle pathogénique de

<sup>132</sup> Deshayes *et al.*, « Steroid-Sparing Effect of Anakinra in Giant-Cell Arteritis ».

<sup>133</sup> Loock *et al.*, « Treatment of Refractory Giant Cell Arteritis with Cyclophosphamide: A Retrospective Analysis of 35 Patients from Three Centres ».

<sup>134</sup> Quartuccio *et al.*, « Role of Oral Cyclophosphamide in the Treatment of Giant Cell Arteritis ».

<sup>135</sup> de Boysson *et al.*, « Is There a Place for Cyclophosphamide in the Treatment of Giant-Cell Arteritis? »

<sup>136</sup> Carbonella *et al.*, « Immunosuppressive Therapy (Methotrexate or Cyclophosphamide) in Combination with Corticosteroids in the Treatment of Giant Cell Arteritis ».

<sup>137</sup> de Boysson *et al.*, « Is There a Place for Cyclophosphamide in the Treatment of Giant-Cell Arteritis? »

ces cellules dans la physiopathologie de l'ACG, et la preuve de l'efficacité du mycophénolate dans d'autres vascularites systémiques a conduit à l'utilisation de ce traitement en pratique clinique. Une étude de cas rapporte trois patients traités par mycophénolate 2g par jour par voie orale, à visée d'épargne cortisonique (diabète de type 2, obésité, ostéoporose sous-jacents). Les trois patients semblaient avoir tiré bénéfice du traitement, avec une diminution plus rapide de la corticothérapie par rapport aux décroissances habituellement réalisées. Le mycophénolate était par ailleurs bien toléré, sans signe de toxicité après une moyenne de 21 mois de suivi.<sup>138</sup> Une série rapporte 37 patients atteints d'ACG de type aorto-artérite traités par mycophénolate. Trente et un patients ont été traités pendant au moins 2 ans, avec une bonne réponse clinicobiologique. Le taux de rechute était de 16,2% à un an, et 27% à deux ans de traitement.<sup>139</sup>

### 3.3.8 Léflunomide

Le léflunomide inhibe l'enzyme dihydro-orotate déshydrogénase (DHODH) et a une action antiprolifératrice. Il a donc un effet immunomodulateur, et son efficacité a été démontrée dans la polyarthrite rhumatoïde et dans certaines vascularites systémiques. Deux séries de cas de patients réfractaires traités par léflunomide ont été rapportées dans la littérature, de 11 et 9 patients, avec une bonne réponse clinicobiologique à 3 mois de traitement. Les effets indésirables rapportés étaient essentiellement digestifs (nausées, diarrhées, vomissements).<sup>140</sup> Une autre étude rétrospective sur l'efficacité du léflunomide dans les vascularites systémiques retrouvait une efficacité de 64% à 6 mois de traitement chez 14 patients présentant une ACG, avec un seul effet secondaire rapporté.<sup>141</sup> Plus récemment, une étude ouverte non randomisée proposait au patient l'adjonction de 10 mg de léflunomide par voie orale, à 3 mois de l'instauration de la corticothérapie. Sur les 76 patients inclus, 30 ont reçus du léflunomide. Le taux de rechute était de 13,3% dans le groupe léflunomide, versus 39,1% dans le groupe corticothérapie seule ( $p=0,02$ ). Les effets secondaires rapportés dans le groupe léflunomide étaient alopécie, diarrhée, perte de poids, et cytolyse hépatique.<sup>142</sup> Une étude rétrospective a rapporté les résultats du léflunomide dans une cohorte anglaise de 70 patients, présentant une ACG avec atteinte extra-crânienne. Cette équipe utilise assez fréquemment ce traitement, puisque ces 70 patients représentent 63% des patients identifiés. Dans la majorité des cas, le léflunomide était le traitement d'épargne de première ligne. A la fin du suivi, 49 patients étaient encore traités. Les arrêts de traitement (21 patients) étaient liés à

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<sup>138</sup> Sciascia et al., « Mycophenolate Mofetil as Steroid-Sparing Treatment for Elderly Patients with Giant Cell Arteritis ».

<sup>139</sup> Karabayas et al., « Evaluation of Adjunctive Mycophenolate for Large Vessel Giant Cell Arteritis ».

<sup>140</sup> Adizie et al., « Efficacy and Tolerability of Leflunomide in Difficult-to-Treat Polymyalgia Rheumatica and Giant Cell Arteritis »; Diamantopoulos, Hetland, et Myklebust, « Leflunomide as a Corticosteroid-Sparing Agent in Giant Cell Arteritis and Polymyalgia Rheumatica ».

<sup>141</sup> Mustapha et al., « Efficacy of Leflunomide in the Treatment of Vasculitis ».

<sup>142</sup> Hočevár et al., « Does Leflunomide Have a Role in Giant Cell Arteritis? »

la rémission soutenue (4 patients), une réaction allergique (3 patients), une infection majeure (2 patients), une intolérance subjective (11 patients) et l'apparition d'un lymphome (1 patient). Aucun arrêt n'était lié à un défaut d'efficacité. Seize patients (23%) ont présenté au moins une rechute clinique avec délai médian de 15 mois (3 – 40 mois).<sup>143</sup>

### 3.3.9 Abatacept

L'abatacept est une protéine de fusion entre le fragment Fc d'IgG1 humaine et la partie extracellulaire de la molécule CTLA-4, permettant d'inhiber l'activation des lymphocytes T, impliqués dans la physiopathologie de l'ACG.<sup>144</sup>

Une étude randomisée en double aveugle, a testé l'abatacept contre placebo. Tous les patients inclus recevaient de l'abatacept à 10mg/kg par voie intraveineuse pendant les 2 premiers mois, puis étaient randomisés en deux bras : abatacept mensuel ou placebo, sous couvert d'une corticothérapie dégressive sur 28 semaines. Quarante-neuf patients ont été inclus, et 41 randomisés à 12 semaines. Le taux de survie sans rechute était de 48% dans le groupe abatacept et 31% dans le groupe placebo ( $p=0,049$ ), avec une durée médiane de rémission de 9,9 mois versus 3,9 mois respectivement ( $p=0,023$ ). Les effets secondaires étaient similaires dans les deux groupes.<sup>145</sup> Curieusement, cette étude a été réalisée en utilisant un test unilatéral, avec un risque alpha à 10% : les résultats sont donc à interpréter avec prudence.

Une étude « en vie réelle » rapporte 28 patients consécutifs (sur 33 patients inclus) dont 17 présentaient une rechute : les patients « impairs » recevaient du tocilizumab par voie intraveineuse ou sous cutanée selon leur préférence, et les patients « pairs » recevaient de l'abatacept par voie sous cutanée, avec une décroissance de la corticothérapie sur 6 mois. Cette étude propose des critères de jugement originaux, distinguant une réponse complète (normalisation des paramètres cliniques, biologiques, et échographiques), et partielle (amélioration substantielle de ces mêmes paramètres). Le taux de réponse complète était de 57% dans le bras tocilizumab intraveineux, 67% dans le bras tocilizumab sous cutané et 31% dans le bras abatacept.<sup>146</sup>

Une étude américaine randomisée contrôlée contre placebo, en double aveugle, testant l'abatacept 125 mg en sous cutané par semaine dans l'ACG nouvellement diagnostiquée ou en rechute (ABAGART, NCT04474847) est actuellement en cours de recrutement.

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<sup>143</sup> Tomelleri et al., « Long-Term Efficacy and Safety of Leflunomide in Large-Vessel Giant Cell Arteritis ».

<sup>144</sup> Samson et al., « Traitement de l'artérite à cellules géantes ».

<sup>145</sup> Langford et al., « A Randomized, Double-Blind Trial of Abatacept (CTLA-4Ig) for the Treatment of Giant Cell Arteritis ».

<sup>146</sup> Rossi et al., « An Agent-to-Agent Real Life Comparison Study of Tocilizumab versus Abatacept in Giant Cell Arteritis ».

### 3.3.10 Anti-TNF $\alpha$

Largement utilisés dans les rhumatismes inflammatoires, les anti-TNF sont des anticorps monoclonaux complètement (adalimumab) ou partiellement humanisés (infliximab), ou des protéines chimériques (etanercept) se comportant comme des récepteurs solubles du TNF $\alpha$ . Ces biomédicaments diminuent le TNF $\alpha$  sérique, une cytokine pro-inflammatoire impliquée dans la physiopathologie de l'ACG. Les essais thérapeutiques conduits dans l'ACG sont malheureusement peu concluants.

- **Infliximab** : un essai randomisé contrôlé contre placebo, en double aveugle a testé l'infliximab 5 mg/kg administré en intraveineux à S0, S2, S6 puis toutes les 8 semaines, chez des patients présentant une ACG nouvellement diagnostiquée. Les patients étaient également sous corticoïdes, avec une décroissance progressive sur 24 semaines. Parmi les 44 patients inclus, 16 recevaient le placebo, et 28 l'infliximab. A 22 semaines, 43% des patients étaient en rémission dans le groupe infliximab, versus 50% dans le groupe placebo ( $p=0,65$ ), avec une dose cumulée dans les deux groupes non statistiquement significatives (3 154 mg vs 3 049 mg,  $p=0,95$ ).<sup>147</sup>
- **Etanercept** : un essai randomisé contrôlé contre placebo, en double aveugle a testé l'etanercept 25 mg administré en sous cutané toutes les 2 semaines. Les patients inclus avaient une ACG cliniquement asymptomatique avec une dose stable de corticoïde, supérieure à 10 mg, et devaient présenter une comorbidité nécessitant une épargne cortisonique (diabète cortico-induit, ostéoporose ou hypertension artérielle). Huit patients ont été randomisés dans le groupe etanercept, et 9 dans le groupe placebo, des effectifs plus faibles que ceux attendus (14 dans chaque groupe). A 12 mois, 50% des patients dans le groupe etanercept et 78% dans le groupe placebo avaient rechutés, mais sans atteindre la significativité ( $p>0,05$ ).<sup>148</sup>
- **Adalimumab** : un essai randomisé contrôlé contre placebo, en double aveugle a testé l'adalimumab 40 mg administré en sous-cutané toutes les 2 semaines, chez des patients présentant une ACG nouvellement diagnostiquée. La corticothérapie associée était progressivement diminuée pour atteindre 0,1 mg/kg à 24 semaines, puis diminuée d'1mg toutes les 4 semaines jusqu'à l'arrêt. Le nombre de patients randomisés, 34 patients dans le groupe adalimumab et 36 dans le groupe placebo, était inférieur à celui attendu (50 entre

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<sup>147</sup> Hoffman et al., « Infliximab for Maintenance of Glucocorticosteroid-Induced Remission of Giant Cell Arteritis ».

<sup>148</sup> Martinez-Taboada et al., « A Double-Blind Placebo Controlled Trial of Etanercept in Patients with Giant Cell Arteritis and Corticosteroid Side Effects ».



chaque groupe). A 26 semaines, 58,9% des patients étaient en rémission dans le groupe adalimumab versus 50,0% dans le groupe placebo (p=0,46).<sup>149</sup>

### 3.3.11 Molécules en cours de développement

Plusieurs voies thérapeutiques sont actuellement en cours de développement .<sup>150</sup>

Molécule	Référence	Design	Type de patients	N prévu	Durée prévue de la corticothérapie	Critère de jugement
Baricitinib	NCT03026504	Phase II Un seul groupe Ouvert	Rechute	15	Non applicable	Effets indésirables et taux de rémission à 52 semaines
Bosentan	NCT03841734	Phase III Ouvert	Diagnostic, atteinte visuelle	8	Non applicable	Acuité visuelle à 12 semaines
Guselkumab (anti IL-23)	THEIA NCT04633447	Phase II Randomisée Double aveugle	Diagnostic ou rechute	60	26 semaines	Taux de rémission à 28 semaines
Mavrilimumab (anti GM-CSF)	NCT03827018	Phase II Double aveugle	Diagnostic, rechute ou réfractaire	70	26 semaines	Taux de rechute à 26 semaines
Secukinumab (anti IL-17A)	NCT04930094	Phase III Randomisée Double aveugle	Diagnostic ou rechute	240	26 semaines (secukinumab) 52 semaines (placebo)	Taux de rémission à 52 semaines
Secukinumab <sup>151</sup>	NCT03765788	Phase II Randomisée Double aveugle	Diagnostic ou rechute	50	27 semaines	Taux de rémission à 28 semaines
Upadacitinib (anti JAK)	SELECT-GCA NCT03725202	Phase III Randomisée Double aveugle	Diagnostic ou rechute	420	52 semaines	Taux de rémission à 52 semaines

GM-CSF : Granulocyte-macrophage colony-stimulating factor; IL : interleukine; JAK : Janus Kinase

<sup>149</sup> Seror et al., « Adalimumab for Steroid Sparing in Patients with Giant-Cell Arteritis ».

<sup>150</sup> Harkins et Conway, « Giant Cell Arteritis ».

<sup>151</sup> Venhoff et al., « Efficacy and Safety of Secukinumab in Patients with Giant Cell Arteritis ».

## 4 Objectifs

Les données disponibles dans l'ACG restent insuffisantes pour proposer une médecine de précision. En effet, le risque de rechute est mal connu, avec une variabilité inter-étude importante. De plus, les facteurs prédictifs de rechute ne sont pas connus. Enfin, l'effet traitement des immunosuppresseurs est sujet d'un défaut de hiérarchisation en l'absence de comparaison directe.

L'objectif de cette thèse est, *in fine*, de réaliser un modèle de connaissance permettant secondairement de modéliser une population virtuelle réaliste de patients présentant une ACG afin d'évaluer, selon les caractéristiques de chaque patient, la meilleure stratégie thérapeutique.

Afin d'atteindre cet objectif, ce travail de thèse se décline sur deux axes :

- Quantifier la morbi-mortalité de la pathologie, afin de modéliser le risque individuel : déterminer la prévalence des rechutes des patients sous corticothérapie seule (méta-analyse), la prévalence des rechutes sévères (méta-analyse), analyser l'évolution de la mortalité au cours du temps en Europe (analyse des données EUROSTAT entre 1994 et 2016).
- Evaluer l'intérêt des thérapeutiques actuelles par réalisation d'une comparaison indirecte (méta-analyse en réseau) des différentes molécules actuellement disponibles.

## 5 Analyse de la morbi-mortalité dans l'artérite à cellules géantes

### 5.1 Méta analyse de la prévalence des rechutes sous corticothérapie

Mainbourg S, Addario A, Samson M, Puéchal X, François M, Durupt S, Gueyffier F, Cucherat M, Durieu I, Reynaud Q, Lega JC. **Prevalence of Giant Cell Arteritis Relapse in Patients Treated With Glucocorticoids: A Meta-Analysis.** *Arthritis Care Res (Hoboken)*. 2020 Jun;72(6):838-849. doi: 10.1002/acr.23901. Epub 2020 May 19. PMID: 30951256.

**Objective:** The relapse rate of patients with giant cell arteritis (GCA) treated with glucocorticoids (GCs) alone varied widely in observational series and randomized controlled trials (RCTs). The purpose of this systematic review was to evaluate the prevalence of relapse and predisposing factors in patients receiving GCs alone.



**Methods:** We searched Medline up to December 2017. The prevalence of relapse was pooled using a random-effects model.

**Results:** A total of 34 studies (2,505 patients), comprising 8 RCTs, were included. The overall prevalence of relapse was 47.2% (95% confidence interval 40.0, 54.3) with a high heterogeneity ( $I^2 = 93\%$ ). Prevalence of relapse was significantly higher for patients included in an RCT compared to those included in an observational study ( $P < 0.0001$ ), but was not significantly different according to design ( $P = 0.06$ ). The relapse rate was associated with year of publication (34 studies, rate increase of 8.3% for 1 decade;  $P < 0.0001$ ) and with shorter GC regimens (17 studies, rate decrease of 1.7% for 1 additional month;  $P < 0.001$ ), the duration of scheduled GC therapy being shorter in RCTs (12.8 months) compared to observational studies (28.8 months). The effective duration of GC therapy ( $P = 0.23$ ), initial GC dose ( $P = 0.49$ ), duration of follow-up ( $P = 0.14$ ), sex ( $P = 0.29$ ), and age ( $P = 0.43$ ) were not associated with the prevalence of relapse.

**Conclusion:** GCA relapses occur in half of patients and without improvement across decades in patients receiving GC alone, and the relapse rate is more related to short duration of GC administration than to the initial dose at induction. These results advocate for trial design with at least 12 months of GC therapy.



# Prevalence of Giant Cell Arteritis Relapse in Patients Treated With Glucocorticoids: A Meta-Analysis

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**Conclusion.** GCA relapses occur in half of patients and without improvement across decades in patients receiving GC alone, and the relapse rate is more related to short duration of GC administration than to the initial dose at induction. These results advocate for trial design with at least 12 months of GC therapy.

## INTRODUCTION

Giant cell arteritis (GCA) is a large vessel vasculitis affecting individuals age >50 years (1). It is characterized by the occurrence of ischemic signs such as headache, visual manifestations, scalp tenderness, jaw claudication, and stroke, together with systemic symptoms such as weight loss or anorexia, fatigue, and fever.

Most studies consider that GCA does not significantly affect survival (2–4). The recommended treatment at diagnosis is high-dose glucocorticoid (GC) therapy (0.7–1 mg/kg/day of prednisone), followed by progressive tapering when the disease is controlled and until GC withdrawal (5). The duration of treatment is

still debated and a significant number of patients remain on long-term low-dose GCs to prevent relapse (6,7). Nevertheless, the risk of relapse remains high, reported to occur in >50% of patients (8) during the course of the disease. There is no consensus about definition of relapse and flare in GCA, but they are commonly defined by a recurrence of clinical or biologic manifestations, leading to the increase or resumption of GC treatment or to the adjunction of an immunosuppressive drug (9). To limit GC-induced side effects while maintaining remission, immunosuppressive drugs, mainly methotrexate (10,11) and tocilizumab (12,13), have been evaluated as GC-sparing agents in randomized controlled trials (RCTs) with rapid GC discontinuation, which leads to a difficulty in

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### SIGNIFICANCE & INNOVATIONS

- Giant cell arteritis relapses occur in half of patients receiving glucocorticoids (GCs) alone.
- The relapse rate may be related to short duration of GC administration.
- The relapse prevalence was higher in randomized controlled trials than in observational studies.

assessing the efficacy of these drugs compared to the GC treatment. Various factors at GCA diagnosis have been retrospectively described as associated with relapses: female sex, hypertension, diabetes mellitus (14), or anemia (15). Decreasing the relapse rate in the GCA course is currently an important challenge. The purpose of this systematic review and meta-analysis was to estimate the relapse rate in GCA patients treated with GC alone and to determine the factors associated with relapse.

## MATERIALS AND METHODS

**Literature search strategy.** We determined the selection criteria for the data collection and identified all the relevant articles published on the subject up to December 2017. We consulted the Medline database with the search criteria of free text, published in all languages and individual medical subject heading (MeSH) terms. The search equation in PubMed was: (“recurrence” [MeSH] OR “randomized controlled trial” [publication type] OR “recurrence” [all fields] OR “relapse” [all fields]) AND “giant cell arteritis” (MeSH). The reference lists of relevant studies and meta-analyses already carried out were examined to identify additional studies. The method used was consistent with the recommendations of the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) (16) and Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (17).

**Study selection.** Two levels of screening for eligibility were performed. The first level was performed by a single reviewer (J-CL) using titles and abstracts and selecting records that included the number of relapsing GCA patients. The second level was performed using the full-text articles (SM and AA). Studies were included if the following criteria were fulfilled: patients with newly diagnosed or relapsing GCA, patients treated with GC alone (whole study or control arm of trials testing GC-sparing agents), and proportion of relapse available. Studies were excluded if the different groups were not well-defined, or if there was doubt on the treatment received. The included studies then underwent data extraction.

**Data extraction and quality assessment.** Data from the included studies were independently extracted by 3 authors (SM, AA, and J-CL). In case of conflict, consensus was reached through discussion. The extracted study characteristics included first author’s name, year of publication, country, design (retro-

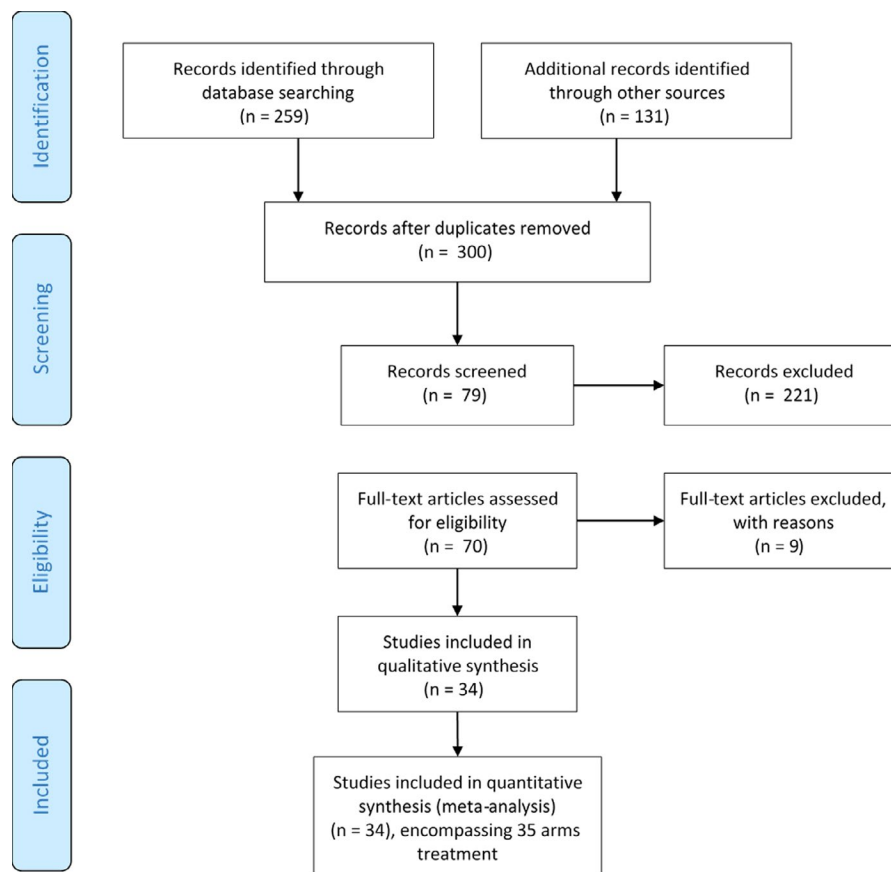
spective or prospective), intervention type (RCT or observational study), type of inclusion (consecutive or nonconsecutive), criteria for GCA diagnosis, relapse definition, number of patients who received GC therapy alone, patient characteristics (mean age at diagnosis, sex), duration of follow-up (mean or median), initial GC dose, duration of scheduled GC therapy estimated by the protocol of GC tapering and withdrawal reported in the methods section, effective duration of GC therapy reported in the results section, number of patients with relapse, and the interval between diagnosis and relapse. The quality of studies was assessed using the MOOSE tool (16), including 6 key domains.

**Data synthesis and analysis.** The pooled prevalence of relapse among patients diagnosed with GCA and its 95% confidence interval (95% CI) were estimated using the raw proportions. Heterogeneity between study-specific estimates was assessed using the inconsistency index  $I^2$  (18). A fixed-effects model was considered for  $I^2$  of  $\leq 50\%$ , while for  $I^2$  of  $>50\%$  substantial heterogeneity was considered, and a random-effects model was used. Once heterogeneity was established, subgroup and meta-regression analyses were performed to further investigate between-study sources of heterogeneity.

Four subgroups were predefined for categorical variables: study design (prospective or retrospective), intervention type (RCT or observational study), type of inclusion (consecutive or nonconsecutive), and target withdrawal of GC therapy ( $\leq$  or  $>12$  months). The continuous variables preselected in the meta-regression were initial GC dose, duration of scheduled GC therapy, effective duration of GC therapy, sex, duration of follow-up, number of included patients in the study, and the year of publication. The risk of publication bias was determined by a funnel plot (19). A  $P$  value less than 0.05 was considered statistically significant. All analyses were performed using R software, version 3.0.2, with Package metafor, version 1.9-5.

## RESULTS

**Study characteristics.** A total of 259 records were identified through electronic searches, and 131 records were extracted from meta-analysis addressing GCA. The results of the systematic review are shown in Figure 1; 34 studies (10–15,20–46) were included (Table 1), encompassing 35 arms with GC treatment and totaling 2,505 patients, with a mean age of 69.9 years at diagnosis and 69% women. Inclusions were consecutive in 13 studies (38%) (13,15,22,25,26,28,34,41–44,46,47), and 19 studies (56%) were prospective (9–13,22,23,27–31,33,35,36,38,44,46). Eight studies (24%) (10–13,33,36,38,46) were RCTs, including 9 arms testing oral GC alone or associated with placebo. Treatments tested in these trials were methotrexate in 3 studies (10,11,33), tocilizumab in 2 studies (12,13), infliximab in 1 study (38), adalimumab in 1 study (46), and intravenous GC in 1 study (36). The duration of scheduled GC therapy ranged from 4 to 29 months; the mean 31



**Figure 1.** Flow diagram of the literature search and study inclusion.

effective duration of GC therapy was 28.8 months in observational studies and 12.8 months in RCTs. In all, 64% of studies were conducted in Europe and 29% in the US. Visual inspection of the funnel plot of prevalence did not indicate publication bias (see Supplementary Figure 1, available on the *Arthritis Care & Research* web site at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23901/abstract>). The quality of the studies is shown in Supplementary Table 1, available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23901/abstract>.

**Prevalence of relapse.** The overall pooled prevalence of GCA relapse was 47.2% (95% CI 40.0, 54.3) using a random-effects model, with a high degree of heterogeneity ( $I^2 = 93\%$ ). The relapse prevalence ranged from 14% to 81.5% in included studies (Figure 2).

**Factors associated with relapse.** The subgroup meta-analysis with the predefined variables was performed to explore heterogeneity between studies. The prevalence of relapse was not significantly different according to study design ( $P = 0.06$ ), or type of inclusion ( $P = 0.19$ ). Prevalence of relapse was significantly higher for patients included in an RCT (65.8% [95% CI 56.9, 74.7]) compared to those included in an observational study (41.7% [95% CI 33.7, 49.7];  $P < 0.0001$ ). Relapses occurred in 65.8%

of patients (95% CI 56.9, 74.7) with targeted withdrawal before 12 months, compared to 34.5% (95% CI 24.8, 44.1) with withdrawal after 12 months ( $P < 0.0001$ ). For all subgroups, heterogeneity remained superior to 50% (Table 2). The year of publication was positively associated with the prevalence of relapse (34 studies, rate increase of 8.3% for 1 decade;  $P < 0.0001$ ) (Figure 3A). The duration of scheduled GC therapy was negatively associated with the prevalence of relapse (17 studies, rate decrease of 1.7% for 1 additional month;  $P < 0.001$ ) (Figure 3B). The effective duration of GC therapy treatment ( $P = 0.23$ ), the initial GC dose ( $P = 0.49$ ), the duration of follow-up ( $P = 0.14$ ), the proportion of women ( $P = 0.29$ ), and the mean of age at diagnosis ( $P = 0.43$ ) were not associated with the percentage of relapse (Table 3).

## DISCUSSION

The systematic literature review and meta-analysis estimated that half of GCA patients treated with GC experience at least 1 relapse during the course of their disease, which is consistent with recent reviews (8,48). The meta-analysis found a significant heterogeneity in relapse prevalence, and the subgroup analysis provided a potential explanation; relapses were more frequent in RCTs than in observational studies, with an absolute difference in risk of approximately 20%. This result can be explained by the

**Table 1.** Summary of studies included in the meta-analysis\*

Authors (ref) year, country	Diagnosis criteria	Relapse definition	Study design/type	GC alone, no.	Follow-up, years	Age, mean years	Women, %	Initial GC dose, mg/day	Scheduled GC therapy, duration months	Relapsing patients, no.	Effective duration of GC, months
Huston et al (20) 1978, US	Biopsy-proven GCA or classic manifestations of TA	Recurrence of symptoms of TA with raised ESR, suppressed by GC	Retro/OS	42	6	75	79	NA	NA	11	15.8
Graham et al (21) 1981, England	Biopsy-proven GCA	Raised ESR and symptoms	Retro/OS	90	5	NA	71	80	NA	18	NA
Behn et al (22) 1983, England	Classic manifestation of TA, raised ESR, and good response to GC	Recurrence of signs or symptoms of TA ± raised ESR	Pros/OS	68	NA	69	74	17.3	20	11	37.7
Andersson et al (23) 1986, Sweden	Biopsy-proven GCA or classic manifestation of TA, raised ESR, and good response to GC	Symptoms of disease after withdrawal of treatment	Pros/OS	90	11.3	71	76	33.2	NA	49	69.6
Gouet et al (24) 1986, France	Biopsy-proven GCA	Recurrence of symptoms of GCA or PMR and raised ESR, suppressed by GC	Retro/OS	87	5	73	60	42	NA	18	36
Delecoeurie et al (25) 1988, France	Classic manifestations of TA and/or raised ESR, orosomucoid, or haptoglobin	Recurrence of clinical symptoms after treatment withdrawal requiring GC reinstatement	Retro/OS	78	NA	76	62	38.1	NA	21	30.9
Dutoit et al (26) 1988, France	NA	NA	Retro/OS	100	NA	71	66	30	24	14	24
Kyle et al (27) 1989, England	Jones and Hazleman criteria	New or persisting event among classical manifestation of GCA	Pros/OS	35	1.3	NA	NA	40	NA	20	NA
Gudmundsson et al (28) 1993, Sweden	Biopsy-proven GCA or Bengtsson and Malmvall criteria	Symptoms requiring increase in GC dose	Pros/OS	31	1	71	24	40	13	10	12
Liozon et al (29) 1994, France	Biopsy-proven GCA	NA	Pros/OS	42	6	74	62	42	NA	22	23.1
Liozon et al (30) 2000, France	Biopsy-proven GCA	Recurrence of symptoms of TA and/or PMR and/or an elevation of the ESR and CRP	Pros/OS	58	3	74	62	42	24	21	24

(Continued)

Table 1. (Cont'd)

Authors (ref.) year, country	Diagnosis criteria	Relapse definition	Study design/ type	GC alone, no.	Follow-up, years	Age, mean years	Women, %	Initial GC dose, mg/day	Scheduled GC therapy, duration months	Relapsing patients, no.	Effective duration of GC, months
Weyand et al (31) 2000, US	Biopsy-proven GCA	Presence of symptoms of TA and/or PMR	Pros/OS	25	1.5	73	80	60	15	15	NA
Hachulla et al (32) 2001, France	NA	Symptoms of TA and/ or increase in ESR and/or CRP requiring increased GC and with good response to GC	Pros/OS	133	5.6	72	71	48	NA	83	40
Jover et al (33) 2001, Spain	Biopsy-proven GCA	Recurrence of symptoms of TA with good response to GC	Pros/RCT	21	2	78	67	60	4	16	23.5
Spiera et al (10) 2001, US	Biopsy-proven GCA or classic manifestations of TA and raised ESR	Recurrence of symptoms of TA with good response to GC	Pros/RCT	9	2	74	44	60	4	3	15
Hoffmann et al (11) 2002, US	Biopsy-proven GCA or classic manifestations of TA or large vessel vasculitis proved	At least one symptom of TA and increase in ESR	Pros/RCT	47	1	75	62	60	6	31	NA
Proven et al (34) 2003, US	1990 ACR criteria (62)	Symptoms of TA with raised ESR	Retro/OS	120	10	75	83	54	NA	57	26.2
Blöckmans et al (35) 2006, Belgium	Biopsy-proven GCA or classic manifestations of TA or PMR	Symptoms of TA with raised inflammatory parameters	Pros/OS	35	NA	73	71	32	13	18	12
Mazlumzadeh et al (36) 2006, US	Biopsy-proven GCA	Recurrence of symptoms of TA and raised inflammatory parameters with good response to GC	Pros/RCT	27	1.5	74	70	40	9	22	18
Narvaez et al (37) 2006, Spain	1990 ACR criteria	Recurrence of symptoms of TA and raised inflammatory parameters with good response to GC	Retro/OS	121	3.6	74	69	50	NA	66	34.7
Hoffman et al (38) 2007, US	1990 ACR criteria	Raised ESR and at least 1 symptom of GCA	Pros/RCT	16	1	69.5	69	49.3	5.5	8	NA

(Continued)



Table 1. (Cont'd)

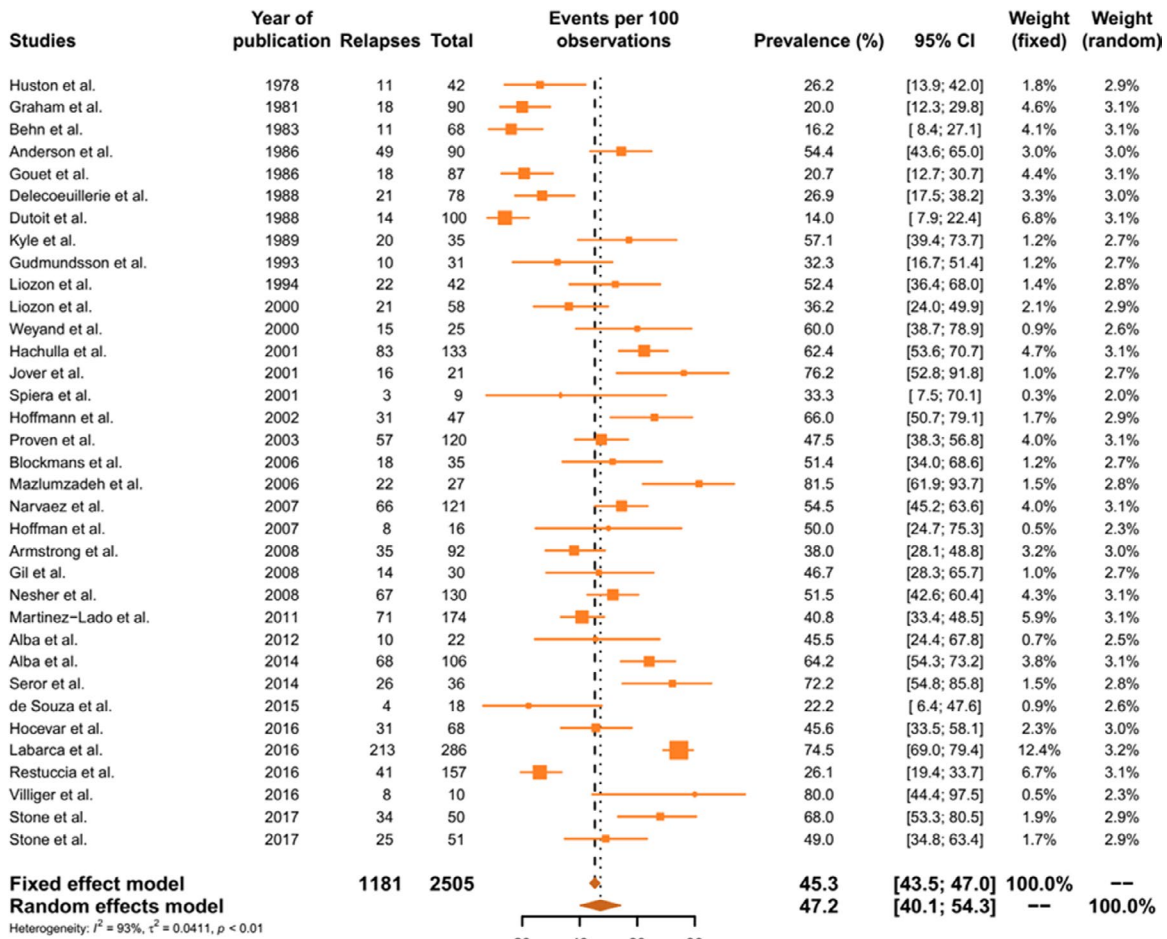
Authors (ref.) year, country	Diagnosis criteria	Relapse definition	Study design/ type	GC alone, no.	Follow-up, years	Age, mean years	Women, %	Initial GC dose, mg/day	Scheduled GC therapy, duration months	Relapsing patients, no.	Effective duration of GC, months
Armstrong et al (39) 2008, US	Biopsy-proven GCA	Return of clinical symptoms or increased ESR that needed to reconstitute GC therapy	Retro/OS	92	NA	75	63	63.5	NA	35	22.5
Gil et al (40) 2008, France	Biopsy-proven GCA and 1990 ACR criteria	NA	Retro/OS	30	NA	75	70	44	NA	14	NA
Nesher et al (41) 2008, Israel	1990 ACR criteria	Symptoms related to GCA that needed to increase GC therapy	Retro/OS	130	3	73	65	55.6	NA	67	NA
Martinez-Lado et al (15) 2011, Spain	Biopsy-proven GCA	Return of clinical symptoms and increased ESR	Retro/OS	174	8.7	75	54	60	29	71	NA
Alba et al (42) 2012, Mexico	1990 ACR criteria	NA	Retro/OS	22	4.7	73	82	50.2	NA	10	23.7
Alba et al (9) 2014, Spain	Biopsy-proven GCA	Return of clinical symptoms and increased ESR that required treatment adjustment	Pros/OS	106	7.8	77	73	60	NA	68	NA
Seror et al (46) 2014, France	1990 ACR criteria	Reappearance of GCA-related clinical symptoms or increase in CRP >15 mg/liter, at 2 time points 1 week apart without any other obvious etiology	Pros/RCT	36	1	74.5	78	42	12	26	12
de Souza et al (43) 2015, Brazil and Netherlands	1990 ACR criteria with large vessel vasculitis by PET	NA	Pros/OS	18	NA	72	78	60	NA	4	NA
Hocevar et al (44) 2016, Slovenia	Biopsy-proven GCA and 1990 ACR criteria	Disease worsening or new disease activity during GC tapering after the initial remission, after exclusion of other reasons	Pros/OS	68	2	73	74	47	28	31	18

(Continued)

**Table 1.** (Cont'd)

Authors (ref.) year, country	Diagnosis criteria	Relapse definition	Study design/ type	GC alone, no.	Follow-up, years	Age, mean years	Women, %	Initial GC dose, mg/day	Scheduled GC therapy, duration months	Relapsing patients, no.	Effective duration of GC, months
Labarca et al (14) 2016, US	Biopsy-proven GCA	New onset or return of clinical symptoms and/or increased ESR that needed to increase GC therapy	Retro/OS	286	5.1	75	74	50.8	NA	213	NA
Restuccia et al (61) 2016, Italy	Biopsy-proven GCA	Recurrence of TA and/or raised inflammatory parameters with good response to GC	Retro/OS	157	7	74	78	46	21	41	40
Villiger et al (12) 2016, Switzerland	1990 ACR criteria	Raised ESR or CRP, and/or at least 1 symptom of GCA	Pros/RCT	10	0.2	69	80	60	6	5	3
Stone et al (13) 2017, US	Biopsy-proven GCA or on evidence of large vessel vasculitis on angiography, computed tomography or MRA or PET	Recurrence of symptoms of GCA or raised ESR attributable to GCA	Pros/RCT	50	1	69	76	30	6	43	6
Stone et al (13) 2017, US	Biopsy-proven GCA or on evidence of large vessel vasculitis on angiography, computed tomography or MRA or PET	Recurrence of symptoms of GCA or raised ESR attributable to GCA	Pros/RCT	51	1	68	73	30	12	42	12

\* GC = glucocorticoids; GCA = giant cell arteritis; TA = temporal arteritis; ESR = erythrocyte sedimentation rate; Retro = retrospective; OS = observational study; NA = not available; Pros = prospective; PMR = polymyalgia rheumatica; RCT = randomized controlled trial; ACR = American College of Rheumatology; CRP = C-reactive protein; PET = positron-emission tomography; MRA = magnetic resonance angiography.



**Figure 2.** Forest plot of relapse prevalence in patients with GCA. Relapses = number of relapsing patients; Total = total number of patients in the study; 95% CI = 95% confidence interval; Weight = study weight in the meta-analysis. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23901/abstract>

longer duration of GC therapy protocol in observational studies; conversely, the early withdrawal of GC was positively associated with the probability of relapse in the meta-regression.

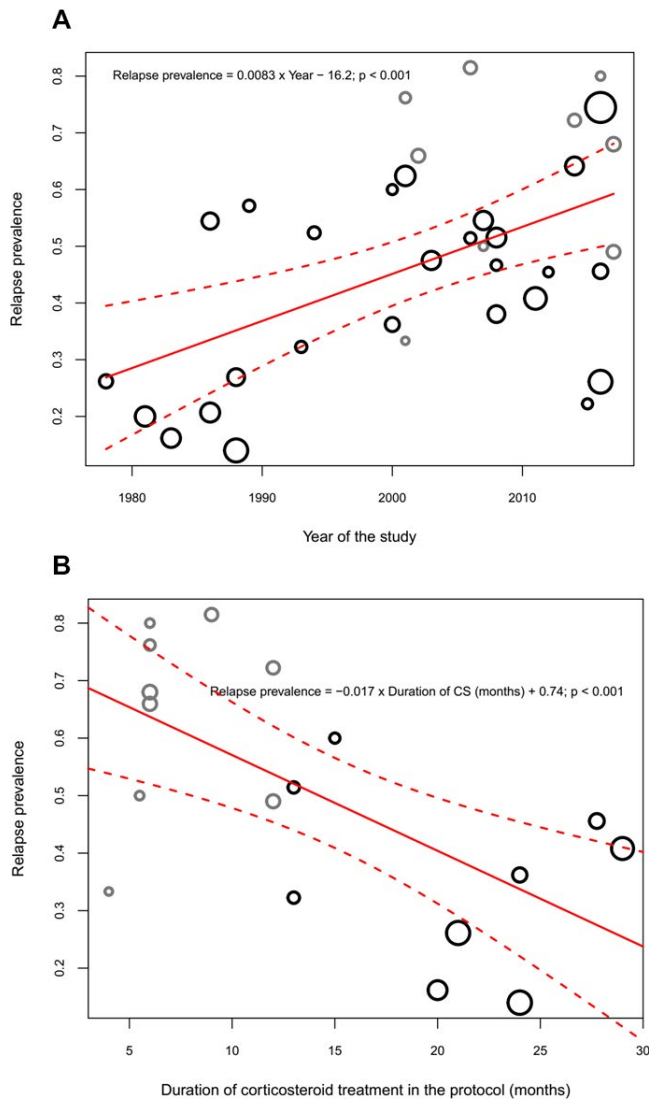
A similar significant association between increased duration of GC therapy and relapse reduction was previously reported in antineutrophil cytoplasmic antibody-associated vasculitis

through meta-analytic approaches (49,50). The proportion of relapse in patients receiving low-dose GC in the long term was 14% compared to 43% in patients with early GC discontinuation; this 30% difference was similar to our results in GCA (49). Multi-variable regression demonstrated that long-term, low-dose GC, and follow-up duration were the only variables associated with

**Table 2.** Exploration of heterogeneity of relapse prevalence by subgroup analysis\*

	Studies	Patients	Prevalence of relapse, % (95% CI)	$I^2$ , %	$P$
Study design					0.06
Prospective	19	843	53.4 (44.6, 62.2)	86.5	–
Retrospective	15	1,662	39.7 (28.6, 50.7)	96.0	–
Inclusion type					0.19
Consecutive	13	981	41.8 (32.0, 51.6)	91.1	–
Nonconsecutive	21	1,524	50.9 (41.4, 60.4)	93.6	–
Intervention type					<0.0001
Randomized controlled trial	8	267	65.8 (56.9, 74.7)	58.6	–
Observational study	26	2,238	41.7 (33.7, 49.7)	94.1	–
Target withdrawal of GC therapy					<0.0001
≤12 months	8	267	65.8 (56.9, 74.7)	58.6	–
>12 months	9	716	34.5 (24.9, 44.0)	87.4	–

\* Values are the number unless indicated otherwise. 95% CI = 95% confidence interval; GC = glucocorticoids.



**Figure 3.** Meta-regression of the relapse probability according to **A**, the year of publication, and **B**, the duration of glucocorticoid treatment according to the tapering schedule. Circles indicate the design of studies included in the meta-regression, black for observational studies and grey for randomized and controlled trials. The red solid curve indicates the model prediction of relapse. The red broken curves indicate the 95% confidence interval of model prediction of relapse. CS = corticosteroids. Color figure can be viewed in the online issue, which is available at <http://onlinelibrary.wiley.com/doi/10.1002/acr.23901/abstract>

relapse in the meta-analysis, including long-term follow-up of studies included in the previous analysis (49) and incorporating prospective cohort studies and RCT (50). A comparable finding was reported in a cohort study suggesting that a fast GC tapering regimen is a predictor of relapse in patients with polymyalgia rheumatica (51). Therefore, the results of the present meta-analysis suggest a potential benefit of sustaining a prescription of low-dose GC for the maintenance of GCA remission.

Notably, however, the net clinical benefit of the administration of low-dose GC after 12 months has been poorly studied in GCA, and the prevalence of severe relapse is not described.

The side effects of sustained low-dose GC in GCA are not well assessed (27,52). In rheumatoid arthritis, the burden of low-dose GC exposure is well known and includes weight gain, diabetes mellitus, increased blood pressure, decreased bone mineral density, increased risk for fractures, cognitive dysfunction, infections, and cataracts (53). In GCA, the analysis of a health care insurance database found associations between increased GC exposure and osteoporosis, cataracts, glaucoma, pneumonia, and diabetes mellitus (52). However, the size of this association seemed to be small, the relative risk of adverse events increasing by 3% for each 1,000-mg prednisone exposure (i.e., 0.46 adverse events per 100 patient-years for 12 additional months of prednisone at 5 mg/day compared to 0.43 adverse events per 100 patient-years). Moreover, the net clinical benefit of administration of low-dose GCs for longer duration of time should be determined by weighting the risk of severe relapse against the risk of GC side effects, a minor relapse (increase of inflammatory markers, headache) being less serious compared to major relapse (myocardial infarction, stroke, blindness).

Our meta-analysis did not report any association between initial GC dose and prevalence of relapse, suggesting no benefit in the use of high-dose GC at GCA induction. This finding is congruent with the result of a 12-month open-label RCT including new onset GCA patients that reported no benefit of GC intravenous pulses over oral prednisone (54). In addition, an RCT compared 40 mg/day to 20 mg/day of oral prednisone, without a significant reduction of relapse rate among those receiving the high-dose regimen (55). Although a small RCT reported an oral GC-sparing effect and a decrease in relapse rate related to 3 consecutive daily intravenous methylprednisolone pulses (15 mg/kg/day) before oral GCs (36), guidelines and a systematic review did not retain high doses of GC as a standard of care for induction of remission in GCA (5,56,57). Overall, the results of RCTs and the present meta-analysis suggest that longer duration of exposure rather than the initial dose of GC at diagnosis contribute to the persistence of remission. The European recommendations did not address the question of GC tapering and cessation (7), except for British and French guidelines that suggest stopping GC after 7–12 and 18–24 months of administration, respectively (5,56).

The meta-regression also suggested that relapse prevalence was positively associated with the year of publication. This finding evidences the absence of a secular trend in relapse reduction related to a better knowledge of GC management. The relapse prevalence was higher in recent studies. Notably, all RCTs were published after 2000 and often evaluated short courses of GC to prevent side effects, which could explain, at least partially, these results. One consequence of the use of short GC courses in RCTs is allowing a sufficient number of relapses to occur in control arms so that a significant difference is detected with investigational drugs. Thus, the estimation of effect size of treatment effect (i.e., relative risk or hazard ratio) of immunosuppressive drugs reported to be effective in GCA, mainly tocilizumab and methotrexate, may 38

**Table 3.** Exploration of heterogeneity of relapse prevalence by meta-regression\*

	Studies	Patients	Beta (95% CI)†	P
Year of publication	34	2,505	0.0083 (0.0036, 0.013)	<0.0001
Duration of scheduled GC therapy, months	17	983	-0.017 (-0.026, -0.007)	<0.001
Effective duration of GC therapy, months	23	1,548	-0.0035 (-0.0092, 0.0022)	0.23
Initial GC dose, mg/day	33	2,463	0.0018 (-0.0033, 0.0069)	0.49
Duration of follow-up, years	27	2,084	-0.016 (-0.0383, 0.0055)	0.14
Proportion of female sex, %	33	2,470	0.0045 (-0.00380, 0.0127)	0.29
Mean age at diagnosis, years	32	2,380	0.011 (-0.0167, 0.0396)	0.42

\* Values are the number unless indicated otherwise. 95% CI = 95% confidence interval; GC = glucocorticoids.

† Beta indicates a relapse rate increase or decrease for the augmentation of 1 unit of the variable tested.

be challenged with a longer duration of GC. Indeed, the comparison of the efficacy of the immunosuppressive drugs with a short duration of prednisone administration (i.e., <12 months) may lead to an increase of the apparent efficacy of tocilizumab and methotrexate compared to late withdrawal (i.e., >12–24 months) commonly used in daily clinical practice (27,58). In another words, the number of flares in the comparator arm may be higher, and the time to first flare shorter, than in clinical practice in European countries (5,56). This weakness of the Giant Cell Arteritis Clinical Research Study design has been discussed by French and English regulatory authorities for tocilizumab approval (59,60). These results did not call into question the GC-sparing effect of methotrexate and tocilizumab but challenged the estimation of the effect size of treatment effects, allowing the computation of the number needed to treat to prevent 1 GCA relapse, which depends on the absolute risk difference between 2 therapeutic strategies.

Our study has some substantial limitations. First, the heterogeneity between studies, including both observational studies and RCTs, was confirmed by the high  $I^2$  index. The prespecified subgroup analysis and meta-regression explained a part of this heterogeneity. However, we can not rule out heterogeneity related to discrepancies in the definition of GCA relapse and recurrence that varied between included studies. This point underlined the need of widely accepted international criteria for this outcome. Second, the estimate of relapse rate encompassed 2 relapse subtypes: 1) severe relapses yielding organ damage (i.e., myocardial infarction, stroke, blindness) or leading to aggressive treatment, and 2) minor relapses, such as arthralgia, requiring a small and temporary increment in the daily dose of prednisone without consequence for the patient. Unfortunately, available data providing the rate of minor and major relapses and their consequences were sparse and did not permit us to address this important issue. Third, a meta-analysis of observational studies or arms of RCTs provides relatively low-grade evidence. In addition, we included in the present meta-analysis studies with a risk of information or confounding bias. Only a dedicated RCT comparing 2 durations of GC administration (e.g., 12 versus 24 months) may provide strong evidence. Nevertheless, the present meta-analysis justifies the conduct of such a study and could help to determine its design and sample size calculation. Finally, we only searched the Medline

database, which could have induced a bias. However, there was no publication bias by visual inspection of the funnel plot.

In conclusion, GCA relapses occur in half of patients receiving GC alone, without improvement across decades. The relapse rate is more related to short duration of GC administration than to the initial dose at induction. The results challenge the GC regimen used in RCTs and thereby question the extent of the real effect of methotrexate and tocilizumab. These results support RCTs designed with control arms treated with GC for at least 12 months.

#### AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Mainbourg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

**Study conception and design.** Mainbourg, Addario, Puéchal, Lega.

**Acquisition of data.** Mainbourg, Addario, Lega.

**Analysis and interpretation of data.** Mainbourg, Addario, Samson, Puéchal, François, Durupt, Gueyffier, Cucherat, Durieu, Reynaud, Lega.

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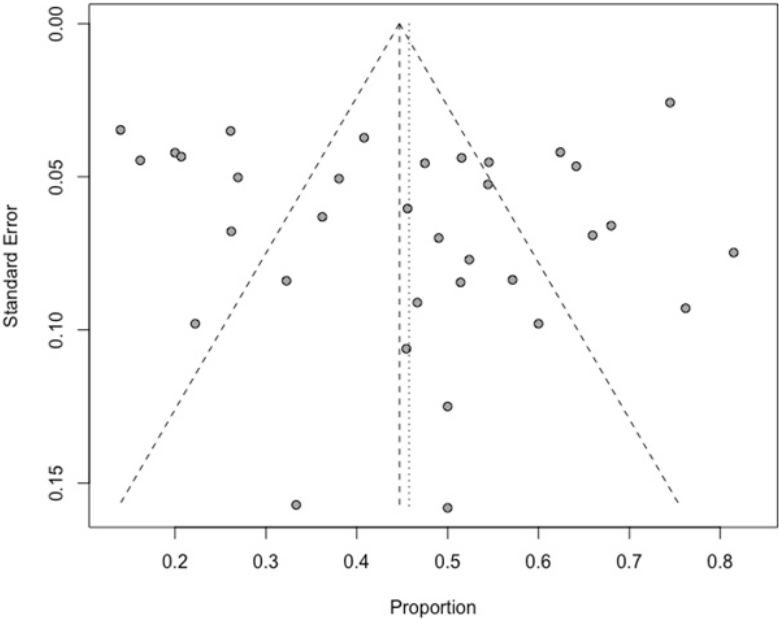
Mainbourg S et al, *Arthritis Care Res (Hoboken)*, 2020 - **Supplementary Table 1.** Quality assessment using the MOOSE tools (16).

	Clear definition of study population?	Clear definition of outcomes and outcome assessment?	Independent assessment of outcome parameters?	Sufficient duration of follow-up*?	No selective loss during follow-up?	Important confounders and prognostic factors identified?
<b>Huston et al. 1978</b>	Yes	Yes	No	Yes	No	No
<b>Graham et al. 1981</b>	Yes	Yes	No	Yes	No	No
<b>Behn et al. 1983</b>	Yes	Yes	No	Yes	No	No
<b>Andersson et al. 1986</b>	Yes	Yes	No	Yes	No	No
<b>Gouet et al. 1986</b>	Yes	Yes	No	Yes	No	No
<b>Delecoeuillerie et al. 1988</b>	Yes	Yes	No	Yes	No	No
<b>Dutoit et al. 1988</b>	No	No	No	Yes	No	No
<b>Kyle et al. 1989</b>	Yes	Yes	No	Yes	No	No
<b>Gudmundsson et al. 1993</b>	Yes	Yes	No	Yes	No	No
<b>Liozon et al. 1994</b>	Yes	No	No	Yes	No	No
<b>Liozon et al. 2000</b>	Yes	Yes	No	Yes	No	No
<b>Weyand et al. 2000</b>	Yes	Yes	No	Yes	No	No
<b>Hachulla et al. 2001</b>	Yes	Yes	No	Yes	No	No
<b>Jover et al. 2001</b>	Yes	Yes	Yes	Yes	No	No
<b>Spiera et al. 2001</b>	Yes	Yes	Yes	Yes	No	No
<b>Hoffmann et al. 2002</b>	Yes	Yes	Yes	Yes	No	No
<b>Proven et al. 2003</b>	Yes	Yes	No	Yes	No	No
<b>Blöckmans et al. 2006</b>	Yes	Yes	No	Yes	No	No
<b>Mazlumzadeh et al. 2006</b>	Yes	Yes	Yes	Yes	No	No
<b>Narvaez et al. 2006</b>	Yes	Yes	No	Yes	No	No
<b>Hoffman et al. 2007</b>	Yes	Yes	Yes	No	No	No
<b>Armstrong et al. 2008</b>	Yes	Yes	No	NA	No	No
<b>Gil et al. 2008</b>	Yes	No	No	Yes	No	No
<b>Nesher et al. 2008</b>	Yes	Yes	No	Yes	No	No
<b>Martinez-Lado et al. 2011</b>	Yes	Yes	No	Yes	No	No
<b>Alba et al. 2012</b>	Yes	No	No	Yes	No	No
<b>Alba et al. 2014</b>	Yes	Yes	No	Yes	No	No
<b>Seror et al. 2014</b>	Yes	Yes	Yes	Yes	No	No
<b>de Souza et al. 2015</b>	Yes	No	No	No	No	No
<b>Hocevar et al. 2016</b>	Yes	Yes	No	Yes	No	No
<b>Labarca et al. 2016</b>	Yes	Yes	No	Yes	No	No
<b>Restuccia et al. 2016</b>	Yes	Yes	No	Yes	No	No
<b>Villiger et al. 2016</b>	Yes	Yes	Yes	Yes	No	No
<b>Stone et al. 2017</b>	Yes	Yes	Yes	Yes	No	No
<b>Stone et al. 2017</b>	Yes	Yes	Yes	Yes	No	No

\* One year follow-up was considered sufficient in this meta-analysis.



Mainbourg S et al, *Arthritis Care Res (Hoboken)*, 2020 - **Supplementary Figure 1**. Funnel plot of relapse prevalence for the search of publication bias. The symmetry of the figure suggests the absence of publication bias.



## 5.2 Méta analyse de la prévalence des rechutes sévères

Aussedat M, Lobbes H, Samson M, Euvrard R, Lega JC, Mainbourg S. **Epidemiology of major relapse in giant cell arteritis: A study-level meta-analysis.** *Autoimmun Rev.* 2021 Sep 2:102930. doi: 10.1016/j.autrev.2021.102930. Epub ahead of print. PMID: 34481940.

**Objective:** The relapse rate of giant cell arteritis (GCA) is around 48%. Major relapse of GCA is defined by the European League Against Rheumatism as severe ischemic or aortic (stenosis, aneurysm, or aortic dissection) disease of GCA. The objective of the present study was to determine the prevalence and incidence, as well as the spectrum of major relapse in GCA using published data.

**Methods:** The MEDLINE and Cochrane databases were searched up to March 2020. Studies that included patients with newly diagnosed or relapsed GCA receiving glucocorticoids (GC) alone and/or GC-sparing therapy, detailing the number of relapsing patients and the characteristics of relapses were included. The prevalence and incidence of major relapse were pooled using a random-effects model.

**Results:** Twenty-six studies (including eight randomised controlled trials) involving 2754 patients with GCA were included. The prevalence and incidence of major relapse in this population was 3.3% (95%CI [1.7;5.6]; I<sup>2</sup> = 86%) and 14.5/100 patient-years (95%CI [5.2;27.2]; I<sup>2</sup> = 90%). The clinical manifestations were jaw claudication (44.3%), ophthalmological involvement (32.7%), peripheral limb ischemia (12.5%), aortic (7.7%), and neurological involvements (4.8%). In the meta-regression analysis, the duration of follow-up was negatively associated with the incidence of major relapse (Beta = -0.015, 95%CI [-0.026; -0.0042]; p = 0.0063). The incidence of major relapse was significantly higher in prospective studies (55.2/100 person-years, 95%CI [15.3;114.3]) than in retrospective studies (4.1/100 patient-years, 95%CI[1.1;8.4]; p<sub>interaction</sub> = 0.000.2).

**Conclusion:** This study found that there was heterogeneity among studies, and this is partially related to study design. Jaw claudication was frequent and increases the prevalence and incidence of relapses major.

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## Review

## Epidemiology of major relapse in giant cell arteritis: A study-level meta-analysis

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## ABSTRACT

**Objective:** The relapse rate of giant cell arteritis (GCA) is around 48%. Major relapse of GCA is defined by the European League Against Rheumatism as severe ischemic or aortic (stenosis, aneurysm, or aortic dissection) disease of GCA. The objective of the present study was to determine the prevalence and incidence, as well as the spectrum of major relapse in GCA using published data.**Methods:** The MEDLINE and Cochrane databases were searched up to March 2020. Studies that included patients with newly diagnosed or relapsed GCA receiving glucocorticoids (GC) alone and/or GC-sparing therapy, detailing the number of relapsing patients and the characteristics of relapses were included. The prevalence and incidence of major relapse were pooled using a random-effects model.**Results:** Twenty-six studies (including eight randomised controlled trials) involving 2754 patients with GCA were included. The prevalence and incidence of major relapse in this population was 3.3% (95%CI [1.7;5.6];  $I^2 = 86\%$ ) and 14.5/100 patient-years (95%CI [5.2;27.2];  $I^2 = 90\%$ ). The clinical manifestations were jaw claudication (44.3%), ophthalmological involvement (32.7%), peripheral limb ischemia (12.5%), aortic (7.7%), and neurological involvements (4.8%). In the meta-regression analysis, the duration of follow-up was negatively associated with the incidence of major relapse (Beta = -0.015, 95%CI [-0.026; -0.0042];  $p = 0.0063$ ). The incidence of major relapse was significantly higher in prospective studies (55.2/100 person-years, 95%CI [15.3;114.3]) than in retrospective studies (4.1/100 patient-years, 95%CI[1.1;8.4];  $p_{interaction} = 0.0002$ ).**Conclusion:** This study found that there was heterogeneity among studies, and this is partially related to study design. Jaw claudication was frequent and increases the prevalence and incidence of relapses major.

## 1. Introduction

Giant cell arteritis (GCA) is a large vessel vasculitis affecting patients aged over 50 years, with a higher incidence for those aged 70–80 years [1,2]. The pathogenesis is not fully understood but results in inflammation and vascular remodelling [3] of large arteries, mainly the branches of the external carotid arteries, as well as the ophthalmic and

vertebral arteries [4]. It is characterised by the occurrence of ischemic symptoms such as headache, visual manifestations, scalp tenderness, jaw claudication, and/or stroke, together with systemic symptoms such as weight loss, anorexia, fatigue, fever, polymyalgia rheumatica (PMR), and/or aortitis. Aortic involvement can be complicated by aneurysm and aortic dissection, the incidence of which is estimated to be around 19 per 1000 patient-years [5]. Nevertheless, the mortality rate is not higher in

**Abbreviations:** GCA, giant cell arteritis; EULAR, European League Against Rheumatism; GC, glucocorticoids; ION, ischemic optic neuropathy; CRAO, central retinal artery occlusion; ON, optic neuritis; PMR, polymyalgia rheumatica; RCT, randomised controlled trial; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

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patients with GCA than in the general population [6].

Glucocorticoid (GC) therapy (0.7–1 mg/kg/day) remains the first-line therapy. The duration of treatment is not clearly established, but it is admitted that GC therapy should be gradually reduced for about 18 months to avoid relapse [7]. In recent years, the addition of immunosuppressive drugs, mainly methotrexate and tocilizumab (anti-IL-6 receptor), has shown its efficacy in preventing relapse or reducing the cumulative dose of GC therapy [8–10].

Relapse is commonly defined by a recurrence of  $\geq 1$  GCA symptom(s) or the reappearance of a biological inflammatory syndrome without a cause other than GCA, requiring an increase or a resumption of GC therapy and that is improved by the latter [11,12]. The rate of relapse under GC therapy alone was estimated to be around 47% in a recent meta-analysis [13]. The European League Against Rheumatism (EULAR) has recently defined major relapse as the occurrence of clinical signs of ischemia (ophthalmological damage, jaw claudication, scalp necrosis, stroke, limb ischemia) as well as aortic damage (stenosis and aortic aneurysms, aortic dissections) [11]. Most relapses are minor, for example, recurrence of headache, PMR, biological inflammatory syndrome or asymptomatic aortitis detected by vascular imaging [14]; major relapse is rare, the epidemiology of major relapse is currently poorly known.

The objective of this meta-analysis was therefore to define the prevalence and the incidence of major relapses in GCA and to report their characteristics.

## 2. Material and methods

The protocol of the present study was registered in PROSPERO (<https://www.crd.yotk.ac.uk/PROSPERO>, registration CRD4201914 8051).

### 2.1. Literature search strategy

We consulted the MEDLINE database for papers published in all languages (up to March 2020) using the following search string in PubMed: (“Giant Cell Arteritis”[MeSH] AND (“relapse”[All Fields] OR “recurrence”[All Fields])). A snowballing procedure was conducted to examine the references cited in the articles reporting the included studies and in relevant meta-analysis. The Clinical Trials database was also searched, using the keyword “Giant Cell Arteritis”. The present report is in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) recommendations.

### 2.2. Study selection

The first level of selection was performed by a single reviewer (MA) by reading the title and abstract; to be selected, studies had to describe a standard GCA population with the mention of a follow-up allowing relapse analysis. The second level of selection was performed by two independent reviewers (MA, SM) by reading the full text; to be selected, studies had to include patients with newly diagnosed or recurrent GCA, receiving GC therapy alone or/and an immunosuppressive drug, the number of relapsed patients, and the clinical description of the relapse. Major relapse was defined as ophthalmological (permanent loss of vision, amaurosis fugax, ischemic optic neuropathy [ION], central retinal artery occlusion [CRAO], optic neuritis [ON], and diplopia), neurological (stroke or transient ischemic attack clearly related to GCA), or other ischemic impairment clearly related to GCA (jaw claudication, myocardial infarction, limb claudication, artery occlusion of upper or lower extremities), and aortic complications defined as a relapse (surgery for an active aneurysm or aortic dissection). Studies that included patients refractory to treatment or a targeted population of GCA (for example focusing on visual or neurological impairment) were excluded. If the description of relapses was missing, we contacted the authors

when possible to collect the data. Both observational studies and randomised controlled trials (RCTs) were included.

### 2.3. Data extraction and quality assessment

Study data were independently extracted by two authors (MA, SM). The study characteristics included the following parameters: the first author's name, year of publication, country, journal of publication, study type (observational or randomised), design (prospective or retrospective), type of inclusion (consecutive or not), presence of an experimental arm, number of patients, follow-up in years, age, sex, definition and description of the GCA diagnosis, level of inflammatory syndrome at diagnosis: C-reactive protein (CRP; mg/L) and erythrocyte sedimentation rate (ESR; mm/h), initial dose of GC, and expected scheduled of GC therapy, as well as the number of relapsed patients, definition and description of relapse, time between diagnosis and relapse in weeks, number of patients with major relapse (classified as jaw claudication, ophthalmological, neurological, aortic, or other), treatment received by the patient at the time of the major relapse, level of inflammatory syndrome at the time of the relapse, and treatment of major relapse. It is to note that we collected aortic complications that are not formerly included in the definition of relapse used herein.

The quality of the studies was assessed using the MOOSE tool, which includes six key areas [15].

### 2.4. Data synthesis and analysis

The pooled prevalence and incidence of major relapse among patients diagnosed with GCA and its 95% confidence interval (95%CI) were estimated using the double arcsine transformation to stabilise the variance [16]. Heterogeneity between study-specific estimates was assessed using inconsistency index  $I^2$  [17]. A fixed-effects model was used when  $I^2 \leq 50\%$ , while for  $I^2 > 50\%$  substantial heterogeneity was considered, and a random-effects model was used. Once heterogeneity was established, subgroup and meta-regression analyses were performed to further investigate between-study sources of heterogeneity. Four subgroups were predefined for categorical variables: study design (prospective or retrospective), type of inclusion (consecutive or non-consecutive), intervention (RCT or observational study) and the use of methotrexate or tocilizumab (yes or no). The continuous variables pre-selected in the meta-regression were year of publication, duration of scheduled GC therapy, proportion of relapsing patients at inclusion, as well as ESR and CRP levels at diagnosis. The risk of publication bias was determined by funnel plot [18]. A  $p$ -value lower than 0.05 was considered statistically significant. All analyses were performed using R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) with the metafor package (version 1.9–5).

## 3. Results

### 3.1. Study characteristics

A total of 293 records were identified in electronic databases and 135 records were extracted from the meta-analysis addressing GCA (Fig. 1). Twenty-six studies were included in the final analysis (Table 1), encompassing 36 arms with GC treatment or other treatments, and totalising 2754 patients. The mean age of patients at diagnosis was 69.5 years and 70.3% were women. Inclusions were consecutive in 11 (42.3%) studies [9,19–28] and 15 (57.7%) studies [9,12,19,21,22,26–35] were prospective. Eight (30.8%) studies were RCTs [9,22,27–30,32,33]; the treatments tested in these trials were methotrexate in three studies [22,29,33], tocilizumab in two studies [9,27], infliximab in one study [32], abatacept in one study [30], and etanercept in one study [28]. Fifteen studies were conducted in Europe, eight in the United States of America, one in Israel, and one in Mexico. The visual inspection of the funnel plot suggests the absence of

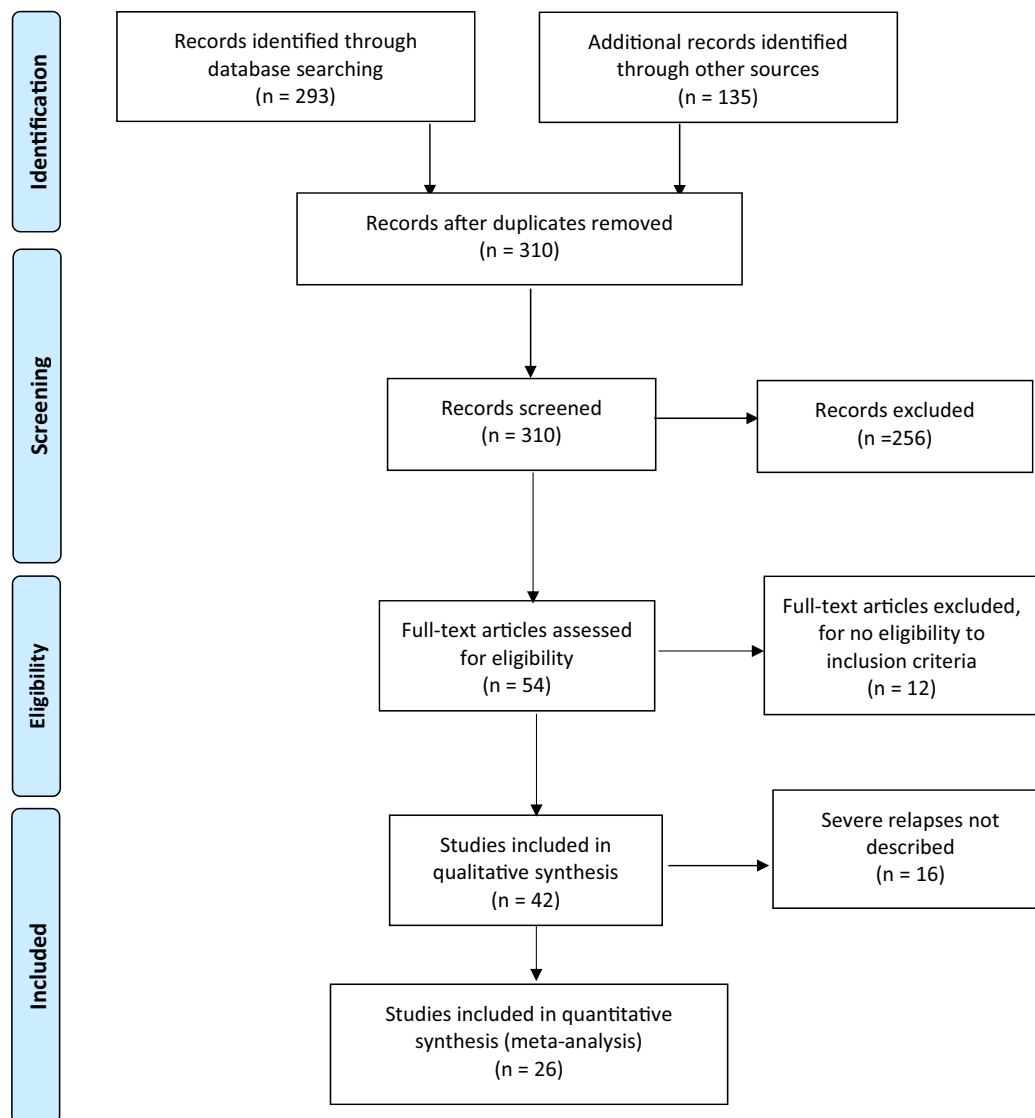


Fig. 1. Flow diagram of the literature search and study inclusion.

publication bias (Fig. S1). The quality of studies is reported in the supplementary material (Table S1). The prevalence of relapse ranged from 16.2 to 90.9% in included studies. The overall pooled prevalence of GCA relapse was 46.5% (95%CI 39.5–53.5) using a random-effects model; there was a high degree of heterogeneity ( $I^2 = 92.2\%$ ).

### 3.2. Prevalence of major relapse

Among the 2754 patients, 104 major relapses were retrieved. The prevalence of major relapse ranged from 0 to 34.1% in included studies (Fig. 2). The overall pooled prevalence of major relapse was 3.3% (95% CI [1.7;5.6] in the overall population using a random-effects model; there was a high degree of heterogeneity ( $I^2 = 86\%$ ). The proportion of major GCA relapse among all cases of relapse ranged from 0 to 40.9% in included studies; the pooled estimate was 7.8% (95%CI [3.9;12.8];  $I^2=87\%$ , Fig. S2).

The design of the study ( $p = 0.18$ ), the type of inclusion ( $p = 0.35$ ) or intervention ( $p = 0.22$ ), or the use of methotrexate or tocilizumab ( $p = 0.99$ ) were not associated with the prevalence of major relapse (Table S2). In meta-regression, the prevalence of major relapse was not significantly different according to year of publication ( $p = 0.38$ ), duration of scheduled GC therapy ( $p = 0.28$ ), proportion of relapsing patient at inclusion ( $p = 0.33$ ), ESR level at diagnosis ( $p = 0.65$ ), and

CRP level at diagnosis ( $p = 0.07$ ; Table S3).

### 3.3. Incidence of major relapses

The length of follow-up was available for 24 studies, totalising 885.6 patient-years. The pooled incidence of relapse was 240.4/100 patient-years (95%CI [185.2;302.4], Fig. S4). The pooled incidence of major relapses was 14.5/100 patient-years (95%CI [5.2;27.2] using a random-effects model; there was a high degree of heterogeneity ( $I^2 = 90\%$ , Fig. S3). The incidence of major relapse was significantly higher in prospective studies than in retrospective studies (55.2/100 patient-years, 95%CI [15.3;114.3] vs 4.1/100 patient-years, 95%CI [1.1;8.4],  $p_{\text{interaction}} = 0.0002$ , Fig. S5). The incidence of major relapse was also significantly higher in RCTs than in observational studies (106.6/100 patient-years, 95%CI [14.5; 264.1] vs 7.9/100 patient-years, 95%CI [2.3;15.8],  $p = 0.007$ ). The type of inclusion ( $p = 0.93$ ) and the use of methotrexate or tocilizumab ( $p = 0.33$ ) were not associated with the incidence of major relapse (Table 2). In meta-regression, the incidence of major relapse was negatively associated with the duration of follow-up (Beta =  $-0.015$ , 95%CI [ $-0.026$ ;  $-0.0042$ ],  $p = 0.0063$ , Fig. 3), and with CRP level at diagnosis (Beta =  $-0.0079$ , 95%CI [ $-0.013$ ;  $-0.0028$ ],  $p = 0.0026$ , Table S4). There was no association between incidence of major relapse and year of publication ( $p = 0.49$ ), proportion of relapsing

**Table 1**  
Summary of studies included in the meta-analysis.

Authors/Year published/Country	Population studied/diagnosis criteria	Study design/type	Patients included/Relapsing patients at inclusion	Relapses	Major relapses	Follow-up (years)	Mean age (years)	Sex (% women)	Initial GC dose (mg/day)	Duration of scheduled GC therapy (months)	Mean ESR (mm/h) /mean CRP (mg/l)
Huston et al. [45]/1978/USA	Newly GCA/ biopsy-proven GCA or classic manifestation of GCA and raised ESR	Retro/OS	42/0	0	2	6	75	79	NA	NA	96/NA
Graham et al. [46]/1981/England	Newly GCA/ biopsy-proven GCA	Retro/OS	90/0	18	4	5	NA	71	80	NA	81/NA
Behn et al. [19]/1983/England	Newly GCA/ Classic manifestation of TA, raised ESR and good response to GC	Pros/OS	68/0	11	0	NA	69	74	17.3	20	66/NA
Gouet et al. [47]/1986/France	Newly GCA/ biopsy-proven GCA	Retro/OS	87/0	18	1	5	73	60	42	NA	90/NA
Delecoeuillerie et al. [20]/1988/France	Newly GCA/ Classic manifestations of TA and/or raised ESR, orosomucoid or haptoglobin	Retro/OS	78/0	21	3	NA	76	62	38.1	NA	104/NA
Kyle et al. [21]/1989/England	Newly GCA/Jones and Hazleman criteria	Pros/OS	35/0	20	2	1.3	NA	NA	40	NA	NA/NA
Liozon et al. [35]/1994/France	Newly GCA/ biopsy-proven GCA	Pros/OS	42/0	22	0	5.91	74	62	42	16	100/95
Weyand et al. [34]/2000/USA	Newly GCA/ biopsy-proven GCA	Pros/OS	25/0	15	0	1.5	72.9	80	60	15	65/NA
Jover et al. [22]/2001/Spain	Newly GCA/biopsy-proven GCA	Pros/RCT	42/0	22	0	2	78	69	60	4	95.5/NA
Spiera et al. [33]/2001/USA	Newly GCA/1990 ACR criteria	Pros/RCT	21/0	9	2	2	72.9	66.7	60	4	71/NA
Hachulla et al. [39]/2001/France	Newly GCA/1990 ACR criteria [48] or biopsy-proven GCA	Retro/OS	133/0	83	0	5.55	72	71	48	4	89/80
Hoffmann et al. [29]/2002/USA	Newly GCA/ biopsy-proven GCA or classic manifestations of TA or large vessel vasculitis proved	Pros/RCT	98/0	46	8	1	74.5	71.3	60	6	NA/NA
Hoffman et al. [32]/2007/USA	Newly GCA/1990 ACR criteria	Pros/RCT	44/0	40	15	0.4	70.8	79.8	49.3	6	77.5/NA
Martinez-Taboada et al [28]/2008/Spain	controlled GCA and side effects to GC/ biopsy-proven GCA	Pros/RCT	17/0	11	0	1	74.5	82.4	18	3	16.5/11
Nesher et al. [23]/2008/Israel	Newly GCA /1990 ACR criteria	Retro/OS	130/0	67	5	3	73	65	55.6	NA	NA/NA
Martinez-Lado et al. [24]/2011/Spain	Newly GCA /1990 ACR criteria or biopsy-proven GCA	Retro/OS	174/0	71	0	8.6	75	54	60	29	90/NA
Alba et al. [25]/2012/Mexico	Newly GCA /1990 ACR criteria	Retro/OS	22	10	2	4.7	73	82	50.2	NA	NA/NA
Alba et al. [12]/2014/Spain	Newly GCA/ biopsy-proven GCA	Pros/OS	106/0	68	1	7.8	75	73	60	34	90/100
Kermani et al. [31]/2015/USA	Newly or established GCA/ modified 1990 ACR criteria	Pros/OS	128/49	44	18	1.78	69.9	80	NA	NA	31/16
Hocevar et al. [26]/2016/Slovenia	Newly GCA/ 1990 ACR criteria and biopsy-proven GCA or halo sign or large vessel vasculitis proved	Pros/OS	68/0	31	11	2	73.2	74	47	28	82/66
Labarca et al. [49]/2016/USA	Newly GCA/ biopsy-proven GCA	Retro/OS	286/0	213	10	5.1	75	74	50.8	NA	66/54.7
Restuccia et al. [14]/2016/Italy	Newly GCA/ biopsy-proven GCA	Retro/OS	157/0	57	4	6.6	74	78	46	21	87/91

(continued on next page)

Table 1 (continued)

Authors/Year published/Country	Population studied/diagnosis criteria	Study design/type	Patients included/Relapsing patients at inclusion	Relapses	Major relapses	Follow-up (years)	Mean age (years)	Sex (% women)	Initial GC dose (mg/day)	Duration of scheduled GC therapy (months)	Mean ESR (mm/h) /mean CRP (mg/l)
Langford et al. [30] /2017/ USA	Newly or relapsing GCA /1990 ACR criteria	Pros/RCT	41/18	24	8	0.5	66.5	90.2	60	7	NA/NA
Stone et al. [9]/ 2017/USA	Newly or relapsing GCA/ biopsy-proven GCA or on evidence of large vessel vasculitis on angiography, computed tomographic or MRA or PET	Pros/RCT	251/132	95	1	1	69.1	74.7	NA	12 or 6	25/NA
Samson et al. [27]/2018/ France	Newly or relapsing GCA/ 1990 ACR criteria and biopsy proven GCA or aortitis proved	Pros/RCT	20/1	10	2	1	72	75	42	11	82.5/ 54.5
de Boysson et al. [40]/2018/ France	Newly GCA/ 3 of 1990 ACR or 2 criteria and large vessels vasculitis proved in imagery	Retro/ OS	549/0	229	5	4	72	70	48	NA	80/80

GC: glucocorticoid; GCA: Giant Cell Arteritis; CRP: C-reactive-protein; ESR: erythrocyte rate sedimentation; Pros: prospective; Retro: retrospective; RCT: Randomised controlled trial. MRA: Magnetic resonance angiography; PET: Positron Emission Tomography.

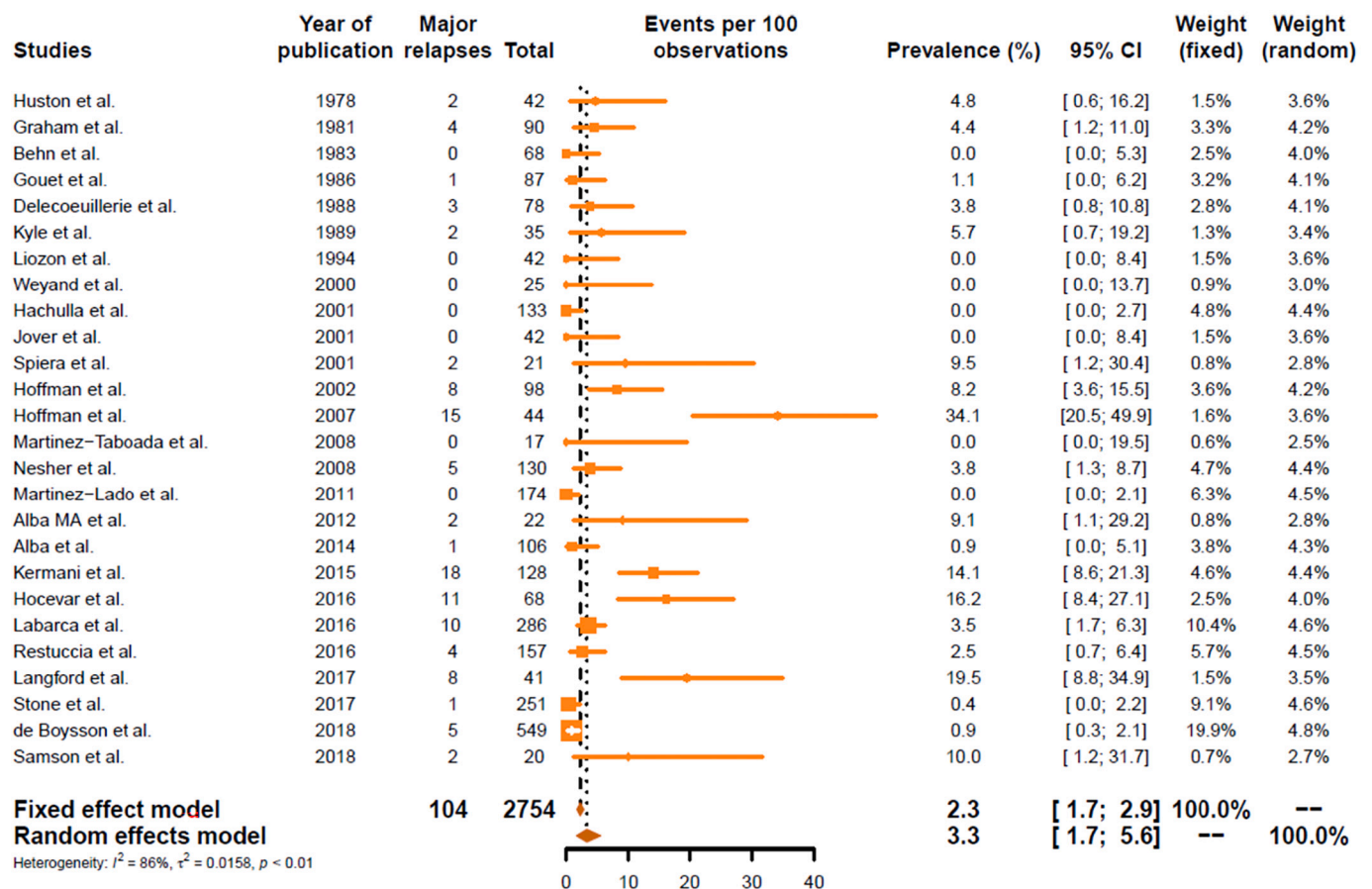


Fig. 2. Forest plot of major relapse prevalence in patients with GCA. Major relapses: number of relapsing patients; total: total number of patients in the study; 95%CI: 95% confidence interval, weight: study weight in the meta-analysis.

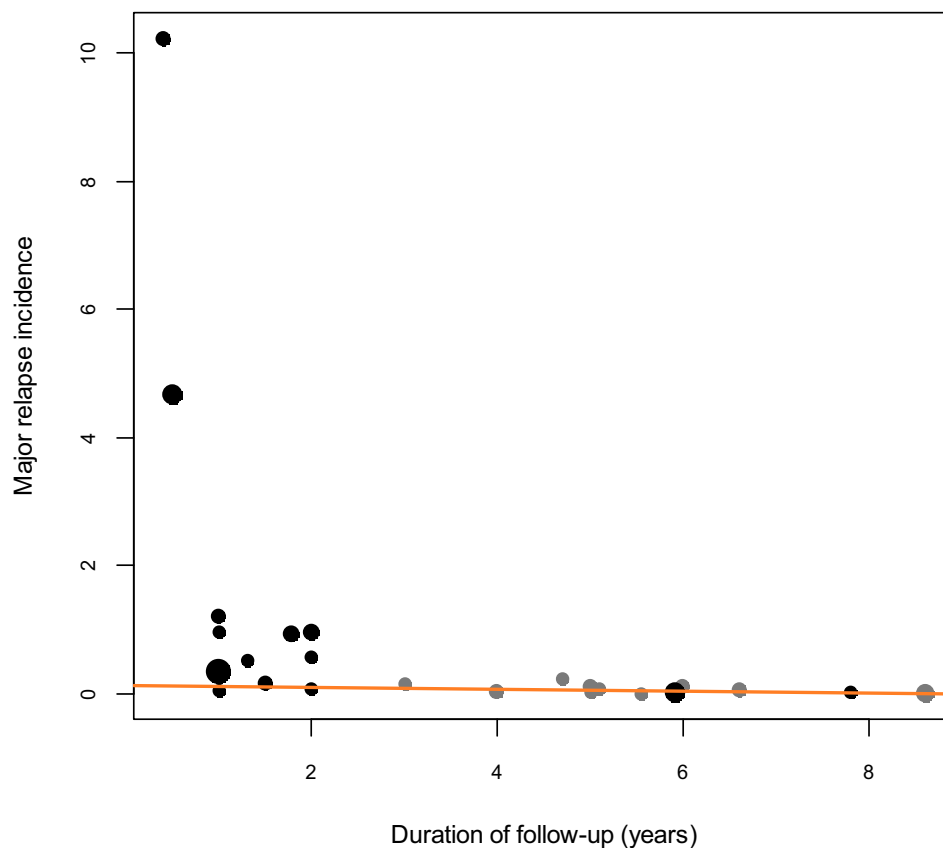
patients at inclusion ( $p = 0.40$ ), or ESR level at diagnosis ( $p = 0.67$ ). The meta-regression found a trend towards a negative association between incidence of major relapse and duration of scheduled glucocorticoid therapy (Beta =  $-0.0024$ , 95%CI [0.0048;0.000],  $p = 0.053$ ).

### 3.4. Sensitivity analysis

A post hoc sensitivity analysis was performed with the exclusion of jaw claudication from the criteria defining major relapse. The

**Table 2**  
Exploration of heterogeneity of major relapse incidence by subgroup analysis.

	Studies (n)	Patients (n)	Incidence of major relapse (/100 patient-years)	95% confidence interval	I <sup>2</sup>	p-value
Study design						
Prospective	14	938	55.2	[15.3;114.3]	92.0%	0.0002
Retrospective	10	1670	4.1	[1.1;8.4]	75.2%	
Inclusion type						0.93
Consecutive	9	759	14.2	[0.006;44.2]	87.5%	
Non-consecutive	15	1849	4.2	[4.5;32.1]	91.6%	
Intervention type						0.007
Randomised controlled trial	8	534	106.6	[14.5;264.1]	91.5%	
Observational study	16	2074	7.9	[2.3;15.8]	87.3%	
Use of methotrexate or tocilizumab						0.33
Yes	5	432	31.0	[0.0;98.3]	81.2%	
No	19	2176	12.1	[3.6;24.8]	91.0%	



**Fig. 3.** Meta-regression of the major relapse incidence according to the duration of follow-up in years. Circles indicate studies included in the meta-regression: black for prospective studies, and grey for retrospective studies. The orange curve indicates the model prediction of relapse.

prevalence of major relapse was 1.8% (95%CI [0.9;3.1], I<sup>2</sup> = 77%); the incidence of major relapse was 4.7/100 patient-years (95%CI [0.5;11.7], I<sup>2</sup> = 83%).

### 3.5. Description of 104 major relapses (Table 3)

#### 3.5.1. Jaw claudication

Claudication of the jaw was the most frequent clinical sign of major relapse; it represented 44.3% (44/104) of major relapses.

#### 3.5.2. Ophthalmological relapse

Ophthalmological relapse represented 32.7% (34/104) of major relapses, including five ION, 14 blindness without specified cause, three reversible vision loss under treatment (including one ION), 10 undefined

visual symptoms (no specific description in the articles), one CRAO, and one diplopia.

#### 3.5.3. Peripheral limb ischemia

Peripheral limb ischemia represented 12.5% (13/104) major relapses, including eight in the peripheral arteries of the upper limbs, and five of the lower limbs.

#### 3.5.4. Aortic involvement

Severe aortic involvement represented 7.7% (8/104) relapses, including two aneurysm of which one requiring surgery and six aortic dissection. No myocardial infarction related to GCA was reported. Aortic complications were identified in 13 patients, but not formally considered as relapses; consequently, these were not included in the present



**Table 3**  
Description of the 104 major relapses included.

	N (ref)	Age, sex	Treatment at major relapse	Description	Treatment of MR	Sequelae
<b>Jaw claudication</b>	<b>44</b>					
	1 (27)	–	GC 10 mg/day	Biological inflammatory syndrome	GC 20 mg/day	Remission
	1 (30)	–	–	Jaw and tongue claudication	–	–
	7 (32)	–	–	22 weeks after diagnosis	–	–
	1 (46)	–	GC 15 mg/day	2 years after diagnosis	–	–
	34	–	–	–	–	–
	(26,30,31,33,45,49)	–	–	–	–	–
<b>Ophthalmological</b>	<b>34</b>					
	1 (12)	–	No treatment (ending 2 years ago)	2nd recurrence of ION 4 years after end of follow-up	–	–
	1 (14)	–	GC 12.5 mg/day	13 months after diagnosis	–	Transient vision loss
Ischemic optic neuropathy	1 (9)	–	–	–	–	after GC treatment
	1 (31)	–	–	–	–	–
	1 (26)	–	–	–	–	Permanent vision loss
Blindness (undefined cause)	13 (23,29)	–	–	–	–	Vision loss
	1 (20)	–	–	–	GC 60 mg/day	Unilateral vision loss
Reversible vision loss under treatment	1 (47)	73 years, male	GC 5 mg/day	Unilateral vision loss	Increase of GC dose	Transient
	1 (9)	–	–	ION	–	–
	1 (27)	–	–	Transient loss of vision	–	–
Visuals symptoms	10 (21,31,32)	–	–	–	–	–
Central retinal artery occlusion	1 (30)	–	–	Partial vision loss at 28 weeks then CRAO (branch) 5 months before end of follow-up	–	–
Diplopia	1 (31)	–	–	–	–	–
<b>Peripheral disease</b>	<b>13</b>					
	1 (14)	–	–	Stenosis of subclavian artery	–	–
Upper limb	1 (26)	–	–	Hand claudication, angioplasty of axillar artery	–	–
	6 (31)	–	–	–	–	–
	3 (25,31)	–	–	No detail	–	–
Lower limb	1 (33)	–	under methotrexate (withdrawal of GC)	Ischemia of left lower limb	GC	Transient with GC therapy
	1 (14)	–	–	Left limb claudication, occlusion of superficial femoral artery	–	–
<b>Aortitis</b>	<b>8</b>					
Aneurysm	1 (14)	–	–	Pulsatile mass with aneurysm of ascendant aortitis	–	–
	1 (26)	–	–	Surgery of progressing thoracic aneurysm	–	–
	1 (45)	–	GC 20 mg/day	Dissection and aortic rupture, raised ESR	–	Death
Dissection	2 (40)	–	Methotrexate	Dissection	–	Death
	1 (40)	–	Tocilizumab	Dissection	–	Death
	2 (40)	–	–	Dissection	–	Survival
<b>Neurological</b>	<b>5</b>					
Transient ischemic attack	1 (32)	–	–	–	–	–
	1 (46)	62 years, –	GC 10 mg/day	Left hemiparesia, headache, PMR 5 years after diagnosis	–	–
Stroke	1 (46)	62 years, –	GC 10 mg/day	Right hemiparesia, jaw claudication one year after diagnosis	–	–
	1 (20)	–	GC 20 mg/day stopped by patient	Controlled disease, intra cranial arteritis	–	Death
	1 (23)	–	GC 60 mg/day	Controlled disease	–	Hemiplegia

CRAO: Central retinal artery occlusion, ESR: erythrocyte rate sedimentation, GC: glucocorticoid, ION: Ischemic optic neuropathy, PMR: polymyalgia rheumatica.

analysis.

### 3.5.5. Central neurological relapse

Central neurological relapse represented 4.8% (5/104) major relapses, including four ischemic strokes (territories of ischemia unknown) and one transient ischemic attack.

## 4. Discussion

In GCA, major relapse is a rare event, occurring in only 3.3% of patients and accounted for 7.8% of all relapses. The incidence of relapse was estimated to be 240/100 patient-years, and that of major relapse to be 15/100 patient-years. However, the values of incidence and prevalence of major relapse in GCA were imprecise. For incidence, this was

related to the high level of heterogeneity of estimates extracted from included studies rather than a lack of power. The subgroup analysis partially explained this heterogeneity; the incidence of major relapse being higher in prospective studies and RCTs. Although this must be interpreted with caution because of the high colinearity between the variables, these results raise several hypotheses. For instance, differences in treatment exposure may explain the variation of incidence of major relapse; it was found in a meta-analysis investigating overall relapse that patients included in RCTs received a shorter duration of GC than did those in cohort studies and that this was associated with the prevalence of relapse (incidence was not investigated) [13]. This hypothesis is also supported by the negative association between time of follow-up and incidence of major relapse herein. We may also hypothesize that patients included in RCTs are more severe and were at higher

risk of major relapse. Another explanation may be the underestimation of major relapse in retrospective studies related to information bias; prospective studies, including RCTs may therefore capture the true incidence of major relapse in GCA. For prevalence, this was either due to the high level of heterogeneity of estimates extracted from the included studies but also a lack of power; this lack of power also explains why the subgroup analysis was not informative, and is likely as another meta-analysis found that relapse were more frequent in RCTs than in observational studies [13] which was not found herein.

Major relapse is a composite outcome without weighting of clinical endpoints. It is admitted that composite outcomes should occur with similar frequency and be of comparable clinical importance [36]. This is not the case herein, jaw claudication accounting for almost half of all major relapses and seems clinically less serious than the other manifestations although this has been described as a risk factor for severe cranial ischemic complications [37,38]. The potential association between jaw claudication and ophthalmological relapse is outside the scope of the present study, but the clinical importance of this outcome, compared to other ischemic signs, is questionable. Further studies are needed to compare the prognosis of patients according to the relapse manifestations.

The present study does have several limitations. Firstly, the heterogeneity remained important and was not fully explained by subgroup analysis and meta-regression. One point of interest is that the patients included were heterogeneous as both relapsing and newly diagnosed patients were included in the studies. Nevertheless, the meta-regression was not in favour of a relationship between the prevalence of relapsing patients and the incidence of major relapse. Secondly, some studies included in the present meta-analysis mentioned progressive aortic complications, without specifying the presence of signs in favour of GCA relapse [39,40]. These patients were excluded from the analysis herein; we may therefore have underestimated the prevalence of major relapse. Thirdly, although the funnel plot did not show visual asymmetry [18], we cannot exclude selection or information bias that could overestimate the prevalence of major relapse as only studies in which major relapses were described, or absence of major relapse was specified were included. Fourthly, a meta-analysis of observational studies or arms of RCTs provides relatively low-grade evidence. Lastly, because of individual data were not available, we could not exclude ecological bias for meta-regression analysis [41]. In the context of these limitations, dedicated multicentre studies are needed to confirm the estimations of the prevalence and incidence of major relapse; it would also be of interest to evaluate predictive factors of major relapse in GCA, including initial low systemic inflammation [42,43] or damage to large vessels [43,44], and estimated its consequence in terms of treatment and damage.

In conclusion, the prevalence and incidence of major relapse varied widely across studies, with a potential effect of study design on incidence estimates. Incidence and prevalence estimates are heavily impacted by jaw claudication, the clinical importance of which is questionable.

#### Declaration of Competing Interest

MS: Roche-Chugai (invitation to congress, personal fees for symposium and boards), Abbvie (consulting), None declared for others.

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The protocol of the meta-analysis is registered in the international prospective register of systematic reviews PROSPERO (<https://www.crd.yotk.ac.uk/PROSPERO>, registration CRD42019148051).

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.autrev.2021.102930>.

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*Aussedat et al. Autoimmun Rev. 2021 - Supplementary Table S1. Quality assessment using the MOOSE tools*

	Clear definition of study population?	Clear definition of outcomes and outcome assessment?	Independent assessment of outcome parameters?	Sufficient duration of follow-up?	No selective loss during follow-up?	Important confounders and prognostic factors identified?
Huston <i>et al.</i> (45) 1978	Yes	Yes	No	Yes	No	No
Graham <i>et al.</i> (46) 1981	Yes	Yes	No	Yes	No	No
Behn <i>et al.</i> (19) 1983	Yes	Yes	No	Yes	No	No
Gouet <i>et al.</i> (47) 1986	Yes	Yes	No	Yes	No	No
Delecoeuillerie <i>et al.</i> (20) 1988	Yes	Yes	No	Yes	No	No
Kyle <i>et al.</i> (21) 1989	Yes	Yes	No	Yes	No	No
Liozon <i>et al.</i> (35) 1994	Yes	No	No	Yes	No	No
Weyand <i>et al.</i> (34) 2000	Yes	Yes	No	Yes	No	No
Hachulla <i>et al.</i> (39) 2001	Yes	Yes	No	Yes	No	No
Jover <i>et al.</i> (22) 2001	Yes	Yes	Yes	Yes	No	No
Spira <i>et al.</i> (33) 2001	Yes	Yes	Yes	Yes	No	No
Hoffmann <i>et al.</i> (29) 2002	Yes	Yes	Yes	Yes	No	No
Hoffman <i>et al.</i> (32) 2007	Yes	Yes	Yes	No	No	No
Nesher <i>et al.</i> (23) 2008	Yes	Yes	No	Yes	No	No
Martinez-Taboada <i>et al</i> (32) 2008	Yes	Yes	Yes	Yes	No	No
Martinez-Lado <i>et al.</i> (24) 2011	Yes	Yes	No	Yes	No	No
Alba <i>et al.</i> (25) 2012	Yes	No	No	Yes	No	No
Alba <i>et al.</i> (12) 2014	Yes	Yes	No	Yes	No	No
Kermani <i>et al.</i> (31) 2015	Yes	Yes	Yes	Yes	No	No
Hocevar <i>et al.</i> (26) 2016	Yes	Yes	No	Yes	No	No
Labarca <i>et al.</i> (49) 2016	Yes	Yes	No	Yes	No	No
Restuccia <i>et al.</i> (14) 2016	Yes	Yes	No	Yes	No	No
Stone <i>et al.</i> (9) 2017	Yes	Yes	Yes	Yes	No	No
De Boysson <i>et al.</i> (40) 2017	Yes	Yes	Yes	Yes	No	No
Langford <i>et al.</i> (30) 2017	Yes	Yes	No	No	No	No
Samson <i>et al.</i> (27) 2018	Yes	Yes	Yes	Yes	No	No

*Aussedat et al. Autoimmun Rev. 2021 - Supplementary Table S2. Exploration of heterogeneity of major relapse prevalence by subgroup analysis.*

	Studies (n)	Patients (n)	Prevalence of relapse (%)	95% confidence interval	I <sup>2</sup>	p-value
<b>Study design</b>						0.18
Prospective	15	1006	4.6	[2.3;9.6]	89.4%	
Retrospective	11	1748	1.9	[0.8;3.5]	73.7%	
<b>Inclusion type</b>						0.35
Consecutive	11	905	2.3	[0.5;5.5]	82.6%	
Non-consecutive	15	1849	4.2	[1.8;7.6]	88.4%	
<b>Intervention type</b>						0.22
Randomised controlled trial	8	534	6.6	[1.0;16.4]	90.8%	
Observational study	18	2220	2.4	[0.1;4.4]	83.6%	
<b>Use of methotrexate or tocilizumab</b>						0.99
Yes	5	432	3.4	[0.02;9.7]	82.7%	
No	21	2322	3.4	[1.5;5.9]	87.5%	

*Aussedat et al. Autoimmun Rev. 2021 - Supplementary Table S3. Exploration of heterogeneity of severe relapse prevalence by meta-regression.*

	<b>Studies (n)</b>	<b>Patients (n)</b>	<b>Beta*</b>	<b>95% Confidence interval</b>	<b>p- value</b>
<b>Year of publication</b>	26	2754	0.0014	[-0.0017;0.0046]	0.38
<b>Duration of scheduled glucocorticoid therapy (months)</b>	15	1174	-0.0020	[-0.0055;-0.0016]	0.28
<b>Proportion of relapsing patients at inclusion (%)</b>	25	2205	0.0006	[-0.0006;0.0019]	0.33
<b>Erythrocyte sedimentation rate level at diagnosis</b>	12	942	0.0001	[-0.0004;0.0006]	0.65
<b>C-reactive protein level at diagnosis</b>	10	1530	-0.0013	[-0.0027;0.0001]	0.07

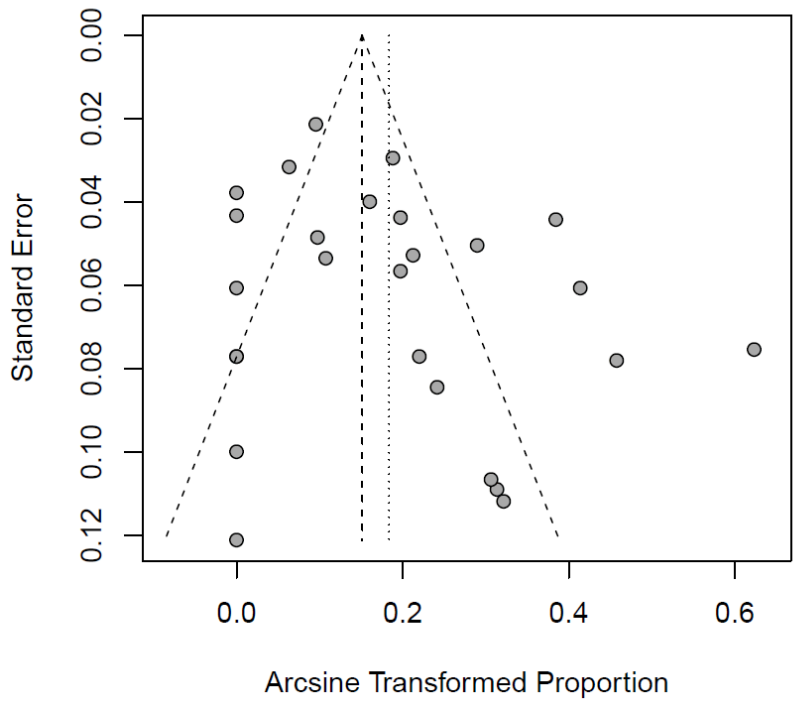
\*Beta signification: relapse rate/incidence increase or decrease for the augmentation of one unit of the variable tested

*Aussedat et al. Autoimmun Rev. 2021 - Supplementary Table S4. Exploration of heterogeneity of severe relapse incidence by meta-regression.*

	<b>Studies (n)</b>	<b>Patients (n)</b>	<b>Beta*</b>	<b>95% Confidence interval</b>	<b>p- value</b>
<b>Year of publication</b>	24	2608	0.023	[-0.043;0.089]	0.49
<b>Duration of follow-up</b>	24	2608	-0.015	[-0.026;-0.0042]	0.0063
<b>Duration of scheduled glucocorticoid therapy (months)</b>	14	1106	-0.0024	[-0.0048;0.000]	0.053
<b>Proportion of relapsing patient at inclusion (%)</b>	23	2059	0.0009	[-0.0013;0.0031]	0.40
<b>Erythrocyte sedimentation rate level at diagnosis</b>	10	796	-0.0004	[-0.0022;0.0014]	0.67
<b>C-reactive protein level at diagnosis</b>	10	1530	-0.0079	[-0.013;-0.0028]	0.0026

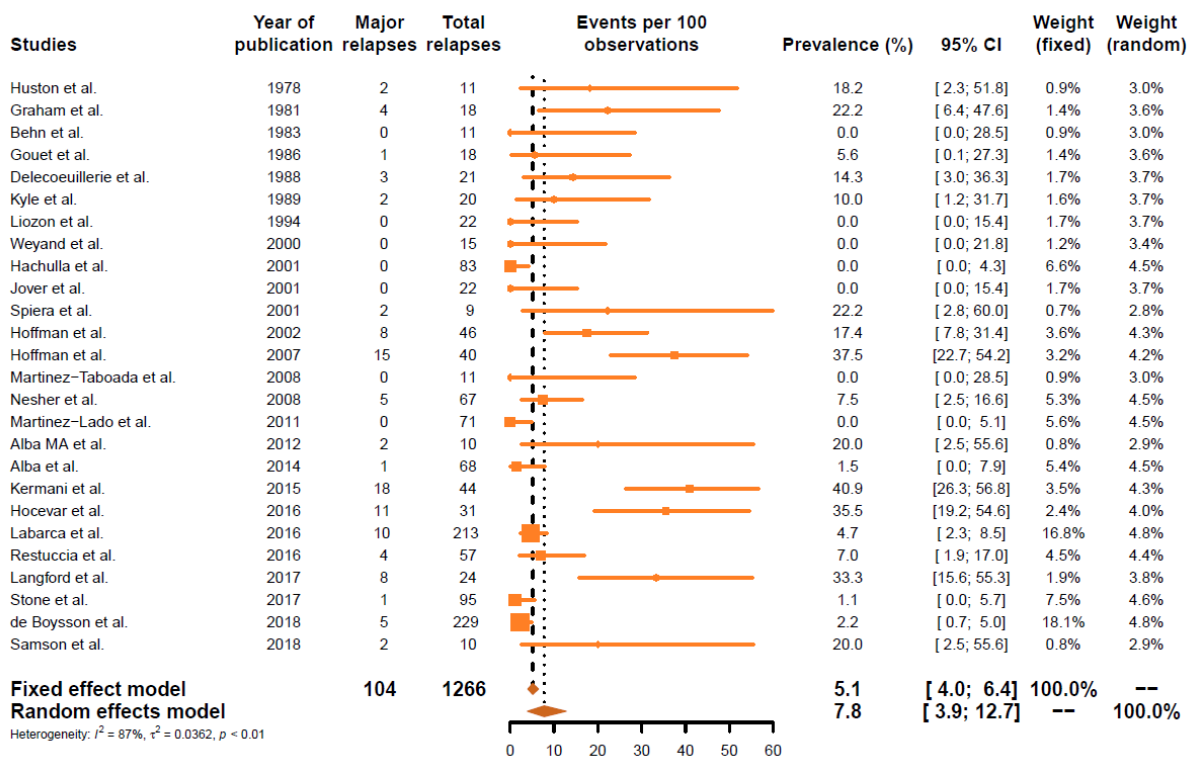
\*Beta signification: relapse rate/incidence increase or decrease for the augmentation of one unit of the variable tested

Aussedat et al. *Autoimmun Rev.* 2021 – **Supplementary Figure S1. Funnel plot of relapse prevalence for the search of publication bias.** The symmetry of the figure suggests the absence of publication bias.

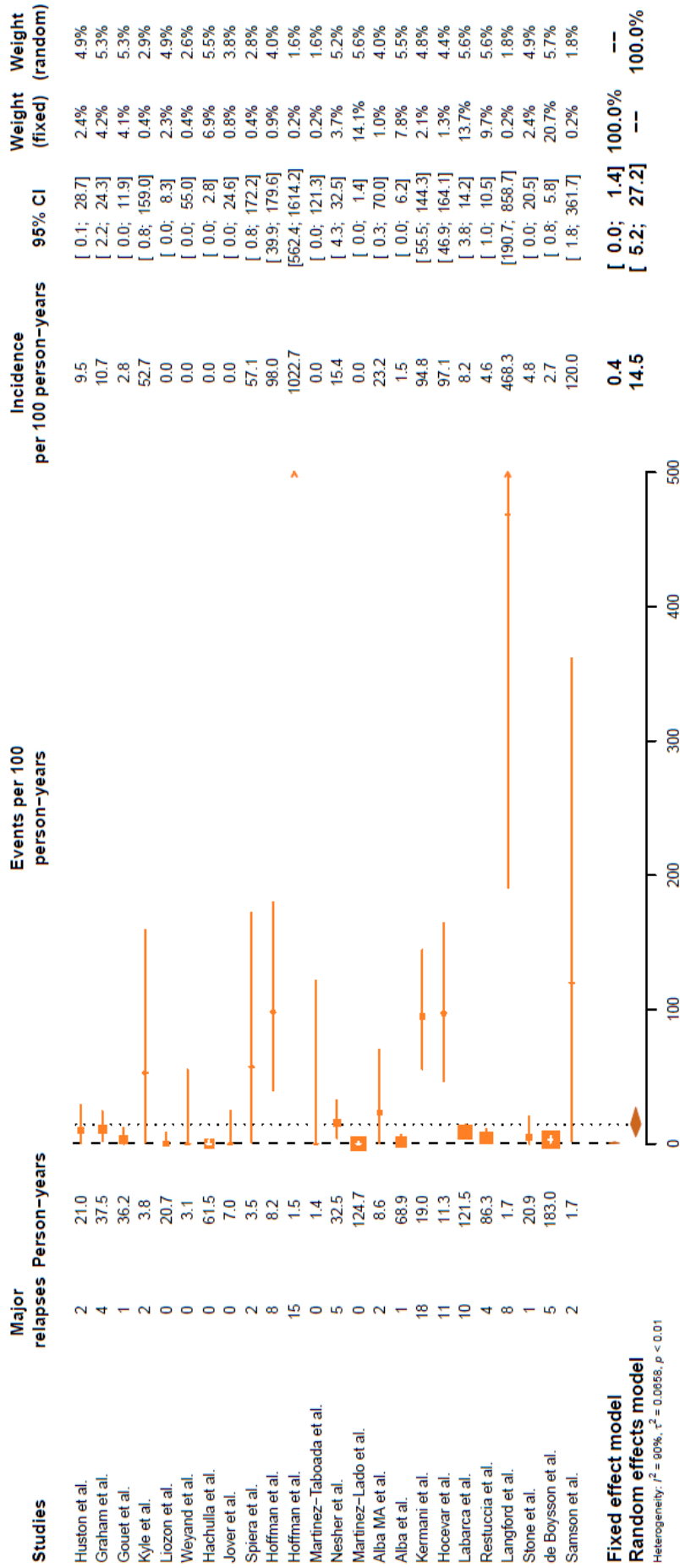




Aussedat et al. Autoimmun Rev. 2021 - Supplementary Figure S2. Forest plot of major relapse prevalence among total relapse in patients with GCA. Major relapses: number of relapsing patients; total relapses: total number of relapsing patients in the study; 95%CI: 95% confidence interval, weight: study weight in the meta-analysis.

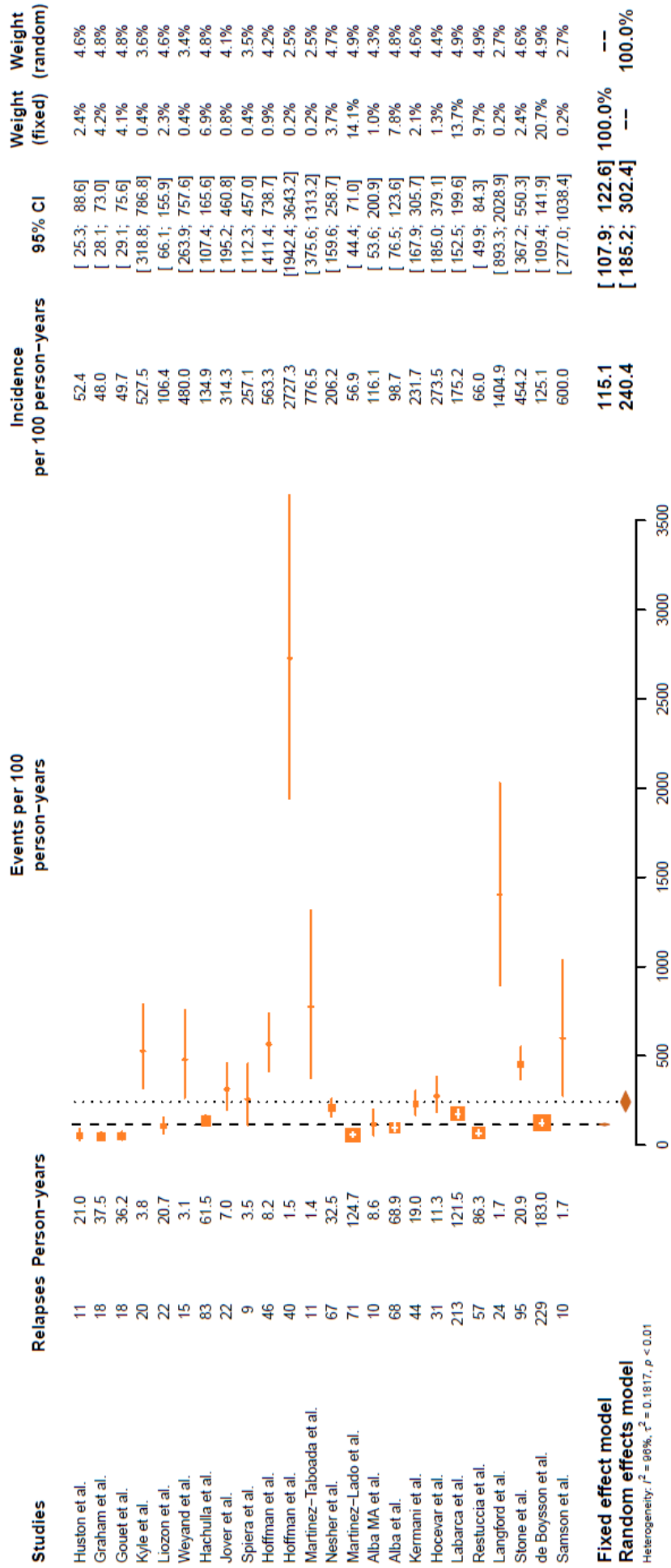


Aussedat et al. *Autoimmun Rev.* 2021 - Supplementary Figure S3. Forest plot of major relapse incidence in patients with GCA. Major relapses: number of relapsing patients; Patient-years: number of patients at risk; 95%CI: 95% confidence interval, weight: study weight in the meta-analysis.

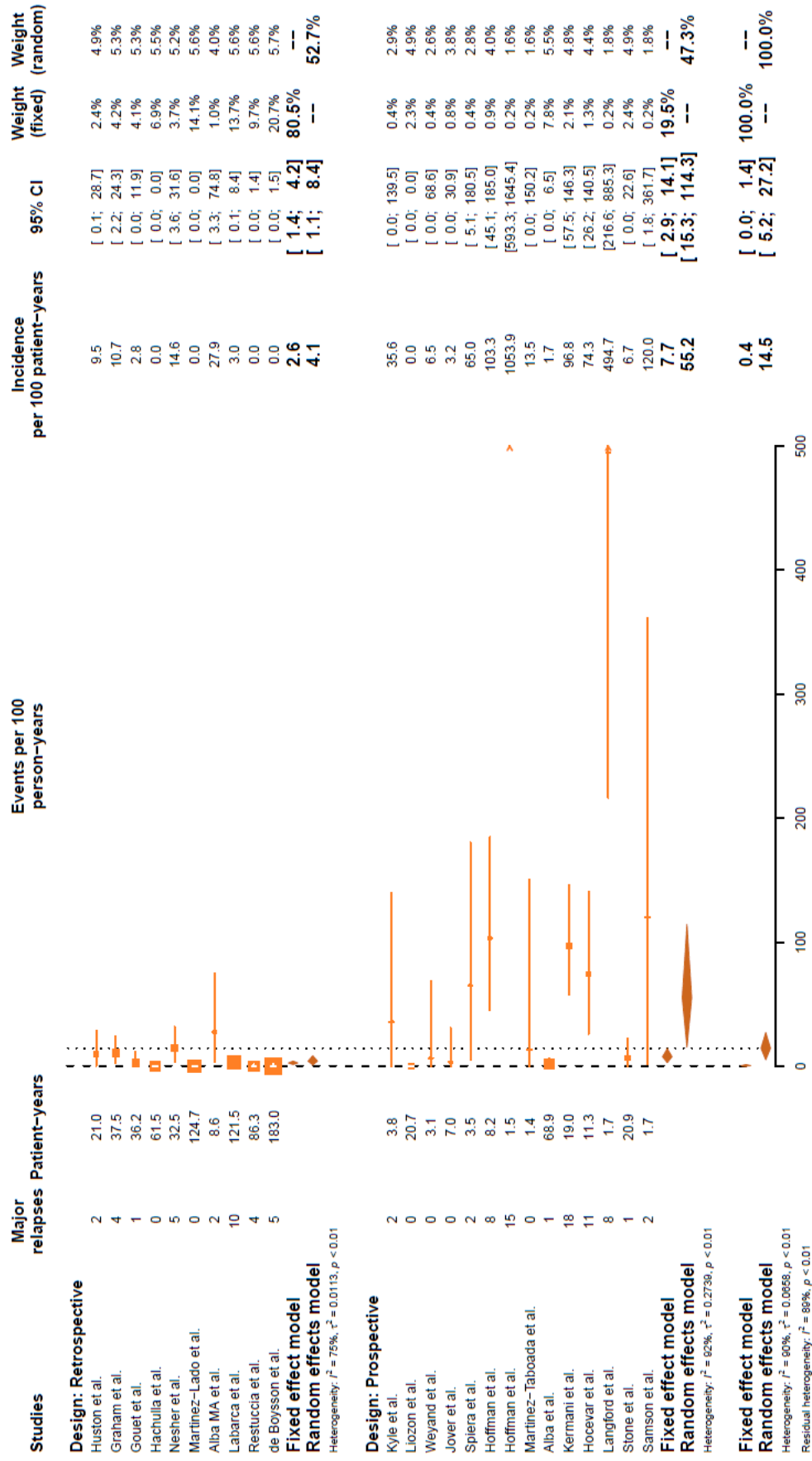


Aussedat et al. *Autoimmun Rev.* 2021 – Supplementary Figure S4. Forest plot of relapse incidence in patients with GCA. Relapses: number of relapsing

patients; Patient-years: number of patients at risk; 95%CI: 95% confidence interval, weight: study weight in the meta-analysis.



Aussedat et al. *Autoimmun Rev.* 2021 - Supplementary Figure S5. Forest plot of major relapse incidence in patients with GCA according to study design



Relapses: number of relapsing patients; Patient-years: number of patients at risk; 95%CI: 95% confidence interval, weight: study weight in the meta-analysis.

### 5.3 Données Eurostat

Mainourg S, Dananché C, Freyssenge J, Hachulla E, Belot A, Lega JC, FAI2R. **Mortality trends in giant cell arteritis in European countries: Eurostat data analysis from 1994 to 2016.**

*En cours de rédaction*

**Objective:** The objective of this study was to describe the evolution of giant cell arteritis-related mortality from 1994 to 2016 in European countries.

**Methods:** Data from death of people and population size from 31 countries were extracted from Eurostat in the period 1994–2016. The International Classification of Diseases 10 (ICD-10) and ICD-9 codes corresponding to giant cell arteritis were selected. Age was aggregated in 5-year groups from 50 years to greater than 85 years. The crude mortality rate was calculated within each country for every, and in the whole European. We estimated age-standardized mortality rates (ASMR), using the 2011 inter-censal estimates of European population as the reference, allowing direct comparisons between countries by adjusting for a reference population.

**Results:** 5 650 deaths related to GCA were reported across the 31 European countries. The crude GCA-related mortality rate of Europe varied from 0.398/100 000 population over 50 years (95% CI 0.351 - 0.450) in 1994 to 0.154/100 000 (95% CI 0.138 - 0.172) in 2016. The crude mortality rate was significantly higher in the age groups over 75 years. ASMR varies from 0.436/100 000 population over 50 years (95%CI 0.384 - 0.494) in 1994 to 0.146/100 000 (95%CI 0.130 - 0.163) in 2016. ASMR significantly decreased over time (-0.017 per year,  $p < 0.001$ ). At visual inspection, ASMR of France, Iceland and Luxembourg were higher than other countries.

**Conclusion:** GCA-related mortality decreased over time in Europe. There was considerable heterogeneity between countries, which raises questions about the quality of the Eurostat data.

# Mortality trends in giant cell arteritis in European countries: Eurostat data analysis from 1994 to 2016

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## Introduction

Giant cell arteritis (GCA) is a large vessel vasculitis affecting people over 50 years of age.[1,2] It is characterized by the occurrence of ischemic signs such as headache, visual manifestations, scalp tenderness, jaw claudication and stroke, together with systemic symptoms such as weight loss or anorexia, fatigue, and fever.

The mortality rate is not higher in patients with GCA than in the general population but some studies reports a mortality increase in the first years following the diagnosis.[3] The main causes of death related to GCA described are infectious, cardiovascular or related to diabetes mellitus.[4–6] Little is known about how GCA-related mortality changes over time excepted from France. Indeed, two studies used French death certificate, the first one between 1980 and 2011 and shows a significant increase in the death rate up to a peak in 1997, then a significant decrease until 2011.[5] The second one was conducted from 2005 to 2014 and shows a stability of mortality over the study period.[4]

The objective of this study was to describe the evolution of the mortality related to giant cell arteritis from 1994 to 2016 in European countries.

## Material and methods

*Population.* Data from death of people from 31 countries were extracted from Eurostat, the statistical office of the European Union (EU), in the period 1994–2016 (<http://ec.europa.eu/eurostat/data/database>). The countries included the 27 member countries of the EU (Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Germany, Greece, Spain, Finland, France, Hungary, Ireland, Italy, Lithuania, Luxemburg, Latvia, Malta, Netherlands, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia), three member of the European Free Trade Association (Norway, Switzerland and Iceland) and United Kingdom. The database was updated on March 8, 2018. The International Classification of Diseases 10 (ICD-10) codes M31.5 (giant cell arteritis with polymyalgia rheumatica) and M31.6 (other giant cell arteritis) and the ICD-9 code 446.5 (giant cell arteritis) were selected. We used the underlying cause of death (UCD) for this analysis, which is defined by Eurostat as “the disease or injury which initiated the train of morbid events leading directly to death, or the circumstances of the accident or violence which produced the fatal injury”. The dataset was not complete because data for one or more calendar years were missing from a few countries. Nevertheless, GCA as UCD is rare, and zero death was possible but was not distinguishable from missing data in the original dataset. Therefore we replaced the missing data with zero when data were available for other more frequent cause of death in the dataset (we use rheumatoid arthritis). No other extrapolation was made for missing data.

The population sizes (number of inhabitants of a given area on 1 January of the year in question) of the 31 countries from 1994 and 2016 have been downloaded from the Eurostat website (<https://ec.europa.eu>). We used the standard European population as reference from the 2011 intercensal estimates by Eurostat.

Because GCA diagnosis is not considered before 50 years, age was aggregated in 5-year groups from 50 years to greater than 85 years. Therefore, results are presented per 100 000 population over 50 years.

*Statistical analysis.* We calculated the crude mortality rate and its 95% confidence interval (CI) within each country for every year (number of deaths divided by population size), and in the whole European population (using the count of population for which number of deaths was available). We also calculated the crude mortality rate and its 95% CI in the whole European population for every year in each age group.

We estimated age-standardized mortality rates (ASMR) and its 95% CI in the European population and within each country for every year studied, using the 2011 standard European population as the reference, giving our findings as number of deaths per 100 000 population over 50 years. Thus, ASMR allowed direct comparisons between countries by adjusting for a reference population.

Univariate and multivariate linear regression adjusted on age group were conducted in the crude mortality rate and univariate linear regression was conducted in the ASMR. All analysis were conducted with R (packages *epitools* and *ggplot2*, R Language and Environment for Statistical Computing, Vienna, Austria).

## Results

*Crude mortality rate.* Between 1994 and 2016, 5 650 deaths related to GCA were reported across the 31 European countries considered. In Europe, the crude mortality rate varied from 0.398/100 000 population (95% CI 0.351 - 0.450) in 1994 to 0.154/100 000 (95% CI 0.138 - 0.172) in 2016 (Table 1 and Supplementary material, Figure S1). In the univariate analysis, the crude mortality rate significantly decreased over time (-0.015 per year,  $p < 0.001$ ), and the result remained significant when adjusting on age group (-0.0092 per year,  $p < 0.001$ , Table 2). The crude mortality rate was significantly higher in the age groups over 75 years (Table 2, Figure 1). Regarding the different countries, the crude mortality rate varies from 0/100 000 population (95% CI 0 - 0.026; Poland, 2016) to 1.604/100 000 (95%CI 0.041 - 8.935; Iceland, 1995) population (Supplementary material, Table S1, and Figure S2).

*ASMR.* In Europe, ASMR varies from 0.436/100 000 population over 50 years (95%CI 0.384 - 0.494) in 1994 to 0.146/100 000 (95%CI 0.130 - 0.163) in 2016 (Table 1). ASMR significantly decreased over time



(-0.017 per year,  $p < 0.001$ , Figure 2). At visual inspection, ASMR of France, Iceland and Luxembourg were higher than other countries (Figure 3 and supplementary material, Table S2).

## Discussion

The result of the present study provide evidence in favor of a significant decrease of the GCA mortality rate over time from 1994 to 2016 in Europe. This is globally consistent with a previous study about French death certificate from 1980 et 2011, in which standardized death rate increased to a peak in 1997 and then decreased[5].

As expected, mortality is predominant in older patients, and remains rare before 65 years. Most studies of mortality in GCA look at the mortality of patients with GCA compared with the general population

The mortality rate, even standardized, is heterogeneous across European countries. Leaving aside Iceland, whose small population explains the inconsistency of mortality rates, the French rates are striking, with an ASMR around 3 times the European average. Data about GCA related mortality in France have been studied before using the French death certificates, and are consistent with our data concerning the absolute number of death listed as the UCD.[4] To our knowledge, no identical study has been conducted in any other European country, which does not allow us to verify the other data. Various hypothesis could explain this discrepancy. First, and most likely, the process of registering causes of death varies among European countries, and may affect comparability. Literature about inter-country variation in coding death is scarce and old, mainly in frequent causes but important differences in certification are reported.[7] Therefore, we can assume that this would be amplified for more rare causes of death like GCA. Secondly, a difference of incidence could explain these variations, but GCA incidence in France does not seem to be that different from its European neighbor[8–14] and cannot explain such discrepancy in mortality rate.

The dataset was not complete for each year and each country, and it was not possible to differentiate zero death from missing data. Even if data imputation led to decrease the missing data, only data from a few countries are available for the earliest years, which may overestimate the mortality rate. Indeed, if some countries had zero related deaths and the population was not included in the denominator, this may artificially increase the incidence rates in some years, and therefore explain, at least in part, why mortality rates are so much higher in the 1990s.

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## TABLE & FIGURE

**Table 1.** GCA related death in the 31 European countries (1994-2016)

**Table 2.** Multivariate analysis of crude mortality rate according to year and age group

**Table 3.** Standardized GCA rate ratios, by countries and years. SRR indicates the number of times that the mortality of a country is increased (if above 1) or decreased (if below 1) as compared with the European average. Results in bold are those superior to 1

**Figure 1.** Crude GCA-mortality rate in Europe according to age group (1994-2016)

**Figure 2.** Evolution of European adjusted mortality rate from 1994 to 2016. Grey line indicate the linear regression of the whole dataset and its confidence interval.

**Figure 3.** Giant cell arteritis age-standardised mortality rate, by country (1994-2016).

## SUPPLEMENTARYL MATERIAL

**Table S1.** Crude mortality rate and its 95% confidence interval, by years and countries (1994-2016). Results are reported for 100 000 population over 50 years.

**Table S2.** Age-standardised GCA-mortality rate and its 95% confidence interval, by years and countries (1994-2016). Data are deaths per 100 000 population over 50 years and rate ratios for individual countries.

**Figure S1.** Evolution of European crude GCA mortality (1994-2016). Grey line indicate the linear regression and its confidence interval.

**Figure S2.** Crude GCA mortality rate, by country (1994-2016).

**Table 1.** GCA related death in the 31 European countries (1994-2016)

Year	N GCA death	N European population*	N countries	Crude mortality rate / 100 000 pop (95% IC)	ASMR /100 000 pop (95% CI)
1994	256	64 258 581	10	0.398 (0.351 – 0.450)	0.436 (0.384 – 0.494)
1995	281	67 152 423	12	0.418 (0.371 – 0.470)	0.45 (0.399 – 0.507)
1996	258	72 914 189	14	0.354 (0.312 – 0.400)	0.383 (0.337 – 0.433)
1997	279	74 973 927	16	0.372 (0.33 – 0.418)	0.402 (0.356 – 0.452)
1998	268	76 222 186	16	0.352 (0.311 – 0.396)	0.374 (0.331 – 0.422)
1999	268	76 738 961	15	0.349 (0.309 – 0.394)	0.375 (0.332 – 0.424)
2000	285	81 340 769	16	0.35 (0.311 – 0.394)	0.375 (0.332 – 0.422)
2001	242	80 178 891	16	0.302 (0.265 – 0.342)	0.323 (0.283 – 0.367)
2002	237	87 886 496	17	0.27 (0.236 – 0.306)	0.302 (0.264 – 0.343)
2003	246	78 981 153	15	0.311 (0.274 – 0.353)	0.331 (0.291 – 0.375)
2004	223	83 792 057	17	0.266 (0.232 – 0.303)	0.291 (0.254 – 0.332)
2005	228	96 816 179	18	0.235 (0.206 – 0.268)	0.263 (0.230 – 0.300)
2006	209	98 870 602	18	0.211 (0.184 – 0.242)	0.229 (0.199 – 0.263)
2007	201	121 261 415	20	0.166 (0.144 – 0.190)	0.171 (0.148 – 0.196)
2008	220	123 183 265	20	0.179 (0.156 – 0.204)	0.182 (0.158 – 0.207)
2009	217	125 005 609	19	0.174 (0.151 – 0.198)	0.173 (0.151 – 0.198)
2010	195	129 182 817	21	0.151 (0.131 – 0.174)	0.149 (0.129 – 0.172)
2011	237	187 982 369	30	0.126 (0.111 – 0.143)	0.126 (0.11 – 0.143)
2012	237	186 264 292	29	0.127 (0.112 – 0.145)	0.125 (0.109 – 0.142)
2013	272	189 131 224	30	0.144 (0.127 – 0.162)	0.139 (0.123 – 0.157)
2014	228	192 200 792	29	0.119 (0.104 – 0.135)	0.114 (0.099 – 0.13)
2015	231	195 326 216	30	0.118 (0.104 – 0.135)	0.113 (0.099 – 0.128)
2016	316	205 174 405	31	0.154 (0.138 – 0.172)	0.146 (0.130 – 0.163)

ASMR: age standardised mortality rate, GCA: giant cell arteritis, pop: population over 50 years, CI: confidence interval, N: number

\*Only countries for which data was available for GCA related death are considered in the count of European population

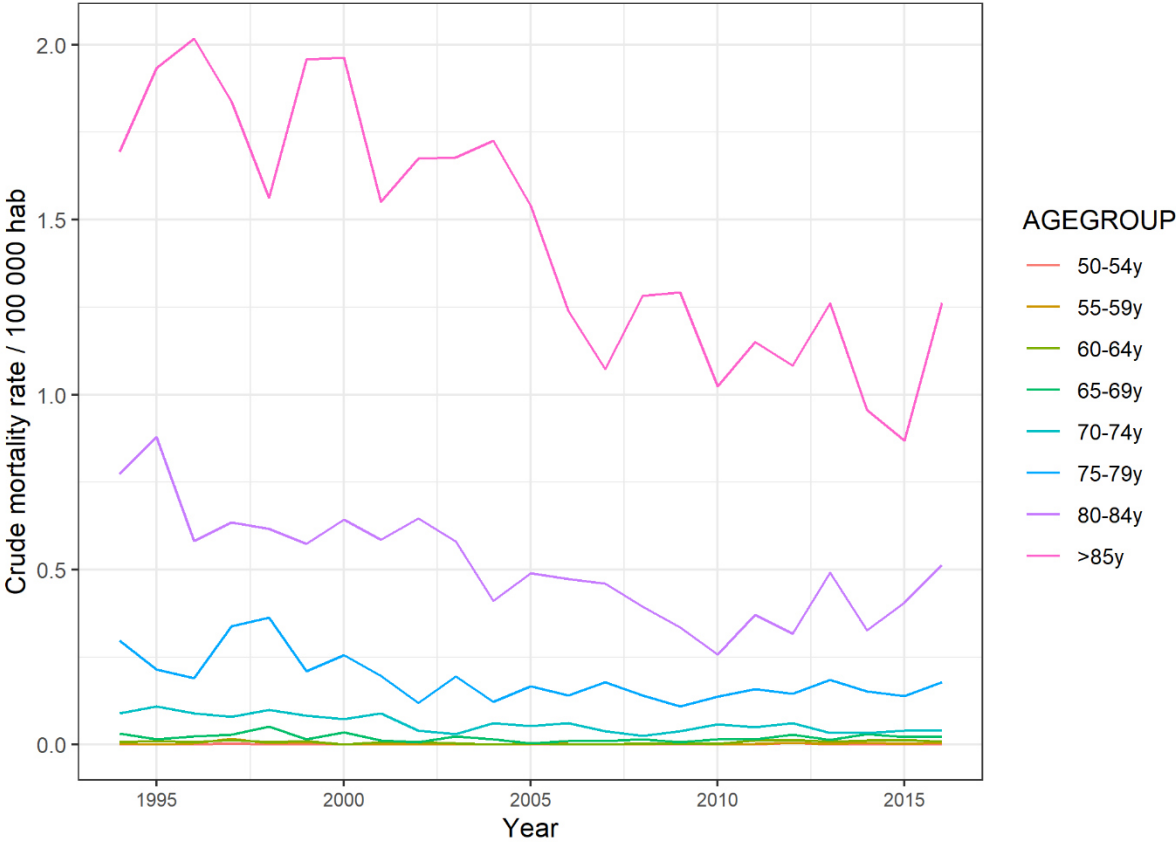
**Table 2.** Multivariate analysis of crude mortality rate according to year and age group

<b>Variable</b>	<b>Estimate<sup>§</sup></b>	<b>p-value</b>
Intercept	18.36	
Year	-0.009158	<0.0001
Age group		
50-55 y	reference	
55-59 y	0.002442	0.947
60-64 y	0.006360	0.863
65-69 y	0.019523	0.598
70-74 y	0.059702	0.108
75-79 y	0.187930	<0.0001
80-84 y	0.511082	<0.0001
≥ 85 y	1.461764	<0.0001

<sup>§</sup>estimate indicates a crude mortality rate decrease for one year, and a crude mortality rate increase for each age group compared to the reference age group

EN COURS DE REDACTION

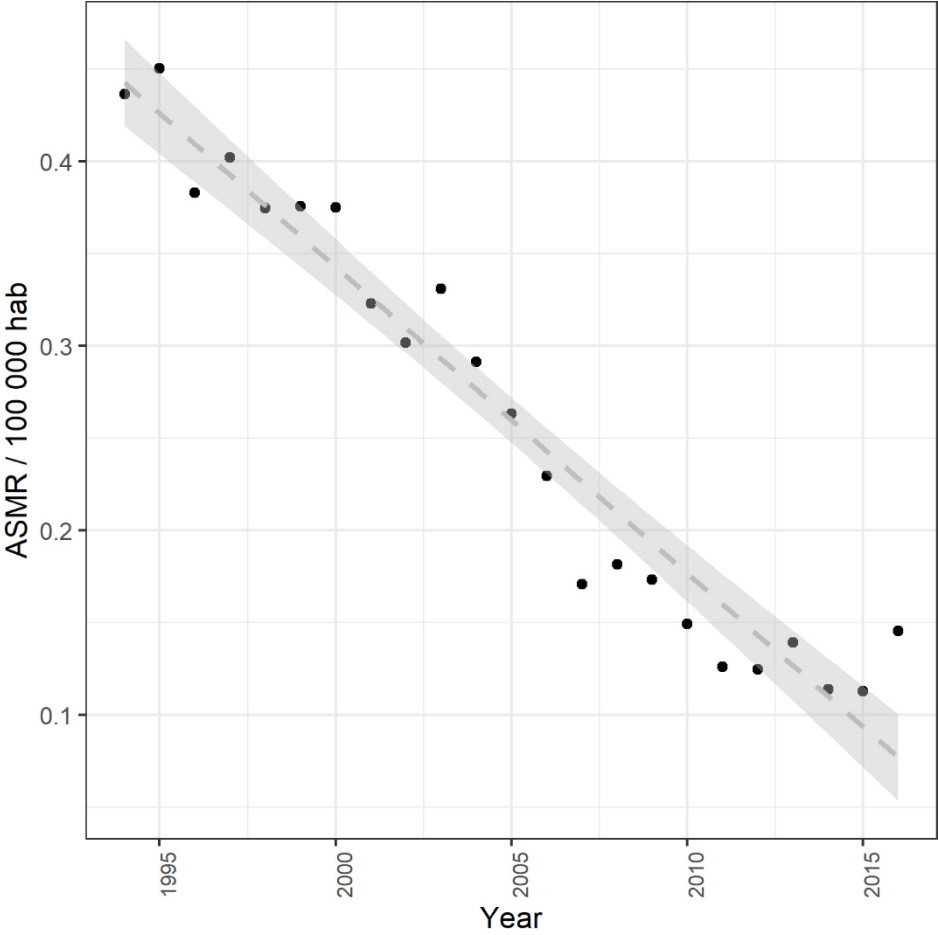
Figure 1. Crude GCA-mortality rate in Europe according to age group (1994-2016)



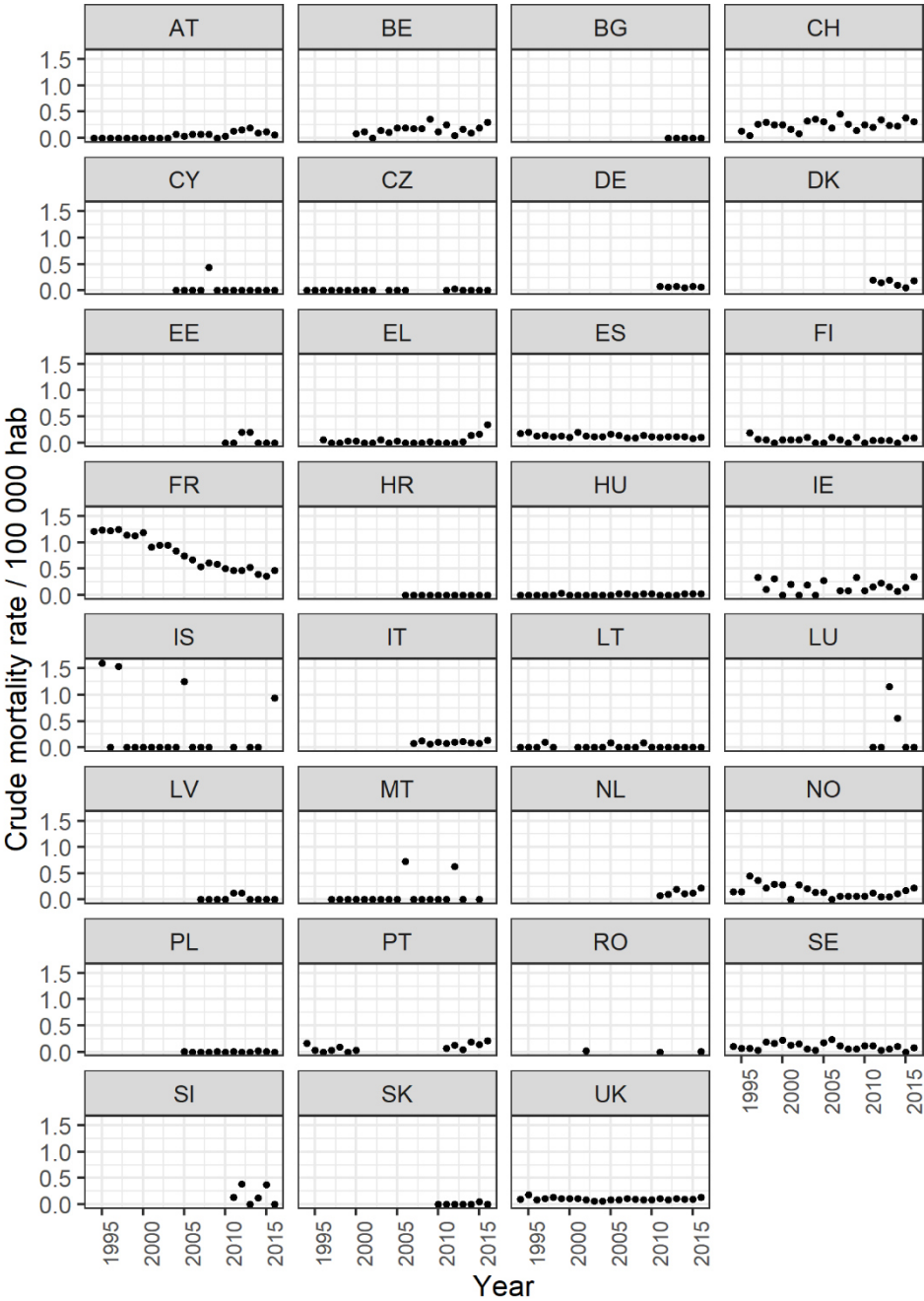
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**Figure 2.** Evolution of European adjusted mortality rate from 1994 to 2016. Grey line indicate the linear regression of the whole dataset and its confidence interval.

$$ASMR = 33.6 - 0.017 \times Year, p < 0.001$$



**Figure 3.** Giant cell arteritis age-standardised mortality rate, by country (1994-2016).



AT: Austria. BE: Belgium. BG: Bulgaria. CH: Switzerland. CY: Cyprus. CZ: Czech Republic. DE: Germany. DK: Denmark. EE: Estonia. EL: Greece. ES: Spain. FI: Finland. FR: France. HR: Croatia. HU: Hungary. IE: Ireland. IS: Iceland. IT: Italia. LT: Lithuania. LU: Luxembourg. LV: Latvia. MT: Malta. NL: Netherlands. NO: Norway. PL: Poland. PT: Portugal. RO: Romania. SE: Sweden. SI: Slovenia. SK: Slovakia. UK: United Kingdom



**Table S1 (1).** Crude mortality rate and its 95% confidence interval, by years and countries (1994–2004). Results are reported for 100 000 population over 50 years.

COUNTRY	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
AT	0 0–0.149	0 0–0.147	0 0–0.147	0 0–0.146	0 0–0.144	0 0–0.143	0 0–0.141	0 0–0.139	0 0–0.138	0 0–0.136	0.073 0.009–0.264
BE	NA	NA	NA	NA	NA	NA	0.087 0.018–0.256	0.115 0.031–0.295	0 0–0.105	0.141 0.046–0.328	0.111 0.03–0.284
BG	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CH	NA	0.137 0.028–0.4	0.045 0.001–0.25	0.266 0.098–0.578	0.306 0.123–0.63	0.258 0.095–0.561	0.254 0.093–0.553	0.167 0.045–0.427	0.082 0.01–0.296	0.323 0.14–0.637	0.359 0.164–0.681
CY	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0
CZ	0 0–0.125	0 0–0.123	0 0–0.122	0 0–0.12	0 0–0.117	0 0–0.114	0 0–0.112	0 0–0.111	0 0–0.109	NA	0 0–0.105
DE	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DK	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EE	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EL	NA	NA	0.056 0.007–0.204	0 0–0.102	0 0–0.101	0.027 0.001–0.15	0.027 0.001–0.149	0 0–0.097	0 0–0.099	0.053 0.006–0.191	0 0–0.097
ES	0.174 0.108–0.267	0.205 0.132–0.302	0.129 0.074–0.209	0.143 0.085–0.226	0.118 0.066–0.194	0.131 0.076–0.21	0.099 0.053–0.169	0.203 0.134–0.295	0.133 0.079–0.211	0.116 0.066–0.189	0.121 0.071–0.194
FI	NA	NA	0.192 0.04–0.562	0.062 0.002–0.347	0.061 0.002–0.338	0 0–0.218	0.058 0.001–0.321	0.056 0.001–0.314	0.055 0.001–0.308	0.108 0.013–0.392	0 0–0.196
FR	1.217 1.057–1.394	1.235 1.075–1.413	1.22 1.061–1.395	1.253 1.094–1.43	1.145 0.994–1.312	1.124 0.977–1.286	1.187 1.038–1.351	0.906 0.778–1.049	0.947 0.818–1.092	0.943 0.815–1.086	0.844 0.724–0.979
HR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HU	0 0–0.115	0 0–0.114	0 0–0.114	0 0–0.113	0 0–0.112	0.03 0.001–0.168	0 0–0.11	0 0–0.109	0 0–0.108	0 0–0.107	0 0–0.105
IE	NA	NA	NA	0.331 0.068–0.967	0.108 0.003–0.601	0.316 0.065–0.925	0 0–0.381	0.202 0.024–0.73	0 0–0.364	0.193 0.023–0.696	0 0–0.347
IS	NA	1.604 0.041–8.935	0 0–5.804	1.543 0.039–8.596	0 0–5.559	0 0–5.422	0 0–5.297	0 0–5.15	0 0–5.01	0 0–4.879	0 0–4.744
IT	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LT	0 0–0.351	0 0–0.354	0 0–0.353	0.096 0.002–0.535	0 0–0.355	NA	NA	0 0–0.352	0 0–0.347	0 0–0.344	0 0–0.342

COUNTRY	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
LU	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LV	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MT	NA	NA	NA	0 0-3.608	0 0-3.481	0 0-3.371	0 0-3.277	0 0-3.11	0 0-3.018	0 0-2.938	0 0-2.863
NL	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NO	0.156 0.019-0.562	0.154 0.019-0.555	0.455 0.167-0.989	0.372 0.121-0.867	0.219 0.045-0.641	0.288 0.079-0.738	0.285 0.078-0.729	0 0-0.259	0.278 0.076-0.711	0.206 0.042-0.601	0.135 0.016-0.489
PL	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PT	0.161 0.052-0.376	0.032 0.001-0.177	0 0-0.116	0.031 0.001-0.173	0.092 0.019-0.268	0 0-0.111	0.03 0.001-0.165	NA	NA	NA	NA
RO	NA	NA	NA	NA	NA	NA	NA	NA	0.015 0-0.084	NA	NA
SE	0.103 0.021-0.301	0.068 0.008-0.244	0.066 0.008-0.24	0.033 0.001-0.182	0.194 0.071-0.422	0.159 0.052-0.372	0.221 0.089-0.454	0.125 0.034-0.319	0.155 0.05-0.361	0.061 0.007-0.222	0.03 0.001-0.169
SI	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SK	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
UK	0.094 0.055-0.15	0.186 0.129-0.26	0.087 0.05-0.141	0.107 0.066-0.166	0.132 0.085-0.195	0.104 0.064-0.161	0.10 0.067-0.166	0.112 0.07-0.17	0.081 0.046-0.132	0.065 0.035-0.112	0.06 0.031-0.104

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**Table S1 (2).** Crude mortality rate and its 95% confidence interval, by years and countries (2005-2016). Results are reported for 100 000 population over 50 years.

COUNTRY	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
AT	0.036 0.001-0.201	0.071 0.009-0.257	0.07 0.008-0.253	0.069 0.008-0.249	0 0-0.125	0.033 0.001-0.185	0.131 0.036-0.334	0.16 0.052-0.373	0.188 0.069-0.41	0.092 0.019-0.269	0.12 0.033-0.308	0.059 0.007-0.213
BE	0.192 0.077-0.395	0.189 0.076-0.389	0.186 0.075-0.383	0.183 0.074-0.377	0.36 0.197-0.605	0.127 0.041-0.295	0.249 0.119-0.458	0.049 0.006-0.177	0.169 0.068-0.349	0.095 0.026-0.244	0.188 0.081-0.37	0.301 0.16-0.515
BG	NA	NA	NA	NA	NA	NA	NA	0	0	0	0	0
CH	0.314 0.135-0.618	0.193 0.063-0.45	0.455 0.235-0.795	0.261 0.105-0.537	0.146 0.04-0.374	0.25 0.101-0.515	0.211 0.077-0.459	0.344 0.165-0.633	0.236 0.095-0.486	0.23 0.093-0.474	0.385 0.199-0.673	0.314 0.151-0.578
CY	0 0-1.775	0 0-1.728	0 0-1.675	0.439 0.011-2.445	0 0-1.561	0 0-1.504	0 0-1.45	0	0	0	0	0
CZ	0 0-0.104	0 0-0.102	NA	NA	NA	NA	0 0-0.097	0.026 0.001-0.145	0	0	0	0
DE	NA	NA	NA	NA	NA	NA	0.077 0.05-0.113	0.06 0.037-0.093	0.077 0.05-0.113	0.055 0.033-0.086	0.072 0.046-0.106	0.07 0.046-0.104
DK	NA	NA	NA	NA	NA	NA	0.199 0.054-0.508	0.147 0.03-0.43	0.193 0.053-0.495	0.095 0.012-0.344	0.047 0.001-0.261	0.184 0.05-0.471
EE	NA	NA	NA	NA	NA	0 0-0.756	0 0-0.749	0.201 0.005-1.119	0.199 0.005-1.11	0	0	0
EL	0.026 0.001-0.145	0 0-0.094	0 0-0.093	0 0-0.092	0.025 0.001-0.137	0 0-0.089	0 0-0.088	0 0-0.087	0.023 0.001-0.13	0.139 0.051-0.303	0.161 0.065-0.331	0.342 0.191-0.564
ES	0.168 0.108-0.25	0.137 0.084-0.212	0.087 0.047-0.149	0.092 0.05-0.154	0.135 0.084-0.206	0.113 0.067-0.179	0.099 0.056-0.16	0.121 0.074-0.187	0.119 0.073-0.183	0.117 0.071-0.18	0.086 0.048-0.141	0.107 0.064-0.167
FI	0 0-0.193	0.103 0.012-0.371	0.05 0.001-0.281	0 0-0.183	0.098 0.012-0.353	0 0-0.178	0.048 0.001-0.265	0.047 0.001-0.262	0.046 0.001-0.258	0	0.09	0.089
FR	0.738 0.627-0.863	0.669 0.564-0.787	0.544 0.451-0.651	0.615 0.517-0.727	0.584 0.489-0.692	0.497 0.411-0.597	0.468 0.385-0.565	0.47 0.387-0.565	0.529 0.441-0.629	0.394 0.319-0.48	0.36 0.289-0.442	0.469 0.389-0.561
HR	NA	0 0-0.233	0 0-0.23	0 0-0.228	0 0-0.226	0 0-0.224	0 0-0.222	0	0	0	0	0
HU	0 0-0.103	0.028 0.001-0.154	0.027 0.001-0.152	0 0-0.1	0.027 0.001-0.151	0.027 0.001-0.151	0 0-0.099	0	0	0.027	0.027	0.027
IE	0.276 0.057-0.805	NA	0.088 0.002-0.491	0.086 0.002-0.478	0.334 0.091-0.856	0.081 0.002-0.454	0.159 0.019-0.575	0.233 0.048-0.681	0.152 0.018-0.548	0.074 0.002-0.412	0.144 0.017-0.521	0.351 0.114-0.82
IS	1.249 0.032-6.96	0 0-4.459	0 0-4.301	0 0-4.176	NA	NA	0 0-3.891	NA	0	0	NA	0.936
IT	NA	NA	0.075 0.044-0.121	0.118 0.078-0.172	0.065 0.036-0.107	0.103 0.066-0.153	0.076 0.045-0.12	0.096 0.061-0.144	0.107 0.07-0.156	0.084 0.052-0.128	0.074 0.045-0.116	0.139 0.097-0.193
LT	0.092 0.002-0.514	0 0-0.34	0 0-0.339	0 0-0.337	0.09 0.002-0.504	0 0-0.33	0 0-0.328	0	0	0	0	0

COUNTRY	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
LU	NA	NA	NA	NA	NA	NA	0 0-2.251	0 0-2.184	1.15 0.139-4.156	0.556 0.014-3.097	0 0-1.98	0 0-1.918
LV	NA	NA	0 0-0.475	0 0-0.473	0 0-0.472	0 0-0.471	0.127 0.003-0.709	0.127 0.003-0.706	0 0-0.466	0 0-0.465	0 0-0.464	0 0-0.465
MT	0 0-2.788	0.727 0.018-4.051	0 0-2.619	0 0-2.55	0 0-2.489	0 0-2.431	0 0-2.373	0.629 0.016-3.507	0 0-2.277	NA	0 0-2.183	NA
NL	NA	NA	NA	NA	NA	NA	0.084 0.027-0.195	0.098 0.036-0.214	0.193 0.1-0.337	0.11 0.044-0.227	0.124 0.053-0.243	0.228 0.127-0.375
NO	0.133 0.016-0.481	0 0-0.242	0.065 0.002-0.359	0.064 0.002-0.354	0.062 0.002-0.348	0.061 0.002-0.342	0.121 0.015-0.437	0.059 0.002-0.331	0.058 0.001-0.326	0.115 0.014-0.415	0.169 0.035-0.494	0.221 0.06-0.567
PL	0.009 0-0.047	0 0-0.031	0 0-0.03	0 0-0.029	0.008 0-0.043	0 0-0.028	0.008 0-0.042	0 0-0.027	0 0-0.027	0.022 0.004-0.064	0.014 0.002-0.052	0 0-0.026
PT	NA	NA	NA	NA	NA	NA	0.075 0.015-0.219	0.123 0.04-0.288	0.049 0.006-0.176	0.193 0.083-0.38	0.143 0.052-0.311	0.212 0.097-0.402
RO	NA	NA	NA	NA	NA	NA	0 0-0.05	NA	NA	NA	NA	0.014 0-0.078
SE	0.181 0.066-0.393	0.239 0.103-0.471	0.118 0.032-0.303	0.059 0.007-0.212	0.058 0.007-0.21	0.115 0.031-0.295	0.114 0.031-0.292	0.028 0.001-0.157	0.056 0.007-0.202	0.11 0.03-0.283	0 0-0.1	0.08 0.017-0.235
SI	NA	NA	NA	NA	NA	NA	0.13 0.003-0.726	0.384 0.079-1.123	0 0-0.466	0.124 0.003-0.693	0.368 0.076-1.075	0 0-0.445
SK	NA	NA	NA	NA	NA	0 0-0.214	0 0-0.21	0 0-0.207	0 0-0.204	0 0-0.201	0.054 0.001-0.299	0 0-0.195
UK	0.079 0.045-0.128	0.088 0.052-0.139	0.107 0.067-0.161	0.096 0.058-0.148	0.08 0.047-0.129	0.084 0.05-0.132	0.11 0.07-0.164	0.081 0.048-0.128	0.106 0.068-0.158	0.091 0.057-0.14	0.094 0.059-0.142	0.134 0.092-0.19

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**Table S2 (1).** Age-standardised GCA-mortality rate and its 95% confidence interval, by years and countries (1994-2004). Data are deaths per 100 000 population over 50 years and rate ratios for individual countries.

Country	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
AT	0 0-0.201	0 0-0.207	0 0-0.187	0 0-0.17	0 0-0.187	0 0-0.209	0 0-0.21	0 0-0.185	0 0-0.159	0 0-0.166	0.069 0.008-0.283
BE	NA	NA	NA	NA	NA	NA	0.089 0.018-0.289	0.126 0.033-0.338	0 0-0.122	0.153 0.049-0.367	0.117 0.031-0.315
BG	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
CH	NA	0.14 0.029-0.419	0.046 0.001-0.267	0.28 0.103-0.612	0.305 0.122-0.637	0.267 0.098-0.592	0.261 0.095-0.58	0.167 0.045-0.44	0.087 0.01-0.317	0.326 0.141-0.648	0.366 0.168-0.698
CY	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	0 0-2.592
CZ	0 0-0.228	0 0-0.217	0 0-0.207	0 0-0.198	0 0-0.198	0 0-0.229	0 0-0.23	0 0-0.204	0 0-0.204	NA 0-0.241	0 0-0.241
DE	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
DK	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EE	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
EL	NA	NA	0.064 0.008-0.243	0 0-0.134	0 0-0.139	0.033 0.001-0.193	0.036 0.001-0.203	0 0-0.133	0 0-0.124	0.057 0.007-0.217	0 0-0.115
ES	0.19 0.117-0.295	0.235 0.152-0.35	0.144 0.081-0.236	0.164 0.097-0.261	0.123 0.068-0.205	0.147 0.086-0.236	0.11 0.058-0.189	0.213 0.14-0.311	0.141 0.083-0.225	0.123 0.07-0.202	0.123 0.072-0.199
FI	NA	NA	0.228 0.046-0.695	0.06 0.002-0.405	0.081 0.002-0.449	0 0-0.289	0.061 0.002-0.383	0.057 0.001-0.37	0.074 0.002-0.41	0.139 0.017-0.509	0 0-0.262
FR	1.21 1.049-1.39	1.182 1.028-1.358	1.164 1.011-1.334	1.224 1.067-1.398	1.128 0.978-1.297	1.102 0.955-1.267	1.179 1.026-1.35	0.907 0.777-1.054	0.973 0.839-1.123	0.971 0.839-1.12	0.895 0.767-1.039
HR	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
HU	0 0-0.216	0 0-0.205	0 0-0.196	0 0-0.189	0 0-0.184	0.025 0.001-0.241	0 0-0.202	0 0-0.174	0 0-0.182	0 0-0.194	0 0-0.205
IE	NA	NA	NA	0.336 0.069-1.11	0.111 0.003-0.759	0.347 0.071-1.107	0 0-0.553	0.292 0.035-1.056	0 0-0.523	0.213 0.025-0.856	0 0-0.503
IS	NA	1.526 0.039-9.558	0 0-6.827	1.608 0.041-9.607	0 0-6.62	0 0-6.525	0 0-6.439	0 0-6.309	0 0-6.092	0 0-5.904	0 0-5.764
IT	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LT	0 0-0.586	0 0-0.596	0 0-0.558	0.086 0.002-0.683	0 0-0.616	NA	NA	0 0-0.631	0 0-0.578	0 0-0.604	0 0-0.62

Country	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
LU	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
LV	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
MT	NA	NA	NA	0 0-6.068	0 0-5.866	0 0-5.766	0 0-5.68	0 0-5.539	0 0-5.437	0 0-5.387	0 0-5.207
NL	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
NO	0.129 0.016-0.546	0.146 0.017-0.577	0.433 0.158-0.984	0.347 0.112-0.86	0.204 0.042-0.657	0.275 0.075-0.756	0.269 0.073-0.737	0 0-0.318	0.267 0.072-0.723	0.197 0.041-0.612	0.128 0.015-0.497
PL	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
PT	0.221 0.068-0.552	0.036 0.001-0.257	0 0-0.188	0.032 0.001-0.228	0.113 0.023-0.35	0 0-0.157	0.041 0.001-0.226	NA	NA	NA	NA
RO	NA	NA	NA	NA	NA	NA	NA	NA	0.034 0.001-0.188	NA	NA
SE	0.097 0.02-0.302	0.062 0.007-0.248	0.063 0.008-0.25	0.031 0.001-0.199	0.181 0.067-0.414	0.15 0.049-0.369	0.202 0.081-0.434	0.115 0.031-0.311	0.14 0.046-0.343	0.058 0.007-0.222	0.028 0.001-0.172
SI	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
SK	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
UK	0.096 0.056-0.154	0.19 0.132-0.266	0.088 0.05-0.143	0.106 0.065-0.165	0.134 0.086-0.198	0.107 0.065-0.166	0.109 0.068-0.168	0.116 0.073-0.177	0.083 0.047-0.135	0.067 0.036-0.115	0.063 0.032-0.11

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**Table S2 (2).** Age-standardised GCA-mortality rate and its 95% confidence interval, by years and countries (2005-2016). Data are deaths per 100 000 population over 50 years and rate ratios for individual countries.

Country	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
AT	0.046 0.001 - 0.256	0.075 0.009 - 0.282	0.074 0.009 - 0.274	0.065 0.008 - 0.255	0 0 - 0.145	0.028 0.001 - 0.179	0.125 0.034 - 0.331	0.166 0.054 - 0.396	0.188 0.069 - 0.422	0.096 0.02 - 0.29	0.115 0.031 - 0.306	0.061 0.007 - 0.228
BE	0.228 0.091 - 0.477	0.192 0.076 - 0.406	0.182 0.073 - 0.382	0.18 0.072 - 0.375	0.356 0.194 - 0.601	0.129 0.042 - 0.304	0.237 0.114 - 0.441	0.047 0.006 - 0.18	0.154 0.062 - 0.329	0.085 0.023 - 0.232	0.178 0.076 - 0.363	0.276 0.147 - 0.483
BG	NA	NA	NA	NA	NA	NA	NA	0 0 - 0.19	0 0 - 0.186	0 0 - 0.178	0 0 - 0.173	0 0 - 0.168
CH	0.32 0.138 - 0.634	0.202 0.066 - 0.474	0.457 0.236 - 0.804	0.254 0.102 - 0.531	0.144 0.039 - 0.378	0.25 0.1 - 0.524	0.204 0.074 - 0.454	0.331 0.159 - 0.619	0.24 0.096 - 0.5	0.229 0.092 - 0.48	0.387 0.199 - 0.684	0.317 0.152 - 0.591
CY	0 0 - 2.619	0 0 - 2.644	0 0 - 2.342	0.617 0.016 - 3.44	0 0 - 2.227	0 0 - 2.149	0 0 - 2.078	0 0 - 2.049	0 0 - 1.998	0 0 - 1.912	0 0 - 1.84	0 0 - 1.822
CZ	0 0 - 0.232	0 0 - 0.214	NA	NA	NA	NA	0 0 - 0.141	0.022 0.001 - 0.166	0 0 - 0.129	0 0 - 0.124	0 0 - 0.119	0 0 - 0.115
DE	NA	NA	NA	NA	NA	NA	0.075 0.048 - 0.111	0.057 0.035 - 0.089	0.076 0.049 - 0.112	0.054 0.032 - 0.085	0.069 0.045 - 0.103	0.067 0.043 - 0.1
DK	NA	NA	NA	NA	NA	NA	0.234 0.064 - 0.605	0.165 0.034 - 0.496	0.219 0.059 - 0.573	0.101 0.012 - 0.389	0.05 0.001 - 0.303	0.189 0.051 - 0.506
EE	NA	NA	NA	NA	NA	0 0 - 1.06	0 0 - 0.988	0.198 0.005 - 1.249	0.192 0.005 - 1.179	0 0 - 0.789	0 0 - 0.776	0 0 - 0.812
EL	0.022 0.001 - 0.148	0 0 - 0.111	0 0 - 0.109	0 0 - 0.107	0.021 0.001 - 0.137	0 0 - 0.1	0 0 - 0.096	0 0 - 0.095	0.02 0 - 0.127	0.13 0.048 - 0.291	0.139 0.056 - 0.298	0.285 0.16 - 0.481
ES	0.17 0.109 - 0.255	0.139 0.085 - 0.216	0.088 0.047 - 0.151	0.087 0.048 - 0.148	0.128 0.079 - 0.197	0.103 0.061 - 0.165	0.088 0.05 - 0.144	0.112 0.068 - 0.175	0.105 0.064 - 0.165	0.1 0.061 - 0.156	0.075 0.042 - 0.127	0.092 0.055 - 0.147
FI	0 0 - 0.26	0.108 0.013 - 0.42	0.056 0.001 - 0.331	0 0 - 0.22	0.098 0.012 - 0.374	0 0 - 0.199	0.051 0.001 - 0.294	0.049 0.001 - 0.287	0.049 0.001 - 0.284	0 0 - 0.187	0.093 0.011 - 0.344	0.092 0.011 - 0.343
FR	0.771 0.655 - 0.904	0.666 0.562 - 0.786	0.521 0.432 - 0.624	0.573 0.481 - 0.678	0.529 0.443 - 0.628	0.446 0.368 - 0.537	0.413 0.339 - 0.499	0.404 0.332 - 0.489	0.444 0.37 - 0.53	0.329 0.266 - 0.404	0.301 0.241 - 0.373	0.384 0.317 - 0.463
HR	NA	0 0 - 0.523	0 0 - 0.471	0 0 - 0.438	0 0 - 0.407	0 0 - 0.382	0 0 - 0.361	0 0 - 0.34	0 0 - 0.327	0 0 - 0.309	0 0 - 0.292	0 0 - 0.278
HU	0 0 - 0.191	0.028 0.001 - 0.216	0.043 0.001 - 0.241	0 0 - 0.148	0.038 0.001 - 0.21	0.029 0.001 - 0.183	0 0 - 0.127	0 0 - 0.131	0 0 - 0.128	0.029 0.001 - 0.176	0.03 0.001 - 0.174	0.03 0.001 - 0.174
IE	0.372 0.076 - 1.102	NA	0.1 0.003 - 0.615	0.114 0.003 - 0.638	0.425 0.116 - 1.097	0.099 0.003 - 0.57	0.172 0.02 - 0.668	0.298 0.061 - 0.873	0.196 0.024 - 0.708	0.095 0.002 - 0.527	0.182 0.022 - 0.66	0.435 0.141 - 1.019
IS	1.512 0.038 - 8.426	0 0 - 5.339	0 0 - 5.048	0 0 - 5.077	NA	NA	0 0 - 5.116	NA	0 0 - 4.768	0 0 - 4.726	NA	1.257 0.032 - 7.006
IT	NA	NA	0.069 0.04 - 0.112	0.11 0.072 - 0.161	0.059 0.033 - 0.099	0.092 0.059 - 0.139	0.067 0.04 - 0.108	0.085 0.054 - 0.129	0.092 0.06 - 0.137	0.072 0.044 - 0.111	0.063 0.038 - 0.101	0.112 0.079 - 0.158
LT	0.081 0.002 - 0.721	0 0 - 0.595	0 0 - 0.561	0 0 - 0.524	0.093 0.002 - 0.636	0 0 - 0.458	0 0 - 0.43	0 0 - 0.403	0 0 - 0.38	0 0 - 0.357	0 0 - 0.353	0 0 - 0.35

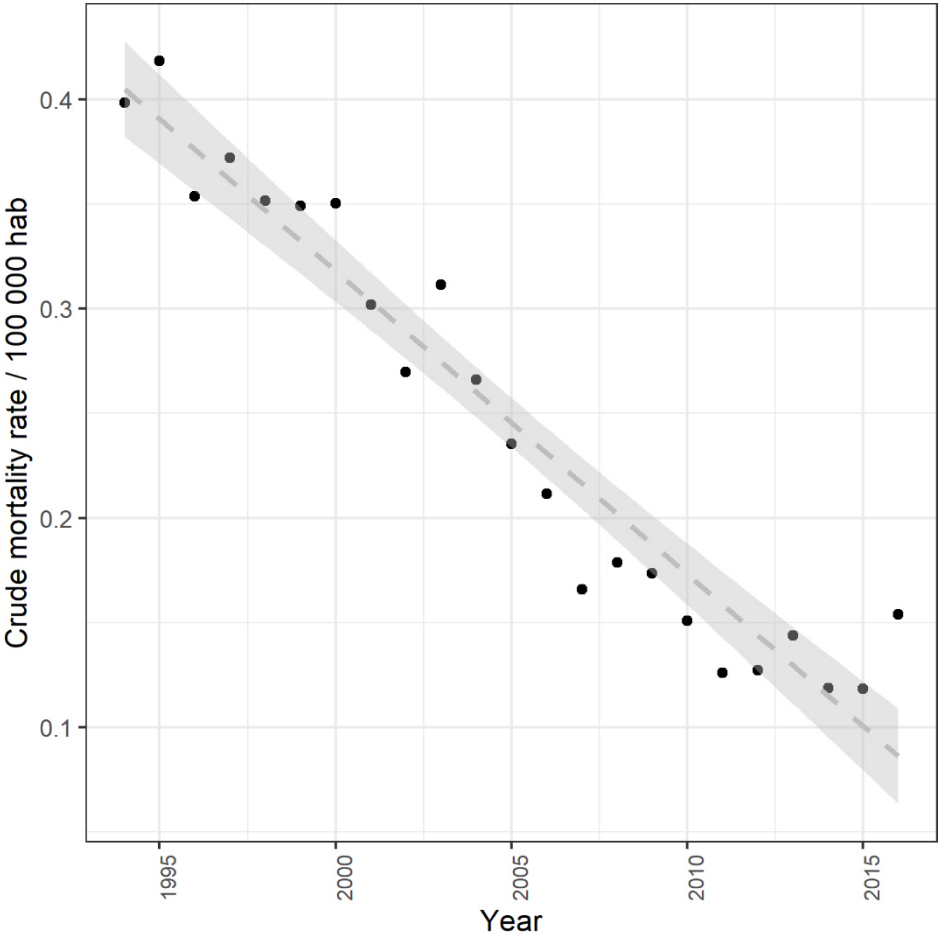
Country	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
LU	NA	NA	NA	NA	NA	NA	0 0 - 2.825	0 0 - 2.498	1.243 0.15 - 4.601	0.608 0.015 - 3.512	0 0 - 2.39	0 0 - 2.366
LV	NA	NA	0 0 - 0.858	0 0 - 0.814	0 0 - 0.755	0 0 - 0.706	0.136 0.003 - 0.882	0.108 0.003 - 0.777	0 0 - 0.576	0 0 - 0.54	0 0 - 0.517	0 0 - 0.494
MT	0 0 - 4.842	0.888 0.022 - 6.057	0 0 - 4.408	0 0 - 4.161	0 0 - 3.99	0 0 - 3.732	0 0 - 3.486	0.531 0.013 - 4.08	0 0 - 3.185	NA	0 0 - 2.925	NA
NL	NA	NA	NA	NA	NA	NA	0.098 0.032 - 0.228	0.107 0.039 - 0.237	0.219 0.113 - 0.384	0.127 0.051 - 0.263	0.136 0.058 - 0.271	0.257 0.144 - 0.426
NO	0.118 0.014 - 0.475	0	0.07 0.002 - 0.42	0.063 0.002 - 0.402	0.054 0.001 - 0.373	0.073 0.002 - 0.414	0.127 0.015 - 0.488	0.052 0.001 - 0.356	0.066 0.002 - 0.392	0.118 0.014 - 0.462	0.17 0.034 - 0.529	0.255 0.069 - 0.665
PL	0.009 0 - 0.077	0 0 - 0.061	0 0 - 0.057	0 0 - 0.052	0.006 0 - 0.056	0 0 - 0.045	0.008 0 - 0.055	0 0 - 0.039	0 0 - 0.037	0.023 0.005 - 0.072	0.016 0.002 - 0.062	0 0 - 0.037
PT	NA	NA	NA	NA	NA	NA	0.076 0.016 - 0.225	0.12 0.039 - 0.284	0.046 0.006 - 0.173	0.179 0.077 - 0.359	0.133 0.049 - 0.296	0.195 0.089 - 0.376
RO	NA	NA	NA	NA	NA	NA	0 0 - 0.083	NA	NA	NA	NA	0.015 0 - 0.09
SE	0.17 0.062 - 0.382	0.219 0.094 - 0.444	0.103 0.028 - 0.282	0.049 0.006 - 0.201	0.048 0.006 - 0.196	0.108 0.029 - 0.289	0.106 0.029 - 0.285	0.023 0.001 - 0.156	0.06 0.007 - 0.222	0.112 0.03 - 0.295	0 0 - 0.112	0.08 0.016 - 0.242
SI	NA	NA	NA	NA	NA	NA	0.172 0.004 - 0.959	0.455 0.093 - 1.354	0 0 - 0.559	0.115 0.003 - 0.721	0.4 0.082 - 1.173	0 0 - 0.514
SK	NA	NA	NA	NA	NA	0 0 - 0.376	0 0 - 0.362	0 0 - 0.347	0 0 - 0.334	0 0 - 0.32	0.046 0.001 - 0.37	0 0 - 0.295
UK	0.079 0.045 - 0.129	0.089 0.052 - 0.14	0.107 0.067 - 0.162	0.094 0.058 - 0.146	0.079 0.046 - 0.127	0.083 0.049 - 0.131	0.107 0.069 - 0.16	0.08 0.048 - 0.128	0.103 0.066 - 0.154	0.088 0.054 - 0.135	0.092 0.057 - 0.139	0.128 0.088 - 0.182

AT: Austria, BE: Belgium, CH: Switzerland, CY: Cyprus, CZ: Czech Republic, DE: Germany, DK: Denmark, EE: Estonia, EL: Greece, ES: Spain, FI: Finland, FR: France, HR: Croatia, HU: Hungary, IE: Ireland, IS: Iceland, IT: Italia, LT: Lithuania, LU: Luxembourg, LV: Latvia, MT: Malta, NL: Netherlands, NO: Norway, PL: Poland, PT: Portugal, RO: Romania, SE: Sweden, SI: Slovenia, SK: Slovakia, UK: United Kingdom

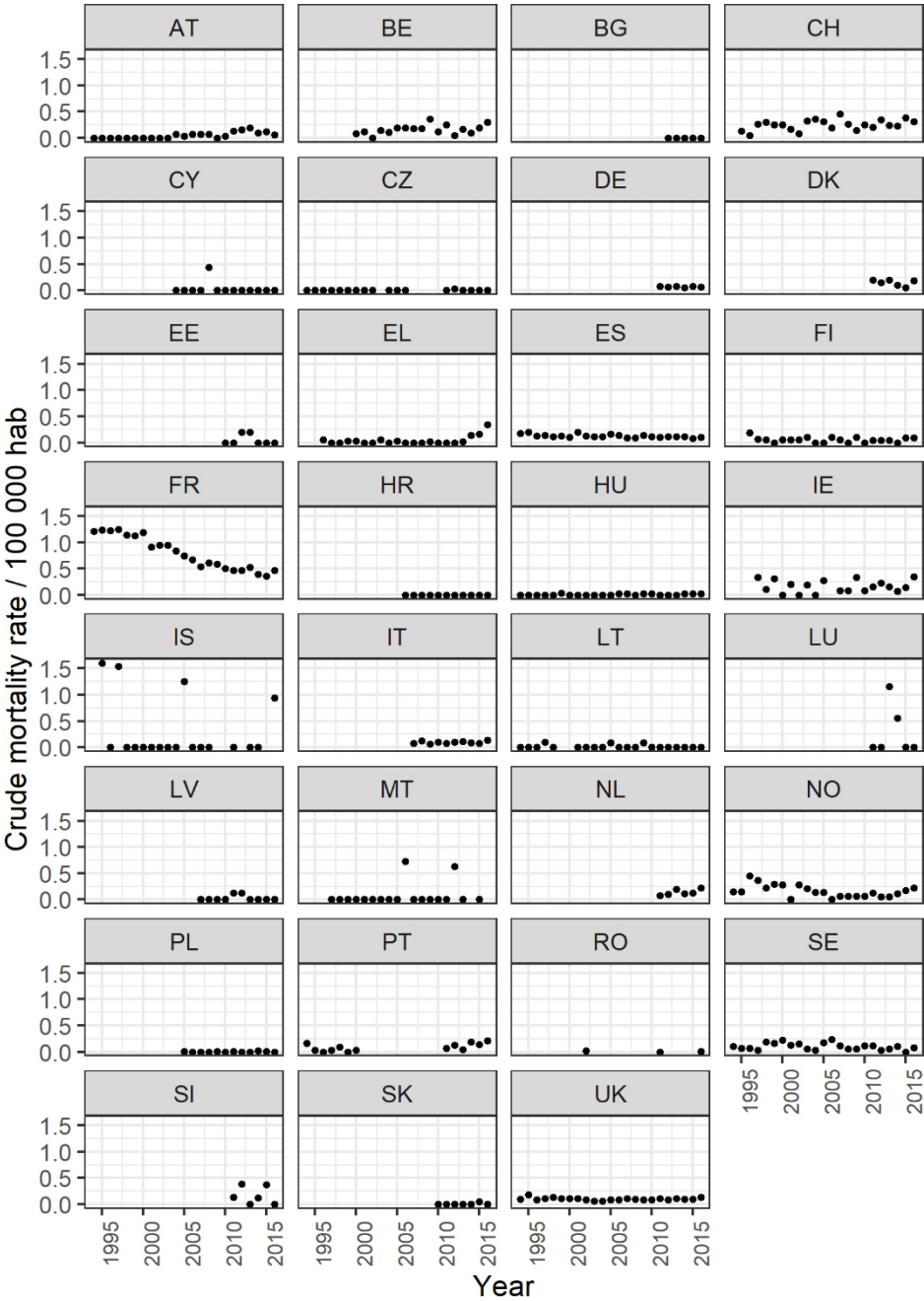


**Figure S1.** Evolution of European crude GCA mortality (1994-2016). Grey line indicate the linear regression and its confidence interval.

$Crude\ mortality\ rate = 29.3 - 0.014 \times Year, p < 0.001$



**Figure S2.** Crude GCA mortality rate, by country (1994-2016).



AT: Austria. BE: Belgium. BG: Bulgaria. CH: Switzerland. CY: Cyprus. CZ: Czech Republic. DE: Germany. DK: Denmark. EE: Estonia. EL: Greece. ES: Spain. FI: Finland. FR: France. HR: Croatia. HU: Hungary. IE :Ireland. IS: Iceland. IT: Italia. LT: Lithuania. LU: Luxembourg. LV: Latvia. MT: Malta. NL: Netherlands. NO :Norway. PL: Poland. PT: Portugal. RO: Romania. SE: Sweden. SI: Slovenia. SK: Slovakia. UK: United Kingdom

## 6 Impact des thérapeutiques dans l'artérite à cellules géantes

Mainbourg S, Tabary A, Cucherat M, Gueyffier F, Lobbes H, Aussedat M, Grenet G, Durieu I, Samson M, Lega JC. **Indirect comparison of glucocorticoid sparing agents for the remission maintenance in giant cell arteritis: a network meta-analysis.**

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**Objective.** Several glucocorticoid-sparing agents have been evaluated with the aim to limit glucocorticoid side effects and maintain remission in patients suffering from giant cell arteritis (GCA). However, their benefits and risk remain unclear. We aimed to compare and rank the effect of glucocorticoid-sparing agents in GCA using a network meta-analysis

**Methods.** The MEDLINE and Clinical Trials databases were searched up to January 2020; all randomized controlled trials (RCT) investigating glucocorticoid in GCA were included. The glucocorticoid regimen was dichotomized in to short ( $\leq 6$  months) or prolonged ( $> 6$  months) use. Risk of relapse and safety were estimated using network meta-analysis with frequentist random-effects models.

**Results.** Among the 96 records screened, 8 studies were included (572 patients). The studies compared glucocorticoid and a sparing-agent: tocilizumab (2 studies), oral methotrexate (3 studies), infliximab (1 study), etanercept (1 study), and adalimumab 1 study). The pooled prevalence of GCA relapse was 52.6% (95%CI 38.1 to 66.9). The risk of relapse was significantly lower with tocilizumab compared to methotrexate (RR=0.41, 95%CI 0.17 to 0.97), prolonged (RR=0.41, 95%CI 0.20 to 0.83), and short glucocorticoid (RR=0.32, 95%CI 0.16 to 0.66) use. The risk of relapse was not significantly different with methotrexate compared to short (RR=0.79, 95%CI 0.48 to 1.31) and prolonged glucocorticoid use (RR=0.95, 95%CI 0.31 to 2.89). The frequency of serious adverse events and serious infection were comparable between the different drugs.

**Conclusion.** This meta-analysis suggests that tocilizumab is currently the best option to prevent GCA relapse among the sparing-agents, with safety that is comparable to the other drugs.

# Indirect comparison of glucocorticoid sparing agents for remission maintenance in giant cell arteritis: a network meta-analysis

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The protocol of the meta-analysis is registered in the international prospective register of systematic reviews PROSPERO (<https://www.crd.york.ac.uk/prospéro/>; registration CRD42020112387).

## INTRODUCTION

Giant cell arteritis (GCA) is a large vessel vasculitis affecting people over 50 years of age.<sup>1,2</sup> It is characterised by the occurrence of ischemic signs such as headache, visual manifestations, scalp tenderness, jaw claudication and stroke, together with systemic symptoms such as weight loss or anorexia, fatigue, and fever. The pathogenesis of GCA involves dendritic cell activation followed by the activation of CD4+ T cells, their proliferation and polarisation into Th1 and Th17 cells driven by pro-inflammatory cytokines (interleukin [IL]-12, IL-18, IL-23, IL-6, and IL-1 $\beta$ ) present in the microenvironment. Then, interferon- $\gamma$  produced by Th1 cells trigger the recruitment and activation of monocytes and their differentiation into macrophages and multinuclear giant cells that produce IL-1 $\beta$  and IL-6 which are responsible for systemic symptoms of GCA, and cytotoxic mediators and growth factors that trigger vascular remodelling of the arterial wall leading to stenosis of the affected arteries and ischemic manifestations of GCA.<sup>3,4</sup> The recommended treatment at GCA diagnosis remains high-dose glucocorticoid therapy, followed by progressive tapering until glucocorticoid withdrawal.<sup>5</sup> However, the long-term use of glucocorticoids leads to numerous side effects; the most frequent are osteoporosis and bone fracture, hyperglycaemia and type 2 diabetes, hypertension, cardiovascular disease, cataract.<sup>6</sup> In addition, the risk of relapse remains high; it is reported to occur in more than 50% of patients during the course of the disease<sup>7</sup>. Notably, glucocorticoid impair Th17 polarization but have a weak effect on Th1 polarisation and do not restore a normal Treg response, which is supposed to be critical in the occurrence of relapse when glucocorticoid are tapered<sup>8,9</sup>.

Therefore, to limit glucocorticoid-induced side effects while maintaining remission is the therapeutic challenge of GCA. Thus, several immunosuppressive drugs and biological agents have been evaluated as glucocorticoid-sparing agents in randomized controlled trials (RCT) of various designs, but always compared to a control group receiving glucocorticoids. Two drugs, methotrexate<sup>10-12</sup> and tocilizumab<sup>13,14</sup> have been demonstrated to be effective on maintaining remission and are therefore recommended and prescribed in clinical practice.<sup>15-17</sup>

The absence of head-to-head trials for these treatments creates uncertainty for decision makers. The main objective of the present study was to compare the effect of glucocorticoid-sparing agents regarding the risk of relapse in GCA and their safety.

## MATERIAL AND METHODS

This systematic review was conducted in accordance with the methodological guidelines for systematic reviews of randomized controlled trials described in the Cochrane Handbook for Systematic Reviews

of Interventions.<sup>18</sup> It was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).<sup>19</sup> No ethics approval was needed. The protocol of the present study was registered in the international prospective register of systematic reviews PROSPERO (<https://www.crd.york.ac.uk/prospero/>; registration CRD42020112387).

**Literature search strategy.** Relevant records published up to the end of January 2020 were identified. We consulted the MEDLINE database using the search terms ("Randomized Controlled Trial" [Publication Type]) AND "Giant Cell Arteritis"[Mesh]. This was completed by searching the Clinical Trials database with the keywords "Giant Cell Arteritis" and "interventional".

**Outcome measures.** The outcomes were number of patients experiencing relapse and the number of major relapses. Relapse was defined by a recurrence of symptoms or reappearance of a biological inflammatory syndrome requiring an increase or resumption of glucocorticoid therapy and improved by the latter. Major relapse was adjudicated *a posteriori* and defined according to the 2018 European League Against Rheumatism (EULAR) definition by recurrence of active disease with either of the following: (i) clinical features of ischaemia (including jaw claudication, visual symptoms, visual loss attributable to GCA, scalp necrosis, stroke, limb claudication); (ii) evidence of active aortic inflammation resulting in progressive aortic or large vessel dilatation, stenosis or dissection.<sup>15</sup>

The safety outcomes were serious adverse events (SAE), defined as potentially life-threatening adverse events, requiring hospitalisation or its prolongation, causing significant disability, or resulting in death,<sup>20</sup> and serious infections.

**Study selection and data extraction.** Two reviewers (S.M. and A.T.) independently selected trials and data were extracted using a standardised data abstraction form. Trials were included in the systematic review if they met inclusion criteria defined a priori: 1) enrolment of patients with diagnosis of GCA according to the American College of Rheumatology (ACR) criteria,<sup>2</sup> newly-diagnosed or relapsing; 2) patients randomized to receive a glucocorticoid-sparing agent versus glucocorticoids; 3) report one of the outcomes of interest of the present systematic review. Primary analyses were conducted on all retrieved trials. Two reviewers (S.M. and A.T.) independently extracted information from all trials retained in the meta-analysis, including 1) the trial design, 2) patient characteristics, 3) duration of glucocorticoid treatment,<sup>7</sup> dichotomised between short (less than or equal to 6 months), and prolonged (more than 6 months) 4) efficacy, and 5) safety data. Disagreements were resolved by discussion.

**Quality assessment.** The risk of bias of trials was assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).<sup>21</sup> Publication bias was assessed with funnel plots. The certainty of evidence in the overall judgement was assessed using the Grading of Recommendations, Assessment,

Development, and Evaluation (GRADE) process, and was estimated to be high, moderate, low, or very low. We used the online tool CINeMA (<http://cinema.ispm.ch/>)<sup>22,23</sup> to evaluate confidence in evidence from the network meta-analysis, and the process described in the Cochrane Training (<https://training.cochrane.org/resource/SoF-tables-nma>).<sup>24</sup>

**Statistical analysis.** First, the pooled prevalence of events and its 95% confidence interval (95% CI) was estimated using the arcsine transformation. Heterogeneity between trial-specific estimates was assessed using the inconsistency index  $I^2$ .<sup>25</sup> A fixed-effect model was used when  $I^2 \leq 50\%$ , while a random-effects models was used when  $I^2 > 50\%$ . Then, a frequentist network meta-analysis using a random-effects model was constructed to assess the relative efficacy to reduce the relapse rate of all treatments simultaneously.<sup>26</sup> Results were expressed as relative risk (RR) and 95% confidence interval (95%CI).

Network meta-analysis combines direct (pairwise) and indirect comparisons for the same outcome, allowing the estimation of the relative efficacy among all interventions and rank ordering of the interventions. For a given comparison, direct evidence is provided by trials that compare the drugs directly. Indirect evidence refers to the evidence obtained through one or more common comparators. For example, in the absence of an RCT that directly evaluates A and B, interventions A and B can be compared indirectly if both have been compared to C (forming an A-B-C “loop” of evidence).<sup>27</sup>

The probability that each drug had the most efficacious regimen was calculated using the p-score, which can be considered as a frequentist analogue of the surface under the cumulative ranking curve for a Bayesian approach.<sup>28</sup> Sensitivity analyses were planned focusing on drugs with demonstrated efficacy (i.e. methotrexate and tocilizumab),<sup>29</sup> and by fusing the two glucocorticoid regimens. All analyses were performed using R (netmeta package version 1.2–1 for treatment comparison, meta package version 4.8–2 for pooled prevalence, R Language and Environment for Statistical Computing, Vienna, Austria).<sup>30</sup>

## RESULTS

**Study selection and characteristics of the included randomized controlled trials.** The reviewers screened 96 records, and eight trials were selected for extraction (figure 1); these included a total of 572 patients (median sample size: 42.5 patients). All the trials compared glucocorticoids to a glucocorticoid-sparing agent: tocilizumab (2 trials),<sup>13,14</sup> oral methotrexate (3 trials),<sup>10–12</sup> infliximab (1 trial),<sup>31</sup> etanercept (1 trial),<sup>32</sup> and adalimumab (1 trial).<sup>33</sup> Patients with newly diagnosed GCA

represented 72.7% of patients (416/572). The duration of glucocorticoid therapy ranged from 3 to 12 months; the mean  $\pm$  standard deviation duration was  $6.9 \pm 2.9$  months (table 1).

**Quality assessment.** Two trials testing etanercept and tocilizumab were at high risk of bias because information about the measurement of the primary endpoint was either missing,<sup>32</sup> or imprecise.<sup>14</sup> A third trial testing methotrexate<sup>10</sup> was at high risk of bias because the measure of the primary endpoint appeared to be missing for a significant proportion of the patients included (figure S1). The visual inspection of funnel plot suggests the absence of publication bias (figure S2). The certainty of evidence as assessed using the GRADE process is summarised in Table 3 (details in Appendix 1) for the comparison of interest. The final rating was low for tocilizumab versus short glucocorticoid as well as tocilizumab versus prolonged glucocorticoid, and very low for tocilizumab versus methotrexate, methotrexate versus short glucocorticoid, methotrexate versus prolonged glucocorticoid, as well as short glucocorticoid versus prolonged glucocorticoid.

**Risk of relapse.** The analysis of relapse included eight trials<sup>10-14,31-33</sup> (572 patients) testing five glucocorticoid-sparing agents (tocilizumab, methotrexate, etanercept, adalimumab, and infliximab) and the two glucocorticoid regimens (short and prolonged). The pooled prevalence of patients with relapse was 52.6% (95% CI 38.1 to 66.9), with a high heterogeneity ( $I^2=87\%$ ) leading to a random-effects model being used for the network meta-analysis. There were a median 24.5 (range: 6 to 95) relapses per trial, and 285 relapses were reported. The risk of relapse was significantly lower with tocilizumab compared to methotrexate (RR=0.41, 95% CI 0.17 to 0.97), prolonged glucocorticoid (RR=0.41, 95% CI 0.20 to 0.83), and short glucocorticoid (RR=0.32, 95% CI 0.16 to 0.66). The risk of relapse was not significantly different with methotrexate compared to short glucocorticoid (RR=0.79, 95% CI 0.48 to 1.31), and to prolonged glucocorticoid (RR=0.95, 95% CI 0.31 to 2.89); or with prolonged glucocorticoid compared to short glucocorticoid (RR=0.79, 95% CI 0.39 to 1.60; table 2, figure 2A).

**Major relapse.** The analysis of major relapse included five trials<sup>10-13,31</sup> (234 patients); three trials were not included because of missing data. The network consisted of two separate sub-networks; glucocorticoid regimen fusion led to a stellar network, and tested three glucocorticoid-sparing agents (tocilizumab, methotrexate, and infliximab). Forty-three major relapses were reported; there were a median 8 (range: 1 to 18) major relapses per trial. The pooled prevalence of major relapse was 18.3% (95% CI 7.3 to 32.8), with a high heterogeneity ( $I^2=84\%$ ). The risk of major relapse was significantly lower with tocilizumab compared to infliximab (RR=0.06, 95% CI 0.01 to 0.48) and glucocorticoid (RR=0.08, 95% CI 0.01 to 0.66), and there was a trend towards this when compared to methotrexate (RR=0.14, 95% CI 0.01 to 1.38). Other comparisons were not significant (figure 2B and online supplementary table S1).



**Serious adverse events.** SAE were reported in six trials<sup>10,13,14,31-33</sup> (510 patients) testing five glucocorticoid-sparing agents (tocilizumab, methotrexate, adalimumab, etanercept, and infliximab) and the two glucocorticoid regimens. A total of 101 SAE were reported; there was a median 12 (range: 3 to 46) SAE per trial. Adalimumab was associated with lower risk of SAE compared to prolonged glucocorticoid (RR=0.31, 95% CI 0.13 to 0.75). All other comparisons were not significant (table 2 and figure 2C).

**Serious infections.** Serious infections were reported in 6 trials<sup>10,12-14,31,33</sup> (534 patients) testing 4 glucocorticoid-sparing agents (tocilizumab, methotrexate, adalimumab, and infliximab) and the two glucocorticoid regimens. Fifty serious infections were reported; there were a median 7.5 serious infections per trial (range: 3 to 17). No comparison was significant (figure 2D and online supplementary table S2).

**Sensitivity analysis.** The sensitivity analysis was conducted among trials that compared methotrexate and tocilizumab to glucocorticoid. The results were similar to those obtained with the complete network (see online supplementary figure S3A). The pre-specified analysis with the fusion of the two glucocorticoid regimens was also conducted. The network was stellar. The risk of relapse was significantly lower with tocilizumab compared to glucocorticoid (RR=0.36, 95% CI 0.19 to 0.68), and there was a trend towards this when compared to methotrexate (RR=0.45, 95% CI 0.21 to 1.001; see online supplementary figure S3B). The risk of relapse was not significantly different between methotrexate and glucocorticoid (RR=0.75, 95% CI 0.34 to 1.66). A post-hoc analysis was conducted, removing the trial reported by Villiger *et al.*,<sup>13</sup> because relapse may be related only to an increase in inflammatory parameters. Tocilizumab suppresses C-reactive protein (CRP) levels,<sup>35</sup> and therefore the efficacy of tocilizumab may be overestimated. Results are shown in online supplementary table S3, and are superimposable to the previous ones.

## DISCUSSION

The results of the present study provide indirect evidence in favour of the superiority of tocilizumab over oral methotrexate in terms of efficacy and that these have comparable safety. Nevertheless, the superior efficacy of tocilizumab compared to methotrexate was not found for major relapse. The superiority of tocilizumab was also confirmed, compared to short or prolonged glucocorticoid therapy, both in terms of reducing relapses and major relapses.

Tocilizumab is now an adjunctive treatment admitted during the course of GCA, and is recommended in refractory disease or in case of unsustainable glucocorticoid side effects.<sup>15,17</sup> Numerous retrospective cohorts also suggest tocilizumab effectiveness in GCA treatment in “real-life”

conditions.<sup>36–39</sup> Nevertheless, data regarding safety of this drug do not concord with that reported herein as infections are more frequently reported.<sup>37,38,40</sup> Moreover, GCA patients treated by tocilizumab seem to have more frequently adverse events than rheumatoid arthritis patients: underlying disease but also age and glucocorticoid use may influence the safety.<sup>41</sup> The time to stop tocilizumab is today unclear, and effect seems to be suspensive with 50% of relapse when stopping,<sup>42,43</sup> similarly as those treated by glucocorticoid alone.<sup>7</sup>

The results of the present study suggest that methotrexate, which is currently prescribed as a glucocorticoid-sparing agent in GCA, could be less effective than tocilizumab. However, clinical trials that investigated the efficacy of methotrexate in GCA used mild doses (7.5 to 15 mg/week) and always the oral form,<sup>10–12</sup> which is known to have a poorer bioavailability than subcutaneous injection.<sup>44</sup> In addition, the results also suggest that the efficacy of methotrexate is not superior to glucocorticoid, unlike that found in an individual patient data meta-analysis from the 3 RCT available and which reported a pooled hazard ratio for a first relapse of 0.65 (95% CI 0.44 to 0.98).<sup>45</sup> A lack of power in our network meta-analysis probably explains this discrepancy, as the point estimates are quite close.

The present meta-analysis provides original data to rank the sparing-agents in the absence of head-to-head trials. A higher level of evidence of the superiority of tocilizumab compared to methotrexate will be provided by the METOGiA trial that compares 12-month tocilizumab (162 mg/week subcutaneous) and 12-month subcutaneous methotrexate (0.3 mg/kg/week, maximum 20 mg/week) in association with tapering glucocorticoid in active GCA (clinicaltrials.gov: NCT03892785).

In a previous meta-analysis, our group demonstrated that the prevalence of relapse in patients treated by glucocorticoid alone was 47%,<sup>7</sup> representing the baseline risk of relapse. Using the RR estimated by indirect comparison, we can therefore calculate the absolute risk difference according to drug exposure. Within the limitations of the approach used herein, it is expected that there would be 28 fewer relapses per 100 patients treated with tocilizumab than with prolonged glucocorticoid therapy and 32 fewer than with short glucocorticoid therapy; there would be no benefit for oral methotrexate compared to prolonged glucocorticoid therapy, and 10 fewer relapses per 100 patients treated with oral methotrexate than with short glucocorticoid therapy. Another application of the result of this meta-analysis, combined with the individual patient data meta-analysis that investigated the efficacy of methotrexate,<sup>45</sup> and the meta-analysis of prevalence of relapse on glucocorticoids,<sup>7</sup> is the calculation of the expected relapse rates on methotrexate and tocilizumab, that are estimated at 30% and 17%, respectively. These results should be used to calculate the number of patients to be included in future trials.

This network meta-analysis has several limitations. First, the definition of relapse is not homogenous, particularly concerning the place of clinical and laboratory criteria, with some trials authorizing relapse based only on inflammatory parameters. This point is particularly problematic for the estimation of tocilizumab efficacy, the mechanism of action which leads to negative CRP.<sup>35</sup> It was not possible with the available data to separate clinical and laboratory-based relapse, and the efficacy of tocilizumab may therefore be overestimated despite reassuring results from the post-hoc analysis. Secondly, the number of patients included was generally low, leading to a lack of power, especially for the analysis of major relapse. Moreover, it was therefore not possible to analyse factors potentially modifying the effect of the treatment, such as newly diagnosed patients versus relapsed patients, or the precise duration of glucocorticoid therapy. Thirdly, the transitivity hypothesis may be questioned by the absence of a similar design, different initial patient characteristics, and a different control group treatment among the included trials. Because of the small size of studies, it was not possible to conduct subgroup analysis. Fourthly, the results put etanercept in second place regarding the p-score, whereas this biological agent was assessed in only one trial that reported negative results, included a very low number of patients (n=17), had a high risk of bias according to the ROB2 evaluation, and very short glucocorticoid regimen (3 months).<sup>32</sup> The choice to include all trials in GCA, even negative ones, was motivated by the improved accuracy of the final estimate when adding treatments to the network.<sup>29</sup> However, the sensitivity analysis found that this was not the case, and the estimate provided by the indirect comparison for etanercept should not be considered in the clinical interpretation. Moreover, in absence of confidence intervals, p-score should be interpreted with great caution.

To conclude, this meta-analysis provides new data drawing a ranking of glucocorticoid-sparing agents, and places tocilizumab at the top. These results may be informative for the treatment of GCA and ongoing or future design of randomized clinical trials testing methotrexate and tocilizumab in GCA, even if the certainty of evidence is low.

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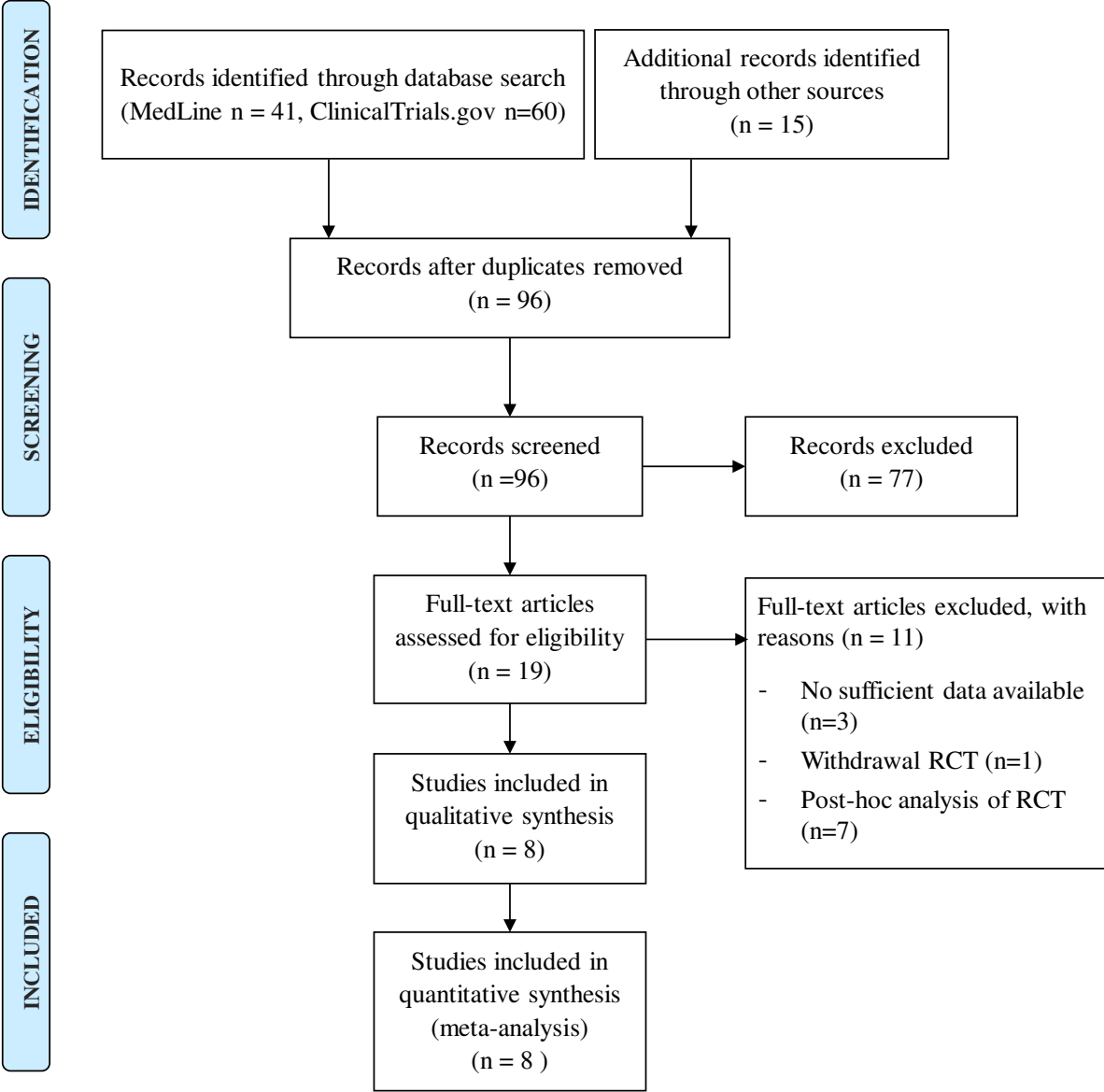
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SUMMARY

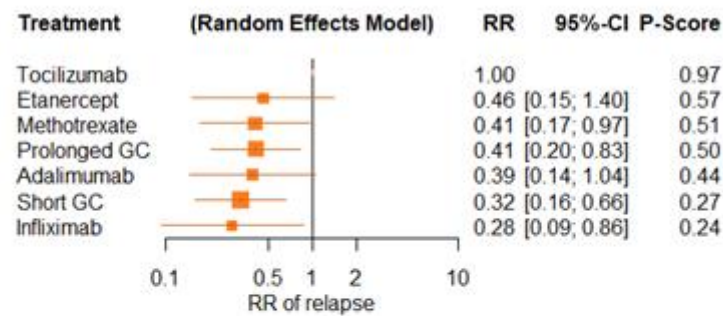
**FIGURE**

**Figure 1.** Flow chart

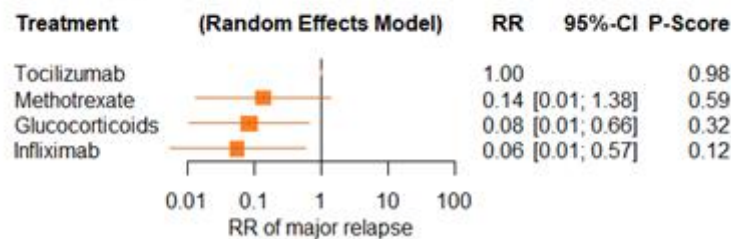


**Figure 2.** Forest plots of relative risks (RR) of the different treatments versus tocilizumab for (A) relapse, (B) major relapse, (C) serious adverse event (SAE), and (D) infections in the network meta-analysis. P-score represents the probability to be the best treatment, but in absence of confidence intervals, it should be interpreted with great caution. GC: glucocorticoids.

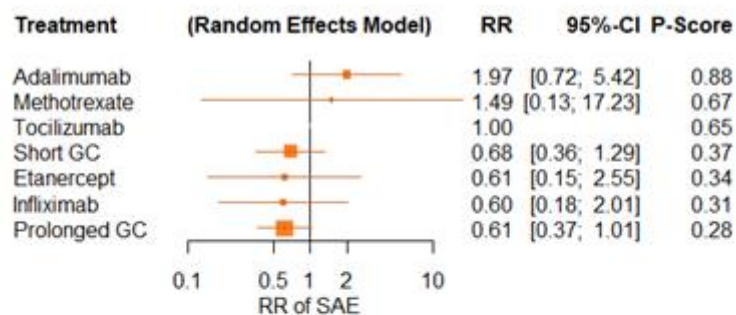
### A. Relapse



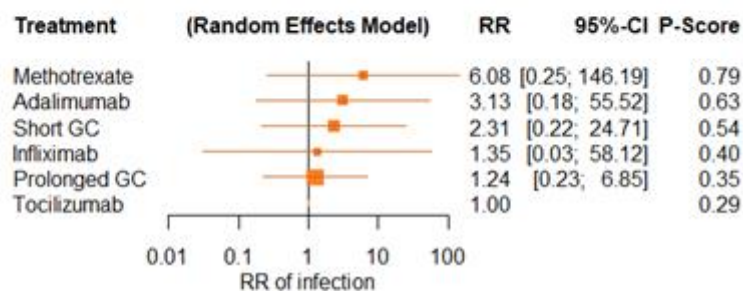
### B. Major relapse



### C. Serious adverse events



### D. Infections





**TABLES**

**Table 1.** Baseline characteristics and results of included trials.

Trial	Design	GCA definition	Relapse definition	Intervention group	N	Wom (%)	Mean age, years	TAB+ (%)	Newly diagnosed (%)	N relapsing (%)	Cumulative dose of GC, mg/kg <sup>s</sup>	SAEs (%)	Infections (%)
<b>Villiger et al. 2016</b> <sup>13</sup>	Double blinded, randomized, ITT	1990 ACR criteria	Raised ESR or CRP, and/or at least one of symptoms of GCA	Tocilizumab	20	13 (65)	71.3	13 (65)	16 (80)	1 (5)	43	7 (35)	10 (50)
<b>Stone et al. 2017</b> <sup>14</sup>	Double blinded, randomized, ITT	Biopsy-proven GCA or on evidence of large vessel vasculitis	Recurrence of symptoms of GCA or raised ESR attributable to GCA	Tocilizumab <sup>€</sup>	150	113 (75)	69.5	91 (61)	73 (49)	36 (24)	27	22 (15)	9 (6)
		on angiography, computed tomographic or MRA or PET		GC 6 m	50	38 (76)	69.3	36 (72)	23 (46)	34 (68)	47	11 (22)	2 (4)
<b>Spiers et al. 2001</b> <sup>11</sup>	Double blinded, randomized, PP	Biopsy-proven GCA or classic manifestations of TA and raised ESR	Recurrence of symptoms of TA with good response to GC	GC 12 m	51	37 (73)	67.8	29 (57)	23 (45)	25 (49)	52	13 (25)	6 (12)
		TA and raised ESR		Oral methotrexate	12	9 (75)	72.0	10 (75)	12 (100)	5 (42)	99	NA	NA
<b>Hoffman et al. 2002</b> <sup>10</sup>	Double blinded, randomized, ITT	Biopsy-proven GCA or classic manifestations of TA or large vessel vasculitis proved	At least one symptom of TA and increase in ESR	GC 4 months	9	4 (44)	74.0	7 (78)	9 (100)	3 (33)	89	NA	NA
		Biopsy-proven GCA or classic manifestations of TA or large vessel vasculitis proved		Oral methotrexate	51	41 (80)	73.5	41 (80)	51 (100)	31 (61)	NA	NA	1 (2)
<b>Jover et al. 2001</b> <sup>12</sup>	Double blinded, randomized, PP	Biopsy-proven GCA	At least one symptom of TA and increase in ESR	GC 6 months	47	29 (62)	75.0	38 (81)	47 (100)	31 (66)	NA	NA	2 (4)
		Biopsy-proven GCA		Oral methotrexate	21	14 (67)	78.0	16 (76)	21 (100)	9 (43)	70	NA	NA

Trial	Design	GCA definition	Relapse definition	Intervention group	N	Wo-men (%)	Mean age, years	TAB+ (%)	Newly diagnosed (%)	N relapsing (%)	Cumulative dose of GC, mg/kg <sup>§</sup>	SAEs (%)	Infections (%)
			Recurrence of symptoms of TA with good response to GC	GC 6 months	20	15 (75)	77.6	15 (75)	20 (100)	16 (80)	95	NA	3 (15)
			Reappearance of GCA-related clinical symptoms or increase in CRP greater than 15 mg/L, at two time points at 1 week apart without any other obvious etiology	Adalimumab	34	24 (71)	74.5	22 (65)	34 (100)	20 (59)	NA	5 (15)	3 (9)
<b>Seror et al. 2014</b> <sup>33</sup>	Double blinded, randomized, ITT	1990 ACR Criteria		GC 12 months	36	28 (78)	74.5	28 (78)	36 (100)	26 (72)	NA	17 (47)	8 (22)
			Symptoms and/or signs of GCA with elevations in at least one of ESR and/or CRP	Etanercept	8	6 (75)	74.5	8 (100)	0 (0)	5 (63)	25	3 (38)	NA
<b>Martinez-Taboada et al. 2007</b> <sup>32</sup>	Double blinded, randomized, ITT	Biopsy-proven GCA		GC 3 months	9	8 (89)	74.4	9 (100)	0 (0)	8 (89)	50	3 (33)	NA
			Raised ESR and at least 1 symptom of GCA	Infliximab	28	24 (86)	71.5	24 (86)	28 (100)	16 (57)	47	8 (29)	3 (11)
<b>Hoffman et al. 2007</b> <sup>31</sup>	Double blinded, randomized, ITT	1990 ACR Criteria		GC 6 months	16	11 (69)	69.5	10 (63)	16 (100)	8 (50)	45	4 (25)	1 (6)

<sup>§</sup> if the cumulative dose was not available in mg/kg, the dose was related to the mean weight if available or by default to a weight of 60 kg. <sup>¶</sup>Data from tocilizumab weekly and every other week were pooled. ACR: American College of Rheumatology; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; GC: glucocorticoids; GCA: giant cell arteritis; ITT: intention to treat; MRA: magnetic resonance angiography; PET: positron-emission tomography; PP: per-protocol; SAE: serious adverse event; TA: temporal arteritis; TAB: temporal artery biopsy; Toci: tocilizumab

**Table 2. Relative risk (95% confidence interval) of relapse and serious adverse events from network meta-analysis for all pairwise comparisons.** Relative risks (RR) for relapse are below the diagonal line, whereas relative risks for serious adverse events are above the diagonal line. For example, below the diagonal,  $RR_{\text{tocilizumab/methotrexate}} = 0.41$  means that RR of relapse for patients treated by tocilizumab is 0.41 compared to patients treated by methotrexate. Above the diagonal,  $RR_{\text{tocilizumab/methotrexate}} = 0.67$  means that RR of serious adverse events for patients treated by tocilizumab is 0.67 compared to patients treated by methotrexate. Significant results are highlighted in bold. GC: glucocorticoid.

<b>Tocilizumab</b>	0.67 (0.06 to 7.81)	1.63 (0.99 to 2.67)	1.46 (0.78 to 2.75)	1.64 (0.39 to 6.89)	0.51 (0.18 to 1.39)	1.67 (0.50 to 5.60)
<b>0.41</b> <b>(0.17 to 0.97)</b>	<b>Methotrexate</b>	2.42 (0.21 to 28.32)	2.17 (0.20 to 23.16)	2.44 (0.17 to 36.12)	0.75 (0.06 to 10.28)	2.48 (0.19 to 32.81)
<b>0.41</b> <b>(0.20 to 0.83)</b>	1.01 (0.42 to 2.40)	<b>Prolonged GC</b>	0.90 (0.46 to 1.75)	1.01 (0.24 to 4.30)	<b>0.31</b> <b>(0.13 to 0.75)</b>	1.03 (0.30 to 3.51)
<b>0.32</b> <b>(0.16 to 0.66)</b>	0.79 (0.48 to 1.31)	0.79 (0.39 to 1.60)	<b>Short GC</b>	1.12 (0.31 to 4.07)	0.35 (0.11 to 1.05)	1.14 (0.41 to 3.20)
0.46 (0.15 to 1.40)	1.13 (0.42 to 3.06)	1.12 (0.37 to 3.43)	1.42 (0.60 to 3.37)	<b>Etanercept</b>	0.31 (0.06 to 1.68)	1.02 (0.20 to 5.28)
0.39 (0.14 to 1.04)	0.95 (0.31 to 2.89)	0.94 (0.47 to 1.89)	1.20 (0.44 to 3.23)	0.84 (0.23 to 3.14)	<b>Adalimumab</b>	3.29 (0.73 to 14.94)
<b>0.28</b> <b>(0.09 to 0.86)</b>	0.70 (0.26 to 1.88)	0.69 (0.23 to 2.11)	0.88 (0.37 to 2.08)	0.62 (0.18 to 2.09)	0.73 (0.20 to 2.72)	<b>Infliximab</b>

**Table 3. Summary of findings and quality of evidence assessment**

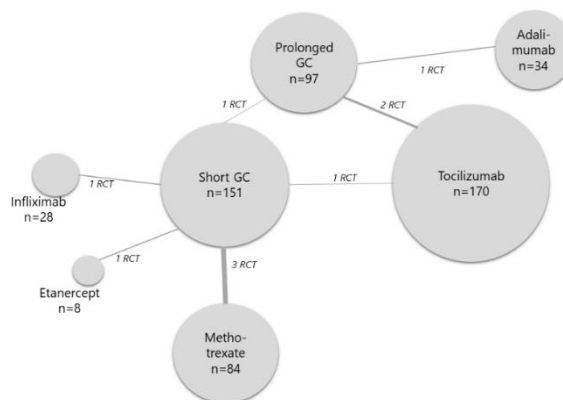
**Patients:** with giant cell arteritis, newly diagnosed

or relapsing

**Interventions:** GC sparing-agent

**Comparator :** GC

**Outcome:** relapse rate



*Geometry of the network\**

Comparison	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence <sup>§</sup> (GRADE)	Comments
Tocilizumab vs Methotrexate	<b>RR 0.41</b> (0.17 to 0.97)	No direct evidence, indirect evidence only	⊕○○○ VERY LOW	Risk of bias, imprecision
Tocilizumab vs short GC	<b>RR 0.32</b> (0.16 to 0.66)	200 (1 RCT)	⊕⊕○○ LOW	Risk of bias
Tocilizumab vs prolonged GC	<b>RR 0.41</b> (0.20 to 0.83)	230 (2 RCTs)	⊕⊕○○ LOW	Risk of bias
Methotrexate vs short GC	<b>RR 0.79</b> (0.48 to 1.31)	160 (3 RCTs)	⊕○○○ VERY LOW	Risk of bias, imprecision
Methotrexate vs prolonged GC	<b>RR 1.01</b> (0.42 to 2.40)	No direct evidence, indirect evidence only	⊕○○○ VERY LOW	Risk of bias, imprecision
Short GC vs prolonged GC	<b>RR 1.27</b> (0.62 to 2.58)	101 (1 RCT)	⊕○○○ VERY LOW	Risk of bias, imprecision

**CI:** Confidence interval; **GC:** Glucocorticoids; **RR:** Risk ratio

\*The width of lines for each connection in the evidence network are proportional to the number of randomized controlled trials (RCT) comparing each pair of treatments. The size of each treatment node is proportional to the number of randomized participants (sample size).

<sup>§</sup>Details of GRADE evaluation are available in appendix.

**GRADE Working Group grades of evidence (or certainty in the evidence)**

**High quality:** We are very confident that the true effect lies close to that of the estimate of the effect.

**Moderate quality:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

**Low quality:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

**Very low quality:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

**SUPPLEMENTARY MATERIAL**

**Table S1. Relative risk (95% confidence interval) of major relapse from network meta-analysis for all pairwise comparisons.** For example, relative risk (RR)<sub>tocilizumab/methotrexate</sub> = 0.14 means that RR of major relapse for patients treated by tocilizumab is 0.14 compared to patients treated by methotrexate. Significant results are highlighted in bold.

<b>Tocilizumab</b>			
0.14 (0.01 to 1.38)	<b>Methotrexate</b>		
<b>0.08</b> <b>(0.01 to 0.66)</b>	0.61 (0.22 to 1.69)	<b>Glucocorticoids</b>	
<b>0.06</b> <b>(0.01 to 0.57)</b>	0.41 (0.10 to 1.76)	0.67 (0.24 to 1.91)	<b>Infliximab</b>

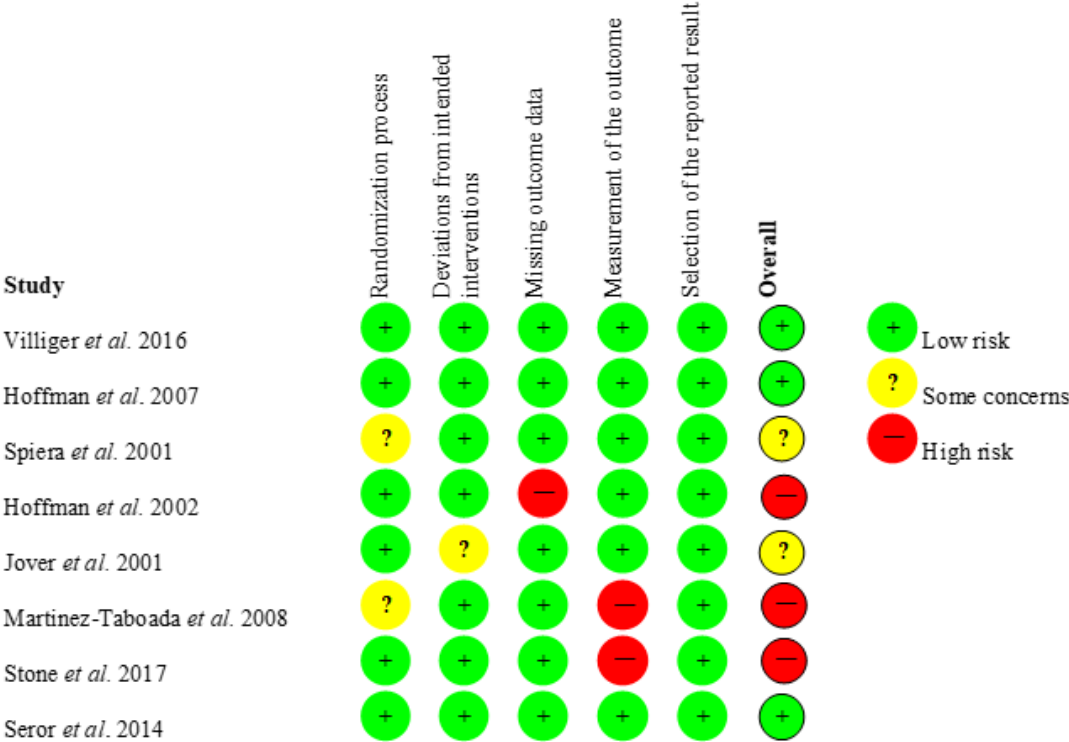
**Table S2. Relative risk (95% confidence interval) of infections from network meta-analysis for all pairwise comparisons.** For example, relative risk (RR)<sub>methotrexate/tocilizumab</sub> = 0.16 means that RR of infection for patients treated by methotrexate is 0.16 compared to patients treated by tocilizumab. GC: glucocorticoid

<b>Methotrexate</b>					
0.51 (0.01 to 26.59)	<b>Adalimumab</b>				
0.38 (0.05 to 3.15)	0.74 (0.03 to 20.54)	<b>Short GC</b>			
0.22 (0.01 to 8.18)	0.43 (0.01 to 36.10)	0.58 (0.03 to 10.87)	<b>Infliximab</b>		
0.20 (0.01 to 4.99)	0.40 (0.04 to 4.02)	0.54 (0.05 to 5.90)	0.92 (0.02 to 40.44)	<b>Prolonged GC</b>	
0.16 (0.01 to 3.95)	0.32 (0.02 to 5.66)	0.43 (0.04 to 4.64)	0.74 (0.02 to 32.10)	0.80 (0.15 to 4.43)	<b>Tocilizumab</b>

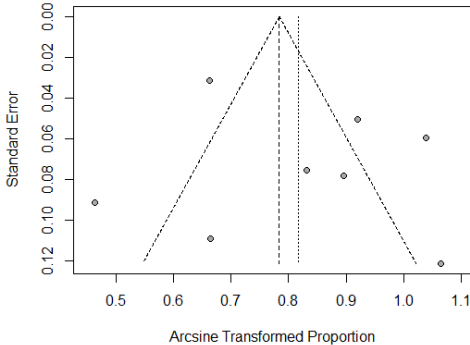
**Table S3.** Sensitivity analysis of relative risk (95% confidence interval) of relapse from network meta-analysis without results of Villiger *et al.* Relative risks for relapse are below the diagonal line, whereas relative risks for serious adverse events are above the diagonal line. For example, below the diagonal, relative risk( $RR$ )<sub>tocilizumab/methotrexate</sub> = 0.44 means that RR of relapse for patients treated by tocilizumab is 0.44 compared to patients treated by methotrexate. Significant results are highlighted in bold.

<b>Tocilizumab</b>						
<b>0.44</b> <b>(0.22 to 0.92)</b>	<b>Methotrexate</b>					
<b>0.49</b> <b>(0.26 to 0.91)</b>	1.10 (0.54 to 2.27)	<b>Prolonged GC</b>				
<b>0.35</b> <b>(0.20 to 0.64)</b>	0.79 (0.52 to 1.21)	0.72 (0.40 to 1.30)	<b>Short GC</b>			
0.50 (0.19 to 1.31)	1.13 (0.48 to 2.69)	1.03 (0.39 to 2.67)	1.42 (0.67 to 3.03)	<b>Etanercept</b>		
0.46 (0.20 to 1.07)	1.04 (0.42 to 2.59)	0.94 (0.54 to 1.64)	1.31 (0.58 to 2.94)	0.92 (0.30 to 2.78)	<b>Adalimumab</b>	
<b>0.31</b> <b>(0.12 to 0.81)</b>	0.70 (0.29 to 1.65)	0.63 (0.24 to 1.64)	0.88 (0.41 to 1.87)	0.62 (0.21 to 1.79)	0.67 (0.22 to 2.02)	<b>Infliximab</b>

**Figure S1.** Risk of bias summary: review authors' judgements about each risk of bias item for each included study (Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)).

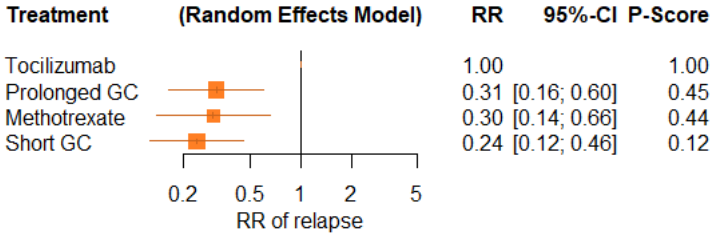


**Figure S2.** Funnel plot

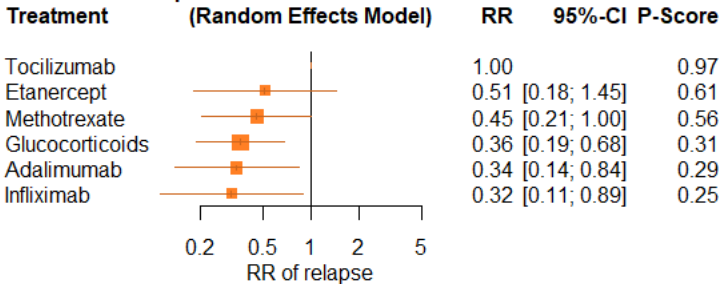


**Figure S3.** Sensitivity analysis: forest plots of relative risks (RR) for relapse in network meta-analysis of (A) methotrexate and glucocorticoid (GC) versus tocilizumab, and (B) tocilizumab compared to other treatment with GC regimens fused. P-score represents the probability to be the best treatment, but in absence of confidence intervals, it should be interpreted with great caution. GC: glucocorticoids.

**A. Tocilizumab, methotrexate and glucocorticoids**



**B. Glucocorticoid regimens merged**





## Appendix 1 - GRADE process

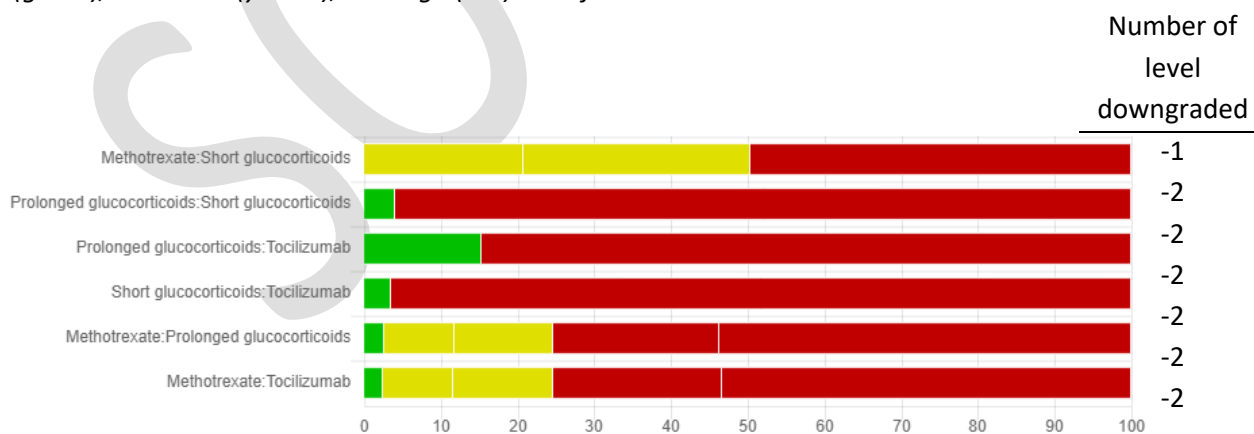
We describe here the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process resulting in the overall judgement of the certainty of evidence of a specific network estimate to be high, moderate, low, or very low. The online tool CINeMA (<http://cinema.ispm.ch/>)<sup>1,2</sup> was used to evaluate confidence in evidence from the network meta-analysis, and the process described by the Cochrane Training (<https://training.cochrane.org/resource/SoF-tables-nma>).<sup>3</sup> The criteria for downgrading the certainty of evidence for a specific comparison within a certain GRADE domain are described below.

### Rating certainty in direct estimates

#### Risk of bias

Risk of bias was estimated using the Revised Cochrane risk-of-bias tool for randomized trials (RoB2)<sup>4</sup> for each study, classifying risk of bias as low risk, some concern, or high risk. The per-study contribution matrix<sup>5</sup> was used to evaluate the contribution of each study and each direct comparison to the estimation of each relative effect. The confidence rating was downgraded for a network estimate by one level when the contributions came mostly from comparisons with a risk of bias of “some concern” or by two levels when the contributions came mostly from comparisons with a “high” risk of bias. Results are illustrated in Figure A1.

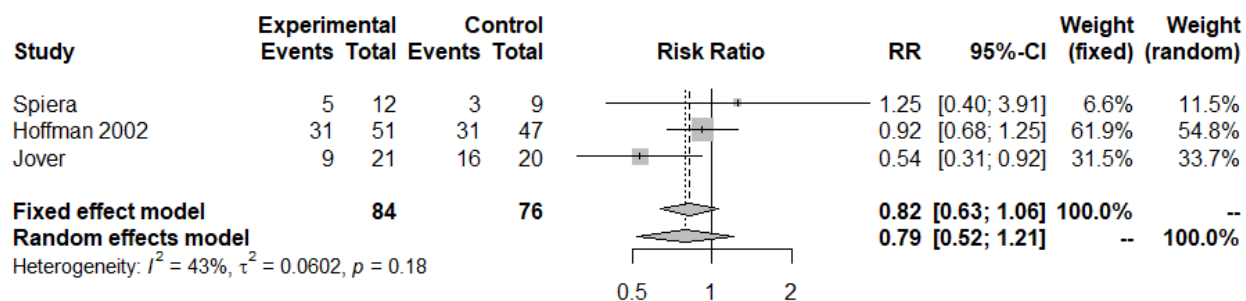
**Figure A1.** Risk of bias bar chart for the network meta-analysis of treatment in GCA. Each bar represents the evidence for a relative treatment effect. White vertical lines separate colored areas which refer to the contribution of each study. Each bar shows the percentage contribution from studies judged to be at low (green), moderate (yellow), and high (red) risk of bias.



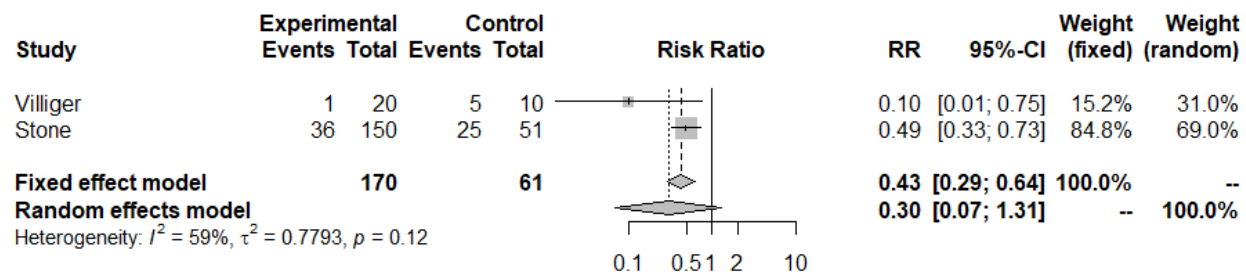
#### Inconsistency

Inconsistency was assessed using the GRADE guidelines.<sup>6</sup> Meta-analysis of direct comparison are presented below (Figure A2 and A3).

**Figure A2.** Forest plot of studies that compared methotrexate and glucocorticoids. RR: relative risk, 95%-CI: 95% confidence interval



**Figure A3.** Forest plot of studies that compared tocilizumab and glucocorticoids. RR: relative risk, 95%-CI: 95% confidence interval



Concerning methotrexate,  $I^2$  was 43%, and even if the 95% confidence interval (CI) of studies overlapped, the direction of the results was not consistent; the quality of evidence was therefore downgraded (one level). Concerning tocilizumab,  $I^2$  was 59%, but the 95%CI of the two studies overlapped, and results are both in the same direction; the quality was therefore not downgraded the quality of evidence.

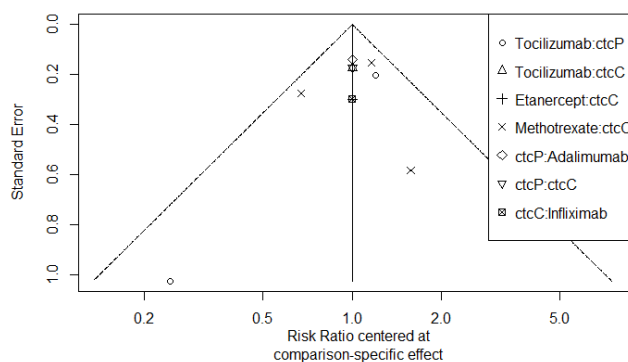
### Indirectness

The four sources of indirectness identified in the GRADE handbook were reviewed: differences in population, differences in interventions, differences in outcome measures (surrogate outcomes), and indirect comparisons (see transitivity in rating estimate in indirect estimate). It was not considered that there were significant differences between study populations or between study interventions (see Table 1 of the manuscript), and the outcome measure was relapse in all studies, which is a clinical outcome; quality was therefore not downgraded.

### Publication bias

Visual inspection of the funnel plot (Figure A4) did not indicate publication bias, and quality of evidence was not downgraded.

**Figure A4.** Funnel plot dedicated to network meta-analysis. ctcC: short glucocorticoids, ctcP: prolonged glucocorticoids.



### Rating certainty in indirect estimates:

In the most dominant first-order loop the rating of each of the direct estimates was considered and the lowest of the two ratings chosen.

### Transitivity

Transitivity was evaluated by comparing the distribution of effect modifiers across the different comparisons. The main effect modifiers taking into consideration was age, sex distribution, and proportion of newly diagnosed GCA patients vs. relapsing patients. These effect modifiers were not considered as different among studies (see Table 1) and the quality of evidence was therefore not downgraded.

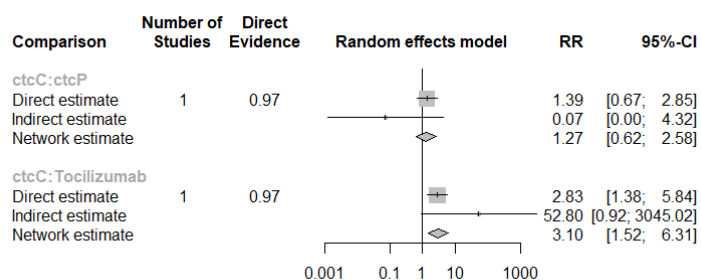
### Rating certainty in network meta-analysis estimates:

The rating of the evidence that contributed the most, either direct or indirect comparison, was chosen and incoherence and imprecision examined.

### Incoherence

Incoherence was assessed with the node-splitting method proposed by Dias et al.<sup>7</sup> Incoherence was estimated as not serious if the 95%CI of estimate of direct estimation and indirect estimation overlapped, and serious if not (Figure A5). The confidence intervals overlap, and the quality was not downgraded.

**Figure A5.** Node-splitting method to assess incoherence. Results are available when direct and indirect comparison are available for the same comparison. ctcC: short glucocorticoids, ctcP: prolonged glucocorticoids.



## Imprecision

Imprecision was assessed using the optimal information size criterion (OIS) as described in the GRADE handbook. The conventional sample size was calculated for a single adequately powered trial, using the estimate risk of relapse presented below:

Risk of relapse		Details
$R_{\text{glucocorticoid}}$	0.47	Meta-analysis of prevalence of relapse <sup>8</sup>
$R_{\text{short glucocorticoid (6 months)}}$	0.64	Meta regression: <sup>8</sup> 0.74-0.017xDuration of GC in months
$R_{\text{prolonged glucocorticoid (12 months)}}$	0.54	
$R_{\text{methotrexate}}$	0.30	$R_{\text{metho}} = RR_{\text{metho/GC}}^9 \times R_{\text{GC}}^8$
$R_{\text{tocilizumab}}$	0.17	$R_{\text{toci}} = RR_{\text{toci/GC}}^{\$} \times R_{\text{GC}}^8$ §Result of the present network meta-analysis

The steps proposed in the Cochrane handbook in deciding whether to rate down the quality of evidence for imprecision considered: if the optimal information size criterion is not met, rate down for imprecision, unless the sample size is very large (at least 2000, and perhaps 4000 patients); if the OIS criterion is met and the 95%CI excludes no effect (i.e. CI around RR excludes 1.0), do not rate down for imprecision; if OIS criterion is met, and the 95%CI overlaps no effect (i.e. CI includes RR of 1.0) rate down for imprecision if the CI fails to exclude important benefit or important harm: results are detailed below.

Comparison	OIS	NMA	Yes or No	If Yes, 95% CI excludes no effect?	Rate down for imprecision?
Tocilizumab vs methotrexate	260	0	No	NA	Yes
Tocilizumab vs short GC	25	200	Yes	Yes	No
Tocilizumab vs pGC	40	230	Yes	Yes	No
Metho vs sGC	50	160	Yes	No	Yes
Metho vs pGC	100	0	No	NA	Yes
cGC vs pGC	600	101	No	NA	Yes

Summary of the GRADE evaluation results.

Comparison	Tocilizumab vs methotrexate	Tocilizumab vs sGC	Tocilizumab vs pGC	Metho vs sGC	Metho vs pGC	cGC vs pGC
Number of studies	no study	1 study	2 studies	3 studies	0 study	1 study
<b>1. Rating direct estimate</b>		0.35 95%CI (0.17-0.73)	0.41 95%CI(0.20-0.83)	0.79 95%CI (0.48-1.31)		1.39 95%CI (0.67-2.85)
a. Assess risk of bias	2	2	2	1	1	2
b. Asses inconsistency	NA	NA	0	1	NA	NA
c. Assess indirectness	NA	0	0	0	NA	0
d. Assess publication bias	NA	0	0	0	NA	0
<b>TOTAL</b>	2	2	2	2	1	2
<b>2. Rating indirect estimate</b>		0.17 95%CI (0.00-1.09)	NA (multi-arm trial)	NA	1.01 95%CI (0.42-2.40)	13.61 95%CI(0.23-800.16)
a. Choose the most dominant first-order loop	0.41 95%CI (0.17-0.97)		NA	NA		
b. Look at the rating of each of the direct estimates from that loop	toci-shortGC-metho	toci-prolonged-short	NA	NA	metho-short-prolonged	short-toci-prolonged
c. Choose the lowest of the two ratings	2	2	NA	NA	2	2
d. Examine for intransitivity	0	0	NA	NA	0	0
<b>TOTAL</b>	2	2	NA	NA	2	2
<b>3. Rating network estimate</b>		0.32 95%CI (0.16-0.66)	0.41 95%CI (0.20-0.83)	0.79 95%CI (0.48-1.31)	1.01 95%CI (0.42-2.40)	1.27 95%CI (0.62-2.58)
a. Choose the rating of the evidence that contributes the most	indirect	direct	NA	direct	indirect	direct
b. Examine for incoherence	NA	0	NA	NA	NA	0
c. Examine for imprecision	1	0	0	1	1	1
<b>TOTAL</b>	3	2	2	3	3	3
<b>FINAL RATING</b>	VERY LOW	LOW	LOW	VERY LOW	VERY LOW	VERY LOW

3=very low; 2=low; 1=moderate; 0=high.

sGC: short glucocorticoids, pGC: prolonged glucocorticoids

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## 7 Discussion et perspectives

### 7.1 Synthèse des résultats obtenus

L'ACG est une vascularite des gros vaisseaux, touchant préférentiellement les femmes de plus de 70 ans. L'atteinte clinique est variée, allant d'un syndrome inflammatoire nu à des évènements ischémiques sévères mettant en jeu le pronostic vital ou fonctionnel des patients. La pathologie est particulièrement présente dans les pays occidentaux, avec un gradient Nord Sud assez marqué.

La mortalité des patients atteints d'ACG semble similaire à celle de la population générale, avec néanmoins plusieurs signaux en faveur d'un excès de mortalité dans les premières années suivant le diagnostic. Sur le plan européen, l'analyse du registre Eurostat est en faveur d'une diminution du taux de mortalité au cours du temps sur la période 1994-2016, avec une importante hétérogénéité selon les pays, difficile à interpréter car la qualité des données Eurostat est délicate à certifier.

La physiopathologie n'est pas complètement élucidée, mais un modèle en 4 phases est actuellement proposé, avec la sécrétion de plusieurs cytokines pro-inflammatoires, associée à un important remodelage vasculaire entraînant les manifestations ischémiques.

La corticothérapie est un traitement constamment efficace, mais qui s'accompagne d'importants effets secondaires lors de la prise prolongée. Surtout, la méta-analyse présentée dans ce travail établit que 47,2% (IC 95% 40,0 – 54,3) des patients traités par corticothérapie seule vont présenter une rechute au cours de leur suivi. Le taux de rechute est associé à la durée de la corticothérapie, et diminue lorsque cette dernière augmente. La prévalence des rechutes sévères est quant à elle estimée à 3,3% (IC 95% 1,7 – 5,6), avec un rôle majeur dans ce chiffre des claudications de la mâchoire, dont l'impact clinique est encore à démontrer.

La nécessité d'un traitement d'épargne cortisonique se fait donc pressante, et deux molécules ont montré une efficacité pour prévenir les rechutes, d'une part le méthotrexate et d'autre part le tocilizumab. La comparaison indirecte des différents essais par méta-analyse en réseau positionne le tocilizumab en première ligne comme traitement d'épargne cortisonique, même si le niveau de certitude demeure faible.

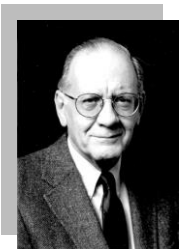
De nombreuses questions restent en suspens dans l'ACG :

- Sur le plan physiopathologique : quel trigger est à l'origine de la rupture de tolérance initiale ?

- Sur le plan pronostique : quels sont les facteurs de risque de rechute ? quels sont les facteurs de risque de corticorésistance, de corticodépendance, de mauvaise tolérance de la corticothérapie ?
- Sur le plan thérapeutique : place exacte des traitements d'épargne (en première ligne ? en cas de corticorésistance ? en cas d'effet indésirable sévère lié à la corticothérapie ?), schémas de traitement, et développement de nouvelles molécules qui nécessiteront des essais thérapeutiques.

Pour permettre de limiter les essais à ceux qui ont le plus de chance de succès, des méthodes d'essais cliniques *in silico* se développent de nos jours, et nécessitent en premier lieu la création d'une population virtuelle.

## 7.2 Définition et intérêt d'une population virtuelle



*"The essence of tragedy has been described as the destructive collision of two sets of protagonists, both of whom are correct. The statisticians are right in denouncing subgroups that are formed post hoc from exercises in pure data dredging. The clinicians are also right, however, in insisting that a subgroup is respectable and worthwhile when established a priori from pathophysiological principles."*

A R Feinstein, 1998

L'auteur de la citation ci-dessous, clinicien, chercheur et épidémiologiste, pointe du doigt une des limites des essais cliniques comme source de décision unique par le clinicien. En effet, les données issues des essais sont basées sur des estimations moyennes d'effet traitement, appliquées à des populations moyennes, alors que le clinicien doit traiter le patient dans son individualité. Le clinicien est alors tenté de rechercher le sous-groupe correspondant aux caractéristiques de son patient et de déterminer sa conduite à tenir sur les résultats issus de ces sous-groupes. Malheureusement, ces résultats en sous-groupe sont la plupart du temps exploratoires, avec un risque non négligeable d'inflation du risque alpha, conduisant à une probabilité élevée de conclure à tort à une différence alors qu'elle n'existe pas.

Les contraintes liées à la réalisation d'un essai clinique de bonne qualité, qu'elles soient d'ordre financier, éthique, ou matériel limitent en général l'obtention de données probantes sur les sous-groupes d'intérêt.



Une population virtuelle est une population simulée à partir des connaissances disponibles (données épidémiologiques, environnementales) pour générer une image *in silico* d'une population réelle et son évolution au cours du temps.<sup>152</sup> Cette population virtuelle, reflétant les caractéristiques individuelles des sujets et populationnelles d'une cohorte clinique typique permet de réaliser des simulations prospectives de réponse aux nouvelles thérapies prenant en compte la variabilité inter-sujets observée dans la pratique clinique, et pourrait aider à identifier les patients qui répondent et ceux qui ne répondent pas au traitement<sup>153</sup>.

La population virtuelle est particulièrement adaptée lorsque le rapport global bénéfice/risque au niveau de la population, obtenu par l'agrégation des rapports bénéfices/risques individuels, n'est pas directement calculable à partir d'un profil moyen représentatif, en raison de la complexité des règles d'association et de la multiplicité des dimensions des fonctions en jeu.

L'exploration de différents scénarios d'utilisation d'un médicament ou d'une stratégie thérapeutique est supportée par la réalisation d'une population virtuelle. En fonction des contraintes externes, ces analyses de différentes stratégies peuvent conduire à identifier des seuils de bénéfices, fournissant ainsi une référence pour des décisions thérapeutiques rationnelles. La génération d'une population virtuelle doit viser à obtenir une population *in silico* aussi réaliste que possible, et à capturer les caractéristiques les plus pertinentes de la population réelle : c'est ce qui définit le concept de population virtuelle réaliste (PVR)<sup>154</sup>.

Par ailleurs, la PVR peut également permettre d'optimiser les critères d'inclusion pour maximiser les chances d'un essai conclusif.<sup>155</sup>

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<sup>152</sup> Gueyffier et al., « Contribution of Modeling Approaches and Virtual Populations in Transposing the Results of Clinical Trials into Real Life and in Enlightening Public Health Decisions ».

<sup>153</sup> Allen, Rieger, et Musante, « Efficient Generation and Selection of Virtual Populations in Quantitative Systems Pharmacology Models ».

<sup>154</sup> Gueyffier et al., « Contribution of Modeling Approaches and Virtual Populations in Transposing the Results of Clinical Trials into Real Life and in Enlightening Public Health Decisions ».

<sup>155</sup> Duffull et Gulati, « Potential Issues With Virtual Populations When Applied to Nonlinear Quantitative Systems Pharmacology Models ».

### 7.3 Conclusion

La revue de la littérature proposée ainsi que les différents résultats issus des études menées visent à réaliser un « modèle de connaissance » de l'ACG. Ce modèle est amené à s'enrichir au fil du temps, en fonction des nouvelles données disponibles, tant sur le plan physiopathologique qu'épidémiologique.

C'est à partir de ce modèle de connaissance qu'un « modèle computationnel », c'est-à-dire traduisant les données connues en équations mathématiques, qu'une population virtuelle peut être construite, associant des caractéristiques démographiques à des modèles d'effets des médicaments, permettant ensuite de réaliser des essais thérapeutiques *in silico*.

