Efficacité et tolérance des agents biologiques dans les rhumatismes inflammatoires à début juvénile dans les essais cliniques randomisés et les études observationnelles

Natalia Cabrera Rojas

N° d'ordre NNT : 2019LYSE1191

THESE de DOCTORAT DE L'UNIVERSITE DE LYON
Opérée au sein de
L'Université Claude Bernard Lyon 1

École Doctorale N° 341
(E2M2 Écosystèmes Évolution Modélisation Microbiologie)

Spécialité de doctorat : Pharmacologie Clinique
Discipline : Rhumatologie Pédiatrique

Soutenue publiquement le 30/09/2019, par :
Natalia Margarita Cabrera Rojas

Efficacité et tolérance des agents biologiques dans les rhumatismes inflammatoires à début juvénile dans les essais cliniques randomisés et les études observationnelles

Devant le jury composé de :		
Belot, Alexandre	PU-PH, Hospices Civils de Lyon, Hôpital Lyon Sud /Université Lyon 1	Président
Cimaz, Rolando	Professeur, *Department of Clinical Sciences and Community Health, University of Milan*	Rapporteur
Quartier, Pierre	PU-PH, Assistance Publique-Hôpitaux de Paris, Hôpital Necker / Université Paris	Rapporteur
Kone-Paut, Isabelle	PU-PH, Assistance Publique-Hôpitaux de Paris, Hôpital Kremlin-Bicêtre / Université de Paris	Examinatrice
Bader-Meunier, Brigitte	PH, Assistance Publique-Hôpitaux de Paris, Hôpital Necker / Université de Paris	Examinatrice
Berard, Anick	PU-PH, Hospices Civils de Lyon, Hôpital Lyon Sud /Université Lyon 1	Examinatrice
Lega, Jean-Christophe	PU-PH, Hospices Civils de Lyon, Hôpital Lyon Sud /Université Lyon 1	Directeur de thèse
Kassai, Behrouz	PU-PH, Hospices Civils de Lyon, Hôpital Femme Mère Enfant / Université Lyon 1	Co-directeur de thèse

UNIVERSITE CLAUDE BERNARD - LYON 1

Président de l'Université	**M. le Professeur Frédéric FLEURY**
Président du Conseil Académique	M. le Professeur Hamda BEN HADID
Vice-président du Conseil d'Administration	M. le Professeur Didier REVEL
Vice-président du Conseil Formation et Vie Universitaire	M. le Professeur Philippe CHEVALIER
Vice-président de la Commission Recherche	M. Fabrice VALLÉE
Directeur Général des Services	M. Alain HELLEU

COMPOSANTES SANTE

Faculté de Médecine Lyon Est – Claude Bernard	Directeur : M. le Professeur J. ETIENNE
Faculté de Médecine et de Maïeutique Lyon Sud – Charles Mérieux	Directeur : Mme la Professeure C. BURILLON
Faculté d'Odontologie	Directeur : M. le Professeur D. BOURGEOIS
Institut des Sciences Pharmaceutiques et Biologiques	Directeur : Mme la Professeure C.
Institut des Sciences et Techniques de la Réadaptation	VINCIGUERRA
Département de formation et Centre de Recherche en Biologie Humaine	Directeur : M. le Professeur Y. MATILLON Directeur : Mme la Professeure A-M. SCHOTT

COMPOSANTES ET DEPARTEMENTS DE SCIENCES ET TECHNOLOGIE

Faculté des Sciences et Technologies	Directeur : M. F. DE MARCHI
Département Biologie	Directeur : M. le Professeur F. THEVENARD
Département Chimie Biochimie	Directeur : Mme C. FELIX
Département GEP	Directeur : M. Hassan HAMMOURI
Département Informatique	Directeur : M. le Professeur S. AKKOUCHE
Département Mathématiques	Directeur : M. le Professeur G. TOMANOV
Département Mécanique	Directeur : M. le Professeur H. BEN HADID
Département Physique	Directeur : M. le Professeur J-C PLENET
UFR Sciences et Techniques des Activités Physiques et Sportives	Directeur : M. Y.VANPOULLE
Observatoire des Sciences de l'Univers de Lyon	Directeur : M. B. GUIDERDONI
Polytech Lyon	Directeur : M. le Professeur E.PERRIN
Ecole Supérieure de Chimie Physique Electronique	Directeur : M. G. PIGNAULT
Institut Universitaire de Technologie de Lyon 1	Directeur : M. le Professeur C. VITON
Ecole Supérieure du Professorat et de l'Education	Directeur : M. le Professeur A. MOUGNIOTTE
Institut de Science Financière et d'Assurances	Directeur : M. N. LEBOISNE

Résumé

Efficacité et tolérance à long terme des agents biologiques dans les rhumatismes inflammatoires à début juvénile dans les essais cliniques randomisés et les études observationnelles

Les rhumatismes inflammatoires juvéniles sont des maladies auto-immunes chroniques débutant avant l'âge de 16 ans. Ils comprennent des pathologies classées dans un *continuum*, allant de la dérégulation de l'immunité innée à la dérégulation de l'immunité adaptative. L'arthrite juvénile idiopathique (AJI) reste la plus fréquemment diagnostiquée. Les options thérapeutiques se sont élargies depuis les années 2000, avec le développement des thérapies ciblées, les biothérapies, associées aux traitements standard utilisés en rhumatologie pédiatrique, incluant anti-inflammatoires non stéroïdiens, corticostéroïdes, méthotrexate, et autres immunosuppresseurs. L'objectif de ce travail de thèse était d'estimer la relation bénéfice-risque des biothérapies utilisées dans les rhumatismes inflammatoires juvéniles, à partir des essais contrôlés randomisés (ECR), et d'explorer la tolérance au long cours à partir d'essais observationnels.

Dans un premier temps, en utilisant une approche méta-analytique, les données des ECR en double aveugle contre placebo, ou en ouvert dans l'AJI, ont été analysées pour modéliser la relation bénéfice-risque des biothérapies avec le bénéfice net. Pour cela, l'efficacité clinique, mesurée par un score composite clinique et biologique (ACRpedi30), a été confrontée à la tolérance clinique pendant la phase randomisée des ECR. Le critère de tolérance était la survenue d'un évènement indésirable (EI) grave. Le modèle du bénéfice net présenté, est adapté pour utiliser les données résumées des ECR réalisés avec les biothérapies dans l'AJI. Nos résultats suggèrent qu'un plus grand nombre de patients ont connu un succès thérapeutique (sans EI grave) dans l'AJI à début systémique, comparativement aux autres catégories d'AJI.

Cependant, ces résultats sont limités par le suivi clinique de courte durée et par la sélection des patients, qui peut sous-estimer l'incidence des EI. Le risque de base de la population d'étude, le plan d'expérience de l'essai clinique, et les catégories de la maladie ont une incidence sur la mesure du bénéfice net des biothérapies chez les patients atteints d'AJI.

Dans un second temps, nous avons conduit une étude observationnelle pour étudier la tolérance à moyen et long-terme des biothérapies utilisant les EI et les EI graves décrits dans une base de données multicentrique rétrospective. La tolérance globale des biothérapies a été acceptable chez les enfants atteints de rhumatismes inflammatoires. Nous avons observé un effet des immunosuppresseurs sur la survenue des EI. Afin d'améliorer la précision de l'estimation de l'incidence des EI graves sous biothérapies, une méta-analyse des études observationnelles a été faite. Les résultats de ces méta-analyses suggèrent que le taux d'incidence des EI graves, associé à l'utilisation des biothérapies dans l'AJI, est faible. Bien que l'interprétation et la généralisation des résultats soient limitées par des biais potentiels, les données sur l'innocuité des biothérapies dans les AJI sont rassurantes. Les infections graves, le cancer et le décès ne représentent qu'une partie des EI graves. Le suivi à long terme des patients atteints d'AJI n'est pas encore optimal dans la plupart des cohortes incluses dans la méta-analyse. En fin, une série mono-centrique de patients avec AJI et double traitement simultané par biothérapie a été décrite.

Mots clés : arthrite juvénile idiopathique, biothérapie, essais contrôlés randomisés, études observationnels, tolérance, balance bénéfice-risque, méta-analyse

Abstract

Efficacy and safety of biological agents in juvenile inflammatory rheumatic diseases: from randomized clinical trials and observational studies

Juvenile inflammatory rheumatisms are chronic autoimmune diseases that begin before the age of 16. They include pathologies classified along a *continuum*, ranging from the deregulation of innate immunity to the deregulation of adaptive immunity. Juvenile idiopathic arthritis (JIA) remains the most frequently diagnosed disease. Therapeutic options have expanded since the 2000s with the development of targeted therapies, biological agents (BAs), combined with standard treatments used in paediatric rheumatology, including non-steroidal anti-inflammatory drugs, corticosteroids, methotrexate, and other immunosuppressive drugs. The objective of this thesis was to estimate the benefit-risk balance of BAs used in juvenile inflammatory rheumatic diseases from randomized clinical trials (RCTs) and to explore long-term tolerance from observational trials.

First, using a meta-analytical approach, the data from the double-blinded, placebo-controlled or open-RCTs in the JIA, were analysed to model the benefit-risk balance of BAs with net benefit. For this purpose, clinical efficacy, measured by a composite, clinical and biological, score (ACRped30), was compared with clinical safety during the randomised phase of RCTs. The safety criterion was the occurrence of a serious adverse event (SAE). The net benefit model presented is adapted to use data from RCTs conducted with BAs in JIA disease. Our results suggest that a greater number of patients have had therapeutic success (without a SAEs) in systemic-onset JIA, compared to other categories of JIA. However, these results are limited by poor follow-up and patient selection, which may underestimate the incidence of adverse events. The baseline risk of the study population, the clinical trial design and the disease categories, have an impact on the measurement of the net benefit of BAs in JIA patients.

Second, we conducted an observational study to investigate the long-term safety of BAs using the adverse events and SAEs described in a retrospective multicentre database. The overall safety of BAs has been acceptable in children with inflammatory rheumatic diseases. We observed an effect of immunosuppressive drugs on the occurrence of adverse events. In order to improve the accuracy of estimations of the incidence of SAEs under BA treatment, a meta-analysis of observational studies was conducted. The results of these meta-analyses suggest that the incidence rate of SAEs associated with the prescription of BAs in JIA is low. Although the interpretation and generalization of the results are limited by potential biases, the safety data on BAs in JIAs are reassuring. Serious infections, malignancies and death explain only part of the SAEs. Long-term follow-up of JIA patients is not yet optimal in most of the cohorts included in the meta-analysis. Finally, a single center series of patients with JIA disease and double simultaneous BAs treatment has been described.

Keywords: juvenile idiopathic arthritis, biological agents, randomised controlled trials, observational studies, safety, benefit-risk balance, meta-analysis

Laboratoire

UMR CNRS 5558 - Laboratoire de Biométrie et Biologie Évolutive

Service de Pharmacologie Clinique

Bâtiment B, site Laennec- La Buire – Faculté de Médecine Lyon Est

7 Rue Guillaume Paradin 69008 Lyon

Table des matières

Publications et travaux liés à la thèse

Publications en premier auteur :

1. **Safety of biological agents in paediatric rheumatic diseases: A real-life multicenter retrospective study using the JIRcohorte database.**
   Cabrera N, Lega JC, Kassai B, Wouters C, Kondi A, Cannizzaro E, Woerner A, Chausset A, Roethlisberger S, Jeanneret C, Aeschlimann F, Malik S, Duquesne A, Kaiser D, Higel L, Maes A, Berthet G, Hentgen V, Kone-Paut I, Belot A, Hofer M.
   Joint Bone Spine. 2019 May;86(3):343-350.
   doi: 10.1016/j.jbspin.2018.08.003.

2. **The benefit-risk balance for biological agents in juvenile idiopathic arthritis, a meta-analysis of randomized clinical trials.**
   Cabrera N, Avila-Pedretti G, Belot A, Larbre JP, Duquesne A, Kassai B, Lega JC.
   Submitted article, Rheumatology Oxford.

3. **Safety of biological DMARDs in juvenile idiopathic arthritis, a meta-analysis of observational studies.**
   Cabrera N, Avila-Pedretti G, Belot A, Larbre JP, Cattivelli G, Paredes E, Kassai B, Euvrard R, Grenet G, Berard A, Mainbourg S, Lega JC.
   Manuscript in preparation, for submission

Communications orales.

1. **Monogenic childhood-onset systemic lupus erythematosus not related to complement deficiency: A systematic review of 90 cases.**
   P. Nakhleh, **N. Cabrera**, M. Roderick, J-C. Lega, A. Belot.
   Annual European Congress of Rheumatology, 12–15 June 2019.

Communications affichées.

1. **Evaluation of the diagnostic delay and access to remission in JIA patients of the JIR cohort.**
   Freychet C, **Cabrera N**, Lega JC, Hofer M, Belot A and JIRcohorte.
   Pediatr Rheumatol Online J. 2017; 15(Suppl 2): 64.
   doi: 10.1186/s12969-017-0185-x

2. **THU0599 Benefit risk ratio for biological agents in juvenile idiopathic arthritis, a meta-analysis of randomized clinical trials**
   N. Cabrera[1], P. Janiaud[1], A. Belot[2], B. Kassai[1,3], J.-C. Lega
   Annual European Congress of Rheumatology, 14–17 June 2017
   Ann Rheum Dis. June 2017 - Volume 76 - Suppl 2

Autres publications et travaux réalisés au cours de la thèse

1. **Anti-C1q autoantibodies as markers of renal involvement in childhood-onset systemic lupus erythematosus.**
   Picard C, Lega JC, Ranchin B, Cochat P, **Cabrera N**, Fabien N, Belot A.
   Pediatr Nephrol. 2017 Sep;32(9):1537-1545.
   doi: 10.1007/s00467-017-3646-z

2. **Treatment with simultaneous biological agents in juvenile idiopathic arthritis: single-center case series and review of literature.**
   N. Cabrera, P. Nakhleh, M. Desjonquères, J-P. Larbre, J-C. Lega, A. Belot
   Annals of the Rheumatic Diseases 2019; 78: 1940
   http://dx.doi.org/10.1136/annrheumdis-2019-eular.5712

3. **Infectious adverse events in children with Juvenile Idiopathic Arthritis treated with Biological Agents in a real-life setting: data from the JIRcohorte**
   C. Dumaine, S. Bekkar, A. Belot, **N. Cabrera**, S. Malik, A. von Scheven, A. Carbasse, A. Woerner, C. Wouters, K. Bouayed, P. Pillet, S. Schroeder, M. Hofer, V. Hentgen
   Joint Bone Spine. Available online 29 July 2019
   https://doi.org/10.1016/j.jbspin.2019.07.011

Abréviations

AJI : arthrite juvénile idiopathique

AMM : autorisation de mise sur le marché

DMARDs : disease-modifying antirheumatic drugs

ECRs : essais randomisés contrôles

EI : événement indésira leévénementévènement indésirable graves

ICH : *International Council for Harmonisation of Technical Requeriments for Pharmaceutical for Human Use*

LES : lupus érythémateux systémique

MedDRA *: Medical dictionary for regulatory*

MTX : méthotrexate

OMERACT : *Outcome Measure in Rheumatology*

PRCSG : *Pediatric Rheumatology Collaborative Study Group*

PRINTO : *Paediatric Rheumatology International Trials Organisation*

1. Introduction : Problématique et objectifs de la thèse

Les agents biologiques (ou biothérapies ou biomédicaments) ont révolutionné la prise en charge des patients avec de rhumatismes inflammatoires chroniques à début juvénile, notamment dans les arthrites juvéniles idiopathiques (AJI) (1,2) et quelques maladies auto-inflammatoires (3,4), en prévenant les séquelles à long terme, et en améliorant la qualité de vie. D'autres maladies pédiatriques, comme le lupus érythémateux systémique, ont encore des besoins de recherche spécifiques (5).

En rhumatologie pédiatrique, les efforts ont été particulièrement évidents dans le contexte des essais thérapeutiques. Les travaux de recherche clinique en réseaux, initialement développes par le groupe américain *Pediatric Rheumatology Collaborative Study Group* (PRCSG) et par la suite par le réseau international *Paediatric Rheumatology International Trials Organisation* (PRINTO), en lien avec les changements réglementaires des différentes agences de médicaments d'Europe, du Japon, du Canada et des États-Unis (6,7), ont aboutis à l'harmonisation de la méthodologie des essais intéressants les biothérapies. Cela a permis que ces réseaux de recherche aient des pratiques harmonisées pour la conception et la conduite d'essai contrôlé randomisé multicentrique (ECR), dans la population pédiatrique d'intérêt. Ainsi, un ECR est désormais suffisant pour l'enregistrement d'une molécule thérapeutique, contre plusieurs essais antérieurement (2,8). Dans la recherche clinique, l'ECR à double insu est le *gold standard*, qui sert à étudier l'efficacité des nouvelles thérapeutiques (9).

Avec les changements réglementaires pour le développement des médicaments en pédiatrie, les ECR ont augmenté en rhumatologie pédiatrique, notamment dans l'AJI, avec l'autorisation de mise sur le marché (AMM) des biothérapies. Entre les années 2000 et 2018, au moins 20 ECR ont été conduit dans l'AJI. Ces ECR comprenant les 9 biothérapies suivantes : etanercept (10–12), adalimumab (13–15), infliximab (16,17), golimumab (18), anakinra

(19,20), canakinumab (21), rilonacept (22,23), tocilizumab (24,25), et abatacept (26). Parmi ces ECR, deux types de plans d'expérience sont utilisés : essais en bras parallèles et essais de retrait. L'essai « en bras parallèles » correspond au design traditionnel en 2 bras synchronisés par la randomisation comparant le traitement étudié au contrôle (placebo ou traitement standard chez les patients avec AJI). Les essais « de retrait » randomisent les patients qui ont obtenu une réponse clinique initiale pendant une période ouverte où tous les patients reçoivent le traitement actif. Par la suite, les patients répondeurs sont randomisés pour poursuivre soit le traitement actif soit le placebo. Les essais de retrait s'adressent donc à une population différente de celle de l'essai en bras parallèles (27). Bien que des outils de mesure de l'activité clinique continuent à évoluer dans les maladies rhumatologiques pédiatriques (28), l'efficacité des biothérapies est établie pour certaines maladies, dont les maladies auto-inflammatoires (3) et l'AJI, particulièrement pour sa forme poly-articulaire et systémique (2).

Par ailleurs, les besoins de pharmacovigilance et de suivi à long terme des ces patients ont favorisé la création de registres, et de cohortes de suivi. Dans certains centres, des études de cohortes de suivi de patients traités par biothérapies ont été initiées simultanément avec l'AMM de ces nouveaux médicament (29–31). Ces données observationnelles sont intéressantes car elles reflètent plus précisément les complications observées dans la pratique clinique, notamment celles liées à la prescription hors AMM, à l'administration des traitements concomitants, et aux pratiques d'utilisation des médicaments (mésusage). De plus, les études d'observation comprennent un plus grand nombre de patients dont la durée du suivi est plus longue que celle des ECR. Les études observationnelles sont donc plus sensibles pour détecter l'apparition d'événements rares, comme les effets indésirables (EI) graves, dans la pratique clinique quotidienne (9). Du fait de leurs caractère suspensifs, les biothérapies sont habituellement administrées au long cours. Dans le but d'atteindre un meilleur contrôle de

l'activité clinique, voire la rémission des maladies inflammatoires juvéniles, les stratégies thérapeutiques associent d'autres traitements immunosuppresseurs aux biothérapies (32,33).

Définir les bénéfices et les risques connus des médicaments est important, dans le cadre de leur développement, ainsi que dans leur prescription lors de la pratique clinique. En rhumatologie, l'initiative *Outcome Measures in Rheumatology* (OMERACT) a défini le besoin d'un outil mesurant simultanément les bénéfices et les risques pour un patient donné, suffisamment simple pour que le patient puisse le comprendre (et/ou que le clinicien puisse l'expliquer) (34). Le défi actuel en rhumatologie pédiatrique est de quantifier les profils de sécurité de ces médicaments, particulièrement dans les populations à risque, que représentent les patients avec exposition médicamenteuse multiples ou successives, ceux présentant des immuno-déficits associés, ou encore ceux se trouvant en période de transition enfant-adulte. Considérant la supériorité des ECR pour l'étude de l'efficacité des médicaments (comprenant moins de biais avec validité interne élevé, entre autres) ainsi que les avantages des études observationnelles de cohortes, pour le suivi à long terme et la pharmacovigilance, toutes les informations disponibles sont utiles pour étudier la balance bénéfice-risque des biothérapies en rhumatologie pédiatrique (9).

1.1: Étude de la tolérance des biothérapies en rhumatologie pédiatrique

Le profil de tolérance varie pour chaque biothérapie, compte tenu de ses différences pharmacologiques (35). Il n'existe pas, à ce jour, d'essais cliniques comparant leur tolérance de façon directe ('*head-to-head trials*') mais, des principes généraux sont valables pour les biothérapies utilisées en rhumatologie pédiatrique. Toutes les biothérapies peuvent induire la formation d'anticorps anti-biomédicaments (neutralisant ou non-neutralisant), et l'association des immunosuppresseurs, comme le MTX, est parfois nécessaire afin de réduire le risque de

perte de l'effet thérapeutique (36). Parce qu'elles ciblent les protéines de la réponse inflammatoire, toutes les biothérapies augmentent potentiellement, le risque infectieux (37).

Afin de faciliter le partage d'information concernant la surveillance des produits médicaux, le Conseil internationale d'harmonisation des exigences techniques relatives aux produits pharmaceutiques à usage humain (ICH, en anglais) a développé le dictionnaire « MedDRA » pour *Medical dictionary for regulatory activities*. Le codage des EI, dans les ECR, se fait grâce à la standardisation de la terminologie médicale. À la fin d'un essai, les données de tolérance sont catégorisées et résumées, ainsi, les événements indésirables (EI) sont regroupés en 5 grandes catégories, selon les niveaux de hiérarchisation du système MedDRA. Chaque niveau présente un degré de détail variable selon la discipline médicale.

Bien que la tolérance à court terme soit évaluée dans les ECR avec une codification standardisée, la notification des évènements indésirables dans les essais cliniques, n'est pas optimale. Le codage des EI graves est également normalisé par le même dictionnaire MedDRA, et se fait systématiquement pendant les ECR. Les EI graves ont deux évaluations indépendantes l'une par l'investigateur, l'autre par le promoteur de l'étude. Cependant, la gravité d'un EI, survenu sous le traitement en étude, n'a pas une pondération, par la quantité et/ou la fréquence de présentation de l'évènement (38,39). Considérant les limitations des ECR pour l'évaluation de l'innocuité des biothérapies à long terme, la tolérance est mieux explorée par les études observationnelles, comme les registres et les cohortes de suivi de patients. En rhumatologie pédiatrique, ces types d'études, offrent l'avantage d'avoir une population représentative des patients exposés aux biomédicaments dans la pratique clinique quotidienne (données de vie-réelle).

1.2: Objectif de la thèse

Les objectives généraux de la thèse

L'objectif de cette thèse est d'estimer le bénéfice et le risque des biothérapies dans les maladies rhumatismales pédiatriques.

Considérant que toutes les maladies inflammatoires à début juvénile et nécessitant un traitement par biothérapie, sont des maladies rares, nous avons d'abord proposé, l'étude de l'efficacité et la sécurité des biothérapies dans l'AJI, car elle représente l'affectation la plus documentée. Par la suite, nous nous sommes intéressés à explorer les effets indésirables à long-terme et les risques associés à la survenue des EI graves sous traitement par biothérapie. Nous nous sommes penchées notamment sur l'incidence des EI graves, comme les infections graves, les cancers et les décès.

Étapes du travail de thèse

Ce travail de thèse s'appuie sur l'exploration de deux types d'études en pharmacologie, les ECR et les études observationnelles.

Premièrement, afin de connaître la balance bénéfice-risque des biothérapies, nous avons modélisé leur bénéfice net, en utilisant les données de la phase randomisée des ECR réalisées dans l'AJI. Dans une étape préliminaire, nous avons résumé, par un approche méta-analytique, l'effet thérapeutique d'efficacité et de sécurité clinique des biothérapies, par l'estimation du risque relatif. Ensuite, nous avons calculé le risque absolu sous traitement à partir du risque de base de la population (patients du groupe contrôle des ECR). Le bénéfice net est ainsi estimé en soustrayant le risque absolu de présenter un EI grave à la possibilité d'obtenir une réponse clinique.

Deuxièmement, afin d'étudier la tolérance à long terme des traitements par biothérapie, nous avons exploité les données issues des études observationnelles. Nous avons tout d'abord décrit une base de données rétrospective multicentrique de patients présentant des maladies rhumatismales inflammatoires à début juvénile. Cette base nous a servi dans un premier temps à connaitre la prescription de biothérapies en vie-réelle dans de centres francophones spécialisés en rhumatologie pédiatrique. Dans un second temps, elle nous a aidé à estimer l'incidence des EI et EI graves et à analyser les possibles facteurs de risques associés à la survenu de ces évènements.

Afin d'étudier la variabilité de l'estimation des EI graves, l'ensemble des données de la littérature a été utilisé. Nous avons conduit une méta-analyse s'intéressant spécifiquement au taux d'incidence des EI graves, plus précisément les infections graves, le cancer et le décès, chez les patients avec AJI traités par biothérapies. Pour connaître le profil de sécurité des biothérapies dans une population à risque, la description d'une série de cas monocentrique de patients résistants à toutes les lignes thérapeutiques disponibles, et nécessitant le recours à une double biothérapie simultanée, a été conduite.

2 : Méta-analyse des études randomisées

Rapport bénéfice-risque des biothérapies dans l'arthrite juvénile idiopathique à partir des essais contrôles randomisés.

Article soumis

OXFORD UNIVERSITY PRESS | Rheumatology

The benefit-risk balance for biological agents in juvenile idiopathic arthritis, a meta-analysis of randomised clinical trials

Journal:	*Rheumatology*
Manuscript ID	RHE-19-1502.R1
Manuscript Type:	Review Article
Date Submitted by the Author:	01-Dec-2019
Complete List of Authors:	Cabrera, Natalia; University Claude Bernard Lyon 1, UMR - CNRS 5558, Laboratoire de Biométrie et Biologie Évolutive Avila-Pedretti, Gabriela; Universidad Nacional de Asuncion Facultad de Ciencias Medicas, Department of Research Belot, Alexandre; CHU Lyon, National Referral Centre for rare Juvenile Rheumatological and Autoimmune Diseases (RAISE) Larbre, Jean-Paul; CHU Lyon, Department of Rheumatology - Lyon Sud Mainbourg, Sabine; University Claude Bernard Lyon 1, UMR - CNRS 5558, Laboratoire de Biométrie et Biologie Évolutive Duquesne, Agnès; CHU Lyon, Department of Paediatric Rheumatology Janiaud, Perrine; University Claude Bernard Lyon 1, UMR - CNRS 5558, Laboratoire de Biométrie et Biologie Évolutive Kassai, Behrouz; University Claude Bernard Lyon 1, UMR - CNRS 5558, Laboratoire de Biométrie et Biologie Évolutive; CHU Lyon, Clinical Investigation Centre 1407, INSERM, Hospices Civils de Lyon Cucherat, Michel; University Claude Bernard Lyon 1, UMR - CNRS 5558, Laboratoire de Biométrie et Biologie Évolutive Lega, Jean-Christophe; CHU Lyon, Department of Internal and Vascular Medicine; University Claude Bernard Lyon 1, UMR - CNRS 5558, Laboratoire de Biométrie et Biologie Évolutive
Keywords Please select a minimum FIVE keywords from the list provided. These keywords will be used to select reviewers for this manuscript. The keywords in the main text of your paper do not need to match these words.:	Juvenile idiopathic arthritis < RHEUMATIC DISEASES, Metaanalysis < BASIC & CLINICAL SCIENCES, Systematic review < MISCELLANEOUS, Pharmacology < BASIC & CLINICAL SCIENCES, Biological therapies < THERAPIES

The benefit-risk balance for biological agents in juvenile idiopathic arthritis, a meta-analysis of randomised clinical trials

Natalia Cabrera[1], Gabriela Avila-Pedretti[2], Alexandre Belot[3], Jean-Paul Larbre[4], Sabine Mainbourg[1,6], Agnès Duquesne[3], Perrine Janiaud[1], Behrouz Kassai[1,5], Michel Cucherat[1], Jean-Christophe Lega[1,6]

[1]University of Lyon, UMR - CNRS 5558, *Laboratoire de Biométrie et Biologie Évolutive*, Claude Bernard University Lyon 1, F-69100, France.

[2] Department of Research, Universidad Nacional de Asuncion, San Lorenzo 2160, Paraguay.

[3] INSERM U1111, National Referral Centre for rare Juvenile Rheumatological and Autoimmune Diseases (RAISE) and Department of Paediatric Rheumatology, Lyon University Hospital, University of Lyon.

[4] Department of Rheumatology, *Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite*, France

[5] Department of Pharmaco-toxicology, Clinical Investigation Centre 1407, INSERM, Hospices Civils de Lyon, 69003 Lyon, France.

[6] National Referral Centre for rare Juvenile Rheumatological and Autoimmune Diseases (RAISE), Department of Internal and Vascular Medicine, *Centre Hospitalier Lyon Sud, Hospices Civils de Lyon*, *Pierre-Bénite*, France

PROSPERO register number: CRD42018107592.

Corresponding author: Natalia Cabrera, MD

University of Lyon, UMR - CNRS 5558, *Laboratoire de Biométrie et Biologie Évolutive*,

Lyon 1 University, F-69100 – France.

9 Rue Guillaume Paradin, 69008, Lyon – France

e-mail: cabrera.rojas.reumatoped@gmail.com

ABSTRACT

Objective: To assess the net benefit of biological agents (BA) used in juvenile idiopathic arthritis (JIA).

Methods: We systematically searched, up to March 2019, databases for randomised controlled trials (RCT) performed in JIA disease. Separate random-effects meta-analyses were conducted for efficacy (ACRpedi30) and serious adverse events (SAEs) for safety. The net benefit was determined as the risk difference (RD) of efficacy subtracted by the RD of safety.

Results: We included 19 trials: 11 parallel RCTs (754 patients) and 8 withdrawal RCTs (704 patients). The net benefit ranged from 2.4% (adalimumab) to 17.6% (etanercept), and from 2.4% (etanercept) to 36.7%, (abatacept) in parallel and withdrawal trials assessing non-systemic JIA, respectively. In systemic JIA category, the net benefit ranged from 22.8% (rilonacept) to 70.3% (canakinumab), and from 32.3% (canakinumab) to 58.2% (tocilizumab) in parallel and withdrawal trials, respectively. The subgroup analysis of parallel RCTs showed a higher efficacy of BAs in systemic onset JIA (OR=11.50, 95%CI [3.37; 39.21]) than non-systemic JIA (2.19, 95%CI [1.35; 3.56]) (test for subgroup differences p= 0.02). A trend in association between SAE risk and trial design was suggested between parallel (OR= 2.00, 95%CI 0.94; 4.26) and withdrawal (OR= 1.01, 95%CI 0.45; 2.24) trials (test for subgroup differences p= 0.05).

Conclusion: The results suggest that greater number of patients experienced therapeutic success without SAE in the systemic onset JIA category compared to the BAs for non-systemic JIA categories. Baseline risk, design of trial and JIA categories impact the measure of net benefit of BAs in JIA patients.

Keywords: juvenile idiopathic arthritis, benefit/risk balance, absolute net benefit, biological agents, meta-analysis.

Key message:

1. The net benefit of biological agents (BAs) for juvenile idiopathic arthritis (JIA) is favourable, although varied widely according to trial design and JIA categories.

2. Benefit related to efficacy of BAs is higher in systemic onset JIA.

3. Safety of BAs is higher in withdrawal trials than in parallel trials.

INTRODUCTION

Efficacy (benefit) and safety (risk) of therapeutic interventions are analysed separately in most trials and meta-analyses. Many methods have been proposed to promote simultaneous benefit-risk analysis (1). In the field of rheumatology, the Outcome Measures in Rheumatology Conference (OMERACT) group has identified the need of a simple tool that incorporates both benefits and risks in one scale and proposing a table with three rows for different risk severities and three columns for different benefit levels (2). This method uses patient-level data from randomised controlled trials (RCTs).

The JIA American College of Rheumatology response (ACRpedi) is the first clinical tool used to asses an improvement or flare in JIA patients enrolled in clinical trials (3). It is a composite score with six core response variables. The ACRpedi30 response corresponds to a >30% improvement in at least three of the six JIA ACR core response variables without ≥30% worsening in more than one of the remaining JIA ACR core response variables compared with baseline. The ACRpedi30 is accepted by both the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA). Therefore, most RCTs of BAs for JIA use this instrument as an efficacy outcome (4). RCTs are typically designed to measure the efficacy of an intervention whereas measuring its safety (5).

Safety events are usually codified in a standardised way using the Medical Dictionary for Regulatory Activities (MedDRA). At the end of a trial, data are categorised and summarised, and adverse events (AEs) are grouped into 5 broad categories (6). In addition, serious AEs (SAEs) are often assessed independently for causality by the investigator and the sponsor although it may impact the decision to continue, modify or end the trial (7). However, MedDRA does not provide severity descriptors of frequency qualifiers. Considering this quantitative issue, it is justified to initiate a process of quantification of AEs and to assess its impact by modelling the balance of benefit and risk using data from RCTs. Using systematic

review and meta-analyses methods, we aim to assess the benefit/risk balance through the net benefit of biological agents (BAs) versus placebo or standard treatment in JIA disease.

METHODS

Data sources and searches

The protocol of the review was registered on September 5th, 2018 on the International Prospective Register of Ongoing Systematic Review (PROSPERO) database under the register number: CRD42018107592, available at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=107592.

We searched MEDLINE via PubMed, the Cochrane Central Register of Controlled Trials, and ClinicalTrial.gov register up to March 12th, 2019. We restricted our search to reports in English. Conference abstracts and secondary analyses of RCTs were excluded. We also contacted relevant pharmaceutical companies to identify unpublished trial data. The search strategy included keywords related to RCTs, JIA, and BAs as presented in Table 1A and 2A in the 'Additional tables and figures' section. The method used is consistent with the recommendations of the Cochrane Handbook for Systematic Reviews of Intervention (8) and reports according the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA)(9).

Study selection

We included single or double-blinded RCTs of BAs on JIAs fulfilling the established diagnosis criteria by the following international organisations: the American College of Rheumatology Criteria (ACR) since 1997 and the International League of Associations for Rheumatology/European League Against Rheumatism Criteria (ILAR/EULAR) since 2001 (10). Thus, were included: paediatric population, both sexes, aged < 19 years old and diagnosed with JIA disease. All JIA subgroups were eligible.

RCTs comparing BAs alone or in combination with conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) or corticosteroids versus placebo or standard treatments were eligible for inclusion. Participants could take other DMARDs, nonsteroidal anti-inflammatory drugs or corticosteroids with stable doses and were then randomly allocated to treatment with or without BAs. The BAs of interest were: etanercept, adalimumab, infliximab, anakinra, canakinumab, rilonacept (not authorized in European Union), rituximab, and abatacept. There were no restrictions regarding dosage or duration of the intervention.

Inclusion criteria were defined *a priori*, and two outcomes of interests were: (i) the JIA ACR response criteria (ACRpedi30) for efficacy and (ii) SAE for safety. The efficacy outcome depends on the trial design. For parallel RCTs, the ACRpedi30 was considered according to what was explained in the Introduction section and, in withdrawal RCTs, JIA relapse is defined as 30% or greater worsening in three of the six JIA core response variables without more than 30% improvement in more than one remaining JIA core response variables.

We have excluded studies when safety and efficacy analyses reported zero events simultaneously in both arms.

Data extraction and quality assessment

We extracted study characteristics design, inclusion and exclusion criteria, patient characteristics, drug characteristics, and number of events of the two co-primary safety and efficacy outcomes. The quality was assess using the Risk of Bias Tool from The Cochrane Collaboration (11). Two reviewers (NC and GAP) independently extracted data for all eligible articles and assessed if the internal validity of studies was adequate. Any disagreements were resolved by consensus.

Data synthesis and analysis

First, we conducted separate meta-analyses for efficacy and safety outcomes. The efficacy (response or relapse ACRpedi30, according trial design) and the safety outcomes (SAEs) were

chosen based on the confidence and comparability of those measures in RCTs. Summary odds ratio (OR) for efficacy and safety outcomes were calculated using a random-effects model. For the latter, we used Peto's methods to pool ORs which is adequate for very rare events as SAE and which does not require corrections for zero cell count (12). Secondly, we converted the ORs and Peto's OR of the meta-analysis in RR in order to project them on the characteristic baseline risks of sub-population (control group). In order to standardize the baseline risk, we performed a meta-analysis in the control group. The pooled results of efficacy and safety responses were used to obtain the risk difference (RD). Thirdly, the RD for efficacy and RD for safety for each BA was calculated. The overall benefits and risk balance, as criterion of the net benefit, were calculated using the difference between the RD of efficacy and RD of safety (i.e. RD efficacy - RD safety), when appropriate. The net benefit shows in absolutes values the number of patients who experience therapeutic success without SAEs.

The random-effect method was chosen because JIA is a disease with different subtypes that can introduce heterogeneity into the results, in addition the random effects method and the fixed effects method will give identical results when there is no heterogeneity between studies. The index I_2 was estimated to assess the heterogeneity and inconsistency of our meta-analyses. High heterogeneity is usually characterized by an I^2 of 50% or more suggesting the presence of substantial statistical heterogeneity (13). Efficacy meta-analyses were conducted in subgroup analysis depending on the trial design (parallel versus withdrawal RCTs) because withdrawal RCTs select only responding ACRpedi30 patients treated in an open fashion who are then randomised in a double-blind fashion to continue the active treatment or receive placebo, and according JIA disease (SoJIA versus non-systemic JIA). Safety meta-analyses were only separated according to the trial design. Subgroup analysis were also conducted according to the BA type for efficacy and safety meta-analysis. In presence of heterogeneity, a meta-regression and subgroup analysis were conducted to investigate if studies' characteristics

were associated with the treatment benefit. The parameters included in meta-regression were year of publication, trial design, age of patients, JIA categories, duration of randomised phase, total of patients in randomised phase, immunosuppressive drug in the control group during the randomised phase, previous BA treatment during the randomised phase of trial. The risk of publication bias was determined by visual aspect of funnel plot and the Egger test (14). All analyses were performed using R Software and its 'metafor' package (https://cran.r-project.org/web/packages/metafor/metafor.pdf).

RESULTS

Study selection

A total of 184 citations were retrieved in the initial search through the different databases. Seventy records were excluded on titles and abstracts and 113 studies were assessed for eligibility. During the qualitative synthesis, five additional studies were excluded (15–19) (see Figure 1).

Characteristics of included studies

We included 18 articles covering 19 trials (involving 1458 patients) conducted on JIA disease. Their characteristics are described in Table 1. Trials were mainly conducted in the OA and PA JIA categories with 2 trials including patients with early PA JIA (20,21). None of the trials included the undifferentiated JIA category. Among the BAs, trials evaluating anti-IL1s (anakinra, canakinumab and rilonacept) were conducted exclusively for the SoJIA category, while this category was mostly excluded of trials evaluating anti-TNFs (etanercept, adalimumab and infliximab).

When concomitant medications were used such as NSAIDs and/or conventional DMARDs, doses were stable and distributed in both arms. Twelve trials (63%) used methotrexate as comparator in the control group, two of which (11%) were performed in early forms of PA JIA

(20,21). Eleven parallel RCTs (58%) were identified, but 10 were included for efficacy estimates (22–31), as one of them did not report the ACRpedi30 score (21). However, this one trial was included to explore the safety. All eight withdrawal RCTs (42%) assessed the efficacy outcome of interest (30,32–38). Two trials (11%) were excluded for the safety analysis (28,34) due to zero events in both arms.

Ninety-five percent (18/19) of the trials were double blinded (20). A high risk of selective reporting bias was found in four trials (26,29,31,34) (see Figure 2 and 3). The visual inspection of funnel plots exploring publication bias was slightly asymmetrical for both efficacy in parallel trials (ACRpedi30) (see Figure 4). The Egger test were not in favour of publication bias in efficacy meta-analysis from parallel RCTs (p= 0.41). We were not able to assess the publication bias for the efficacy outcomes in withdrawal RCTs because of the low number of studies and for safety outcomes because Fisher scoring algorithm did not converge.

Assessment of efficacy of BAs by meta-analysis

In parallel RCTs, the ACRpedi30 response was significantly improved for non-systemic JIA categories (OA or PA JIA, ERA and psoriasis arthritis) (OR= 2.19, 95%CI [1.35; 3.56]) in the BAs group compared to standard treatments, as for the SoJIA category (OR= 11.50, 95% CI [3.37; 39.21]) compared to placebo. In withdrawal RCTs, significantly fewer relapses (ACRpedi30 worsening response) occurred for non-systemic JIA categories in the BAs group compared to standard treatment (OR= 0.27, 95% CI [0.19; 0.39]) and for SoJIA (OR= 0.13, 95% CI [0.03; 0.63]) compared to placebo (Table 2 and Figure A1). Heterogeneity was substantial and statistically significant (I^2= 74%, Tau^2= 1.37) for SoJIA category from parallel RCTs. Conversely, we did not detect any significant heterogeneity for the other groups.

In meta-regression analysis, the SoJIA category seems to be associated with better efficacy outcome (coefficient 0.46, R^2 = 60.2%, Tau^2= 0.025), as well as the number of patients with

previous BAs in control (coefficient 0.021, R^2 = 71.9%, Tau^2= 0.022) and intervention group (coefficient 0.013, R^2= 100%, Tau^2= 0.0) both, for parallel and withdrawal RCTs. The other tested parameters (year of publication, trial design type, duration of randomized phase, study size, concomitant immunosuppressive treatment and age of patients) were not associated with different treatment effects. These results are shown in Table A3.

We included, as additional analysis, efficacy meta-analysis with ACRpedi50 and ACRpedi70 only with parallel RCTs. Doing this with withdrawal RCTs was not possible because the studies' outcomes do not allow this. Therefore, it was made only with the studies previously mentioned and when compared, the difference was not large (Appendix section, Table A4).

Safety of BAs

There were significantly more SAEs in the BAs group compared to the control group for parallel RCTs (OR= 2.00, 95%CI [0.94; 4.26]). In withdrawal RCTs, the pooled OR was inconclusive (OR = 1.01, 95%CI [0.45; 2.24]). Except anakinra and abatacept, all BAs had at least one SAE during the randomised period of follow-up (Figure A2).

Net benefit estimate

There are large variations in RDs between the different BAs, for efficacy and safety outcomes. The baseline risk of efficacy outcomes (ACRpedi30 or relapses without BA according to trial design) also varied widely. The net benefit was different according to subgroups delimited by JIA categories and trial design.

In general, BAs seemed to show higher efficacy in systemic onset JIA in withdrawal (range 32.3% to 58.2) and parallel (range 22.8% to 70.3%) RCTs compared to non-systemic JIA in withdrawal (2.4% to 36.7%) and parallel (range 2.4% to 17.6%) RCTs (Table 2). However, because of the large confidence interval of estimates, comparisons could not be established.

The two trials assessing anakinra had zero SAE during the randomised period of interest and the net benefit could not be calculated (28,34). The results of the net benefit analysis are summarised in Table 2.

DISCUSION

We included 19 RCTs involving 1458 patients assessing the efficacy and safety of all BAs approved for treating JIA. To our knowledge, this is the first meta-analysis that simultaneously evaluates the benefits and risks of BAs in one scale in patients with JIA disease. Our results suggest a net benefit in favour of BAs in the short-term follow-up assessed RCTs.

There was consistent evidence of efficacy effects for all approved BAs, to prevent relapses in withdrawal RCTs (not worsening ACRpedi score than 30%) and achieve a clinical improvement (ACRpedi30 response) in parallel RCTs. However, the great variability in the estimates of net profit prevents formal comparisons despite having standardized with the control group, the baseline risk of the population.

Differences of treatment effects reported in meta-analysis of safety outcomes were founded, suggesting the influence of trial design in the estimate of treatment effect of JIA in BAs. Pooled estimate of SAEs in withdrawal RCTs were inconclusive. Although the net benefit model for this study uses already published trial data, results suggest that there are differences because of BAs and in between BAs depending on the trial design and categories of JIA. The OMERACT group proposes to use individual patients data but they also used RCTs and the same clinical criteria of efficacy (ACR score) and safety (SAEs) as us (39). Both outcomes are rigorous enough and clinically relevant to be considered for modelling a net benefit assessment.

Parallel and withdrawal RCTs have different objectives. While parallel RCTs asses the efficacy of BAs to achieve clinical remission, withdrawal RCTs evaluate maintenance of remission and inactive disease only in a specific sub-population (i.e. the ACRpedi30 responders) (40). On

that basis, we have decided to analyse these two groups of trials separately. We have grouped the non-systemic JIA categories as a different group from to the SoJIA, then we analysed the efficacy of each BA. For SAE, we have decided to focus on trial design, assuming that the effect-size of safety is in function of each BA and not remarkably related to the underlying disease.

In the meta-analyses for efficacy and safety outcomes, we noted that the effect sizes of clinical responses seem to vary according to the category of JIA in subgroup analyses of BAs. In parallel RCTs, systemic JIA category showed larger effect size to achieve efficacy compared to polyarticular categories of JIA. A possible explanation, supported by the meta-regression results, may be that the efficacy of BAs seems higher in more symptomatic disease, such as systemic JIA category, in comparison with polyarticular JIA. Although direct comparisons between effect size according to JIA categories were not performed, previous meta-analyses have suggested, by indirect comparisons, that the effect size of some BAs could be comparable in SoJIA category or polyarticular JIA categories. Effect size of tocilizumab did not differ from an anti-TNF (adalimumab) in PA JIA (41) and from two anti-IL1s (anakinra and canakinumab) in SoJIA categories (42). In addition, abatacept, anakinra, and tocilizumab not shown significant differences in effect size in order to prevent flare in polyarticular categories of JIA (43). The found effect size variation could be attributed to many factors such as co-prescription drugs, categories of JIA disease, and length of follow-up. The subsequent large variation founded in the absolutes risk, assessed by the RD in efficacy and RD in safety outcomes, justifies the modelling of the net benefit. On the other hand, the ‘number of patients’ previously treated by BAs could explain, at least in part, the heterogeneity found, as suggested by the meta-regression, being significant in both arms (control and intervention).

Differences in baseline risks were found, mainly in systemic JIA from withdrawal and parallel trials. In addition, fewer SAEs with two BAs (adalimumab and abatacept in non-systemic JIA

categories from withdrawal RCTs). This discrepancy could be attributed to the differences in the previous time of exposure to such BAs in withdrawal RCTs and to the fact that some SAEs occur early in the first months of treatment (44). For patients who presented an SAE during the first open phase of withdrawal RCTs, we hypothesised that they have not been included in the randomised phase, and thus their safety data were not analysed (5,45).

In the net benefit model presented here, we assume that an ACRpedi30 has the same weight as an SAE. We decided to use the ACRpedi30 score because most RCTs evaluate it as primary outcome. We used the SAEs for the reason that the causality is methodically verified and are the main way of monitoring safety in RCTs (7). However, trials are not sufficient to fully determine the potential harmful effects of BAs. Although, the accurate coding of the events using MedDRA and the safety evaluation by the sponsor can be difficult, the quality of SAEs reporting in terms of completeness and accuracy are of paramount importance (7). For SAEs, meta-analysis may be the only way to obtain reliable estimates of safety events occurring in randomized trials (12).

The generalisability of these results is subject to certain limitations. First, the assessment of the risk-benefit balance remains a complex issue with no unique method to analyse it. Second, the visual asymmetry found in the forest plots were not assumed as a publication bias in this systematic review but are more likely related to the heterogeneity of the JIA which could have affected the measurements of effect size. To address the issue, we conducted subgroups analyses according to categories of JIA for the efficacy outcome. Third, a risk of selective reporting was present in 19% of trials. Finally, the lack of scoring of SAEs, the short-term follow-up and the relative restricted size of participants may negatively impact the results of the pooled estimates of effect size of BAs. Despite its exploratory nature, our meta-analyses suggest that quantification of the benefit-risk balance of BAs is necessary regardless of the frequency of AEs.

CONCLUSION

We present a net benefit model adapted to summarize data from RCTs performed on BAs in JIA disease. The results suggest that greater number of patients experienced therapeutic success without SAE in the systemic onset JIA category compared to the BAs for non-systemic JIA categories. Baseline risk, design of trial and JIA categories impact the measure of net benefit of BAs in JIA patients.

BIBLIOGRAPHY

1. Najafzadeh M, Schneeweiss S, Choudhry N, Bykov K, Kahler KH, Martin DP, et al. A unified framework for classification of methods for benefit-risk assessment. Value Health J Int Soc Pharmacoeconomics Outcomes Res. 2015 Mar;18(2):250–9.
2. Boers M, Brooks P, Fries JF, Simon LS, Strand V, Tugwell P. A first step to assess harm and benefit in clinical trials in one scale. J Clin Epidemiol. 2010 Jun;63(6):627–32.
3. Giannini EH, Ruperto N, Ravelli A, Lovell DJ, Felson DT, Martini A. Preliminary definition of improvement in juvenile arthritis. Arthritis Rheum. 1997 Jul;40(7):1202–9.
4. Consolaro A, Schiappapietra B, Dalprà S, Calandra S, Martini A, Ravelli A. Optimisation of disease assessments in juvenile idiopathic arthritis. Clin Exp Rheumatol. 2014 Oct;32(5 Suppl 85):S-126-130.
5. Balevic SJ, Becker ML, Cohen-Wolkowiez M, Schanberg LE. Clinical Trial Design in Juvenile Idiopathic Arthritis. Paediatr Drugs. 2017 Oct;19(5):379–89.
6. Schroll JB, Maund E, Gøtzsche PC. Challenges in coding adverse events in clinical trials: a systematic review. PloS One. 2012;7(7):e41174.
7. Crépin S, Villeneuve C, Merle L. Quality of serious adverse events reporting to academic sponsors of clinical trials: far from optimal. Pharmacoepidemiol Drug Saf. 2016;25(6):719–24.
8. Higgins JPT, Green S, Cochrane Collaboration, editors. Cochrane handbook for systematic reviews of interventions. Chichester, England ; Hoboken, NJ: Wiley-Blackwell; 2008. 649 p. (Cochrane book series).
9. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21;6(7):e1000097.
10. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004 Feb;31(2):390–2.
11. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011 Oct 18;343:d5928.
12. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med. 2007 Jan 15;26(1):53–77.
13. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539–58.
14. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629–34.
15. Visvanathan S, Wagner C, Marini JC, Lovell DJ, Martini A, Petty R, et al. The effect of infliximab plus methotrexate on the modulation of inflammatory disease markers in juvenile idiopathic arthritis: analyses from a randomized, placebo-controlled trial. Pediatr Rheumatol Online J. 2010 Sep 7;8:24.
16. Ping Z ZH. A randomized double-blind controlled clinical trial to evaluate the efficacy of Recombinant Human TNF-alpha Receptor II fusion protein in juvenile idiopathic arthritis. Int J Rheum Conf 18th Asia Pac Leag Assoc Rheumatol Congr APLAR China Conf 2016. 2016;
17. Ping Z ZH. Efficacy and safety of Infliximab in juvenile idiopathic arthritis and juvenile ankylosing spondylitis: a randomized, double-blind, controlled study. Int J Rheum Conf 18th Asia Pac Leag Assoc Rheumatol Congr APLAR China Conf 2016. 2016;
18. Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, et al. Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis. N Engl J Med. 2017 27;376(17):1637–46.
19. Smith JA, Thompson DJS, Whitcup SM, Suhler E, Clarke G, Smith S, et al. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. Arthritis Rheum. 2005 Feb 15;53(1):18–23.
20. Tynjala P, Vahasalo P, Tarkiainen M, Kroger L, Aalto K, Malin M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011 Sep;70:1605–12.
21. Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, et al. Trial of Early Aggressive Therapy in Polyarticular Juvenile Idiopathic Arthritis. Arthritis Rheum. 2012 Jun;64(6):2012–21.
22. Burgos-Vargas R, Tse SML, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res. 2015 Nov;67(11):1503–12.
23. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized Trial of Tocilizumab in Systemic Juvenile Idiopathic Arthritis. N Engl J Med. 2012

décembre;367(25):2385–95.
24. Hissink Muller PCE, Brinkman DMC, Schonenberg D, Koopman-Keemink Y, Brederije ICJ, Bekkering WP, et al. A comparison of three treatment strategies in recent onset non-systemic Juvenile Idiopathic Arthritis: initial 3-months results of the BeSt for Kids-study. Pediatr Rheumatol Online J. 2017 Feb 6;15(1):11.
25. Horneff G, Fitter S, Foeldvari I, Minden K, Kuemmerle-Deschner J, Tzaribacev N, et al. Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement. Arthritis Res Ther. 2012 Oct 24;14(5):R230.
26. Ilowite NT, Prather K, Lokhnygina Y, Schanberg LE, Elder M, Milojevic D, et al. Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. Arthritis Rheumatol Hoboken NJ. 2014 Sep;66(9):2570–9.
27. Lovell DJ, Giannini EH, Reiff AO, Kimura Y, Li S, Hashkes PJ, et al. Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. Arthritis Rheum. 2013 Sep;65(9):2486–96.
28. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011 May;70(5):747–54.
29. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2007 Sep;56(9):3096–106.
30. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis. N Engl J Med. 2012 décembre;367(25):2396–406.
31. Tynjälä P, Vähäsalo P, Tarkiainen M, Kröger L, Aalto K, Malin M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011 Sep;70(9):1605–12.
32. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015 Jun;74(6):1110–7.
33. Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kümmerle-Deschner JB, Tenbrock K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol Hoboken NJ. 2015 May;67(8):2240–9.
34. Ilowite N, Porras O, Reiff A, Rudge S, Punaro M, Martin A, et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. Clin Rheumatol. 2009 Feb;28(2):129–37.
35. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000 Mar 16;342(11):763–9.
36. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without Methotrexate in Juvenile Rheumatoid Arthritis. N Engl J Med. 2008;359(8):810–20.
37. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet Lond Engl. 2008 Aug 2;372(9636):383–91.
38. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet Lond Engl. 2008 Mar 22;371(9617):998–1006.
39. Boers M, Singh JA, Cofield SS, Bridges SL, Moreland LW, O'Dell JR, et al. A Novel Method to Combine Assessment of Benefit and Harm: Outcome Measures in Rheumatology 3×3 Methodology Applied to Two Active Comparator Trials. Arthritis Care Res. 2019 Feb;71(2):319–22.
40. Berard RA, Laxer RM. Learning the hard way: clinical trials in juvenile idiopathic arthritis. Ann Rheum Dis. 2018 Jan;77(1):1–2.
41. Amarilyo G, Tarp S, Foeldvari I, Cohen N, Pope TD, Woo JMP, et al. Biological agents in polyarticular juvenile idiopathic arthritis: A meta-analysis of randomized withdrawal trials. Semin Arthritis Rheum. 2016 Dec;46(3):312–8.
42. Tarp S, Amarilyo G, Foeldvari I, Christensen R, Woo JMP, Cohen N, et al. Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials. Rheumatol Oxf Engl. 2016 Apr;55(4):669–79.
43. Otten MH, Anink J, Spronk S, van Suijlekom-Smit LWA. Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons. Ann Rheum Dis. 2013 Nov;72(11):1806–12.
44. Cabrera N, Lega J-C, Kassai B, Wouters C, Kondi A, Cannizzaro E, et al. Safety of biological

agents in paediatric rheumatic diseases: A real-life multicenter retrospective study using the JIRcohorte database. Joint Bone Spine. 2019 May;86(3):343–50.

45. Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J Clin Pharmacol. 2015 Mar;79(3):357–69.

FUNDING

Individual scholarship (Paraguay's BECAL* program) attributed to a one author (NC). None other funding was received from any public, commercial or non-profit organization to carry out the work described in this manuscript.

* BECAL: *Becas Don Carlos Antonio Lopez* (http://www.becal.gov.py)

DISCLOSURES

The authors declare that they have not competing interest.

ACKNOWLEDGEMENTS

The authors express their sincere thanks to Giuliana Cattivelli (University of Asuncion – Paraguay) for help in manuscript preparation.

APPENDIX

Tables and figures

Figure 1: PRISMA 2019 flow chart of literature search process of the systematic review

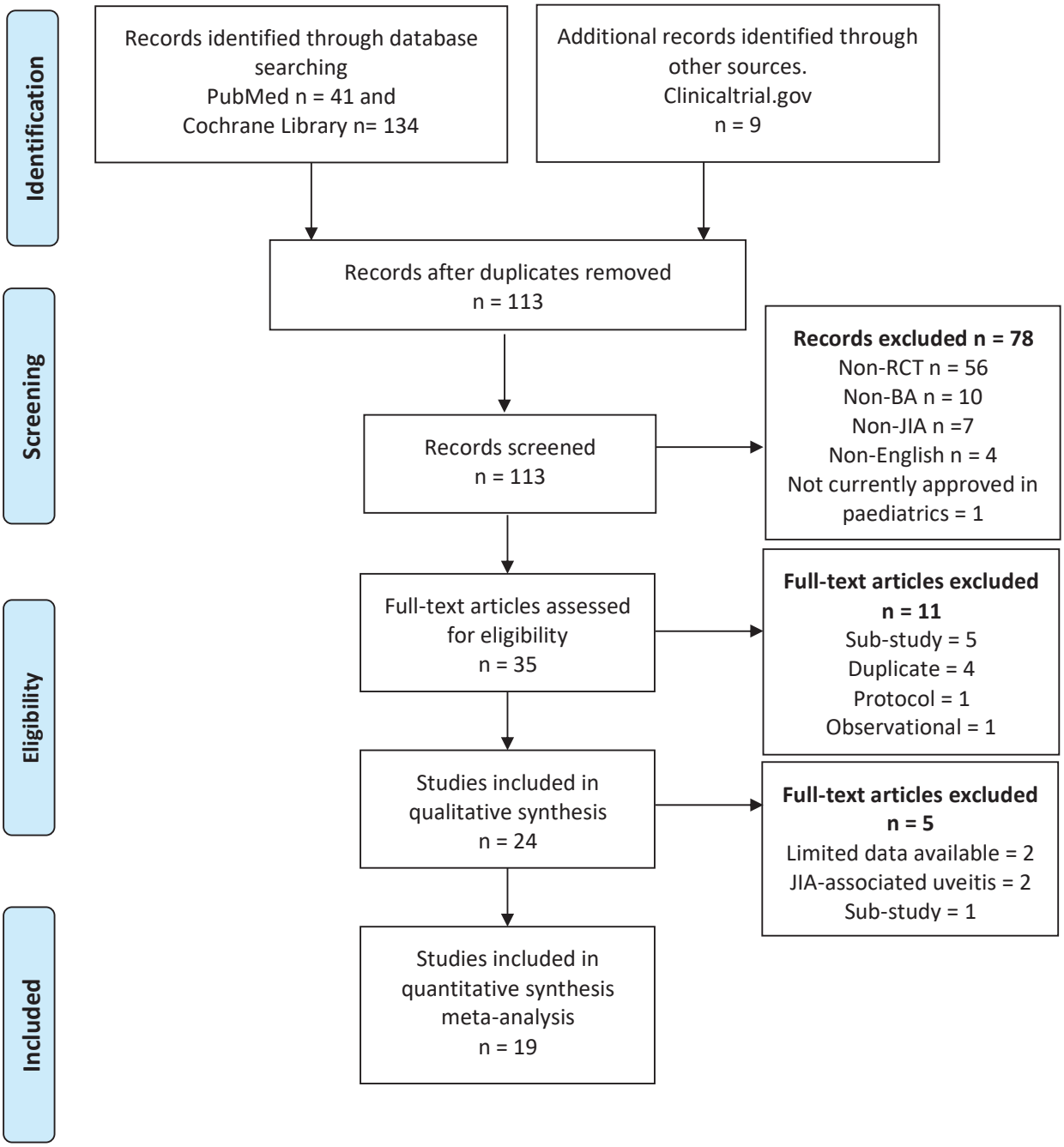


Table 1: Characteristics of included studies

First author, year	Ref	bDMARD	Trial type	Efficacy outcome	Randomised period[E]	JIA subtypes	Randomised patients[F]	Age ± SD (in years)	Disease duration[G]
Lovell et al., 2000	(35)	Etanercept	wRTC	JIA flare	16	OA, PA and SoJIA	51	10.5	5.8
Ruperto et al., 2007	(29)	Infliximab	pRCT	ACRpedi30	14	OA, PA and SoJIA	122	11.2 ±4.0	3.9 ±3.5
Lovell et al., 2008	(36)	Adalimumab	wRTC	JIA flare	32	PA JIA	133	11.2 ±3.7	3.7 ±3.7
Ruperto et al., 2008	(37)	Abatacept	wRTC	JIA flare	24	PA JIA	122	12.3 ±3.0	3.9 ±3.6
Yokota et al., 2008	(38)	Tocilizumab	wRTC	JIA flare	12	SoJIA	44	8.3 ±4.4	2.1 ±1
Ilowite et al., 2009	(34)	Anakinra	wRTC	JIA flare	16	OA, PA and So, JIA	50	11.0	4.1
Quartier et al., 2011	(28)	Anakinra	pRCT	ACRpedi30[C]	4	SoJIA	24	8.5 ±4.5	3.7 ±2.7
Tynjala et al., 2011	(31)	Infliximab	pRCT[B]	ACRpedi30	54	Early PA JIA	60	10.3 ±3.3	0.3 ±0.1
De Benedetti et al., 2012	(23)	Tocilizumab	pRCT	ACRpedi30[C]	12	SoJIA	112	9.6 ±4.5	5.4 ±4.2
Horneff et al., 2012	(25)	Adalimumab	pRCT	ACRpedi30[D]	12	Jo AS	32	15.3 ±1.6	3.2 ±2.3
Ruperto et al., 2012	(30)	Canakinumab	pRCT	ACRpedi30[C]	2	SoJIA	84	8.5	2.2
Ruperto et al., 2012	(30)	Canakinumab	wRTC	JIA flare	56	SoJIA	100	8.0	2.3
Wallace et al., 2012	(21)	Etanercept	pRCT	ACRpedi70	26	Early PA JIA	85	10.5 ±4.4	0.4 ±0.1
Lovell et al., 2013	(27)	Rilonacept	pRCT	ACRpedi30[C]	4	SoJIA	24	12.6 ±4.3	3.1
Ilowite et al., 2014	(26)	Rilonacept	pRCT	ACRpedi30	4	SoJIA	71	10.0 ±4.5	2.6 ±3.4
Brunner et al., 2015	(32)	Tocilizumab	wRTC	JIA flare	24	OA and PA JIA	166	11.0 ±4.0	4.2 ±3.7
Burgos-Vargas et al., 2015	(22)	Adalimumab	pRCT	ACRpedi30	12	ERA JIA	46	12.9 ±2.9	2.6 ±2.3
Horneff et al., 2015	(33)	Etanercept	wRTC	JIA flare	24	ERA JIA	38	13.4 ±2.4	3.2 ±2.8
Hissink-Muller et al., 2017	(24)	Etanercept	pRCT	Inactive disease	12	OA, PA Pso JIA	94	9.2	0.6
Total					**360**		**1458**	**10.8 ± 3.7**	**3.0 ± 2.6**

ACRpedi30: American college of rheumatology paediatric score 30%, bDMARD: biologic disease-modifying antirheumatic drug, JIA: juvenile idiopathic arthritis, NP: Not provided, pRCT: randomised placebo-controlled trial, SD: standard deviation, wRTC: withdrawal randomised controlled trial.

[A]: Trials studied uveitis in JIA patients, eye efficacy outcome according the SUN classification, [B]: RCT in open label fashion, [C]: ACRpedi30 including fever, [D]: Use ASAS40 for the primary outcome but inform also the ACRpedi30, [E]: treatment duration in weeks in randomised period of studies, [F]: Total number of patients who were randomised, [G]: disease duration in weeks ± SD.

Figure 2: Review authors' judgements about each risk of bias item presented as percentages across all included studies

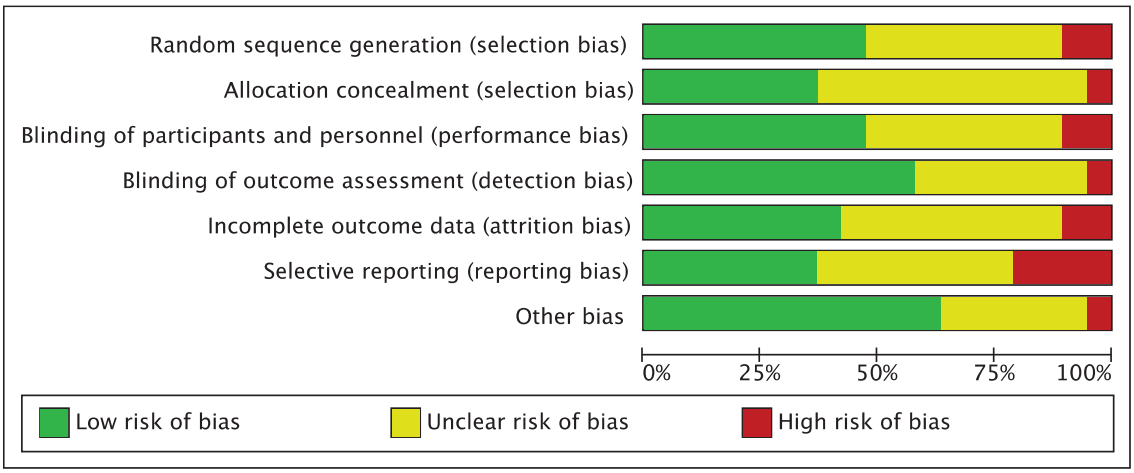


Figure 3: Review authors' judgements about each risk of bias item for included studies.

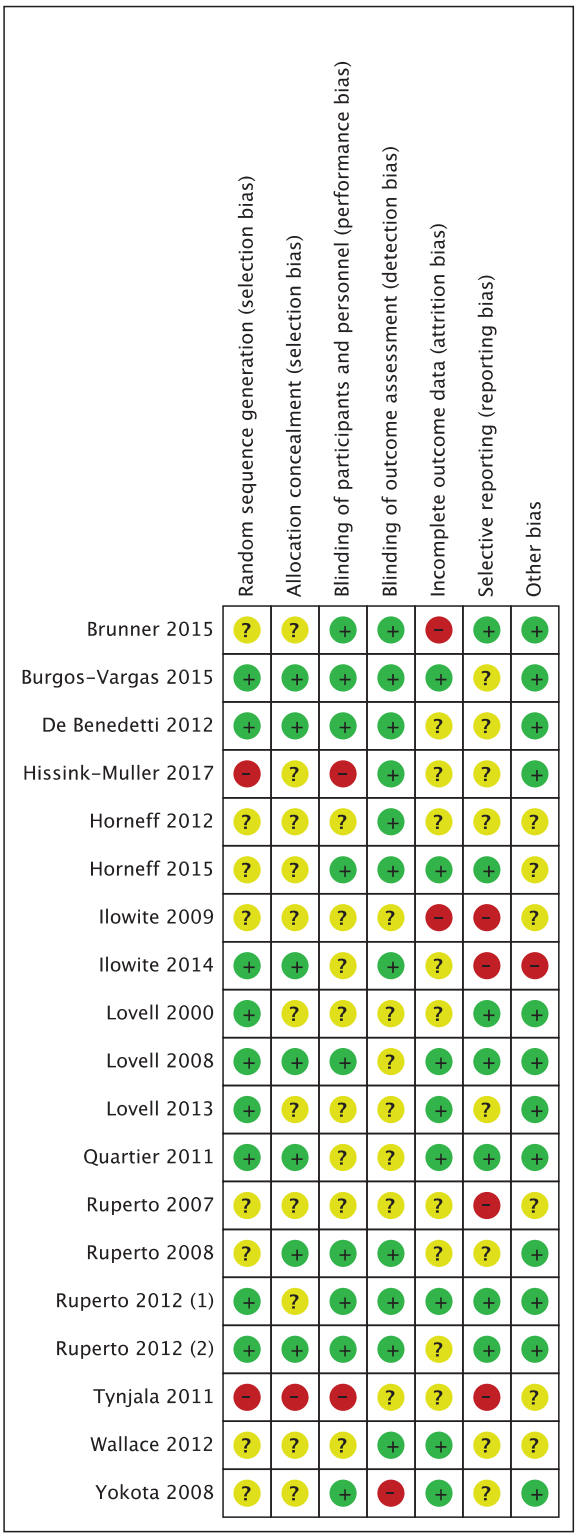
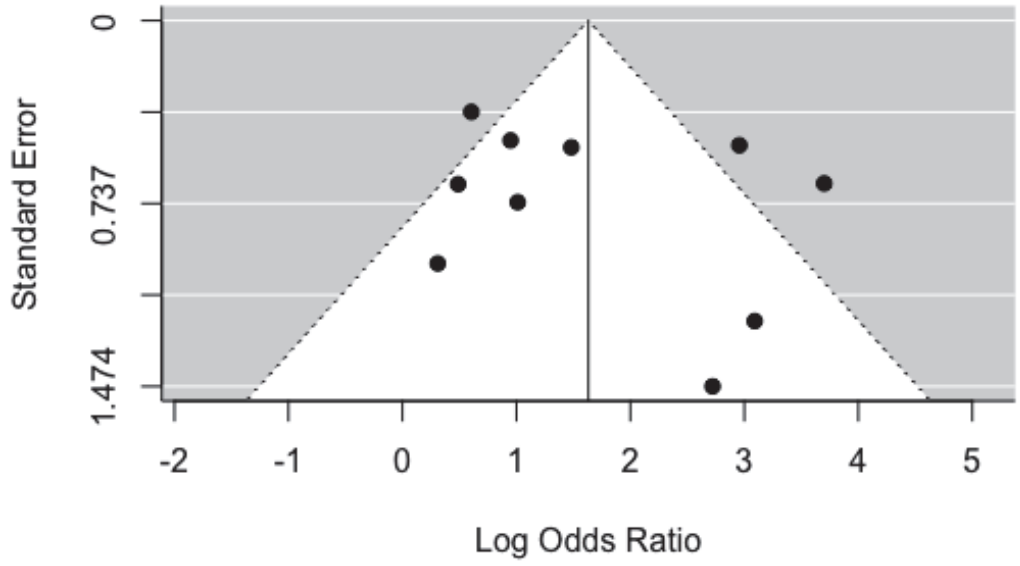


Figure 4: Funnel plots of trials



Test for asymmetry: p= 0.41

Efficacy outcome in ACRpedi30 in parallel RCTs.

.

Table 2: Net benefit for each biological agent according to juvenile idiopathic arthritis disease and trial design. Withdrawal design estimated the rate of relapse whereas parallels trials estimated the rate of response.

Outcome / Intervention	N (ref. of studies)	OR [95% CI]	Anticipated absolute effects [95% CI] Without BAs	With BAs	Difference	N (ref. of studies)	PETO OR [95% CI]	Anticipated absolute effects [95% CI] Without BAs	With BAs	Difference	Net Benefice
Non-systemic JIA											
ACRpedi30 in parallel RCT						*SAEs in parallel RCT*					
Infliximab	n= 181 (29,31)	**3.39** [0.48; 24.11]		**83.9%** [42.5; 97.4]	**23.3%** [1.1; 56.9]	n=181 (29,31)	**2.14** [0.21 to 21.99]		**16.0%** [1.6; 164.2]	**12.4%** [1.3; 64.5]	**10.9%**
Adalimumab	n= 78 (22,25)	**2.06** [0.79; 5.38]	60.6% [46.1; 73.5]	**76.0%** [54.9; 89.2]	**15.4%** [1.0; 52.5]	n= 78 (22,25)	**2.22** [0.29 to 17.15]	3.6% [1.7; 6.3]	**16.6%** [2.2; 128.1]	**13.0%** [1.2; 59.3]	**2.4%**
Etanercept	n= 94 (24)	**2.58** [1.00; 6.65]		**79.9%** [60.6; 91.1]	**19.3%** [1.2; 58.5]	n= 179 (21,24)	**0.70** [0.08 to 6.12]		**5.2%** [0.6; 45.7]	**1.6%** [0.2; 8.9]	**17.6%**
Relapses in withdrawal RCT						*SAEs in withdrawal RCT**					
Etanercept	n= 89 (33,35)	**0.12** [0.05; 0.33]		**13.5%** [6.1; 30.1]	**43.1%** [2.7; 134.4]	n= 89 (33,35)	**7.54** [0.77 to 73.71]		**43.4%** [4.4; 424.7]	**40.6%** [4.1; 206.3]	**2.4%**
Adalimumab	n= 133 (36)	**0.31** [0.15; 0.64]		**28.8%** [16.4; 45.5]	**27.8%** [0.6; 31.7]	n= 133 (36)	**0.13** [0.00 to 6.52]		**0.7%** [3.0% ; 37.6%]	**2.1%** [0.2; 11.3]	**29.9%**
Abatacept	n= 122 (37)	**0.22** [0.10; 0.49]	56.6% [45.7; 67.0]	**22.3%** [15.5; 39.0]	**34.3%** [1.2; 59.2]	n= 122 (37)	**0.14** [0.01 to 2.22]	2.8% [0.07; 6.1]	**0.4%** [0.0; 6.2]	**2.4%** [0.3; 17.3]	**36.7%**
Anakinra	n= 50 (34)	**0.29** [0.08; 1.09]		**27.4%** [9.4; 58.7]	**29.2%** [1.2; 60.8]	-	-		-	-	-
Tocilizumab	n= 163 (32)	**0.37** [0.19; 0.72]		**32.5%** [19.9; 48.4]	**24.1%** [0.5; 27.5]	n= 206 (32,38)	**1.03** [0.25 to 4.19]		**2.9%** [0.7 to 11.7]	**0.1%** [0.0; 0.7]	**24.0%**
Systemic-onset JIA											
ACRpedi30 in parallel RCT						*SAEs in parallel RCT***					
Anakinra	n= 24 (28)	**22.00** [2.05; 236.05]		**85.9%** [36.2; 98.5]	**64.2%** [1.4; 72.2]	-	-		-	-	-
Tocilizumab	n= 112 (23)	**30.22** [10.25; 89.11]	21.7% [12.0; 36.0]	**89.3%** [74.0; 96.1]	**67.6%** [0.8; 38.6]	n= 112 (23)	**4.64** [0.56 to 38.36]	3.6% [1.7; 6.3]	**16.7%** [2.0; 138.1]	**13.1%** [1.2; 62.0]	**54.5%**
Canakinumab	n= 84 (30)	**40.47** [11.18; 146.45]		**91.8%** [75.6; 97.6]	**70.1%** [0.7; 37.4]	n= 84 (30)	**0.95** [0.13 to 7.01]		**3.4%** [0.5; 25.2]	**0.2%** [0.0; 1.4]	**70.3%**
Rilonacept	n= 95 (26,27)	**3.30** [1.23; 8.87]		**47.8%** [25.4; 71.7]	**26.1%** [0.8; 41.1]	n= 95 (26,27)	**1.90** [0.24 to 15.19]		**6.8%** [0.9; 54.7]	**3.2%** [0.3; 15.9]	**22.8%**
Relapses in withdrawal RCT						*SAEs in withdrawal RCT§*					
Tocilizumab	n= 43 (38)	**0.05** [0.01; 0.24]	67.8% [33.2; 89.9]	**9.5%** [2.1; 33.6]	**58.3%** [6.2; 310.5]	n= 206 (32,38)	**1.03** [0.25 to 4.19]	2.8% [0.07; 6.1]	**2.8%** [0.7; 11.3]	**0.1%** [0.0; 0.7]	**58.2%**
Canakinumab	n= 100 (30)	**0.26** [0.11 to 0.62]		**35.4%** [18.8; 56.6]	**32.4%** [0.8; 39.8]	n= 100 (30)	**1.00** [0.30 to 3.32]		**2.8%** [0.8; 9.0]	**0.1%** [0.0, 1.0]	**32.3%**

JIA: juvenile idiopathic arthritis, RCTs: randomised controlled trials, OR: odds ratio, SAE: serious adverse event. * Significant heterogeneity in systemic-onset JIA category from withdrawal RCTs in preliminary efficacy outcomes; **Anakinra with simultaneous zero event in both arms, §Net benefit for tocilizumab using results of preliminary safety analysis from non-systemic and systemic onset JIA categories.

Additional tables and figures

Table A1: Criteria used for including studies using the PICO framework

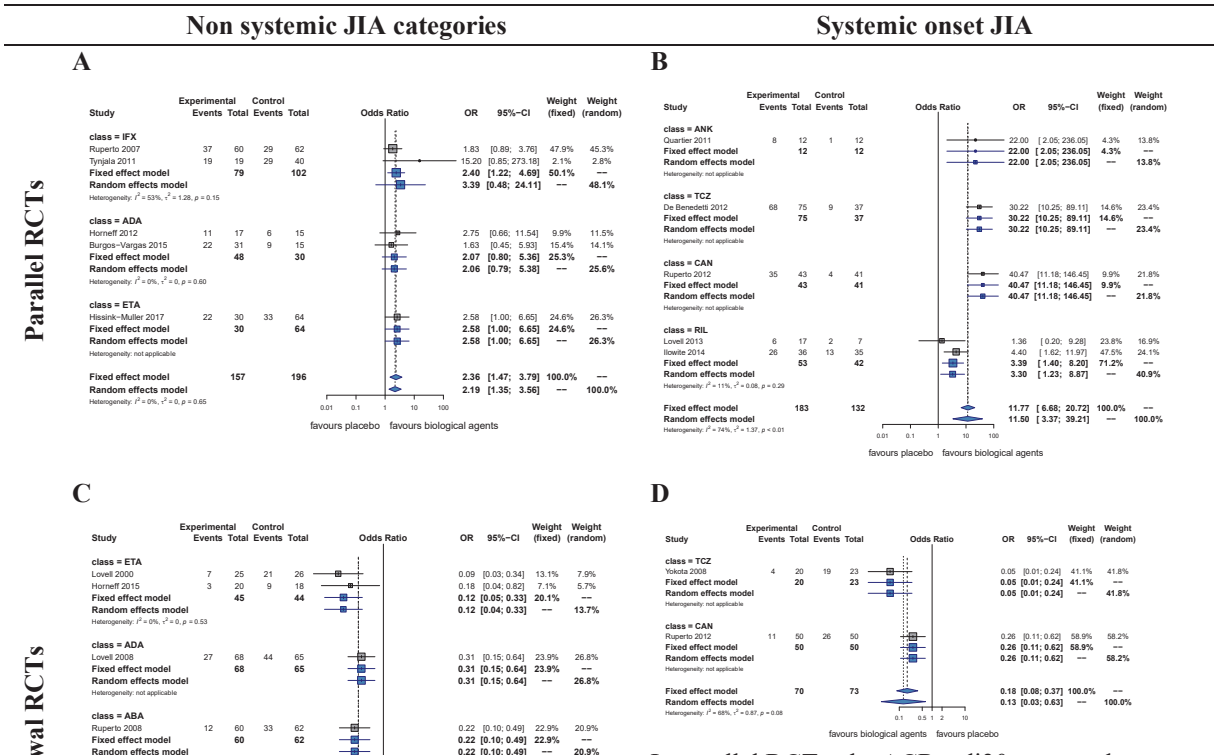
Components	Prespecified criteria
Population	Paediatrics / Juvenile idiopathic arthritis
Intervention	Biologicals agents
Comparator	versus DMARDs* OR versus. placebo
Outcome	Effectiveness AND safety
Type of studies	Randomized clinical trials

*DMARDs: disease-modifying antirheumatic drugs

Table A2: Full electronic search strategy for PudMed database

Database	PubMed
Date	12/03/2019
Result	41
User Query	"juvenile idiopathic arthritis"[All Fields] AND ("TNFR-Fc fusion protein"[All Fields] OR "etanercept"[All Fields] OR "adalimumab"[Supplementary Concept] OR "adalimumab"[All Fields] OR "infliximab"[Supplementary Concept] OR "infliximab"[All Fields] OR "interleukin 1 receptor antagonist protein"[MeSH Terms] OR "interleukin 1 receptor antagonist protein"[All Fields] OR "anakinra"[All Fields] OR "rilonacept"[Supplementary Concept] OR "canakinumab"[All Fields] OR "canakinumab"[Supplementary Concept] OR "canakinumab"[All Fields] OR "tocilizumab"[Supplementary Concept] OR "tocilizumab"[All Fields] OR "rituximab"[Supplementary Concept] OR "rituximab"[All Fields] OR "abatacept"[Supplementary Concept] OR "abatacept"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields] OR "child"[MeSH Terms] OR "child"[All Fields] OR "adolescent"[MeSH Terms] OR "adolescent"[All Fields]) AND ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields])

Figure A1: Meta-analysis of efficacy outcomes of biological agents according to juvenile idiopathic arthritis categories.

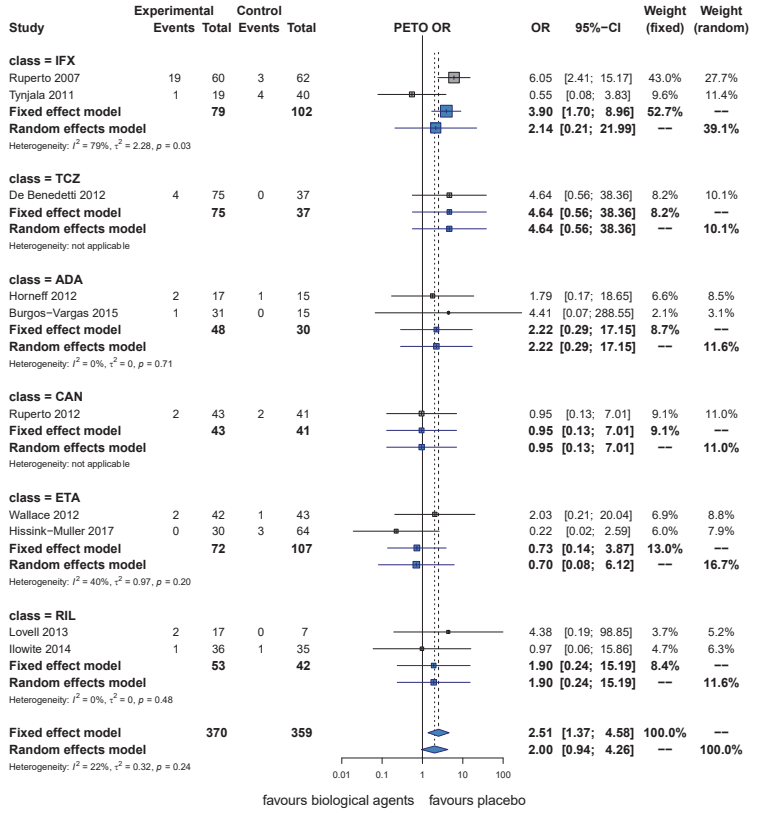


In parallel RCTs, the ACRpedi30 was used to measure the efficacy of BAs in polyarticular, enthesitis-related arthritis and psoriatic arthritis categories (A) and in systemic onset JIA (B). In withdrawal RCTs, relapses of disesases were used to measure mantenance of clinical response of BAs in polyarticular, enthesitis-related arthritis and psoriatic arthritis categories (C) and in systemic onset JIA (D)

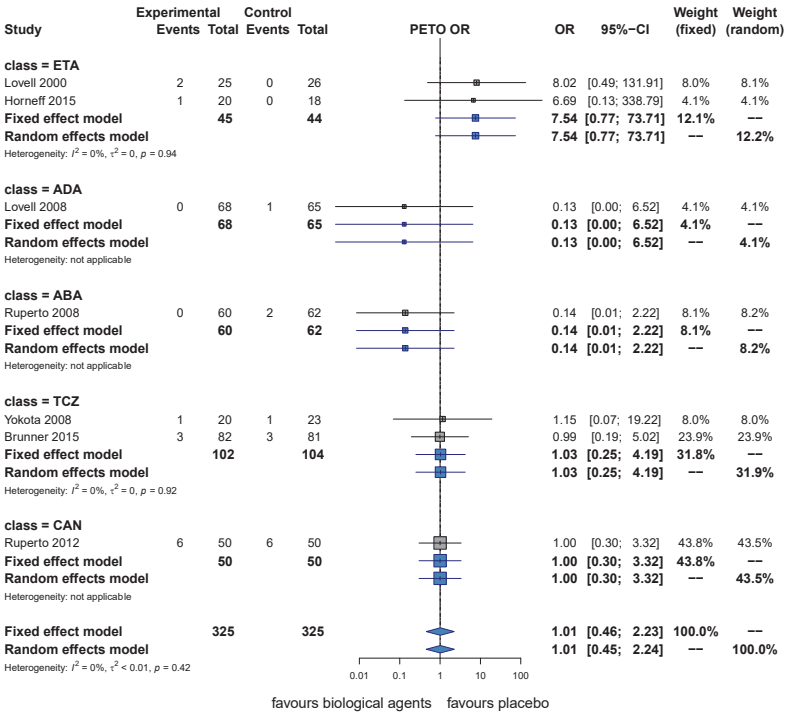
ADA: adalimumab, ANK: anakinra, ABA: abatacept, CAN: canakinumab, CI: confidence interval, ETA: etanercept, IFX: infliximab, JIA: juvenile idiopathic arthritis, OR: odds ratio, RCTs: randomised controlled trials, RIL: rilonacept, TCZ: tocilizumab.

Figure A2: Meta-analysis of safety outcomes of biological agents s in juvenile idiopathic arthritis in parallel (A) and withdrawal (B) randomized controlled trials

A



B



ADA: adalimumab, ANK: anakinra, ABA: abatacept, CAN: canakinumab, CI: confidence interval, ETA: etanercept, IFX: infliximab, OR: odds ratio, RIL: rilonacept, TCZ: tocilizumab.

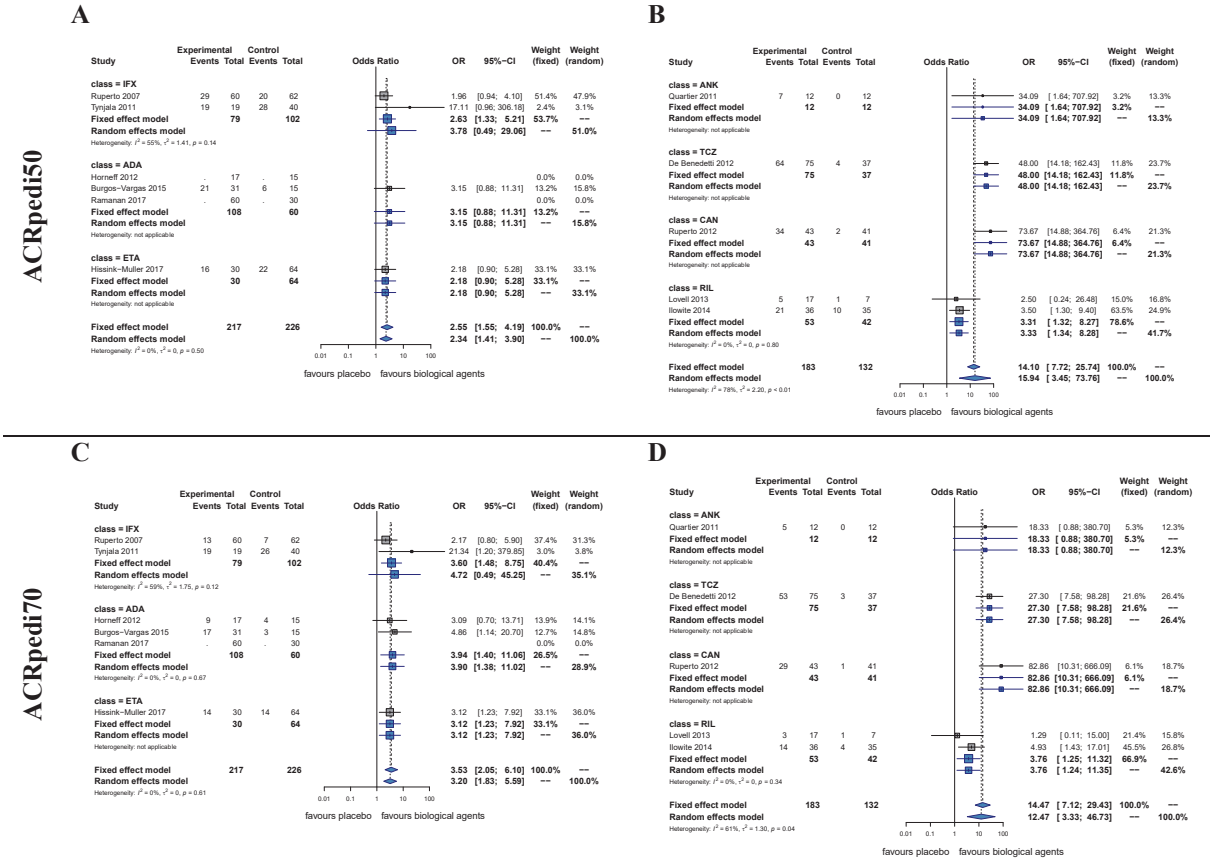
Table A3: Exploration of heterogeneity of clinical response by meta-regression

	k studies*	Coefficient	95% CI	R_2	Tau_2
Year of publication	17	-0.032	[-0.08; 0.02]	0.0%	0.073
Trial design type (withdrawal RCT)	17	-0.037	[-0.42; 0.35]	0.0%	0.089
Age of patients	16	-0.095	[-0.20; 0.01]	0.0%	0.070
Systemic onset JIA disease	**17**	**0.46**	**[0.14; 0.78]**	**60.18%**	**0.025**
Duration of randomised phase	17	-0.001	[-0.02; 0.01]	0.0%	0.093
n of total patients in randomized phase	17	-0.001	[-0.01; 0.003]	0.0%	0.085
Patients receiving IS drugs in the control group	17	-0.130	[-0.77; 0.51]	0.0%	0.077
***n* of patients with previous BA in control group**	**13**	**0.021**	**[0.0057; 0.037]**	**71.9%**	**0.022**
***n* of patients with previous BA in intervention group**	**13**	**0.013**	**[0.0045; 0.021]**	**100%**	**0.00**

*For meta-regression analysis we consider the efficacy outcome measured by the ACRpedi30 score for both, parallel and withdrawal RCTs. This outcome was not used in one trials (37).
CI: confidence interval; IS: immunosuppressive; JIA: juvenile idiopathic arthritis, RCT: randomised controlled trial.

Table A4: Meta-analysis of efficacy outcomes (ACRpedi50 and ACRpedi70) of biological agents according to juvenile idiopathic arthritis categories in parallel RCTs

	Non systemic JIA categories	Systemic onset JIA
ACRpedi50	A	B
ACRpedi70	C	D



Meta-analyses of efficacy outcomes: ACRpedi50 response in non-systemic JIA categories (A) and systemic-onset JIA (B), ACRpedi70 response in non-systemic JIA categories (C) and systemic-onset JIA (D)

3. Études observationnelles

Tolérance des biothérapies chez les patients avec une maladie rhumatismale à début juvéniles à partir des données de la vie réelle : une étude multicentrique

Article publié :

'Safety of biological agents in paediatric rheumatic diseases: A real-life multicenter retrospective study using the JIRcohorte database'

Cabrera N, Lega JC, Kassai B, Wouters C, Kondi A, Cannizzaro E, Woerner A, Chausset A, Roethlisberger S, Jeanneret C, Aeschlimann F, Malik S, Duquesne A, Kaiser D, Higel L, Maes A, Berthet G, Hentgen V, Kone-Paut I, Belot A, Hofer M.

Joint Bone Spine. 2019 May;86(3):343-350.

doi: 10.1016/j.jbspin.2018.08.003

Joint Bone Spine 86 (2019) 343–350

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

Original article

Safety of biological agents in paediatric rheumatic diseases: A real-life multicenter retrospective study using the JIRcohorte database

Natalia Cabrera[a,b,*], Jean-Christophe Lega[a,c], Behrouz Kassai[a,d], Carine Wouters[e,f], Anuela Kondi[g], Elvira Cannizzaro[h], Andreas Woerner[i], Aurelie Chausset[j], Samuel Roethlisberger[k], Cyril Jeanneret[k], Florence Aeschlimann[h], Salma Malik[d], Agnès Duquesne[b], Daniela Kaiser[l], Laetitia Higel[m], Anne Maes[e,f], Gerald Berthet[n], Veronique Hentgen[o], Isabelle Kone-Paut[g], Alexandre Belot[b], Michael Hofer[i]

[a] *UMR CNRS 5558, Laboratoire de Biométrie et Biologie Humaine, Équipe Évaluation et Modélisation des Effets Thérapeutiques, rue Guillaume-Paradin, BP8071, 69376 Lyon cedex 08, France*
[b] *Inserm U1111, National Referral Centre for rare Juvenile Rheumatological and Auto-immune Diseases (RAISE), Department of Paediatric Rheumatology, Lyon University Hospital, University of Lyon, 69677 Bron cedex, France*
[c] *National Referral Centre for rare Juvenile Rheumatological and Auto-immune Diseases (RAISE), Department of Internal and Vascular Medicine, Hôpital Lyon Sud, Lyon University Hospital, University of Lyon, 69495 Pierre-Bénite, France*
[d] *Clinical Investigation Center (CIC1407), Lyon University Hospital, 69003 Lyon, France*
[e] *Department of Paediatrics, University Hospitals Leuven, Leuven, Belgium*
[f] *Department of Immunology and Microbiology, Childhood Immunology, University of Leuven, 3000 Leuven, Belgium*
[g] *Department of Paediatrics and Paediatric Rheumatology, Centre de référence des maladies auto-inflammatoires rares et de l'amylose inflammatoire (CEREMAIA), Bicêtre University, Paris Sud Hospital, 94270 Le Kremlin-Bicêtre, France*
[h] *University Children's Hospital, 8032 Zürich, Switzerland*
[i] *Paediatric Rheumatology, University of Basel, University Children's Hospital, 4031 Basel, Switzerland*
[j] *Department of Paediatrics, Estaing Hospital, Clermont-Ferrand University Hospital, 63100 Clermont-Ferrand, France*
[k] *Paediatric Rheumatology Western Switzerland, Centre Hospitalier Universitaire vaudois (CHUV) 1011 Lausanne and Hospital Universitaire Genève (HUG) 1206 Geneva, Switzerland*
[l] *Department of Paediatrics, Hospital of Lucerne, 6000 Lucerne, Switzerland*
[m] *Hautepierre Hospital, University Hospitals Strasbourg, 67200 Strasbourg, France*
[n] *Department of Paediatrics, Hospital of Aarau, 5001 Aarau, Switzerland*
[o] *Centre de référence des maladies auto-inflammatoires rares et de l'amylose inflammatoire (CEREMAIA), Versailles University Hospital, 78157 Le Chesnay, France*

suppl. Informations

ARTICLE INFO

Article history:
Accepted 28 August 2018
Available online 7 September 2018

Keywords:
Biological agents
Paediatric rheumatology
Juvenile idiopathic arthritis
Adverse events
Serious adverse events
JIRcohorte

ABSTRACT

Objective: To analyse and report the incidence of side effects of biological agents in paediatric patients with inflammatory diseases using of real-life follow-up cohort.
Methods: In this international, observational, retrospective, multicentre study of children treated by biological agents and followed in the Juvenile Inflammatory Rheumatism (JIR) cohort (JIRcohorte) network, a Kaplan–Meier method was used to estimate the occurrence of adverse events. A Cox model was constructed to identify independent predictors of adverse events.
Results: Overall 813 patients totalling 3439 patients–year (PY) of biological agents were included. The main diagnosis was juvenile idiopathic arthritis (84%). A total of 222 patients (27.3%) had 419 adverse events, representing an incidence rate of 12.2 per 100 PY 95% CI [11.0; 13.4]. The overall incidence rate of serious adverse events was 3.9 per 100 PY 95% CI [3.2; 4.6]. Tocilizumab and infliximab were significantly associated with adverse events and canakinumab with serious adverse events. Univariate and multivariable analysis of adverse events and serious adverse events indicated that patients under biological agents with concomitant immunosuppressive drugs (excluding methotrexate) suffered from more of these events.
Conclusion: This study suggests an overall an acceptable safety of biologic agents in children with inflammatory rheumatic diseases treated with biological agents. However, the concomitant prescription of immunosuppressive drugs with biological agents represents a substantial risk of adverse events.

* Corresponding author at: UMR CNRS 5558, Laboratoire de Biométrie et Biologie Humaine, Équipe Évaluation et Modélisation des Effets Thérapeutiques, rue Guillaume-Paradin, BP8071, 69376 Lyon cedex 08, France.
E-mail address: natalia.rojas@etu.univ-lyon1.fr (N. Cabrera).

https://doi.org/10.1016/j.jbspin.2018.08.003
1297-319X/

1. Introduction

At the start of the century, American (FDA) and European (EMA) agencies were concerned with the accessibility of innovative medicines for children, and new regulations on paediatric clinical trials [1] led to several studies investigating biological agents (BA) in the field of paediatric inflammatory diseases [2–4]. The efficacy of BAs has now been well demonstrated in various subtypes of juvenile idiopathic arthritis (JIA) [5–7], in auto-inflammatory diseases such as cryopyrinopathies [8,9], and to a lesser extent in systemic auto-immune diseases such as systemic lupus erythematosus [10,11]. However, there are only a few observational studies that have been conducted in children with rheumatic diseases [12–17] and among these, those that have compared BAs only consider JIA patients [13,16]. Adequate safety has been suggested in both randomised trials [18,19] and observational studies [16,20]. In spite of several other studies that have explored at the risk of cancer associated with anti-TNFs [21,22], there is a lack of information in relation to the long-term immunological consequences of other BAs [23]. For the investigation of such tolerance issues, the Juvenile Inflammatory Rheumatism cohort (JIRcohorte) platform collects prospective and retrospective data, including treatments and their adverse events (AEs), for all patients with juvenile inflammatory rheumatisms reflecting daily practice in paediatric rheumatology departments of tertiary care centres. Therefore, the objective of the present study is to provide real-life data on long-term safety of BAs used in inflammatory rheumatism in the paediatric centres participating in the JIRcohorte network.

2. Methods

2.1. Study design

This was an observational, retrospective, multicentre study. Independent ethics committees in each paediatric rheumatology centre approved the study. Parental or guardian consent was required before the inclusion of patients, in accordance with the respective national regulations.

2.2. Patients

Patients were selected from the JIRcohorte database, which includes all patients with a diagnosis of inflammatory rheumatic (auto-inflammatory or auto-immune) disease starting in childhood. Those who were treated with at least one of either etanercept, adalimumab, infliximab, golimumab, anakinra, canakinumab, rituximab, abatacept, or tocilizumab, regardless of concomitant treatments, up to the 31 August 2014 were included.

The JIRcohorte database includes data collected by chart reviews, comprised of the use of disease-modifying anti-rheumatic drugs (DMARD) and the side effects of the prescribed treatments. The presence of auto-immune diseases in a first-degree relative was also recorded. Outpatient clinic and hospitalisation-related consultations were analysed to extract adverse events (AEs). AEs and serious adverse events (SAEs) were coded and defined in accordance with the International Conference on Harmonization guidelines (using MedDRA) [24] version 17.1. According to MedDRA codes, the intensity of AEs was categorised as mild, moderate, severe, or very severe. SAEs included: hospitalisations, incapacity of life functions, life threatening, and death. Reactivation or relapse of disease was not considered as an AE. All AEs during BA treatment were collected, regardless of concomitant medication.

In the present study, the safety of BAs was also described using the medical important infections (MII) and the immune-mediated diseases (IMD) of each BA, as a way to describe long-term tolerance. The infections leading to hospitalisation or intravenous antibiotic treatment were defined as MIIs; uveitis, intestinal chronic inflammatory disease, psoriasis, lupus-like and haematological disorders including macrophage activation syndrome (MAS), were defined as IMDs.

At the time of the study there were 15 centres participating in the JIRcohorte (Switzerland: Basel, Zurich, Aarau, Lucerne, Vaud, and Graubünden; France: Paris – 2 centres, Lyon, Montpellier, Bordeaux, Strasbourg, Clermont-Ferrand; Morocco: Casablanca; Belgium: Leuven).

2.3. Statistical analysis

Demographic and baseline disease characteristics were summarised with the use of descriptive statistics. Distribution of paediatric inflammatory rheumatic diseases was described. Rheumatic diseases were grouped as follows: JIA and non-JIA (auto-inflammatory diseases, idiopathic uveitis, inflammatory bowel diseases (IBD) related arthritis, vasculitis, connective tissue diseases, chronic recurrent multifocal osteomyelitis, Behçet disease, unclassified auto-inflammatory disease, Blau syndrome, synovitis acne pustulosis hyperostosis and osteitis [SAPHO] syndrome, immune dysregulation polyendocrinopathy enteropathy X–linked [IPEX] syndrome and Castleman disease). JIA was further subdivided according to ILAR classification [25]. The occurrence of MAS and uveitis in JIA in relation to positivity of antinuclear antibodies (ANAs) prior to initiation of BA treatment were also recorded.

To analyse safety, the population was divided according to BA into 9 groups: etanercept, adalimumab, infliximab, golimumab, tocilizumab, rituximab, canakinumab, anakinra and abatacept. In the present study, corticosteroids (CTCs), MTX, and other DMARDs were analysed. We described the AEs (mild, moderate, severe, and very severe) and SAEs of the whole population and then according to the diagnostic group (JIA and non-JIA). To avoid a double analysis of side effects in the survival analysis, mild and moderate AEs were considered together, and severe and very severe AEs were grouped along with the SAEs for the regression model. The Kaplan-Meier estimator was used to estimate the occurrence of AE and SAE; follow-up time and time-to-event outcomes were calculated from the time of initiation of BAs. Curves were compared using the Logrank test, with significance set at $P < 0.05$. To identify independent predictors of AE and SAE a multivariable mixed effects Cox proportional hazards model was constructed using a stepwise approach selecting variables at $P < 0.20$ in univariate analysis. The parameters considered were: sex, MTX, CTCs, other immunosuppressive drugs (azathioprine, cyclosporine, hydroxychloroquine, leflunomide and sulfasalazine), total number of BA and type of disease (JIA vs. non-JIA). Significance was set at $P < 0.05$.

We also described the incidence rate of the side effects considering medical important infections (MII) and immune-mediated diseases (IMD) according to each BA, regardless of the intensity or seriousness. The duration of exposure to BA is heterogeneous and therefore all safety analyses were evaluated using incidence rates, reported as the number of events per 100 patient-years (PY). Statistical analyses were performed using R software version 3.4.4 (R Development Core Team 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org).

2.4. Role of the funding source

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Table 1
Demographic and clinical data of patients.

	Sex	Age at diagnosis (years)			Follow-up (years)
	n (M/F)	Mean ± SD	Min	Max	Mean ± SD
All patients	813 (295/518)	9.4 ± 3.6	0.3	18.4	4.7 ± 3.1
Juvenile idiopathic arthritis	681 (238/443)	7.5 ± 4.7	1.0	18.4	6.8 ± 4.4
RF negative polyarthritis	147 (36/111)	6.7 ± 4.1	1.0	17.2	7.0 ± 4.5
Enthesitis-related arthritis	140 (90/50)	11.2 ± 3.5	0.7	18.4	4.6 ± 3.0
Systemic arthritis	117 (48/69)	6.3 ± 4.8	0.3	17.8	6.2 ± 4.7
Extended oligoarthritis	109 (19/90)	4.3 ± 2.0	1.1	18.4	7.8 ± 4.5
Persistent oligoarthritis	89 (21/68)	5.3 ± 3.7	1.0	16.2	5.9 ± 4.1
Psoriatic arthritis	33 (14/19)	10.7 ± 4.1	1.8	16.5	4.5 ± 2.9
RF positive polyarthritis	30 (3/27)	11.3 ± 2.7	5.2	15.6	4.5 ± 4.1
Unclassified arthritis	16 (7/9)	11.0 ± 5.2	1.9	17.4	4.3 ± 4.1
Non-JIA	132 (57/75)	8.3 ± 4.3	0.3	16.6	4.8 ± 3.4
Auto-inflammatory diseases	52 (25/27)	6.3 ± 4.9	0.3	14.6	5.5 ± 2.5
Cryopyrinopathies	35 (20/15)	5.4 ± 4.8	0.3	14.6	5.7 ± 4.4
TRAPS	6 (2/4)	9.0 ± 4.1	3.9	12.8	5.7 ± 2.0
HIDS	7 (2/5)	4.8 ± 4.1	0.4	9.9	3.2 ± 3.0
FMF	4 (1/3)	6.2 ± 2.7	3.2	9.7	6.5 ± 1.0
Idiopathic uveitis	28 (10/18)	8.7 ± 3.0	4.7	14.8	4.0 ± 2.6
IBD-related arthritis	9 (4/5)	11.0 ± 4.7	4.3	16.6	4.5 ± 2.9
Vasculitis	8 (4/4)	9.6 ± 3.7	5.5	15.9	3.1 ± 2.4
AAV	4 (1/3)	11.7 ± 3.4	7.5	15.9	2.9 ± 1.4
Kawasaki disease	2 (2/0)	5.6 ± 0.1	5.5	5.6	2.5 ± 0.6
Takayasu arteritis	1 (0/1)	6.0	–	–	0.3
Unclassified vasculitis	1 (1/0)	13.5	–	–	8.2
Connective tissue disease	8 (0/8)	12.1 ± 3.1	7.2	16.1	4.5 ± 4.3
Paediatric LES	4 (0/4)	13.7 ± 2.0	11.6	16.1	3.6 ± 2.9
Juvenile dermatomyositis and MCTD	4 (0/4)	12.1 ± 4.3	7.2	15.4	6.1 ± 6
Chronic recurrent multifocal osteomyelitis	8 (5/3)	8.7 ± 4.9	1.5	13.9	6.8 ± 3.5
Behçet disease	8 (4/4)	9.8 ± 5.2	1.7	15.0	3.6 ± 1.6
Unclassified auto-inflammatory diseases[a]	3 (1/2)	6.6 ± 5.3	0.7	11.2	1.3 ± 1.1
Blau syndrome	3 (1/2)	6.9 ± 2.3	4.9	9.4	7.2 ± 2.7
SAPHO syndrome	3 (2/1)	14.5 ± 0.8	13.6	15.1	2.5 ± 2.9
IPEX syndrome	1 (0/1)	25.8	–	–	0,4
Castleman disease	1 (1/0)	6.0	–	–	1.7

AAV: anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; FMF: familial mediterranean fever; HIDS: hyperimmunoglobulinemia D syndrome; IBD: inflammatory bowel diseases; JIA: juvenile idiopathic arthritis; IPEX: immune dysregulation polyendocrinopathy enteropathy X–linked; MCTD: mixed connective tissue disease; RF: rheumatoid factor; SAPHO: synovitis acne pustulosis hyperostosis and osteitis; SD: standard deviation; SLE: systemic lupus erythematosus; TRAPS: tumor necrosis factor receptor associated periodic syndrome; M: male; F: female.

[a] Idiopathic pericarditis and unclassified auto-inflammatory fever.

3. Results

3.1. Baseline characteristics of the patients

A total of 813 patients were included in the study. The mean ± standard deviation (SD) age at disease onset was 9.4 ± 3.6 years (range: 0.3 to 18.4 years). The mean ± SD follow-up was 4.7 ± 3.1 years. The majority of patients had JIA (*n* = 681, 84% of the population; Table 1), followed by auto-inflammatory diseases (*n* = 52, 6% of the total population), mainly cryopyrinopathies (*n* = 35; Table 1).

Uveitis was found in all subtypes of JIA, except in the polyarthritis-rheumatoid factor positive JIA subtype, and occurred in 123 patients (sex ratio 2.1:1). MAS occurred in 33 patients; one episode each and 29 belonging to systemic JIA subtype. History of auto-immune disease in a first-degree relative was found in 16% of patients (*n* = 129/813).

3.2. Biological agents and immunosuppressive drug exposure

In the database, the first BA was prescribed in June 1999. There was a total of 1179 BA prescriptions for 813 patients. The TNFα antagonists represented 75% (*n* = 885/1179) of all BA prescribed, and etanercept was the most frequently used (42%, *n* = 492/1179) followed by adalimumab (20%, *n* = 236/1179), irrespective of the type of rheumatic disease. The total duration of exposure to BAs was 3439 PY (the median exposure of an individual patient was 56.4 months). MTX was frequently associated with etanercept, adalimumab, infliximab, tocilizumab, abatacept, and golimumab. Among the group of anti-IL1 agents, 47% of patients treated by anakinra and 25% of those treated by canakinumab were also prescribed MTX. Corticosteroids were associated with rituximab perfusion in 53% of the cases; for other BAs, CTC co-prescription varied from 22 to 43% [Appendix A, Tables S1–S2; see the supplementary material associated with this article online].

3.3. Safety of biological agents

A total of 222 patients had 419 AEs (without exclusion of SAEs), representing an incidence rate of 12.2 per 100 PY (95% confidence interval, CI [11.0; 13.4]). Seventy-four patients (9.1%) had at least 1 SAE (*n* = 134 SAE), the overall incidence rate of SAE was 3.9 per 100 PY [95% CI: 3.2; 4.6]. No AE was reported with rituximab.

AEs were most frequently mild (46%, 193/419), followed by moderate AEs (39%, 165/419), and severe and very severe AEs represented 15% (61/419). The incidence of AEs was greater among JIA patients (335/419; incidence rate of 9.7 per 100 PY, 95% CI [8.2; 11.3]) than among non-JIA patients (84/419; 2.4 per 100 PY, 95% CI [1.7; 3.2]), and this was the case for all BAs except for canakinumab (Tables 2 and 3).

In regard to very severe AEs, in the JIA group, there were two MAS episodes during tocilizumab treatment (incidence rate 0.8 per 100 PY, 95% CI [0.0; 1.9]) and two events with etanercept treatment in patients with polyarthritis-rheumatoid factor positive JIA subtype: one Hodgkin's lymphoma (nodular sclerosis) in stage IV with bone and lung involvement (incidence rate 0.1 per 100 PY,

Table 2
Incidence of adverse events and serious adverse events in patients treated by anti-TNFs.

	Etanercept	Adalimumab	Infliximab	Golimumab
Total of exposure, PY	1543	627	472	31
Total number of prescriptions	492	236	142	15
Co-prescription MTX (%)[a]	399 (81)	191 (81)	123 (87)	14 (93)
Co-prescription CTC (%)[a]	113 (23)	74 (31)	31 (22)	6 (40)
	n, incidence rate per 100 PY [95% CI]			
AEs[b]	119, 7.7 [6.3; 9.1]	58, 9.3 [6.9; 11.6]	78, 16.5 [12.6; 20.2]	2, 6.5 [0.0; 15.4]
Mild and moderate AEs	106, 6.9 [5.6; 8.2]	52, 8.3 [6.0; 10.5]	59, 12.5 [9.1; 15.7]	2, 6.5 [0.0; 15.4]
Severe and very severe AEs	13, 0.8 [0.4; 1.3]	6, 1.0 [1.7; 60.2]	19, 4.0 [2.1; 5.8]	–
SAE[c]	43, 2.8 [2.0; 3.6]	20, 3.2 [1.8; 4.6]	25, 5.3 [3.1; 7.4]	–
JIA				
Mild and moderate AEs	100, 6.5 [5.2; 7.8]	43, 6.9 [4.8; 8.9]	50, 10.6 [7.5; 13.5]	2, 6.5 [0.0; 15.4]
Severe AEs	11, 0.7 [0.3; 1.1]	5, 0.8 [0.1; 1.5]	16, 3.4 [1.6; 5.1]	–
Very severe AEs[f]	2, 0.1 [0.0; 0.3]	–	1, 0.2 [0.0; 0.6]	–
Hospitalisation	11, 0.7 [0.3; 0.0]	3, 0.5 [0.0; 1.0]	4, 0.8 [0.0; 1.7]	–
Non-JIA				
Mild and moderate AEs	6, 0.4 [0.1 ;0.7]	9, 1.4 [0.5; 2.4]	9, 1.9 [0.6; 3.2]	–
Severe AEs	–	1, 0.2 [0.0; 0.5]	1, 0.2 [0.0; 0.6]	–
Very severe AEs[g]	–	–	1, 0.2 [0.0; 0.6]	–
Hospitalisation	1, 0.1 [0.0 ;0.2]	–	3, 0.6 [0.0; 1.4]	–
All infections	43, 2.8 [2.0; 3.6]	17, 2.7 [1.4; 4.0]	23, 6.1 [3.8; 8.4]	2, 6.5 [0.0; 15.4]
Bacteria	5, 0.3 [0.0; 0.6]	5, 0.8 [0.1; 1.5]	6, 1.7 [0.4; 2.9]	1, 3.2 [0.0; 9.5]
Virus	16, 1.0 [0.5; 1.5]	7, 1.1 [0.3; 1.9]	7, 0.8 [0.0; 1.7]	1, 3.2 [0.0; 9.5]
EBV infection	–	–	–	–
VZV infection	7, 0.4 [0.1; 0.7]	3, 0.5 [0.0; 1.0]	2, 0.4 [0.0; 1.0]	–
Another virus[h]	9, 0.1 [0.0; 0.2]		1, 0.2 [0.0; 0.6]	
Other infections	22, 1.4 [0.8; 2.0]	5, 0.8 [0.1; 1.5]	10, 2.1 [0.7; 3.4]	–
All MII[d]	4, 0.3 [0.0; 0.5]	1, 0.2 [0.0; 0.5]	5, 1.1 [0.1; 2.0]	–
Sepsis	–	–	1, 0.2 [0.0; 0.6]	–
VZV infection	2, 0.1 [0.0; 0.3]	1, 0.2 [0.0; 0.5]	2, 0.4 [0.0; 1.0]	–
Others MII	1, 0.1 [0.0; 0.2]	–	2, 0.6 [0.0; 1.4]	–
Incidence of IMD				
Incident uveitis	5, 0.3 [0.0; 0.6]	–	–	–
Incident IBD	1, 0.1 [0.0; 0.2]	–	–	–
Psoriasiform lesions	1, 0.1 [0.0; 0.2]	6, 1.0 [0.2; 1.7]	2, 0.4 [0.0; 1.0]	–
Lupus[e]	1, 0.1 [0.0; 0.2]	2, 0.3 [0.0; 0.8]	3, 0.6 [0.0; 1.4]	–
All blood disorders	7, 0.5 [0.1; 0.8]	4, 0.6 [0.0; 1.2]	2, 0.4 [0.0; 1.0]	–
Leukopenia	1, 0.1 [0.0; 0.2]	3, 0.5 [0.0; 1.0]	2, 0.2 [0.0; 0.6]	
Thrombocytopenia	–	–	–	
Pancytopenia	1, 0.1 [0.0; 0.2]	–	–	
MAS	1, 0.1 [0.0; 0.2]	–	–	
Other hospitalisations[i]	3, 0.2 [0.0; 0.4]	–	2, 0.2 [0.0; 0.6]	–

AEs: adverse events; CI: confidence interval; EBV: Epstein–Barr virus; HPV: human papillomavirus; IMD: immune-mediated disease; MAS: macrophage activation syndrome; VZV: varicella-zoster virus.

[a] Relative to each biological agent.
[b] All AEs: mild, moderate, severe and very severe AE.
[c] SAE: life threatening, hospitalization, incapacity life functions, cancer, death.
[d] MII: infections that led to hospitalization and/or required intravenous antibiotic treatment.
[e] Lupus-like or positivity of the antinuclear antibodies.
[f] 2 under etanercept (1 Hodgkin's disease, 1 anaphylactic shock) and 1 under infliximab (1 anaphylactic shock).
[g] 1 under infliximab (severe sepsis to *S. epidermidis*).
[h] Measles under adalimumab; enterovirus meningitis under infliximab.
[i] 3 under etanercept (1 poor wound healing, 1 suspected of acute abdomen, 1 anaphylactic shock) and 2 under infliximab (1 syncope episode, 1 paradoxical reaction).

95% CI [0.0; 0.2]) and one JIA associated with familial pulmonary fibrosis died from aggravation of fibrosis and a pulmonary infection. In the non-JIA group, one severe sepsis due to *Staphylococcus epidermidis* that needed two days in an intensive care unit occurred during infliximab perfusion (incidence rate 0.2 per 100 PY, 95% CI [0.0; 0.6]; Table 2) and one demyelinating lesion appeared concomitantly with canakinumab (incidence rate 0.4 per 100 PY, 95% CI 0.4 [0.0; 1.2]; Table 3).

The incidence of hospitalisation during BA treatment in the JIA group were ranged from 0.5 per 100 PY (95% CI [0.0; 1.0]) for adalimumab (Table 2) to 4.5 per 100 PY (95% CI [1.7; 8.1]) for tocilizumab (Table 3).

MII were described for all BAs. The varicella-zoster virus was the main infection reported among the MII events. Two episodes of sepsis were encountered, one with infliximab (Table 2) and another severe sepsis due to *S. epidermidis* during canakinumab treatment (Table 3). No MII was found during abatacept or golimumab treatment. No case of tuberculosis was encountered during BA treatment.

Among the IMDs with BAs, the appearance of lupus-like syndrome and/or a positivity of antinuclear antibodies was found only under anti-TNFα treatments (one for etanercept, two for adalimumab, and three for infliximab; Table 2). Psoriatic lesions had an incidence rate of 0.5 per 100 PY (95% CI [0.0; 1.4]) with anakinra (Table 3) and with the anti-TNFα treatments, the incidence rate ranged from 0.1 per 100 PY (95% CI [0.0; 0.2]) for etanercept to 1.0 per 100 PY (95% CI [0.2; 1.7]) for adalimumab. Uveitis was encountered only in patients treated with etanercept, among whom the incidence rate was 0.3 per 100 PY (95% CI [0.0; 0.6]; Table 2).

Table 3
Incidence of adverse events and serious adverse events in patients treated by another biological agent than anti-TNFs.

	Tocilizumab	Canakinumab	Anakinra	Abatacept
Total of exposure, PY	245	243	207	54
Total number of prescriptions	80	75	85	37
Co-prescription MTX (%)[a]	63 (79)	19 (25)	40 (47)	34 (92)
Co-prescription CTC (%)[a]	34 (43)	17 (23)	20 (24)	11 (30)
	n, incidence rate per 100 PY [95% CI]			
AEs[b]	63, 25.7 [19.4; 32.1]	57, 23.5 [17.4; 29.5]	33, 15.9 [10.5; 21.4]	9, 16.7 [5.8; 27.6]
Mild and moderate AEs	54, 22.0 [16.2; 27.9]	50, 20.6 [14.9; 26.3]	26, 12.6 [7.7; 17.4]	9, 16.7 [5.8; 27.6]
Severe and very severe AEs	9, 3.7 [1.3; 6.1]	7, 2.9 [0.7; 5.0]	7, 3.4 [0.9; 5.9]	–
SAE[c]	20, 8.2 [4.6; 11.7]	12, 4.9 [2.1; 7.7]	10, 4.8 [1.8; 7.8]	4, 7.4 [0.1; 14.7]
JIA				
Mild and moderate AEs	48, 19.6 [14.0; 25.1]	15, 6.2 [3.0; 9.3]	19, 9.2 [5.1; 13.3]	7, 13.0 [3.4; 22.6]
Severe AEs	5, 2.0 [0.0; 3.8]	2, 0.8 [0.0; 2.0]	6, 2.9 [0.6; 5.2]	–
Very severe AEs[f]	3, 1.2 [0.0; 2.6]	–	–	–
Hospitalisation	11, 4.5 [1.8; 7.1]	3, 1.2 [0.0; 2.6]	6, 2.9 [0.6; 5.2]	1, 1.9 [0.0; 5.5]
Non-JIA				
Mild and moderate AEs	6, 2.4 [0.5; 4.4]	35, 14.4 [9.6; 19.2]	7, 3.4 [0.9; 5.9]	2, 3.7 [0.0; 8.8]
Severe AEs	–	4, 1.6 [0.0; 3.3]	1, 0.5 [0.0; 1.4]	–
Very severe AEs[g]	1, 0.4 [0.0; 1.2]	1, 0.4 [0.0; 1.2]	–	–
Hospitalisation	–	2, 0.8 [0.0; 2.0]	–	–
All infections	20, 8.2 [4.3; 11.7]	28, 11.5 [7.3; 15.8]	11, 5.3 [2.2; 8.5]	3, 5.6 [0.0; 11.8]
Bacteria	6, 2.4 [0.5; 4.4]	5, 2.1 [0.3; 3.9]	4, 1.9 [0.0; 3.8]	–
Virus	5, 2.0 [0.3; 3.8]	12, 4.9 [2.1; 7.7]	4, 1.9 [0.0; 3.8]	–
EBV infection	1, 0.4 [0.0; 1.2]	–	1, 0.5 [0.0–1.4]	–
VZV infection	1, 0.4 [0.0; 1.2]	1, 0.4 [0.0; 1.2]	–	–
Another virus[h]	3, 0.4 [0.0; 1.2]	10, 4.1 [1.6; 6.7]	3, 1.4 [0.0; 3.1]	
Other infections	9, 3.7 [1.3; 6.1]	11, 4.5 [1.9; 7.2]	3, 1.4 [0.0; 3.1]	3, 5.6 [0.0; 11.8]
All MII[d]	3, 1.6 [0.0; 3.2]	3, 1.2 [0.0; 2.6]	5, 2.4 [0.3; 4.5]	–
Sepsis	–	1, 0.4 [0.0; 1.2]	–	–
VZV infection	1, 0.4 [0.0; 1.2]	1, 0.4 [0.0; 1.2]	–	–
Others MII	2, 1.2 [0.0; 2.6]	1, 0.4 [0.0; 1.2]	5, 2.4 [0.3; 4.5]	–
Incidence of IMD				
Incident uveitis	–	–	–	–
Incident IBD	–	–	–	–
Psoriasiform lesions	–	–	1, 0.5 [0.0; 1.4]	–
Lupus[e]	–	–	–	–
All Blood disorders	17, 6.9 [3.6; 10.2]	2, 0.8 [0.0; 2.0]	4, 1.9 [0.0; 3.8]	1, 1.9 [0.0; 5.5]
Leukopenia	10, 4.1 [1.6; 6.6]	–	2, 1.0 [0.0; 2.3]	1, 1.9 [0.0; 5.5]
Thrombocytopenia	1, 0.4 [0.0; 1.2]	–	–	–
Pancytopenia	–	–	–	–
MAS	4, 1.6 [0.0; 3.2]	–	1, 0.5 [0.0; 1.4]	–
Other hospitalisations[i]	2, 0.8 [0.0; 1.9]	2, 0.8 [0.0; 2.0]	–	–

Rituximab does not appear in this table because no side effects have been registered under this BAs.
AEs: adverse events; CI: confidence interval; EBV: Epstein–Barr virus; HPV: human papillomavirus; IMD: immune-mediated disease; MAS: macrophage activation syndrome; VZV: varicella-zoster virus.

[a] Relative to each biological agent.
[b] All AEs: mild, moderate, severe and very severe AE.
[c] SAE: life threatening, hospitalization, incapacity life functions, cancer, death.
[d] MII: infections that led to hospitalization and/or required intravenous antibiotic treatment.
[e] Lupus-like or positivity of the antinuclear antibodies.
[f] 3 under tocilizumab (2 MAS, 1 prescription error).
[g] 1 under tocilizumab (MAS) and 1 under canakinumab (demyelinating lesion).
[h] 2 under tocilizumab (1 digestive disorders with hepatic cytolysis, 1 thrombosis of the superior vena cava and subclavian vein).
[i] 2 under canakinumab (1 digestive disorders, 1 demyelinating lesion).

The highest incidence rate of blood disorders was found with tocilizumab (6.9 per 100 PY, 95% CI [3.6; 10.2]); for this drug, the most frequently reported were leukopenia, followed by MAS (Table 3). Mostly MAS occurred in patients with JIA disease (29 in systemic JIA subtype, one in a polyarthritis-rheumatoid factor negative JIA subtype, one in an extended oligoarticular JIA subtype), five had a probable infectious trigger. One episode of central nervous system demyelinating lesion was described during canakinumab treatment. No IMD was found during golimumab treatment, the number of prescriptions of golimumab treatment was 15 (1% of all prescriptions).

3.4. Factors associated with adverse events

In univariate analyses, patients receiving any concomitant treatment suffered from more frequent AE or SAE. This applied to association with azathioprine, cyclosporine, hydroxychloroquine, leflunomide and sulfasalazine for both AE and SAE and CTCs only for AE. Methotrexate was not significantly associated with AE and SAE. Among BAs, tocilizumab and infliximab contributed more than etanercept to the incidence rate of mild and moderate AEs (Appendix A, Table S3). Infliximab and canakinumab also contributed more than etanercept to the incidence rate of severe AEs,

Table 4
Univariate and multivariable analysis of serious adverse events.

	Univariate analysis		Multivariable analysis	
	HR [95% CI]	*P*	HR [95% CI]	*P*
Male sex	0.89 [0.47; 1.70]	NS	–	–
Age at diagnosis	0.99 [0.93; 1.06]	NS	–	–
Corticosteroids	1.02 [0.27; 3.81]	NS	–	–
Methotrexate (MTX)	0.99 [0.51; 1.94]	NS	–	–
Other immunosuppressive drugs[a]	3.50 [1.76; 6.94]	< 0.001	3.45 [1.62; 7.35]	< 0.05
Total number of biological agents[b]	1.20 [0.88; 1.62]	NS	–	–
JIA vs. non-JIA	0.72 [0.31; 1.67]	NS	–	–
Biological agents				
Etanercept	1	–	1	
Adalimumab	1.37 [0.49; 3.71]	NS	1.44 [0.53; 3.92]	NS
Tocilizumab	1.70 [0.55; 5.38]	NS	1.55 [0.47; 5.10]	NS
Infliximab	3.27 [1.42; 7.52]	< 0.05	2.73 [0.89; 5.84]	NS
Anakinra	2.77 [0.85; 9.97]	NS	2.93 [0.90; 9.55]	NS
Canakinumab	3.04 [1.05; 8.84]	< 0.05	3.85 [1.36; 10.90]	< 0.05
Abatacept[c]	NA	–	NA	–
Golimumab[c]	NA	–	NA	–
Rituximab[c]	NA	–	NA	–

Only variables with $P < 0.2$ in the univariate analysis were used as candidate in the multivariate model.
CI: confidence interval; HR: hazard ratio, JIA: juvenile inflammatory arthritis; NA: not available because convergence failure; NS: non-significant.
[a] Other immunosuppressive drugs include: azathioprine, cyclosporine, hydroxychloroquine, leflunomide and sulfasalazine.
[b] Total number of biological agents prescribed during the retrospective period of study. Note that, they are not the previous biological agents to the adverse event.
[c] Lack of convergence in rituximab, golimumab and abatacept.

very severe AEs and SAE (Appendix A, Fig. S1). Sex, age at diagnosis, number of BAs and type of disease (JIA or non-JIA) were not significantly associated with the incidence rate of AE or SAE (Table 4 and Appendix A, Table S3). The multivariable analyses also supported the association between other immunosuppressive drugs with AE (Appendix A, Table S3) and SAE (Table 4). Corticosteroids has been associated only with mild and moderate AEs (Appendix A, Table S3). In the group of anti-IL1, canakinumab was associated with a significant incidence rate of SAE in multivariable analysis (Table 4). Notably, no AE or SAE occurred with rituximab, abatacept, and golimumab, leading to lack of convergence in the statistical regression model of SAEs and AEs.

4. Discussion

The present study found an overall favourable outcome for children with paediatric inflammatory rheumatic diseases treated in real-life with all BAs in terms of severity and intensity of reported side effects, irrespective of the rheumatic disease. Despite the 4% rate for SAE, no sequelae were reported after BA discontinuation.

The incidence of SAE herein was lower for each BA when compared to that reported in the Finnish study which is the only retrospective observational investigation that also compared all BAs [13]. This difference may be in relation to the methodology employed because the Finnish study used at least three sources of information (medical records, as well as notes by nurses and other health professionals) to collect data, which increased the frequency of data collection and consequently multiplied the opportunities to detect an SAE. Conversely, in this study, only the medical records held by the rheumatologist were used. However, owing to the serious nature of these events they are more likely to be notified. Another plausible explanation may come from the difference in coding; the authors of the Finnish study note that the Common Terminology Criteria for AEs (CTCAE) system that they used codes neutropenia and ALT elevation as SAEs, which is not the case for the MedDRA classification used herein. These hypotheses are substantiated by the observation that SAE incidence rates for etanercept and adalimumab found in the present study were comparable to that previously reported in other registers/cohort studies [26–30] that also used a single source of data (for tolerance) and MedDRA.

In the regression model, a significant difference was found in the incidence of AE/SAE between the BAs investigated, irrespective of concomitant drug. Canakinumab in one hand and infliximab and tocilizumab in another hand were associated with an increased frequency of SAE and AE, respectively. Although the latter finding is not in agreement with a network meta-analysis performed in adult rheumatoid arthritis (RA) patients (the indirect comparisons made between the BAs were negative for the BAs analysed in this study), it is of note that there was a significant increase of withdrawal due to AEs in patients receiving infliximab in comparison to the control group [31]. The difference found herein for infliximab not could be explained by its indication as the second-line BA in patients with JIA in regards of our results. Other studies are needed to confirm our finding. Furthermore, the higher incidence of SAEs related to canakinumab treatment could be because these drugs are mainly used in auto-inflammatory diseases in paediatric patients, in particular, for systemic JIA subtype (one of the more severe diseases). Because of possible residual confounding bias (including MAS related to relapse of systemic JIA), these results must be interpreted with caution and should be viewed as exploratory.

In the present study, the combination of BAs and non-MTX immunosuppressive drugs was significantly associated with the incidence rate of AE and SAE. Corticosteroids were only associated with the occurrence of AE. Numerous studies reporting the occurrence of AE related to CTC exposure [32]. However, our study pointed the relation between non-MTX immunosuppressive drugs using a sparing in the burden of the disease. Contrarily to previous study in adults [33], the number of BAs prescribed as a risk factor for AEs or SAEs in juvenile inflammatory diseases was not associated with the occurrence AE. Beyond their efficacy to achieve remission [34,35], the present results question the weight of the non-MTX immunosuppressive drugs in the burden of paediatric rheumatologic diseases. This data suggests that other immunosuppressive drugs are more often associated with AEs and SAEs, irrespective of BAs in paediatric rheumatic disease. This may be because analyses of SAE are often performed in relation to a immunosuppressive drug without consideration of possible combinations [13,14,20]. Furthermore, in a Portuguese cohort of JIA patients [36], concomitant therapy with systemic CTCs was significantly associated with withdrawal of anti-TNFα treatments and was negative after adjusting on clinical covariates. Taken together, the results suggest that

monotherapy with BAs may be preferred when possible as well as de-escalation of immunosuppression after early aggressive therapy in JIA diseases [37–39]. Considering the risk of anti-drug antibody development, mainly in the anti-TNFα group the risk and benefit of a combination therapy should be balanced. A rate of 4% of occurrence of SAE is still unsatisfactory, therefore further investigations by prospective series and randomized trials are needed to help the clinician decide when a combination therapy is useful for the patient.

Additionally we described MII and IMD occurring during BA treatment, regardless of their severity, since they may better reflect long-term tolerance [23]. Focusing on infections, the higher rate of MII found with tocilizumab and anakinra may be explained by the severity of the underlying disease (systemic and polyarticular JIA subtypes and auto-inflammatory diseases), and as we discussed above by the co-prescription [40]. It is interesting to note that we found infections preventable by vaccines (chickenpox and measles). We also provide evidence that the IMDs are present mainly with anti-TNFα treatments; the most frequent IMD in this study with anti-TNFα treatments was clinical and/or biological manifestation of lupus. This would be consistent with a French retrospective series of patients with rheumatoid arthritis, that retrieved 22 patients with lupus-like syndrome induced by anti-TNFα, and who were all positive for antinuclear antibodies [41]. The positivity of antinuclear antibodies with anti-TNFα is also described in the paediatric population treated with infliximab [42] and etanercept [43]; this was also found herein for infliximab, etanercept, and adalimumab. To the best of our knowledge, there is no description of a paediatric series that analyses the incidence of this IMD, probably because it is more infrequent than in the adult population. Therefore, it is the clinical sense of the rheumatologist that directs the search for antinuclear antibodies in patients with paediatric rheumatic diseases treated with some anti-TNFα.

The strength of the study is to report the evaluation of BA safety observed in real life by paediatric rheumatologists from various centres (reference and competence centre) in 4 different countries. Thus, we have shown the safety profile of children treated by all available BAs, including off-label use, for all disease severity levels. We have also to acknowledge several limitations; first the retrospective design might be responsible for potential missing data that may lead to overestimation of the safety profile of BAs. In this sense to ensure the accuracy and consistency of results and to minimise errors, we decided to describe and analyse only severe and very severe AEs and SAEs, because these were most likely the events registered in the medical record. Second, because of the non-randomized design of the present study, we could not draw firm conclusions for the causal relation between AEs or SAEs and drug exposures. Third, the small number of children receiving rituximab, golimumab, and abatacept precludes firm conclusions to be made regarding safety issues. Four, it is noteworthy that, compared to the usual epidemiological data of JIA disease, the oligoarticular subtype was underrepresented in this study. In fact, this subtype is associated with less polyarticular involvement and is known to have a better prognosis and the use of BA was very infrequent in this setting [44]. To improve the quality of data collection, long-term follow-up of children treated with BAs may be undertaken, through national and/or international cohorts, as a way to identify of possible factors predisposing for the occurrence of AEs and SAEs related to BAs exposure in this population.

Disclosure of interest

The following authors: N.C., A.D., D.K., A.C., E.C., F.A., B.K., A.K., A.M., S.R., C.J., S.M., L.H., G.B., V.H., I.K.-P., and A.B. declare that they have no competing interest, J.-C. L. reports personal fees from Roche, during the conduct of the study. A.W. reports grants from Novartis, grants from Roche, grants from Pfizer, outside the submitted work; M.H. reports grants and personal fees from Abbvie, grants and personal fees from Novartis, outside the submitted work; C.W. reports grants from Roche, grants from Pfizer, outside the submitted work.

Acknowledgments

The authors express their sincere thanks to Dr. Maria-Luisa Cabañas (INCAN, Ministry of Public Health and Social Wellbeing of Paraguay), Dr. Paul Lee-Archer (Lady Cilento Children's Hospital, Brisbane, Australia) and Philip Robinson (DRCI, Hospices Civils de Lyon) for help in manuscript preparation.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at https://doi.org/10.1016/j.jbspin.2018.08.003.

References

[1] Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. Br J Clin Pharmacol 2015;79:357–69.
[2] Lovell DJ, Giannini EH, Reiff A, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med 2000;342:763–9.
[3] Ruperto N, Lovell DJ, Cuttica R, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum 2007;56:3096–106.
[4] Ruperto N, Lovell DJ, Quartier P, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet Lond Engl 2008;372:383–91.
[5] Horneff G, Foeldvari I, Minden K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol Hoboken NJ 2015;67:2240–9.
[6] Brunner HI, Ruperto N, Zuber Z, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis 2015;74:1110–7.
[7] Ramanan AV, Dick AD, Jones AP, et al. Adalimumab plus methotrexate for uveitis in juvenile idiopathic arthritis. N Engl J Med 2017;376:1637–46.
[8] Lachmann HJ, Kone-Paut I, Kuemmerle-Deschner JB, et al. Use of canakinumab in the cryopyrin-associated periodic syndrome. N Engl J Med 2009;360:2416–25.
[9] Koné-Paut I, Lachmann HJ, Kuemmerle-Deschner JB, et al. Sustained remission of symptoms and improved health-related quality of life in patients with cryopyrin-associated periodic syndrome treated with canakinumab: results of a double-blind placebo-controlled randomized withdrawal study. Arthritis Res Ther 2011;13:R202.
[10] Merrill J, Buyon J, Furie R, et al. Assessment of flares in lupus patients enrolled in a phase II/III study of rituximab (EXPLORER). Lupus 2011;20:709–16.
[11] Rovin BH, Furie R, Latinis K, et al. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the lupus nephritis assessment with rituximab study. Arthritis Rheum 2012;64:1215–26.
[12] Anton J, Calvo I, Fernández-Martin J, et al. Efficacy and safety of canakinumab in cryopyrin-associated periodic syndromes: results from a Spanish cohort. Clin Exp Rheumatol 2015;33:S67–71.
[13] Tarkiainen M, Tynjälä P, Vähäsalo P, et al. Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting. Rheumatol Oxf Engl 2015;54:1170–6.
[14] Otten MH, Anink J, Prince FHM, et al. Trends in prescription of biological agents and outcomes of juvenile idiopathic arthritis: results of the Dutch national arthritis and biologics in children register. Ann Rheum Dis 2015;74:1379–86.
[15] Kuemmerle-Deschner JB, Hofer F, Endres T, et al. Real-life effectiveness of canakinumab in cryopyrin-associated periodic syndrome. Rheumatol Oxf Engl 2016;55:689–96.
[16] Horneff G, Klein A, Klotsche J, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther 2016;18:272.
[17] Boneparth A, Wenderfer SE, Moorthy LN, et al. Clinical characteristics of children with membranous lupus nephritis: the childhood arthritis and rheumatology research alliance legacy registry. Lupus 2017;26:299–306.
[18] Amarilyo G, Tarp S, Foeldvari I, et al. Biological agents in polyarticular juvenile idiopathic arthritis: A meta-analysis of randomized withdrawal trials. Semin Arthritis Rheum 2016;46:312–8.
[19] Tarp S, Amarilyo G, Foeldvari I, et al. Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials. Rheumatol Oxf Engl 2016;55:669–79.

[20] Klotsche J, Niewerth M, Haas J-P, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis 2016;75:855–61.
[21] Beukelman T, Haynes K, Curtis JR, et al. Rates of malignancy associated with juvenile idiopathic arthritis and its treatment. Arthritis Rheum 2012;64:1263–71.
[22] Zahevi Niaki O, Clarke AE, Ramsey-Goldman R, et al. Malignancy incidence in 5294 patients with juvenile arthritis. RMD Open 2016;2:e000212.
[23] Swart JF, de Roock S, Wulffraat NM. What are the immunological consequences of long-term use of biological therapies for juvenile idiopathic arthritis? Arthritis Res Ther 2013;15:213.
[24] Crépin S, Villeneuve C, Merle L. Quality of serious adverse events reporting to academic sponsors of clinical trials: far from optimal. Pharmacoepidemiol Drug Saf 2016;25:719–24.
[25] Petty RE, Southwood TR, Manners P, et al. International league of associations for rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31:390–2.
[26] Horneff G, Schmeling H, Biedermann T, et al. The German etanercept registry for treatment of juvenile idiopathic arthritis. Ann Rheum Dis 2004;63:1638–44.
[27] Prince FHM, Twilt M, ten Cate R, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. Ann Rheum Dis 2009;68:635–41.
[28] Windschall D, Müller T, Becker I, et al. Safety and efficacy of etanercept in children with the JIA categories extended oligoarthritis, enthesitis-related arthritis and psoriasis arthritis. Clin Rheumatol 2015;34:61–9.
[29] Trachana M, Pratsidou-Gertsi P, Pardalos G, et al. Safety and efficacy of adalimumab treatment in Greek children with juvenile idiopathic arthritis. Scand J Rheumatol 2011;40:101–7.
[30] Schmeling H, Minden K, Foeldvari I, et al. Efficacy and safety of adalimumab as the first and second biologic agent in juvenile idiopathic arthritis: the German biologics JIA registry. Arthritis Rheumatol 2014;66:2580–9.
[31] Singh JA, Wells GA, Christensen R, et al. Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database Syst Rev 2011;16:CD008794.
[32] Hoes JN, Jacobs JWG, Verstappen SMM, et al. Adverse events of low- to medium-dose oral glucocorticoids in inflammatory diseases: a meta-analysis. Ann Rheum Dis 2009;68:1833–8.
[33] Hyrich KL, Lunt M, Watson KD, et al. Society for rheumatology biologics register. Outcomes after switching from one anti-tumor necrosis factor alpha agent to a second anti-tumor necrosis factor alpha agent in patients with rheumatoid arthritis: results from a large UK national cohort study. Arthritis Rheum 2007;56:13–20.
[34] Céspedes-Cruz A, Gutiérrez-Suárez R, Pistorio A, et al. Methotrexate improves the health-related quality of life of children with juvenile idiopathic arthritis. Ann Rheum Dis 2008;67:309–14.
[35] Wipff J, Sparsa L, Lohse A, et al. Impact of juvenile idiopathic arthritis on quality of life during transition period at the era of biotherapies. J Bone Spine Rev Rhum 2016;83:69–74.
[36] Mourão AF, Santos MJ, Melo Gomes JA, et al. Effectiveness and long-term retention of anti-tumour necrosis factor treatment in juvenile and adult patients with juvenile idiopathic arthritis: data from Reuma.pt. Rheumatol Oxf Engl 2016;55:697–703.
[37] Tynjälä P, Vähäsalo P, Tarkiainen M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis 2011;70:1605–12.
[38] Wallace CA, Giannini EH, Spalding SJ, et al. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. Arthritis Rheum 2012;64:2012–21.
[39] Hinze C, Gohar F, Foell D. Management of juvenile idiopathic arthritis: hitting the target. Nat Rev Rheumatol 2015;11:290–300.
[40] Davies HD. Infectious complications with the use of biologic response modifiers in infants and children. Pediatrics 2016;138:e20161209, http://dx.doi.org/10.1542/peds.2016-1209.
[41] De Bandt M, Sibilia J, Le Loët X, et al. Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey. Arthritis Res Ther 2005;7:545–51.
[42] Ruperto N, Lovell DJ, Cuttica R, et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension. Ann Rheum Dis 2009;69:718–22.
[43] Horneff G, Bock FD, Foeldvari I, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA registry. Ann Rheum Dis 2009;68:519–25.
[44] Devauchelle-Pensec V, Thepaut M, Pecquery R, et al. Managing monoarthritis in children. J Bone Spine Rev Rhum 2016;83:25–30.

SUPPLEMENTARY MATERIAL

TABLE S1: Characteristics of patients by index drugs in anti-TNFs at study enrolment

	Etanercept	Adalimumab	Infliximab	Golimumab
All prescription	492 (100)	236 (100)	142 (100)	15 (100)
Juvenile idiopathic arthritis	466 (95)	190 (81)	127 (88)	14 (93)
RF negative polyarthritis	111 (23)	44 (19)	36 (25)	4 (27)
Enthesitis–related arthritis	109 (22)	45 (19)	19 (13)	3 (20)
Systemic arthritis	55 (11)	6 (3)	13 (9)	–
Extended oligoarthritis	83 (17)	24 (10)	23 (16)	1 (7)
Persistent oligoarthritis	45 (9)	36 (15)	25 (18)	5 (33)
Psoriatic arthritis	27 (5)	17 (7)	5 (4)	–
RF positive polyarthritis	23 (5)	11 (5)	5 (4)	–
Unclassified arthritis	13 (3)	7 (3)	1 (1)	1 (7)
Non-JIA	26 (5)	46 (19)	15 (11)	1 (7)
Autoinflammatory diseases	5 (1)	–	–	–
TRAPS	4 (1)	–	–	–
HIDS	1 (0)	–	–	–
Idiopathic uveitis	–	28 (12)	–	–
IBD-related arthritis	3 (1)	6 (3)	6 (4)	–
Vasculitis	1 (0)	–	3 (2)	–
Kawasaki disease	–	–	2 (1)	–
Unclassified vasculitis	1 (0)	–	1 (1)	–
Connective tissue disease	4 (1)	1 (0)	–	–
Paediatric SLE	1 (0)	–	–	–
JDM and MCTD	3 (1)	1 (0)	–	–
CRMO	6 (1)	1 (0)	1 (1)	1 (7)
Behçet disease	2 (0)	4 (2)	4 (3)	–
Blau syndrome	1 (0)	3 (1)	1 (1)	–
SAPHO syndrome	4 (1)	3 (1)	–	–

CRMO: chronic recurrent multifocal osteomyelitis, HIDS: hyperimmunoglobinemia D and periodic fever, IBD: inflammatory bowel disease, JIA: juvenile idiopathic arthritis, JDM: juvenile dermatomyositis, MCTD: mixed connective tissue disease, SAPHO: synovitis, acne, pustulosis, hyperostosis and osteitis, SLE: systemic lupus erythematosus, TRAPS: tumor necrosis factor receptor associated periodic syndrome.

TABLE S2: Characteristics of patients by index drugs at study enrolment in other biological agents than anti-TNFs.

	Anakinra	Tocilizumab	Canakinumab	Abatacept	Rituximab
All prescription	85 (100)	80 (100)	75 (100)	37 (100)	17 (100)
Juvenile idiopathic arthritis	65 (76)	74 (93)	29 (39)	36 (97)	9 (53)
RF negative polyarthritis	1 (1)	16 (20)	1 (1)	18 (49)	3 (18)
Enthesitis–related arthritis	–	–	–	1 (3)	–
Systemic arthritis	62 (73)	45 (56)	28 (37)	4 (11)	4 (24)
Extended oligoarthritis	1 (1)	5 (6)	–	4 (11)	–
Persistent oligoarthritis	1 (1)	1 (1)	–	4 (11)	–
Psoriatic arthritis	–	1 (1)	–	2 (5)	–
RF positive polyarthritis	–	6 (8)	–	3 (8)	2 (12)
Non-JIA	20 (24)	6 (7)	46 (61)	1 (3)	8 (47)
Autoinflammatory diseases	17 (20)	–	45 (60)	–	–
Cryopyrinopathies	8 (9)	–	35 (47)	–	–
TRAPS	3 (4)	–	2 (3)	–	–
HIDS	3 (4)	–	4 (5)	–	–
FMF	3 (4)	–	4 (5)	–	–
Vasculitis	–	–	–	–	5 (29)
AAV	–	–	–	–	4 (24)
Takayasu arteritis	–	–	–	–	1 (6)
Connective tissue disease	–	3 (4)	–	1 (3)	3 (18)
Paediatric SLE	–	–	–	–	3 (18)
JDM and MCTD	–	3 (4)	–	1 (3)	–
CRMO	1 (1)	–	–	–	–
Behçet disease	–	–	–	–	–
Unclassified disease [A]	2 (2)	1 (1)	1 (1)	–	–
IPEX syndrome	–	1 (1)	–	–	–
Castleman disease	–	1 (1)	–	–	–

[A] Idiopathic pericarditis and unclassified autoinflammatory fever.

AAV: anti-neutrophil cytoplasmic antibody (ANCA)- associated *vasculitis*, CRMO: chronic recurrent multifocal osteomyelitis, FMF: familial mediterranean fever, HIDS: hyperimmunoglobinemia D and periodic fever, IBD: inflammatory bowel disease, IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked, JIA: Juvenile idiopathic arthritis, JDM: juvenile dermatomyositis, MCTD: mixed connective tissue disease, SAPHO: synovitis, acne, pustulosis, hyperostosis and osteitis, SLE: systemic lupus erythematosus, TRAPS: tumor necrosis factor receptor associated periodic syndrome.

.

TABLE S3: Univariate and multivariable analysis of adverse events

	Univariate analysis		Multivariable analysis	
	HR [95% CI]	***p***	**HR (95%CI)**	***p***
Male sex	0.97 [0.74; 1.29]	NS	–	–
Age at diagnosis	0.99 [0.96; 1.02]	NS	–	–
Corticosteroids	2.26 [1.64; 3.21]	<0.0001	1.78 [1.11; 2.87]	<0.05
Methotrexate (MTX)	0.98 [0.73; 1.39]	NS	–	–
Other immunosuppressive drugs [A]	1.75 [1.31; 2.35]	<0.001	1.44 [1.03; 2.02]	<0.05
Total number of biological agents [B]	1.27 [1.11; 1.45]	<0.001	1.14 [0.96; 1.35]	NS
JIA vs. non-JIA	0.98 [0.64; 1.49]	NS	–	–
Biological agents				
Etanercept	1	–	1	–
Adalimumab	1.13 [0.79; 1.61]	NS	1.09 [0.77; 1.53]	NS
Tocilizumab	2.20 [1.53; 3.15]	<0.0001	1.56 [0.95; 2.55]	<0.01
Infliximab	2.19 [1.63; 2.94]	<0.0001	1.95 [1.44; 2.64]	<0.0001
Anakinra	1.32 [0.72; 2.40]	NS	1.15 [0.61; 2.17]	NS
Canakinumab	1.57 [0.96; 2.57]	NS	1.55 [0.92; 2.60]	NS
Abatacept	1.32 [0.57; 3.11]	NS	1.13 [0.50; 2.57]	NS
Golimumab	0.75 [0.17; 3.29]	NS	0.77 [0.18; 3.35]	NS
Rituximab [C]	NA	–	NA	–

[A] Other immunosuppressive drugs include: azathioprine, cyclosporine, hydroxychloroquine, leflunomide and sulfasalazine.

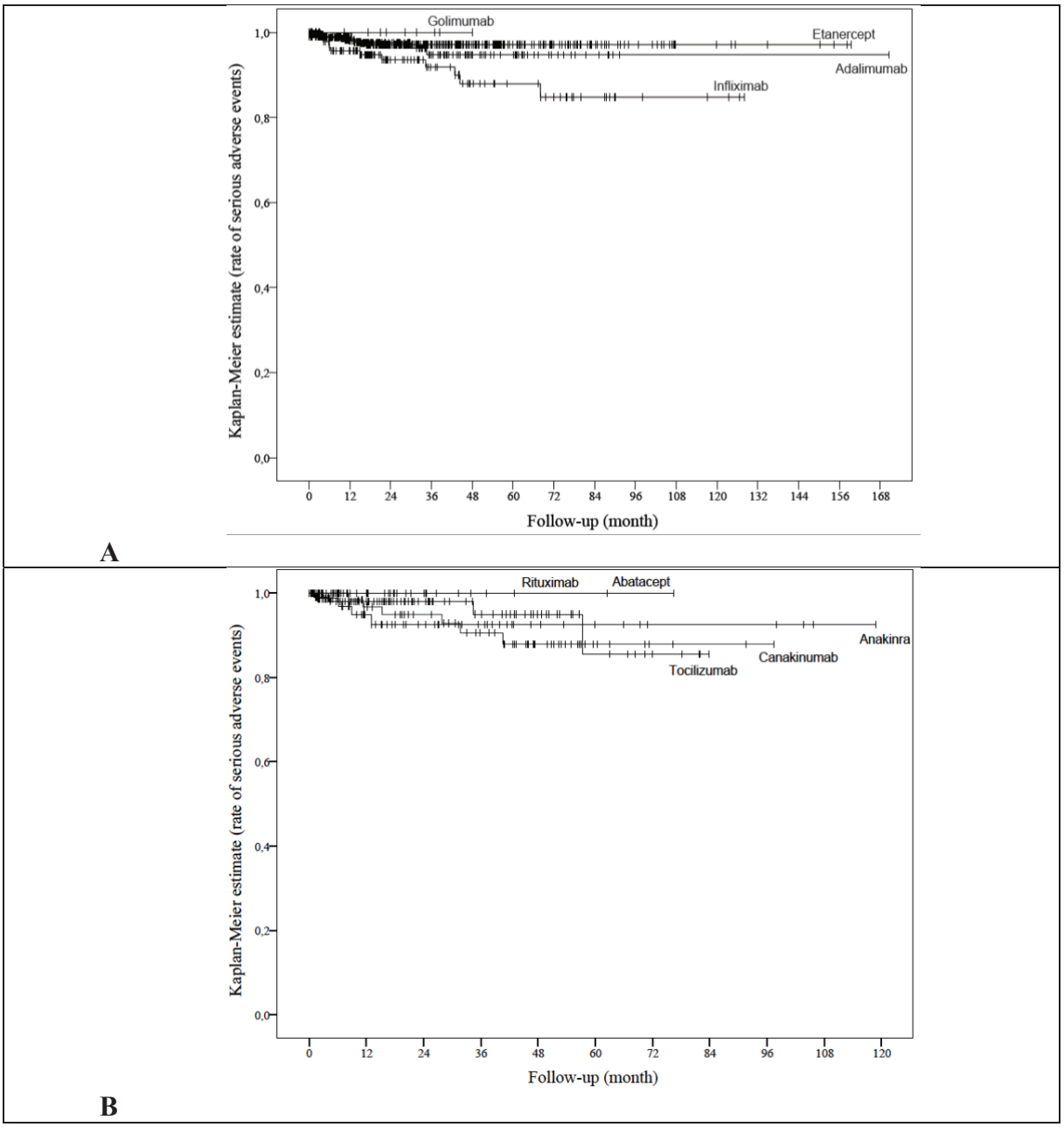
[B] Total number of biological agents prescribed during the retrospective period of study. Note that, they are not the previous biological agents to the adverse event.

[C] Lack of convergence in rituximab.

Only variables with p<0.2 in the univariate analysis were used as candidate in the multivariate model.

CI: confidence interval, HR: hazard ratio, JIA: juvenile inflammatory arthritis, NA: not available because convergence failure, NS: non-significant.

FIGURE S1: Rate of serious adverse events.



Result of the Kaplan-Meier plots of serious adverse events estimate of the probability of staying without serious adverse events in the anti-TNF biological agents' group (Figure A) and in the rest of biological agents (Figure B). Note that no serious adverse event was found under rituximab and golimumab. A lack of convergence in the analysis of serious adverse events for abatacept.

Long-terme tolérance des biothérapies dans l'arthrite juvénile idiopathique à partir des cohortes de suivi de patients

Article en relecture pour soumission

Safety of biological agents in juvenile idiopathic arthritis, a meta-analysis of observational studies

Natalia Cabrera[1], Gabriela Avila-Pedretti[2], Alexandre Belot[3], Jean-Paul Larbre[4], Giuliana Cattivelli[5], Esteban Paredes[5], Behrouz Kassai[1,6], Romain Euvrard[7], Guillaume Grenet[1], Anick Berard[1], Sabine Mainbourg[1,7], Jean-Christophe Lega[1,7]

[1] University of Lyon, UMR - CNRS 5558, *Laboratoire de Biométrie et Biologie Évolutive*, Claude Bernard University Lyon 1, F-69100, France.

[2] Department of Research, *Universidad Nacional de Asuncion*, San Lorenzo 2160, Paraguay.

[3] INSERM U1111, National Referral Centre for rare Juvenile Rheumatological and Autoimmune Diseases (RAISE) and Department of Paediatric Rheumatology, Lyon University Hospital, University of Lyon.

[4] Department of Rheumatology, *Centre Hospitalier Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite*, France

[5]Faculty of Medicine. *Universidad Nacional de Asuncion*, San Lorenzo 2160, Paraguay

[6] Department of Pharmaco-toxicology, Clinical Investigation Centre 1407, INSERM, Hospices Civils de Lyon, 69003 Lyon, France.

[7] National Referral Centre for rare Juvenile Rheumatological and Autoimmune Diseases (RAISE), Department of Internal and Vascular Medicine, *Centre Hospitalier Lyon Sud, Hospices Civils de Lyon*, *Pierre-Bénite*, France.

PROSPERO register number: CRD42019137980

http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42019137980

Corresponding author

Natalia Cabrera, MD

University of Lyon, UMR - CNRS 5558, *Laboratoire de Biométrie et Biologie Évolutive*, *Claude Bernard* University Lyon 1, F-69100, France.

9 Rue Guillaume Paridin, 69008, Lyon – France

e-mail: natalia.rojas@etu.univ-lyon1.fr

ABSTRACT

Objectives: To estimate the incidence of serious adverse events (SAEs), serious infections, malignancies, and death in patients with juvenile idiopathic arthritis (JIA) treated with biological agents (BAs), using meta-analysis techniques.

Methods: We systematically searched, up to May 2019, Medline and Embase databases for observational studies performed in JIA disease under BAs treatment. Outcomes were single reporting of SAEs, serious infections, malignancies and cancer. Complementary, a comparison with the incidence of SAEs from randomised controlled trials (RCTs) was made.

Results: A total of 31 observational studies were included (6811 patients with 17530 patients-years [PY] of follow-up). The incidence rate of SAEs was similar in observational cohorts and withdrawal RCTs (4.46 events per 100 PY, 95% CI [2.85; 6.38]) and 3.71 events per 100 PY, 95% CI [0.0; 13.34], respectively). The incidence rate of serious infections, malignancies and death was estimated at 0.74 events per 100 PY, 95% CI [0.32; 1.30]), 0.10 events per 100 PY (95% CI [0.06; 0.16]) and 0.09 events per 100 PY (95% CI [0.05; 0.14]), respectively, from observational cohorts. Infections were the known cause of death in 8 out of 14 patients. In meta-regression and subgroup analysis, variation of serious infections rates was partially explained by follow-up time (R^2= 30.3%, p= 0.0008), JIA categories (all JIA versus polyarticular versus systemic JIA categories, p= 0.001) and cohort quality (Newcastle-Ottawa score ≥ to 6 versus ≤ to 5 stars, p= 0.0025).

Conclusion: Our results suggest that the incidence rate of SAEs related to BAs in JIA disease is similar to those observed in randomised withdrawal trials. The overall incidence remained low. However, there is an unsatisfactory description of SAEs prevents analysis of hospitalisation causes. Infection and, to a lesser extent, cancer and death, explain only part of burden of BAs.

Key words:

Meta-analysis, juvenile idiopathic arthritis, serious adverse events, incidence rate, biological agents

Key messages:

1. Observational studies suggest acceptable safety of biological agents (BAs) in patients with juvenile idiopathic arthritis (JIA).
2. Incidence rate of serious adverse events related to BAs in JIA disease are similar to those observed in randomised withdrawal trials.
3. Unsatisfactory description of SAEs related to BAs in JIA patients prevents analysis of hospitalisation causes.

INTRODUCTION

The changes in legislation in the early 2000s within the U. S. Food and Drugs Administration and the European Medicines Agency, allowed an unprecedented therapeutic advance in juvenile idiopathic arthritis (JIA), including biological agents (BAs) (1). In order to monitor the safety of these new targeted treatments, follow-up cohorts were initiated consecutively or simultaneously to the development of randomised controlled trials (RCTs) in JIA patients. Thus, European and North American countries have established national database registries where the effectiveness and safety are estimated through "real-world data" (2). They help to identify many complications observed only in clinical practice related to off label use, coadministration of treatments, drug misuse, exposition of rare or unexpected event. In addition, observational studies include a higher number of patients with a longer duration of follow-up compared to randomised trials. Hence, they have a higher sensitivity to capture the occurrence of serious adverse events (SAE) in daily clinical practice (3).

Definition of SAEs by the Food and Drugs Administration is the following: death, life-threatening, hospitalisation (initial or prolonged), disability or permanent damage, congenital anomaly, event that required intervention to prevent permanent impairment or other (important medical events) (4). SAEs are non-systematic adverse events and should be reported, may be by participants to investigators or collected in response to open-ended question (5). For regulatory and reporting purposes, ‘severity’ is related to the intensity of adverse event and is not synonymous with ‘seriousness’. In JIA disease, the SAEs of particular interest are serious infections and malignancies (6–8).

Focusing on long-term tolerance, this study aims to assess the incidence of SAEs, serious infections, malignancies and death in patients with JIA treated with BAs, using meta-analysis approaches.

METHODS

We conducted an original systematic review of observational studies of BAs in JIA patients and integrated the results of a concomitant systematic review of RCTs in the same field.

Regarding the systematic review of observational studies

The protocol of the study has been registered before in the International prospective register of systematic reviews (PROSPERO), available in https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=137980, register number: CRD42019137980. Reporting method was consistent with current recommendations of Meta-analysis of observational studies in epidemiology group (MOOSE group) (9). A completed checklist is available in Appendix (Table A4)

Search strategies

A systematic review was conducted in the two major databases of observational studies: MEDLINE and EMBASE database independently by 2 investigators (NC and GAP) from inception March to May 2019. The following keywords were used: "juvenile idiopathic arthritis", "safety", "tolerance". We used names of individual drugs of each of the ten BAs currently prescribed in paediatric rheumatology (etanercept, adalimumab, infliximab, golimumab, anakinra, canakinumab, rilonacept, rituximab, abatacept and tocilizumab) (see Table A1 and A2). The research strategy excludes the key words “randomized controlled trial”. We have not used hand searching or search software and did not contact the authors of the included articles. Articles in English, Spanish and French have been included.

Inclusion criteria were, (i) cohort studies with at least ten patients with JIA or one of the categories of JIA disease (ii) treated by BAs and which (iii) reported safety data of JIA population. Exclusion criteria were : mixed data of several BAs (as they would not allow to estimate incidences of adverse event for each class of BA), cohorts that did not assess the safety

of BAs, and sub-studies of included studies. Eligibility of studies was determinate independently by each investigator (NC and GAP).

Data extraction

The extracted data were: first author's last name, title of the article, year and journal of publication, country where the study was conducted (or countries, in the case of multicentre studies), population size, age, gender, BAs drugs, follow-up time and patients-years (PY) of follow-up. We also extracted data of potential confounders, including previous BAs, co-prescription of immunosuppressant drugs and time of disease progression. The safety data for the analysis included the following: number of any adverse events, number of SAEs including (i) cancer, (ii) severe infections, (ii) hospitalizations for non-infectious causes, and (iv) death. The definition of SAEs used for this study was that recommended by the Medical Dictionary for Regulatory Activities (MedDRA: https://www.meddra.org). Regarding the diagnosis, JIA categories were considered separately. Data extraction was performed independently by 3 investigators (NC, GC and EP) and independently verified by a 4th investigator (GA), differences were resolved by consensus.

Quality assessment

Quality of included studies was also independently evaluated by two investigators (NC and GAP) using the Newcastle-Ottawa quality assessment scale (NOS scale) that explores three board areas: selection, comparability, and ascertainment of the exposure or outcome of interest in cohort studies (10).

Statistical analysis

The pooled incidence rate of SAE of interest, and its 95% confidence interval (95% CI) among JIA patients treated with BAs, were estimated using inverse variance method and Freeman-Tukey arcsine transformation (11,12). For the analysis of events of interest, in which most of the studies contained zero events because they were very rare events (scarcity of data in

malignancies and death), we used a generalized linear mixed (GLM) model based on the Poisson regression with random effect term for the variant component (13,14).

Heterogeneity between study-specific estimates was assessed using inconsistency index (I_2). If substantial heterogeneity was observed (I_2 >50%), a random-effects model was used. Once heterogeneity was established, subgroup and meta-regression analyses were performed to investigate further between-study sources of heterogeneity with random-effects model (15,16). Meta-regression was performed only if number of studies was superior to 10, in order to avoid overfitting.

The risk of publication bias was determined by funnel plot aspect and Egger regression test for asymmetry analysis (17). A p-value below 0.05 was considered statistically significant in all analyses, without adjustment for multiple testing. These analyses were conducted in observational and experimental (e.g. randomised controlled trial) separately. All analyses were performed with R version 3.4 (R Development Core Team [2008]. R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria with package 'meta' [version 4.9-2] and 'metafor' [version 2.0-0]).

Regarding the systematic review of randomised controlled trials

In addition, to compare incidence from pivotal study and real-life data, we used a database of randomised trials conducted by the same author of this study. Details of inclusion criteria, data extraction and quality assessment of these other study are described in the registered protocol (PROSPERO registered number CRD42018107592). This review contains randomised trials of BAs in the JIA. For this present study, we use only SAEs during the randomised period in the experimental group from RCTs (patients treated with BAs). The pooled incidence rate of SAEs from RCTs, was conducted following the same methodology described above for observational studies.

RESULTS

Search results and study quality

The initial search strategy identified a total of 478 publications from the two consulted databases. After automatic removal of duplicates, 428 studies are remained, of which 107 appeared relevant after title and abstract screening. Seventy articles did not meet the inclusion criteria after full-text reading. The flowchart is detailed in Figure 1.

On the quality assessment, the mean score was 4.8 ± 1.0 standard deviation (SD) in the whole included cohorts. Prospective cohorts (n= 13) and retrospective cohorts (n= 18) have a mean score equal to 4.8 ± 1.0 SD, each. Most of the studies had four stars: seven prospective (18–24) and six retrospective (25–30) cohorts. One retrospective cohort had two stars (31), one cohort has the maximum scale score with seven stars (32) and the rest had five (33–44) or six stars (45–50).

Study characteristics

A total of 31 observational studies were included, of which 13 (42%) cohorts were prospective and 18 (58%) cohorts were retrospective (Table 1). We included four studies that considered anti-TNFs as a group because they have clear safety data (22,37,42,44). We excluded three studies in which safety results were pooled without discriminating the type of BAs (2,43,45).

The included cohorts comprised a total of 6811 patients: 32% (n= 2169) in prospective cohorts and 68% (n= 4642) in retrospective cohorts. Total follow-up of whole cohorts was 17530 PY. The mean age of patients in prospective cohorts was 10.2 years with a mean follow-up of 35.4 months (7146 PY) and the mean age of patients in retrospective cohorts was 9.7 years with a mean follow-up of 32.4 months (10384 PY) (Table 1). Nearly two-third of patients were female (n= 4571, 67%). Most patients had polyarticular forms of JIA (n= 3637, 53.4%), including rheumatoid factor (RF) negative polyarticular JIA (n= 2035, 29.9%), extended polyarticular (n= 927, 13.6%), polyarticular without RF specification (n= 214, 3.1%) and RF positive

polyarticular JIA (n= 461; 6.8%) categories. Systemic onset JIA represented 16.5% (n= 1122), enthesitis-related arthritis JIA 8.3% (n= 566), persistent oligoarticular 7.1%, (n= 483), psoriatic arthritis 4.5% (n= 304) and undifferentiated JIA 2.0% (n= 134) of included patients in cohorts. Two articles (n= 565, 8.3% patients) did not provide distribution by category of the included JIA patients (33,37). Ten articles specified the use of MedDRA to define and codify adverse events in patients treated with BAs (2,20,32,35,40,45,47,49–51). However, all included cohorts defined serious infections in the same way as 'life-threatening, requiring intravenous antibiotics or hospitalisation'.

Three cohorts were international with patients from Switzerland, France, Morocco, Italy, United States, Belgium, Canada and The Netherlands (34,50,52). Seven studies were from Germany (18–20,32,35,36,46), four from Italy (26,31,44,47), three from Finland (22,41,42), two from France (28,38) and five from other European countries (21,27,39,40,49). Three cohorts were from the United States of America (30,37,45), two from Japan (23,48), 2 from Russia (24,25) one from Korea (33) and one from Brazil (43) (Table 1).

Hospitalisations were not described enough to separate those related to an infection and those related to other causes. Within the group of SAEs, only serious infections, malignancies and death could be analysed. Funnel plots and Egger test for SAEs (p= 0.039) and serious infections (p= 0.006) showed a potential pattern of publication bias. Visual interpretation was in favour of an under-representation of small studies with low incidence of SAE and serious infection (Figure A2, A and B), and of a p hacking phenomenon regarding Figure A2(B), where greater proportion of studies with significant effect size were published.

Concerning the systematic review of RCTs, we identified 18 randomised studies with BAs in JIA. To perform meta-analysis of incidence of SAEs, we decided to separate the 11 parallel RCTs (53–63) from the eight withdrawal RCTs (64–71), because they had a different study design.

Incidence of serious adverse events

Observational studies - The incidence rate of SAEs for the studies BAs was 4.46 events per 100 PY, 95% CI [2.85; 6.38]). A high heterogeneity was found (I^2= 95%, p<0.01). Pooled incidence of SAEs according to BAs ranged from 2.11 events per 100 PY, 95% CI [0.70; 4.12] (etanercept) to 18.14 events per 100 PY, 95% CI [12.92; 24.23] (canakinumab), with high heterogeneity for each BAs (Figure 2).

Randomised trials - Incidence rate of SAEs from parallel and withdrawal RCTs was 29.03 events per 100 PY, 95% CI [6.51; 62.73] and 3.71 events per 100 PY, 95% CI [0.0; 13.34], respectively. Significant heterogeneity was observed in both meta-analyses (I^2 = 74%, p= <0.01 and I^2= 56%, p= 0.03, respectively) (Table A3).

Incidence of serious infections, malignancies and deaths

Observational studies - The incidence rate of serious infections was estimated at 0.74 events per 100 PY, 95% CI [0.32; 1.30]) with high heterogeneity (I^2= 83%) (Figure 3). The incidence rate of malignancies and death was estimated at 0.10 events per 100 PY (95% CI [0.06; 0.16], I^2= 0%) and 0.09 events per 100 PY (95% CI [0.05; 0.14], I^2= 0%), respectively (Figure A1). Pooled incidence of serious infections according to BAs ranged from 0.22 events per 100 PY, 95% CI [0.0; 5.66], I^2= 40%) for tocilizumab to 2.42 events per 100 PY, 95% CI [0.0; 18.56] for anakinra.

In total, 16 cases of malignancies and 14 deaths were found in this meta-analysis. Hodgkin's disease was the most frequently described malignancy in cohorts. Infections were the known cause of death in 8 patients. Death cases occurred with etanercept and adalimumab (Table 5).

Heterogeneity analysis

Serious adverse event - The meta-regression and subgroup analyses did not show variable that could explain heterogeneity for SAEs (Tables 3 and 4).

Serious infection - The time of follow-up was negatively associated with the rate of incidence of serious infections (coefficient = -0.018, R_2= 30.3%, p= 0.0008) in meta-regression (Table 3). In subgroup analysis, the differences in the incidence rate of serious infections were significantly associated with JIA categories (all JIA categories together versus polyarticular JIA versus systemic JIA category has 0.37events per 100 PY, 95% CI [0.11; 0.72], 2.62 events per 100 PY, 95% CI [0.87; 5.02] and 2.10 events per 100 PY, 95% CI [0.0; 20.78], respectively with p= 0.001) and quality of studies (NOS score ≥ to 6 with 0.34 serious infections per 100 PY, 95% CI [0.18; 0.54] and NOS score ≤ 5 with 1.25 serious infections per 100 PY, 95% CI [0.51; 2.19], respectively with p= 0.0025) (Table 4).

In subgroup analyses according to JIA categories, significant heterogeneity (I_2>50%) was observed for incidence rate of SAEs and serious infections. Most cohorts present their data considering all categories together (Figure 2 and 3).

DISCUSSION

The incidence of SAEs is estimated at 4.46 events per 100 PY, and mainly corresponds to non-infectious events. The incidence of malignancies and death in patients receiving BAs was very low. These estimations are limited by the large heterogeneity that is partially explained by the time of follow-up, the categories of JIA and quality of included cohorts for serious infection. To the best of our knowledge, this is the first meta-analysis interested in the incidence of SAEs from observational data from cohorts of patients with JIA treated with available BAs.

The considerable heterogeneity could somewhat explain the asymmetry in the funnel plot (72). In addition, publication bias may be present. We observed large sample size cohorts that reported high incidence of SAEs and serious infections (absence of dots in the lower left corner of the funnel plot). As a consequence, the incidence of SAE related to BAs may be over-estimated by the present meta-analysis.

The overall incidence rate of SAEs found in this meta-analysis for all included BAs (4.46 events per 100 PY) was comparable to the incidence rate observed from pooled estimates of withdrawal RCTs (3.71 events per 100 PY, 95% CI [0.0; 13.34]). The pooled estimates of incidence of SAEs from parallel RCTs is greater (29.03 events per 100 PY). The differences founded between the parallel RCTs and observational studies or between RTCs (e.g. parallel versus withdrawal RCTs) were according to their designs and the fact that only the responders (to the clinical efficacy criterion) participate in the randomised phase of the trial. We assume that the responders would have been patients who have tolerated well the BAs during the open phase of the withdrawal RCTs (73).

The incidence of serious infections with etanercept and infliximab of this meta-analysis appears to be lower compared to the results of a systematic review from open-phase randomised trials in JIA patients (incidence ratio: 3.7 and 3.1 per 100 PY, respectively). The open phase studies have patients that participated in the randomised phase of the trial, so they are probably the

most symptomatic subgroup of patients and risk of infections are increased in JIA patients independently of immunosuppressive treatment (74). For adalimumab, the incidence of serious infections that we found was similar to the one reported by a study that analysed data from controlled trials including randomised phase, open-label phase, and long-term follow-up (75). This discrepancy could be attributed to the length of follow-up. In both studies, the follow-up was a maximum of 2 years for most of the patients, only in the case of adalimumab, 30% of the patients were followed for more than 5 years. All available biotherapies do not have observational safety studies, we found only one cohort of patients with JIA on rituximab (24) and another one cohort on canakinumab (34). Long-term follow-up of patients with JIA is still not optimal in most included cohorts.

Nonetheless, none of the articles cited above described cases of death or malignancy with etanercept and adalimumab, contrary to our results (75,76). More data are available to analyse rare effects, such as malignancies in JIA patients, from anti-TNFs than other BAs. They are the BAs group with the longest follow-up time in paediatric rheumatology, as etanercept was the first BA used in JIA disease and the one with the longest observation follow-up time (77). Studies that considered anti-TNFs as a group were included because clearly safety allowed the meta-analysis (22,37,42,44). Summarised data from general United States population (a database from clinical trials and post marketing reports) founded an incidence rate of 0.016 malignancies per 100 PY in paediatric population under etanercept treatment (78). Investigations from a multicentric study (4 paediatric rheumatology cohorts in Canada and 2 in the United States, with 5108 JIA patients and 34224 PY of observation across 1971-2011), found an over-all standardised incidence risk of malignancies of 0.89 in JIA patients (7). Serious infections, malignancies and death do not explain most of the SAEs with BAs in JIA patients. Perhaps there are other events to take into account such as immunological ones (uveitis, lupus-like syndrome, allergic reactions or cytopenia) (3). The SAEs ideally should be

described in detail, in order to be analysed. In these days, the growing dependence on safety data generated by these observational cohorts, led to the establishment of guidelines in an attempt to standardise safety analysis and reporting for new and existing registries in rheumatology (79). No follow-up data found from JIA patients treated by rituximab. One article including less than ten patients reported the safety of abatacept or golimumab (50).

The heterogeneity observed in this meta-analysis could be due to several causes. First, most of studies analyse the JIA categories all together. As suggested by the subgroup analysis, in the categories group of JIA there are autoimmune forms and other auto-inflammatory forms with very different ages and clinical presentations. In addition, the quality of included cohorts (assessed by the NOS score) was significantly associated with differences in the incidence rate of serious infections. Second, as discussed above, the asymmetry of the funnel plot probably represents the heterogeneity in BAs effects into the incidence of serious infections and also may be a publication bias (72). Third, differences in sample size of the included cohorts, and the fact that they are observational data could explain some of the heterogeneity found.

In order to perform a meta-analysis, we used only variables that we considered would be best defined in all cohorts, those were: serious adverse events, serious infections, malignancies and death. We exclusively used cohorts' studies in order to harmonize as much as possible with the data collection methodology. For the same reason, we conducted a subgroup analysis according to the study design (prospective or retrospective). We have not considered the open phase extension of the randomised controlled trials because it mainly contains responders and represents a subpopulation of patients with JIA disease (80). Nevertheless, results must be interpreted considering all the weaknesses of observational studies and bearing in mind the large heterogeneity discussed above. We acknowledge some limitations such as that we did not contact the authors of the articles, in case of doubt we resolved them by consensus, and we have not analysed opportunistic infections, since in some studies there was no detail of them.

In conclusion, the results of this meta-analysis suggest that the incidence rate of SAEs with the use of BAs in JIA disease is low. Long-term follow-up of patients with JIA is still not optimal in observational studies. Although the interpretation and generalizability of results are limited by potential biases, safety data are reassuring. Serious infections, cancer and death explain only part of the SAEs.

REFERENCES

1. Berard RA, Laxer RM. Learning the hard way: clinical trials in juvenile idiopathic arthritis. Ann Rheum Dis. 2018;77(1):1–2.

2. Swart J, Giancane G, Horneff G, Magnusson B, Hofer M, Alexeeva E, et al. Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: combined data of more than 15,000 patients from Pharmachild and national registries. Arthritis Res Ther. 2018 27;20(1):285.

3. Swart JF, de Roock S, Wulffraat NM. What are the immunological consequences of long-term use of biological therapies for juvenile idiopathic arthritis? Arthritis Res Ther. 2013;15(3):213.

4. FDA O of the. What is a Serious Adverse Event? FDA [Internet]. 2019 Jan 8 [cited 2019 Aug 28]; Available from: http://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event

5. Mayo-Wilson E, Fusco N, Li T, Hong H, Canner JK, Dickersin K, et al. Harms are assessed inconsistently and reported inadequately Part 2: nonsystematic adverse events. J Clin Epidemiol. 2019 Sep;113:11–9.

6. Delcoigne B, Horne A, Askling J. OP0001 Risk of malignancy in children with juvenile idiopathic arthritis: a register-based cohort study. Ann Rheum Dis. 2018 Jun 1;77(Suppl 2):50–50.

7. Sasha Bernatsky OZN. Cancer Risk in 5,108 Patients with Juvenile Idiopathic Arthritis (JIA). ACR Meeting Abstracts.

8. Horneff G. Biologic-associated infections in pediatric rheumatology. Curr Rheumatol Rep. 2015 Nov;17(11):66.

9. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000 Apr 19;283(15):2008–12.

10. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010 Sep;25(9):603–5.

11. Miller JJ. The Inverse of the Freeman – Tukey Double Arcsine Transformation. Am Stat. 1978 Nov;32(4):138–138.

12. Munn Z, Moola S, Lisy K, Riitano D, Tufanaru C. Methodological guidance for systematic reviews of observational epidemiological studies reporting prevalence and cumulative incidence data. Int J Evid Based Healthc. 2015 Sep;13(3):147–53.

13. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. Res Synth Methods. 2019 Apr 4;

14. Spittal MJ, Pirkis J, Gurrin LC. Meta-analysis of incidence rate data in the presence of zero events. BMC Med Res Methodol. 2015 Apr 30;15(1):42.

15. Thompson SG, Higgins JPT. How should meta-regression analyses be undertaken and interpreted? Stat Med. 2002 Jun 15;21(11):1559–73.

16. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002 Jun 15;21(11):1539–58.

17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629–34.

18. Windschall D, Müller T, Becker I, Horneff G. Safety and efficacy of etanercept in children with juvenile idiopathic arthritis below the age of 2 years. Rheumatol Int. 2015 Apr;35(4):613–8.

19. Windschall D, Horneff G. Safety and efficacy of etanercept and adalimumab in children aged 2 to 4 years with juvenile idiopathic arthritis. Clin Rheumatol. 2016 Dec;35(12):2925–31.

20. Tzaribachev N, Kuemmerle-Deschner J, Eichner M, Horneff G. Safety and efficacy of etanercept in children with juvenile idiopathic arthritis below the age of 4 years. Rheumatol Int. 2008 Aug;28(10):1031–4.

21. Otten MH, Prince FHM, Armbrust W, ten Cate R, Hoppenreijs EPAH, Twilt M, et al. Factors associated with treatment response to etanercept in juvenile idiopathic arthritis. JAMA. 2011 Dec 7;306(21):2340–7.

22. Lahdenne P, Vähäsalo P, Honkanen V. Infliximab or etanercept in the treatment of children with refractory juvenile idiopathic arthritis: an open label study. Ann Rheum Dis. 2003 Mar;62(3):245–7.

23. Imagawa T, Takei S, Umebayashi H, Yamaguchi K, Itoh Y, Kawai T, et al. Efficacy, pharmacokinetics, and safety of adalimumab in pediatric patients with juvenile idiopathic arthritis in Japan. Clin Rheumatol. 2012 Dec;31(12):1713–21.

24. Alexeeva EI, Valieva SI, Bzarova TM, Semikina EL, Isaeva KB, Lisitsyn AO, et al. Efficacy and safety of repeat courses of rituximab treatment in patients with severe refractory juvenile idiopathic arthritis. Clin Rheumatol. 2011

Sep;30(9):1163–72.

25. Alexeeva E, Dvoryakovskaya T, Denisova R, Sleptsova T, Isaeva K, Chomahidze A, et al. Comparative analysis of the etanercept efficacy in children with juvenile idiopathic arthritis under the age of 4 years and children of older age groups using the propensity score matching method. Mod Rheumatol. 2019 Jan 3;1–8.

26. Bracaglia C, Buonuomo PS, Tozzi AE, Pardeo M, Nicolai R, Campana A, et al. Safety and efficacy of etanercept in a cohort of patients with juvenile idiopathic arthritis under 4 years of age. J Rheumatol. 2012 Jun;39(6):1287–90.

27. De Inocencio Arocena J, Merino Muñoz R, Alvarez Madrid C, García-Consuegra Molina J. [Efficacy of etanercept in the treatment of juvenile idiopathic arthritis]. An Pediatr Barc Spain 2003. 2009 Apr;70(4):354–61.

28. Lequerré T, Quartier P, Rosellini D, Alaoui F, De Bandt M, Mejjad O, et al. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis. 2008 Mar;67(3):302–8.

29. Nigrovic PA, Mannion M, Prince FHM, Zeft A, Rabinovich CE, van Rossum MAJ, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum. 2011 Feb;63(2):545–55.

30. Tambralli A, Beukelman T, Weiser P, Atkinson TP, Cron RQ, Stoll ML. High doses of infliximab in the management of juvenile idiopathic arthritis. J Rheumatol. 2013 Oct;40(10):1749–55.

31. Verazza S, Davì S, Consolaro A, Bovis F, Insalaco A, Magni-Manzoni S, et al. Disease status, reasons for discontinuation and adverse events in 1038 Italian children with juvenile idiopathic arthritis treated with etanercept. Pediatr Rheumatol Online J. 2016 Dec 20;14(1):68.

32. Klotsche J, Niewerth M, Haas J-P, Huppertz H-I, Zink A, Horneff G, et al. Long-term safety of etanercept and adalimumab compared to methotrexate in patients with juvenile idiopathic arthritis (JIA). Ann Rheum Dis. 2016 May;75(5):855–61.

33. Choi JY, Chung JE, Park JH, Cho YS, Jung YW, Choi SA. Surveillance of adverse drug events associated with etanercept prescribed for juvenile idiopathic arthritis in a single center up to 9-years: A retrospective observational study. PloS One. 2018;13(11):e0204573.

34. Horneff G, Ruperto N, Brunner H, Quartier P, Constantin T, Alexeeva E, et al. Long term efficacy and safety of canakinumab in children with systemic juvenile idiopathic arthritis with and without fever. Pediatr Rheumatol Online J. 2015 Sep 28;13(Suppl 1):O83.

35. Horneff G, Klein A, Klotsche J, Minden K, Huppertz H-I, Weller-Heinemann F, et al. Comparison of treatment response, remission rate and drug adherence in polyarticular juvenile idiopathic arthritis patients treated with etanercept, adalimumab or tocilizumab. Arthritis Res Ther. 2016.

36. Horneff G, Schulz AC, Klotsche J, Hospach A, Minden K, Foeldvari I, et al. Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. Arthritis Res Ther. 2017

37. Lee W-J, Lee TA, Suda KJ, Calip GS, Briars L, Schumock GT. Risk of serious bacterial infection associated with tumour necrosis factor-alpha inhibitors in children with juvenile idiopathic arthritis. Rheumatol Oxf Engl. 2018 Feb 1;57(2):273–82.

38. Quartier P, Taupin P, Bourdeaut F, Lemelle I, Pillet P, Bost M, et al. Efficacy of etanercept for the treatment of juvenile idiopathic arthritis according to the onset type. Arthritis Rheum. 2003 Apr;48(4):1093–101.

39. Southwood TR, Foster HE, Davidson JE, Hyrich KL, Cotter CB, Wedderburn LR, et al. Duration of etanercept treatment and reasons for discontinuation in a cohort of juvenile idiopathic arthritis patients. Rheumatol Oxf Engl. 2011 Jan;50(1):189–95.

40. Trachana M, Pratsidou-Gertsi P, Pardalos G, Kozeis N, Badouraki M, Kanakoudi-Tsakalidou F. Safety and efficacy of adalimumab treatment in Greek children with juvenile idiopathic arthritis. Scand J Rheumatol. 2011 Mar;40(2):101–7.

41. Tynjälä P, Vähäsalo P, Honkanen V, Lahdenne P. Drug survival of the first and second course of anti-tumour necrosis factor agents in juvenile idiopathic arthritis. Ann Rheum Dis. 2009 Apr;68(4):552–7.

42. Tarkiainen M, Tynjälä P, Vähäsalo P, Lahdenne P. Occurrence of adverse events in patients with JIA receiving biologic agents: long-term follow-up in a real-life setting. Rheumatol Oxf Engl. 2015 Jul;54(7):1170–6.

43. Brunelli JB, Schmidt AR, Sallum AME, Goldenstein-Schainberg C, Bonfá E, Silva CA, et al. High rate of serious infection in juvenile idiopathic arthritis patients under biologic therapy in a real-life setting. Mod Rheumatol. 2018 Mar;28(2):264–70.

44. Pastore S, Naviglio S, Canuto A, Lepore L, Martelossi S, Ventura A, et al. Serious Adverse

Events Associated with Anti-Tumor Necrosis Factor Alpha Agents in Pediatric-Onset Inflammatory Bowel Disease and Juvenile Idiopathic Arthritis in A Real-Life Setting. Paediatr Drugs. 2018 Apr;20(2):165–71.

45. Beukelman T, Kimura Y, Ilowite NT, Mieszkalski K, Natter MD, Burrell G, et al. The new Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry: design, rationale, and characteristics of patients enrolled in the first 12 months. Pediatr Rheumatol Online J. 2017 Apr 17;15(1):30.

46. Bielak M, Husmann E, Weyandt N, Haas J-P, Hügle B, Horneff G, et al. IL-6 blockade in systemic juvenile idiopathic arthritis - achievement of inactive disease and remission (data from the German AID-registry). Pediatr Rheumatol Online J. 2018 Apr 5;16(1):22.

47. Gerloni V, Pontikaki I, Gattinara M, Fantini F. Focus on adverse events of tumour necrosis factor alpha blockade in juvenile idiopathic arthritis in an open monocentric long-term prospective study of 163 patients. Ann Rheum Dis. 2008 Aug;67(8):1145–52.

48. Mori M, Sugiyama N, Morishima Y, Sugiyama N, Kokubo T, Takei S, et al. Safety and effectiveness of etanercept for treatment of juvenile idiopathic arthritis: Results from a postmarketing surveillance. Mod Rheumatol. 2018 Jan;28(1):101–7.

49. Zuber Z, Rutkowska-Sak L, Postępski J, Dobrzyniecka B, Opoka-Winiarska V, Kobusińska K, et al. Etanercept treatment in juvenile idiopathic arthritis: the Polish registry. Med Sci Monit Int Med J Exp Clin Res. 2011 Dec;17(12):SR35-42.

50. Cabrera N, Lega J-C, Kassai B, Wouters C, Kondi A, Cannizzaro E, et al. Safety of biological agents in paediatric rheumatic diseases: A real-life multicenter retrospective study using the JIRcohorte database. Jt Bone Spine Rev Rhum. 2019 May;86(3):343–50.

51. Mori M, Nakagawa M, Tsuchida N, Kawada K, Sato J, Sakiyama M, et al. Proposal for the development of biologics in pediatric rheumatology. Pediatr Int Off J Jpn Pediatr Soc. 2018 Feb;60(2):108–14.

52. Nigrovic PA, Mannion M, Prince FHM, Zeft A, Rabinovich CE, van Rossum MAJ, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum. 2011 Feb;63(2):545–55.

53. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2007 Sep;56(9):3096–106.

54. Tynjälä P, Vähäsalo P, Tarkiainen M, Kröger L, Aalto K, Malin M, et al. Aggressive Combination Drug Therapy in Very Early Polyarticular Juvenile Idiopathic Arthritis (ACUTE–JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011 Sep 1;70(9):1605–12.

55. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011 May;70(5):747–54.

56. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized Trial of Tocilizumab in Systemic Juvenile Idiopathic Arthritis. N Engl J Med. 2012 Dec 20;367(25):2385–95.

57. Horneff G, Fitter S, Foeldvari I, Minden K, Kuemmerle-Deschner J, Tzaribacev N, et al. Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement. Arthritis Res Ther. 2012 Oct 24;14(5):R230.

58. Burgos-Vargas R, Tse SML, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res. 2015 Nov;67(11):1503–12.

59. Ramanan AV, Dick AD, Jones AP, McKay A, Williamson PR, Compeyrot-Lacassagne S, et al. Adalimumab plus Methotrexate for Uveitis in Juvenile Idiopathic Arthritis. N Engl J Med. 2017 27;376(17):1637–46.

60. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis. N Engl J Med. 2012 Dec 20;367(25):2396–406.

61. Lovell DJ, Giannini EH, Reiff AO, Kimura Y, Li S, Hashkes PJ, et al. Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. Arthritis Rheum. 2013 Sep;65(9):2486–96.

62. Ilowite NT, Prather K, Lokhnygina Y, Schanberg LE, Elder M, Milojevic D, et al. Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. Arthritis Rheumatol Hoboken NJ. 2014 Sep;66(9):2570–9.

63. Hissink Muller PCE, Brinkman DMC, Schonenberg D, Koopman-Keemink Y, Brederije ICJ, Bekkering WP, et al. A comparison of three treatment strategies in recent onset non-systemic Juvenile Idiopathic Arthritis: initial 3-months results of the BeSt for Kids-study. Pediatr Rheumatol Online J. 2017 Feb 6;15(1):11.

64. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. Pediatric Rheumatology Collaborative Study Group. N Engl J Med. 2000 Mar 16;342(11):763–9.

65. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008 Aug 21;359(8):810–20.

66. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum. 2010 Jun;62(6):1792–802.

67. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet Lond Engl. 2008 Mar 22;371(9617):998–1006.

68. Ilowite N, Porras O, Reiff A, Rudge S, Punaro M, Martin A, et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. Clin Rheumatol. 2009 Feb;28(2):129–37.

69. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis. N Engl J Med. 2012 Dec 20;367(25):2396–406.

70. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015 Jun 1;74(6):1110–7.

71. Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kümmerle-Deschner JB, Tenbrock K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol Hoboken NJ. 2015 May;67(8):2240–9.

72. Lau J, Ioannidis JPA, Terrin N, Schmid CH, Olkin I. The case of the misleading funnel plot. BMJ. 2006 Sep 16;333(7568):597–600.

73. Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J Clin Pharmacol. 2015 Mar;79(3):357–69.

74. Hurd A, Beukelman T. Infectious complications in juvenile idiopathic arthritis. Curr Rheumatol Rep. 2013 May;15(5):327.

75. Diener C, Horneff G. Comparison of adverse events of biologicals for treatment of juvenile idiopathic arthritis: a systematic review. Expert Opin Drug Saf. 2019 Aug;18(8):719–32.

76. Burmester GR, Panaccione R, Gordon KB, McIlraith MJ, Lacerda APM. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2012 May 5;72(4):517–24.

77. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in Children with Polyarticular Juvenile Rheumatoid Arthritis. N Engl J Med. 2000 Mar 16;342(11):763–9.

78. Hooper M, Wenkert D, Bitman B, Dias VC, Bartley Y. Malignancies in children and young adults on etanercept: summary of cases from clinical trials and post marketing reports. Pediatr Rheumatol Online J. 2013 Oct 2;11(1):35.

79. Dixon WG, Carmona L, Finckh A, Hetland ML, Kvien TK, Landewe R, et al. EULAR points to consider when establishing, analysing and reporting safety data of biologics registers in rheumatology. Ann Rheum Dis. 2010 Sep;69(9):1596–602.

80. Brunner HI, Rider LG, Kingsbury DJ, Co D, Schneider R, Goldmuntz E, et al. Pediatric Rheumatology Collaborative Study Group - over four decades of pivotal clinical drug research in pediatric rheumatology. Pediatr Rheumatol Online J. 2018 Jul 11;16(1):45.

81. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2007;56(9):3096–106.

82. Tynjälä P, Vähäsalo P, Tarkiainen M, Kröger L, Aalto K, Malin M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011 Sep;70(9):1605–12.

83. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra

in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011 May;70(5):747–54.

84. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized Trial of Tocilizumab in Systemic Juvenile Idiopathic Arthritis. N Engl J Med. 2012 Dec 20;367(25):2385–95.

85. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis. N Engl J Med. 2012 Dec 20;367(25):2396–406.

86. Horneff G, Foeldvari I, Minden K, Trauzeddel R, Kümmerle-Deschner JB, Tenbrock K, et al. Efficacy and safety of etanercept in patients with the enthesitis-related arthritis category of juvenile idiopathic arthritis: results from a phase III randomized, double-blind study. Arthritis Rheumatol Hoboken NJ. 2015 May;67(8):2240–9.

87. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without Methotrexate in Juvenile Rheumatoid Arthritis. N Engl J Med. 2008;359(8):810–20.

88. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. Lancet Lond Engl. 2008 Aug 2;372(9636):383–91.

89. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015 Jun;74(6):1110–7.

FUNDING

Individual scholarship (Paraguay's BECAL* program) attributed to a one author (NC). None other funding was received from any public, commercial or non-profit organization to carry out the work described in this manuscript.

* BECAL: *Becas Don Carlos Antonio Lopez* (http://www.becal.gov.py)

DISCLOSURES

The authors declare that they have not competing interest

TABLES AND FIGURES

FIGURE 1: Flowchart of search strategy

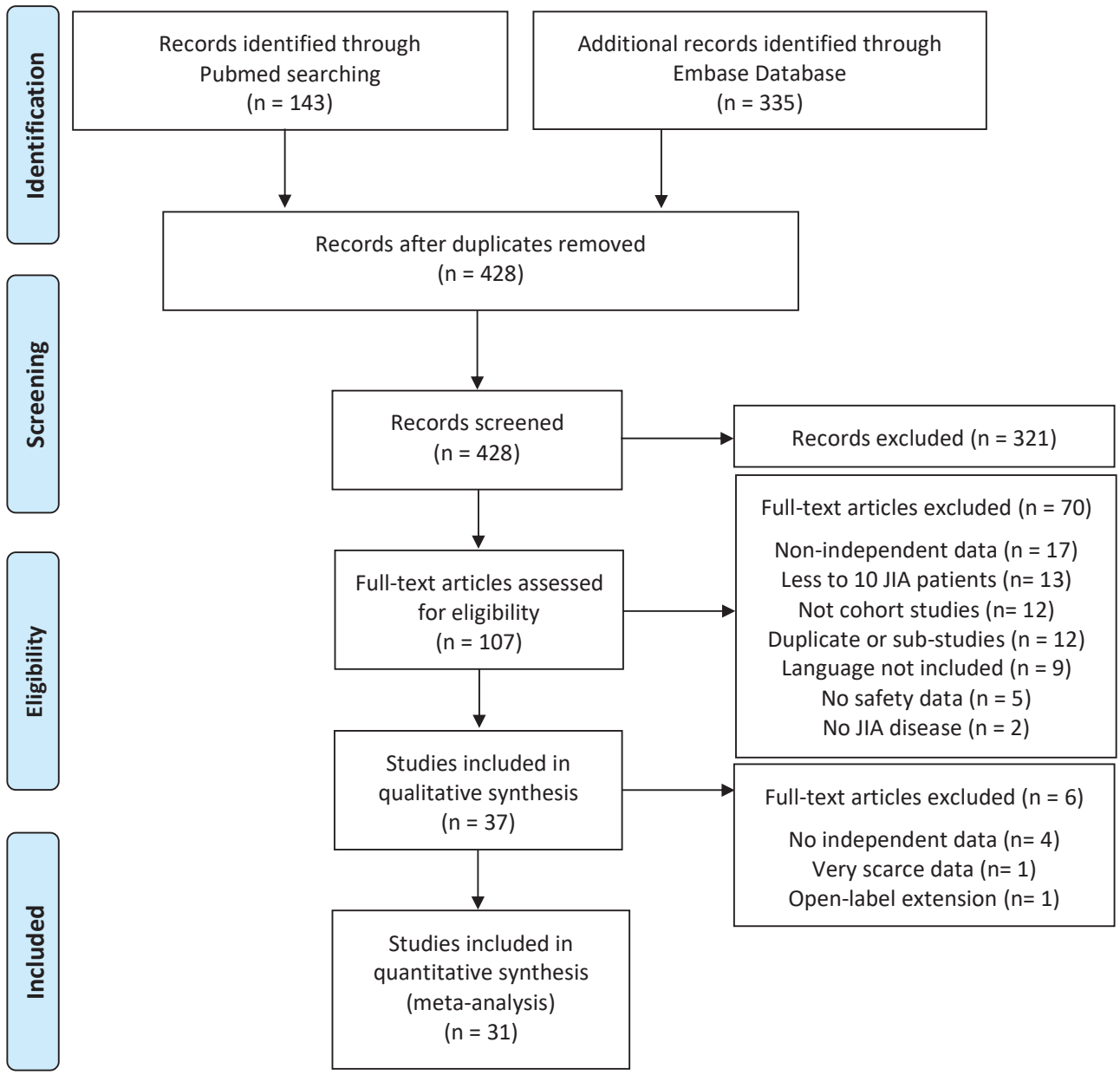


Table 1: Study characteristics of included cohorts

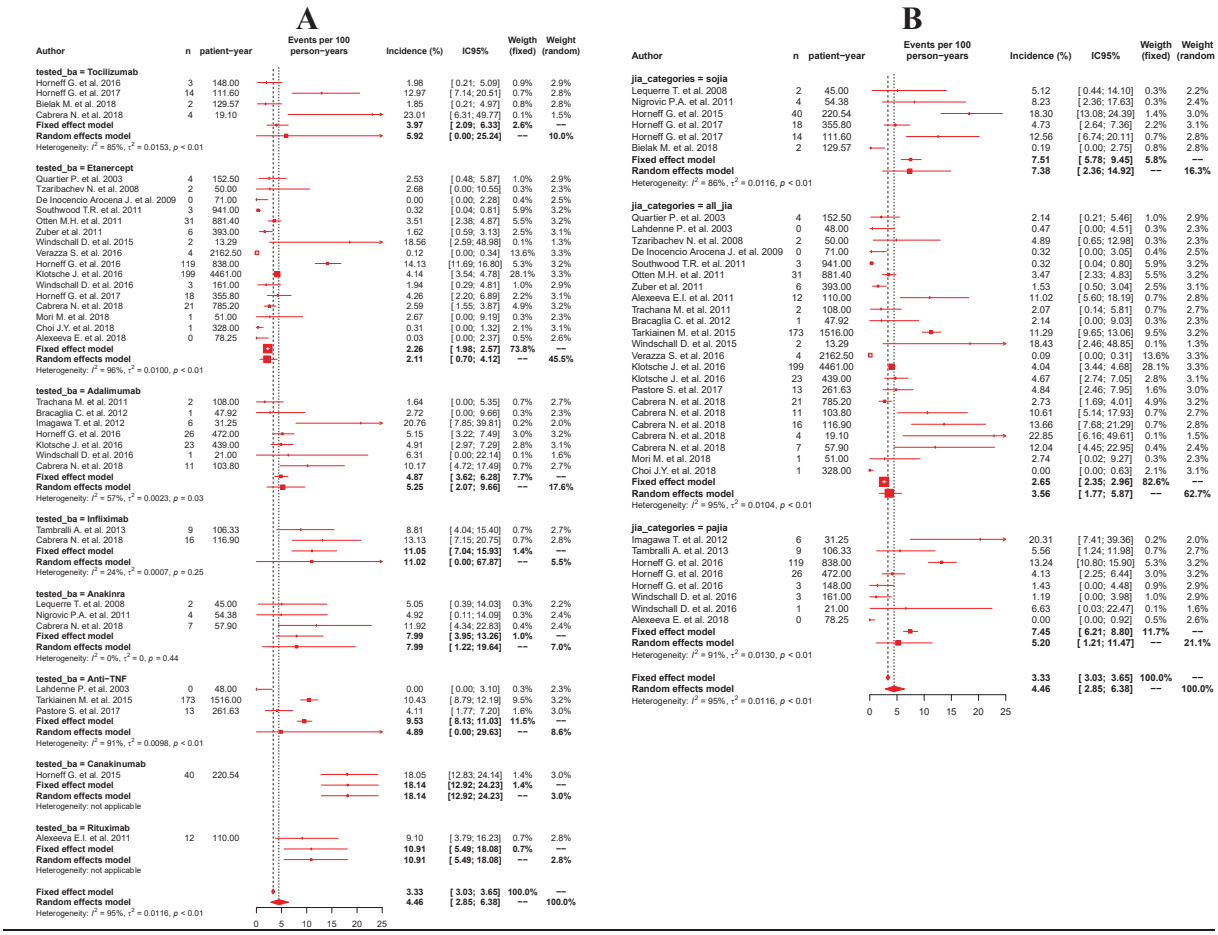
Author and year of publication(ref)	Type of cohort	Country of study	Biological agents	N	Mean age	Disease duration§	Follow-up§
Lahdenne, P., et al. 2003 (22)	Prosp	Finland	Anti-TNFA	24	10.2	1.0	48
Quartier, P., et al. 2003 (38)	Prosp	France	Etanercept	61	12.2	5.6	30
Gerloni, V., et al. 2008 (47)	Prosp	Italy	Etanercept	95	17.1	10.7	72
Gerloni, V., et al. 2008 (47)	Prosp	Italy	Infliximab	68	17.1	10.7	72
Lequerre, T., et al. 2008 (28)	Retro	France	Anakinra	20	12.4	7.0	27
Tzaribachev, N., et al. 2008 (20)	Prosp	Germany	Etanercept	25	1.7	0.6	24
De Inocencio A, J., et al. 2009 (27)	Retro	Spain	Etanercept	71	11.3	NA	12
Tynjälä, P., et al. 2009 (41)	Retro	Finland	Etanercept	105	10.1	5.0	48
Tynjälä, P., et al. 2009 (41)	Retro	Finland	Infliximab	104	10.1	5.0	48
Alexeeva, E. I., et al. 2011 (24)	Prosp	Russian	Rituximab	55	9.3	4.5	24
Otten, M. H., et al. 2011 (21)	Prosp	Netherland	Etanercept	262	12.4	3.0	36
Trachana, M., et al. 2011 (40)	Prosp	Greece	Adalimumab	26	12.6	NA	48
Nigrovic, P. A., et al. 2011 (29)	Retro	International	Anakinra	46	NA	7.6	15
Southwood, T. R., et al. 2011* (39)	Retro	England	Etanercept	483	12.0	NA	60
Żuber., et al. 2011 (49)	Retro	Poland	Etanercept	188	10.0	4.3	25
Bracaglia, C., et al. 2012 (26)	Retro	Italy	Etanercept	25	3.3	1.2	23
Imagawa, T., et al. 2012 (23)	Prosp	Japan	Adalimumab	25	13.0	4.5	15
Tambralli, A., et al. 2013 (30)	Retro	USA	Infliximab	58	11.9	3.0	22
Horneff, G., et al. 2015 (23)	Prosp	International	Canakinumab	122	NA	NA	94
Windschall, D., et al. 2015 (18)	Prosp	Germany	Etanercept	11	1.7	0.6	15
Tarkiainen M. et al. 2015 (42)	Retro	Finland	Anti-TNFB	348	10.8	6.1	51
Klotsche, J., et al. 2016 (32)	Prosp	Germany	Etanercept	1162	12.3	4.8	66
Klotsche, J., et al. 2016 (32)	Prosp	Germany	Adalimumab	46	12.9	5.3	66
Windschall, D. et al. 2016 (19)	Prosp	Germany	Etanercept	74	3.1	1.3	24
Horneff, G., et al. 2016 (35)	Retro	Germany	Etanercept	419	10.5	3.6	24
Horneff, G., et al. 2016 (35)	Retro	Germany	Adalimumab	236	11.8	5.8	24
Horneff, G., et al. 2016 (35)	Retro	Germany	Tocilizumab	74	12.9	6.1	24
Verazza, S., et al. 2016 (31)	Retro	Italy	Etanercept	1038	10.1	3.5	25
Windschall, D. et al. 2016 (19)	Prosp	Germany	Adalimumab	11	3.5	1.8	24
Horneff, G., et al. 2017 (36)	Retro	Germany	Etanercept	143	NA	9.4	24
Horneff, G., et al. 2017 (36)	Retro	Germany	Tocilizumab	71	NA	9.3	24
Pastore S., et al. 2017 (44)	Retro	Italy	Anti-TNFsB	78	5.1	3.1	NA
Alexeeva, E., et al. 2018 (25)	Retro	Russian	Etanercept	49	2.8	0.6	24
Bielak, M., et al. 2018 (46)	Retro	Germany	Tocilizumab	46	11.0	2.0	34
Cabrera N., et al. 2018 (50)	Retro	International	Available BAsC	681	7.5	NA	82
Choi, J. Y., et al. 2018 (33)	Retro	Korea	Etanercept	83	10.5	NA	74
Lee, W. J., et al. 2018 (37)	Retro	USA	Anti-TNFsD	482	10.4	NA	10
Mori, M., et al. 2018 (48)	Prosp	Japan	Etanercept	102	13.3	NA	6
Total (mean ± SD)				**6811**	**9.9 ± 4.0**	**4.6 ± 2.9**	**33.7 ± 19.5**

*Cohort that started retrospectively and then continue to include patients prospectively. §Disease duration in years and follow-up in months.

A: etanercept and infliximab, B: etanercept, adalimumab and infliximab, C: available BAs: etanercept, adalimumab, infliximab, tocilizumab and anakinra, D: all available anti-TNFs (etanercept, adalimumab, infliximab, golimumab and certolizumab).

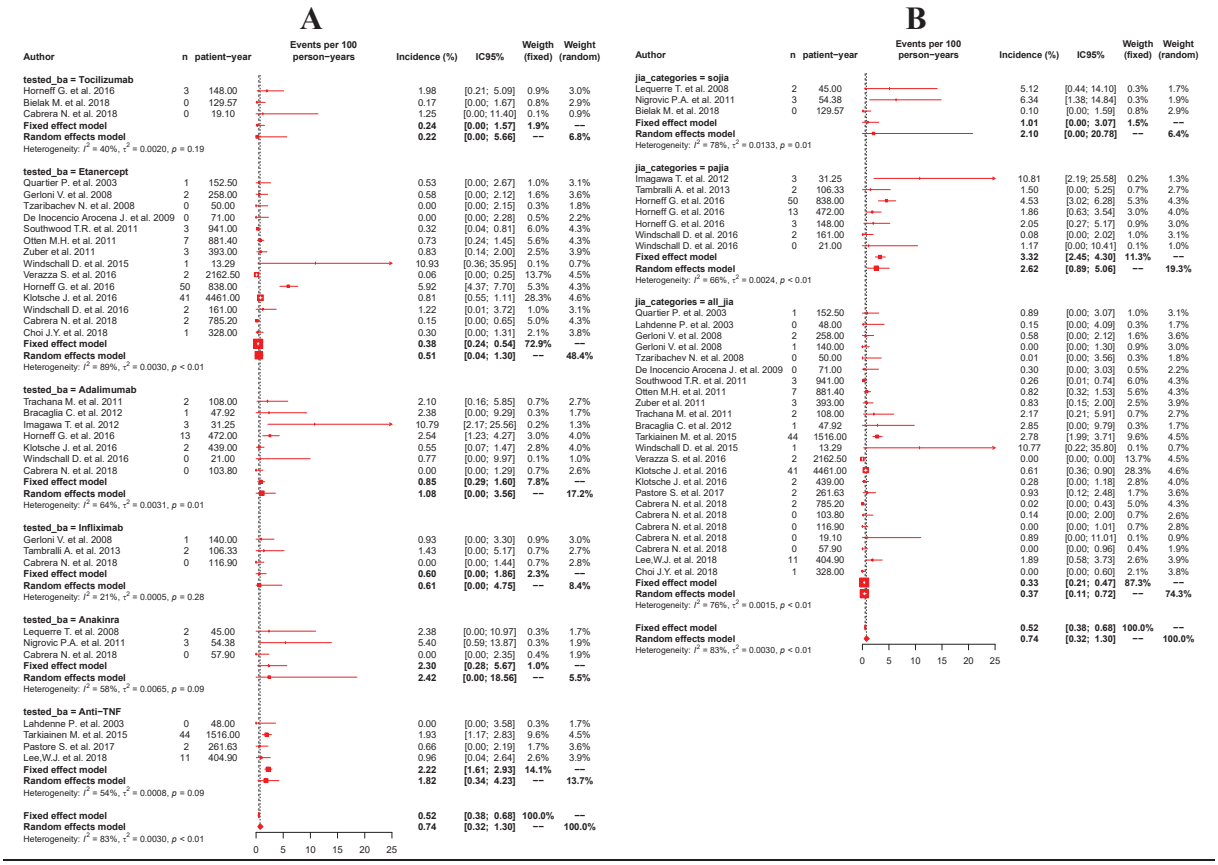
BAs: biological agents, NA: not available, Prosp: prospective, SD: standard deviation, Retro: retrospective, SAEs: serious adverse events, USA: Unite States of America.

Figure 2: Forest plots for incidence rate of serious adverse events according to group of biological agents (A) and juvenile idiopathic arthritis categories (B)



Meta-analysis made according to Freeman-Tukey arcsine transformation and method of inverse of variance (11). For each study, the square indicates the effect size and whiskers, the 95% CI of the study. The diamond indicates the overall effect size of all studies combined.
all_jia: all JIA categories analysed together, ba: biological agent, CI: confidence interval, pajia: polyarticular JIA categories, sojia: systemic onset JIA category, TNF: tumor necrosis factor

Figure 3: Forest plots for incidence rate of serious infections according to group of biological agents (A) and juvenile idiopathic arthritis categories (B)



Meta-analysis made according to Freeman-Tukey arcsine transformation and method of inverse of variance (11). For each study, the square indicates the effect size and whiskers, the 95% CI of the study. The diamond indicates the overall effect size of all studies combined.
all_jia: all JIA categories analysed together, ba: biological agent, CI: confidence interval, pajia: polyarticular JIA categories, sojia: systemic onset JIA category, TNF: tumor necrosis factor

Table 3: Heterogeneity analysis of serious adverse events and serious infections by meta-regression

	k	Coefficient* [95% CI]	R_2	p
Serious adverse events				
Follow-up (in years)	36	-0.0064 [-0.029; 0.016]	0.0%	0.58
Mean-age (in years)	29	0.0002 [-0.011; 0.011]	0.0%	0.99
Year of publication	37	0.0051 [-0.0041; 0.014]	0.03%	0.28
Co-prescription				
Corticosteroids	31	0.0007 [-0.0006; 0.0021]	0.0%	0.30
Methotrexate	27	0.0007 [-0.0006; 0.0021]	0.0%	0.86
Serious infections				
Follow-up (in years)	33	**-0.018 [-0.029; -0.0075]**	**30.3%**	**0.0008**
Mean-age (in years)	29	-0.0016 [-0.0085; 0.0053]	0.0%	0.82
Year of publication	34	-0.0008 [-0.0062; 0.0046]	0.0%	0.77
Co-prescription				
Corticosteroids	26	-0.0001 [-0.0010; 0.0012]	0.0%	0.86
Methotrexate	22	-0.0001 [-0.0011; 0.0009]	0.0%	0.86

Coefficient interpretation: incidence rate increase or decrease for the augmentations of one unit of the variable tested.

Table 4: Exploring heterogeneity of serious adverse events and serious infections by subgroup analysis

	k	Incidence rate per 100 PY [95% CI]	I_2	p-value
Serious adverse events				
Study design				0.71
Retrospective cohorts	23	4.37[2.31; 7.00]	96.3%	
Prospective cohorts	14	4.61 [2.15; 7.85]	81.4%	
JIA categories				0.28
All JIA categories	23	2.65 [2.35; 2.96]	95.3%	
PA JIA categories	8	5.20 [1.21; 11.47]	90.8%%	
SoJIA category	6	7.38 [2.36; 14.92]	86.5%	
NOS score quality				0.78
≥ to 6 stars	10	4.75 [1.97; 8.56]	82.1%	
≤ to 5 stars	27	4.18 [2.31; 6.54]	95.9%	
Serious infections				
Study design				0.29
Retrospective cohorts	21	0.91 [0.31; 1.74]	89.2%	
Prospective cohorts	14	0.28 [0.068; 0.59]	6.8%	
JIA categories				**0.001**
All JIA categories	24	0.37 [0.11; 0.72]	75.7%	
PA JIA categories	7	2.62 [0.87; 5.02]	66.0%	
SoJIA category	3	2.10 [0.0; 20.78]	78.0%	
NOS score quality				**0.0025**
≥ to 6 stars	11	0.34 [0.18; 0.54]	0%%	
≤ to 5 stars	23	1.25 [0.51; 2.19]	87.7%	

BAs= biological agents, JIA: juvenile idiopathic arthritis, NOS: Newcastle-Ottawa score, PA: polyarticular, SoJIA: systemic-onset JIA category, TNF: tumor necrosis factor.

Table 5: Description of malignancies and causes of death found in the review

Biological agent / Outcome	N of patients	Description
Malignancies		
Etanercept	6	Hodgkin's disease (18,20,32,36,50)(42)
	2	Thyroid carcinomas (31,32)
	1	EBV induced lymphoma (35)
	1	Urothelial carcinoma (31)
	1	Ovarian yolk sac tumor (32)
	1	Anaplastic oligodendroglioma (32)
	1	Non-Hodgkin lymphoma (32)
Adalimumab	1	Non-Hodgkin lymphoma (32)
	1	Anaplastic oligodendroglioma (32)
Tocilizumab	1	Hodgkin's disease (46)
Death		
Etanercept	4	Shock septic (31,32,36)
	2	Unknown (21,36)
	2	Unknown [A] (39)
	1	Macrophage activation syndrome (32)
	1	Carditis (32)
	1	Pneumonia [B] and hypoplastic bone marrow (42)
	1	Pneumonia and septicaemia (42)
	1	Pneumonia [C] (50)
Adalimumab	1	Shock septic (40)

A: according to the textual transcription of the article 'after discontinuation of etanercept use, one while admitted to hospital before bone marrow transplant and one after bone marrow transplant'.
B: pneumonia due to *Pneumocystis jirovecii*.

APPENDIX

ADDITIONAL TABLES AND FIGURES

Table A1: Criteria used for including studies using the PICO framework

Components	Pre-specified criteria
Population	paediatrics / juvenile idiopathic arthritis
Intervention	biologicals agents (bDMARDs)
Comparator§	versus cDMARDs* OR versus placebo
Outcome	Safety
Type studies	Observational studies

§if available. *bDMARDs: biological disease-modifying antirheumatic drugs, cDMARDs: conventional disease-modifying antirheumatic drugs

Table A2: Full electronic search strategy for EMBASE database

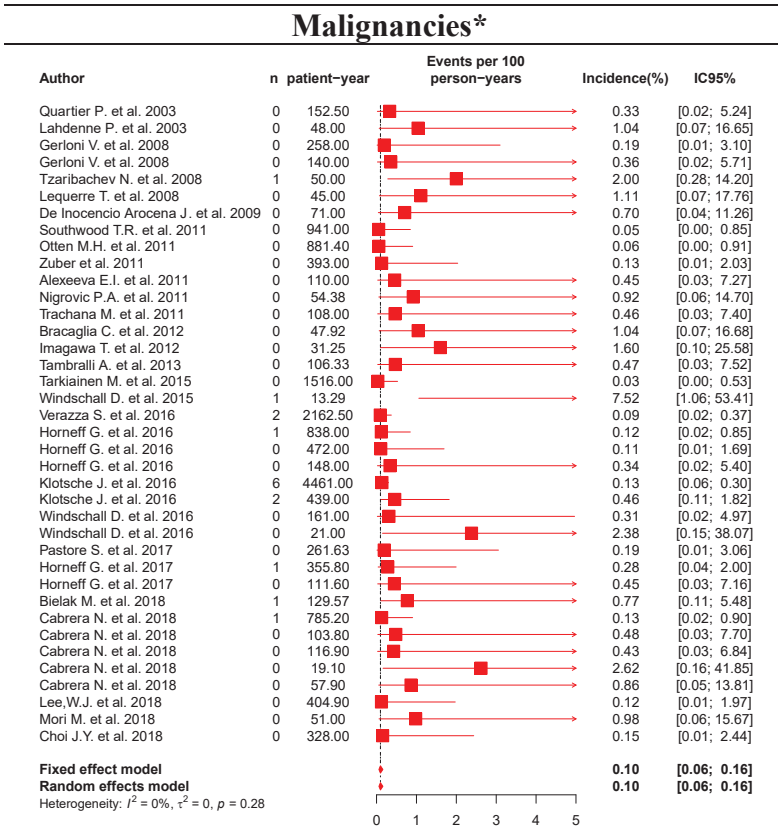
Database	EMBASE (Scopus)
Date	29/03/2019
Result	335
User Query	**(** TITLE-ABS-KEY ("juvenile idiopathic arthritis") AND TITLE-ABS-KEY (safety) OR TITLE-ABS-KEY (tolerance) AND TITLE-ABS-KEY (etanercept) OR TITLE-ABS KEY (adalimumab) OR TITLE-ABS-KEY (infliximab) OR TITLE-ABS KEY (golimumab) OR TITLE-ABS-KEY (anakinra) OR TITLE-ABS KEY (canakinumab) OR TITLE-ABS-KEY (rilonacept) OR TITLE-ABS KEY (rituximab) OR TITLE-ABS-KEY (abatacept) OR TITLE-ABS-KEY (tocilimumab) AND NOT TITLE-ABS-KEY ("randomised controlled trial") AND NOT TITLE-ABS-KEY ("randomized controlled trial"))

Table A3: Incidence rate of serious adverse events in randomise controlled trials

	k	*Ref*	*Incidence rate per 100 PY [95% CI]*	I_2	*p*
Parallel RCTs	11	(57–59,61–63,81–85)	29.03 [6.51; 62.73]	74%	<0.01
Withdrawal RCTs	8	(67,68,77,85–89)	3.71 [0.0; 13.34]	56%	0.03

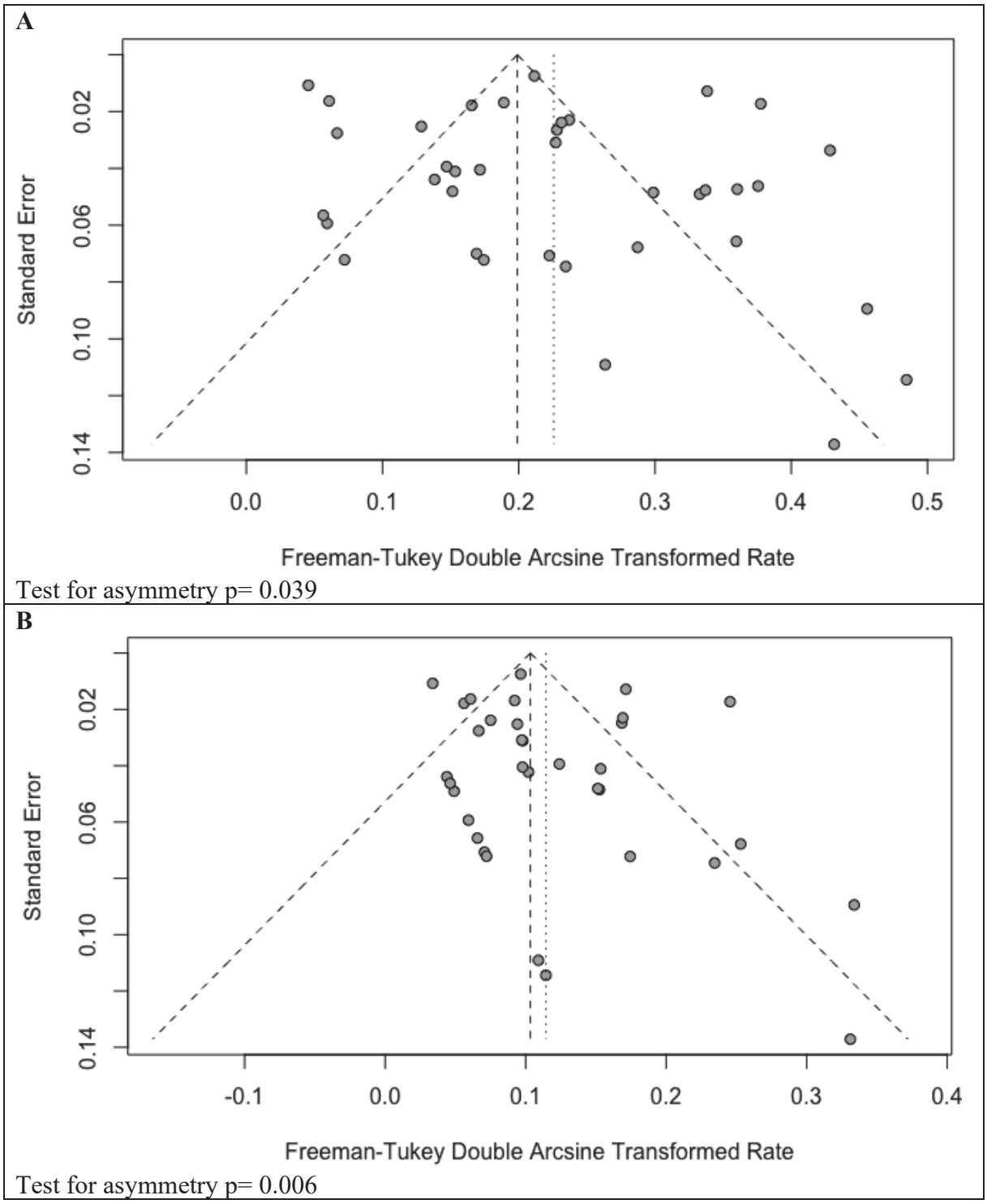
NA: not applicable, PY: patient-year, RCT: randomised controlled trials, TNF: tumor necrosis factor.

Figure A1: Forest plots of incidence rate of serious adverse events of interest.



* Meta-analysis of malignancies and death were made with the generalised linear mixed model therefore individual study weights and subgroup analysis are not available (13,14).

Figure A2: Funnel plot of incidence rate of serious adverse events (A) and serious infections (B)



Patients en double biothérapie simultanée : série des cas monocentrique

Résumé publié :

‘Treatment with simultaneous biological agents in juvenile idiopathic arthritis: single-center case series and review of literature (AB0947)’

Cabrera N, Nakhleh P, Desjonqueres M*, et al*

Annals of the Rheumatic Diseases 2019; 78:1940

http://dx.doi.org/10.1136/annrheumdis-2019-eular.5712

work in collaborative teams to ensure participation and sustainability of processes. Next steps would be to add additional quality and disease outcome measures.

REFERENCES

[1] Harris, J. et al. Improving Care Delivery Outcomes in Pediatric Rheumatic Diseases. Curr Opin Rheumatol. 2016 March; 28(2): 110–116.

Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2019-eular.6188

AB0947 TREATMENT WITH SIMULTANEOUS BIOLOGICAL AGENTS IN JUVENILE IDIOPATHIC ARTHRITIS: SINGLE-CENTER CASE SERIES AND REVIEW OF LITERATURE

Natalia Cabrera[1], Pauline Nakhleh[2], Marine Desjonqueres[2], Jean-Paul Larbre[3], Alexandre Belot[2], Jean-Christophe Lega[1]. *[1]Claude Bernard University Lyon 1, UMR-CNRS 5558 Laboratoire de Biométrie et Biologie Humaine (LBBE), Villeurbanne, France*; *[2]Hospital Woman Mère Enfant – Hcl, Paediatric Rheumatology, Bron, France*; *[3]Lyon Sud Hospital Center, Rheumatology, Pierre-Bénite, France*

Background: Several therapeutic choices are currently available for juvenile idiopathic arthritis (JIA) patients. The classical first line therapies are NSAIDs and corticosteroids (CTCs) and the second line encompasses synthetical and biological DMARDs. The clinical efficacy of DMARDs (alone or in combination) has been well demonstrated in RCTs and the treatment is often tailored on an individual basis. Combination of bDMARDs has not been formally evaluated in rheumatology and few publications are available concerning the combination of bDMARDs in patients with severe active forms of JIA, mainly systemic [SoJIA] and polyarticular [PA] categories. (1)
Objectives: To describe efficacy and safety of JIA patients resistant to MTX and bDMARDs requiring a simultaneous bDMARDs treatment.
Methods: Retrospective analysis of 7 (4.7 ± 2.1 years, male sex 75%) patients with JIA of a single tertiary center. A systematic review of literature was made to search observational studies from MEDLINE database (January 1946 to January 2019).
Results: All patients in the Paediatric Rheumatology Department (Lyon University Hospital) receiving combination therapy with bDMARDs were eligible. Seven patients with JIA diagnosis (4 SoJIA and 3 PA) were included. Genetic studies were performed in three patients, with positive LACC1 mutation in one. The exposure to the bDMARDs of the whole cohort was 79 patient-years (PY), including 16.5 PY of combination with simultaneous bDMARDs. The delay between the date of diagnosis and the first prescription of a combination of simultaneous bDMARDs treatment was 8.3 ± 4.8 years. Nine bDMARDs drugs were prescribed: anti-TNFs, tocilizumab and rituximab (nine times each). Ten co-prescriptions of the bDMARDs were administrated with 5 possible types of combinations between them, the most frequent associating tocilizumab/rituximab. Rituximab was used most frequently in combination with another bDMARD. The rituximab schedule was different between patients. Disease activity decreased for all patients, primarily at the biological level without reaching complete clinical remission.
In general, the clinical tolerance to the co-prescription of bDMARDs was acceptable. One patient (P2) experienced a severe hepatitis event in adulthood attributed to the treatment (tocilizumab), dropping the bDMARDs combination. During the exposure time, the most frequent adverse events were infections: repeated otitis media (P1), persisting vaginitis and fungal urinary infection (P3) not requiring hospitalization. One patient (P6) had 2 episodes of purpuric rash on the days of the canakinumab injection requiring oral CTC treatment. No severe acute reactions were found and no patients died.
The systematic review found a publication: retrospective series of 4 patients (SoJIA) combining abatacept and canakinumab (2).
Conclusion: Severe forms of JIA that are refractory to the current therapeutic options available could benefit from the combination of bDMARDs. The combination of bDMARDs may be an alternative therapy to explore in this group of patients.

REFERENCES

[1] Cimaz R, Marino A, Martini A. How I treat juvenile idiopathic arthritis: A state of the art review. Autoimmun Rev. 2017 Oct;16(10):1008–15.
[2] Record JL, Beukelman T, Cron RQ. Combination Therapy of Abatacept and Anakinra in Children with Refractory Systemic Juvenile Idiopathic Arthritis: A Retrospective Case Series. J Rheumatol. 2011 Jan;38(1): 180–1.

Acknowledgement: Sincere thanks to Dr. Maria-Luisa Cabañas (INCAN, Ministry of Health of Paraguay)
Disclosure of Interests: None declared
DOI: 10.1136/annrheumdis-2019-eular.5712

AB0948 PARADOXICAL TINEA AMIANTACEA IN A PATIENT WITH JUVENILE IDIOPATHIC ARTHRITIS RECEIVING ADALIMUMAB

Maria Costanza Caparello[1], Francesca Tirelli[1], Gabriele Simonini[1], Rolando Cimaz[1], Teresa Giani[1,2]. *[1]AOU Meyer, Rheumatology, Florence, Italy*; *[2]University of Siena, Siena, Italy*

Background: Tinea amiantacea is a papulo-squamous condition of the scalp that can lead to scalp fibrosis and subsequent permanent hair loss. It is thought to represent a reaction pattern to inflammatory skin disease as psoriasis or seborrheic dermatitis (1).
Objectives: To highlight an adverse reaction which involved the skin in the disease course of a young JIA (juvenile idiopathic arthritis) patient, during treatment with adalimumab.
Methods: A 16-month-old female patient presented to our clinic with a 4-week history of knee swelling, associated with functional limitation and morning stiffness. Family history was unremarkable, while past medical history revealed atopic dermatitis in the first year of life. The baby was initially treated with NSAIDs, but one month later, due the persistence of arthritis and the appearance of uveitis, subcutaneous methotrexate was started (15 mg/m^2/weekly). However 5 months later, given the persistence of uveitis and the onset of a severe hypertransaminasemia, methotrexate was interrupted and adalimumab (24 mg/m^2 every 2 weeks) was introduced with a prompt and stable control of ocular and articular disease and a gradual normalization of transaminases. One year later the patient developed dry, itchy, red and cracked skin behind her ears, with fissuring in the lower attachment of the ear lobe, and presented right parietal yellowish scalp lesions which were pruriginous, thick, and scaly, attached both to the scalp and to the proximal hair shafts. A first diagnosis of pityriasis amiantacea secondary to atopic dermatitis was made. A paradoxical cutaneous reaction to the anti-TNF therapy was later hypothesized (2), and 7 months later adalimumab was interrupted with quick resolution of the dermatologic lesions. However, both arthritis and uveitis rapidly recurred, showing an inadequate response to a six month cycle of abatacept treatment (10 mg/kg/month). Adalimumab was than reintroduced with a rapid improvement.
Results: Currently, after 16 months of adalimumab treatment, the patient still shows complete disease control, without any new dermatologic lesions up to now.
Conclusion: TNF antagonist-induced tinea amiantacea is a rare adverse reaction that may require the drug discontinuation. Although the exact pathogenetic mechanism is unclear, an imbalance in the cytokine milieu with a selective overexpression of type I interferon has been hypothesized.

REFERENCES

[1] F. Osório, F. Magro, C. Lisboa, S. Lopes, G. Macedo, H. Bettencourt, F. Azevedo, S. Magina, Anti-TNF-Alpha induced psoriasiform eruptions with severe scalp involvement and alopecia: report of five cases and review of the literature. Dermatology. 2012;225(2):163-7. doi: 10.1159/000342503
[2] J. Ettler, D.A. Wetter, M.R. Pittelkow. Pityriasis amiantacea: a distinctive presentation of psoriasis associated with tumour necrosis factor-α inhibitor therapy. Clin Exp Dermatol. 2012 Aug;37(6):639-41. doi: 10.1111/j.1365-2230.2011.04286.x.

Disclosure of Interests: Maria Costanza Caparello: None declared, Francesca Tirelli: None declared, Gabriele Simonini Grant/research support from: Abbvie, Speakers bureau: Abbvie, Rolando Cimaz: None declared, Teresa Giani: None declared
DOI: 10.1136/annrheumdis-2019-eular.4311

AB0949 IS PEDIATRIC ONSET LUPUS MORE SEVERE IN BOYS? OUR EXPERIENCE AT A TERTIARY CARE CENTER IN NORTH-WEST INDIA

Himanshi Chaudhary, Pandiarajan Vignesh, Ankur Jindal, Deepti Suri, Anju Gupta, Amit Rawat, Surjit Singh. *Post Graduate Institute of Medical Education and Research, Chandigarh, allergy immunology unit, Chandigarh, India*

Background: There is diversity in clinical presentation of pediatric onset SLE (pSLE) and the manifestations are more severe as compared to

Table 1: Clinical characteristics of patients treated with a combination of simultaneous therapy of biological agents

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6
Sex	F	M	F	M	M	F
Age at diagnosis§	2.8	3.4	1	8.4	1.5	5.0
Clinical diagnosis	So JIA	So JIA	PA RF Neg	PA RF Pos	So JIA	PA RF Neg
Genetic study	NOD2 Neg	Not done	Positive LACC 1 mutation Absence of HLA DR1 DR4	Not done	Not done	Negative LACC1 And NOD2 mutation
Age at first bDMARDs§	3.0	5.0	3.2	8.1	1.9	5.6
bDMARDs used (age at start and stop§)	Tocilizumab (3.0 - 3.5) Etanercept (3.7 - 4.0) Anakinra (4.0 - 4.1) Tocilizumab (4.6)* Canakinumab (7.2 - 7.3) * Rituximab (7.4)*	Etanercept (5.0 - 7.6) Anakinra (6.0 - 14.2) Tocilizumab [b] (14.2 - 20.0)* Canakinumab (16. 1 - 17. 6)* Rituximab (18.0 – 20.1)* Anakinra (20.1)	Etanercept (3.2 - 3.8) Infliximab (5.7 - 6.0) Abatacept (6.1 - 7.2) Rituximab (7.3 - 12.1) Tocilizumab (12.5 - 16.4)* Rituximab (15.8 - 16.3)* Canakinumab (16.5 - 17.0) Tocilizumab (17.1 - 17.7)* Rituximab (17.1)* Secukinumab (17.7)*	Etanercept (8.8 - 13.0) Tocilizumab (13.9 -14.1) Rituximab (15.4) * Abatacept (17.2)*	Etanercept (1.9 - 2.5) Adalimumab (2.6 - 3.2) Anakinra (3.2 - 5.5) Tocilizumab (5.1)* Rituximab (11.8)*	Etanercept (5.7 - 7.0) Adalimumab (7.0 - 8.3) Tocilizumab (9.3- 10.2) Abatacept (10.2 - 11.0 Rituximab (10.7)* Anakinra (11.0 - 11.1) Canakinumab (11.1)*
Number of switches	3	5	7	2	3	5
Simultaneous bDMARDs (age§)	8.2	16.1	15.8	17.3	11.8	10.7
Rituximab schedule	1g 1.73m2	1g 1.73m2	500 mg/m2	1g 1.73m2 x 2	1g 1.73m2	500 mg/m2 x 2
Compliance	According at the clinic and CD20+ lymphocytes	Every 6 months	According at the clinic [c]	According at the clinic	According at the clinic	According at the clinic
NSAIDs	*Per os*	No effect	Infusion at relapses	No effect	Dispensable	No effect
Corticosteroids	Dependence	Dependence	Dependence	Dependence	Dependence	Dependence
MTX	Since 3.3 years	Stopped at 16.9 years [c]	Since the age of 1.2 y [c]	During etanercept	Since the age of 1.9 y [e]	Stopped at 8.1 y [g]
Other treatments Received §	ACE inhibitor (3.2) GH (5.9) Zoledronate (8.1) Orthopaedic surgery (9.5)[a] Knee infiltration (10.9) Enteral nutrition (9.0)	Cyclosporine (4.7) Thalidomide (7.6) Aredia® (10.7) GH (11.5) Knees infiltr (several)	Azathioprine (3.3) Ciclosporine (4.4) IVIG (7.8)[d] GH (9.4) Many infiltrations	Knee infiltr (15.8) Elbows infiltr (17.0)	GH (stopped at 9.1) Many infiltrations	-
Autoimmune status						
ANA	Neg	Neg	Neg	Neg	Neg	Neg
RF	Neg	Neg	Neg	Pos	Neg	Neg
Other autoantibodies	Neg	Neg	Neg	Neg	Neg	Neg
Serious adverse event	CIO	CIO Drug-induced liver injury [b]	CIO	-	CIO	Skin purpura with canakinumab injections

§ age in years, *bDMARD combined. ACE: angiotensin-converting-enzyme, ANA: antinuclear antibodies, Aredia® : pamidronate disodium pentahydrate, bDMARDs: biological disease-modifying antirheumatic drugs, CIO: corticosteroid-induced osteoporosis, CRP: C reactive protein, ESR: erythrocyte sedimentation rate, GH : growth hormone, IVIG: intravenous immunoglobulin, JIA: juvenile idiopathic arthritis, MTX: methotrexate, Neg: negative, NSAIDs: non-steroidal anti-inflammatory drugs, P: patient, Pos: positive, RF: Rheumatoid factor, So JIA (systemic-onset juvenile idiopathic arthritis)

a: genu valgus bilateral, b: serious adverse event: Acute cholestatic hepatitis, tocilizumab was stopped (liver biopsy revealed an inflammatory infiltrate with hepatocellular drop out suggesting drug induced liver injury), c: complicated therapeutic compliance by the family, d: substitutive dose (replacement therapy), e: stopped during treatment with anakinra, f: infiltrations at knees, ankles and elbows, g: serious adverse event: No clinical (vomiting) and biological (hepatic cytolysis) tolerance.

4. Discussion générale

Ce travail s'est concentré sur l'évaluation de l'efficacité et la tolérance des biothérapies dans les rhumatismes inflammatoires à début juvénile.

Balance bénéfice/risque des biothérapies dans l'arthrite juvénile idiopathique

L'évaluation de la balance bénéfice/risque des biothérapies, en rhumatologie pédiatrique, a été faite par la modélisation du bénéfice net à partir des données méta-analytiques des ECR. Le modèle de bénéfice net présenté, comporte, dans une seule échelle, des résultats d'efficacité et de tolérance des biothérapies utilisées chez les patients avec AJI. Il est adapté aux données résumées telles qu'elles sont présentées dans les ECR. Les résultats de cette méta-analyse sont à considérer comme étant exploratoires, et indiquent un bénéfice net favorable pour les biothérapies. Cependant, cette évaluation est marquée par une hétérogénéité importante des effets et par des limites quant au niveau de preuve.

Une des difficultés de ce travail était d'examiner la grande variabilité des estimations d'efficacité et de sécurité, ainsi que le risque de base de la population. Les étapes préliminaires à la construction du modèle ont suggéré que, le plan d'expérience de l'essai, la catégorie de la maladie, et la variabilité du risque de base, influencent l'efficacité clinique des biothérapies. En conséquence, les éléments cités ont un impact, sur la mesure du bénéfice net des biothérapies, chez les patients avec AJI.

Concernant l'étude de l'innocuité des biothérapies, les EI graves ont été choisi car ils sont systématiquement vérifiés, et la notification est standardisé avec dictionnaire de terminologie médicale MedDRA. Cependant, même si ces événements sont catégorisés et jugés aussi objectivement que possible dans les ECR, ils comportent des limites au moment de les résumer pour les analyser (40). D'un part, le fait de limiter l'évaluation de l'innocuité des biothérapies à des événements graves, est susceptible de surestimer leur tolérance globale.

D’autre part, une sous-estimation de la sécurité des biothérapies est également à considérer car, dans les ECR des biothérapies dans l’AJI, le suivi d’innocuité est à court terme et évalue une taille relativement restreinte de participants. À cela s’ajoute les limites du dictionnaire MedDRA telles que l'absence d’une valeur numérique de pondération dans les résultats de sécurité et d’évaluation de fréquence des EI, ou encore l’absence d’une terminologie standardisée décrivant la sévérité des EI graves (38,41–43).

D’autres méta-analyses étudiant les biothérapies dans l’AJI soulèvent le fait que, (i) l’hétérogénéité de la maladie et du plan d’expérience des ECR empêchent de tirer des conclusions définitives, et que (ii) des difficultés de comparabilité existent, vis-à-vis de l’efficacité et de la tolérance des biothérapies (44,45). Nous suggérons que la balance bénéfice/risque, pour chacune des biothérapies, doit être quantifiée en considérant des éléments de variabilité individuelle des patients (co-prescription des immunosuppresseurs, corticoïdes et séquence d’utilisation des biothérapies). Malheureusement, il n’existe pas de *score* de stratification du risque d’EI grave, sous biothérapies dans l’AJI. De la même manière, aucun outil permettant de délimiter des populations à risque, de non-réponse ou de rechute sous traitement, n’est disponible. À ce jour, seul des effets moyens sont quantifiables et appliqués à l’ensemble de la population souffrant d’AJI, limitant ainsi la perspective d’une médecine personnalisée dans ce champ thématique. Seule la constitution de cohortes de très grandes tailles (à une échelle internationale) permettra de modéliser la balance bénéfice/risque à un niveau individuel (46).

Tolérance des biothérapies à partir des données observationnelles

Le suivi à long terme permet d’étudier les EI rares, comme les EI graves. Les études observationnelles de cohorte de suivi représentent la meilleure source de données pour les EI graves (9). L’étude de la base de données rétrospective multicentrique, de prescription en vie réelle ‘JIRcohorte’, suggère que, la prescription concomitante de biothérapies et de

médicaments immunosuppresseurs, représente un risque de survenue des EI graves. En général, la sécurité globale des biothérapies, est acceptable chez les patients atteints de rhumatismes inflammatoires à début juvénile.

L'incidence des EI graves, des infections graves, des décès et des cancers sous traitement par biothérapie chez les patients avec AJI a été étudié à partir de données de cohortes prospectives et rétrospectives, avec une méta-analyse. Nous avons observé des incidences similaires des EI graves, à partir de cohortes observationnelles et d'ECR de retrait (*withdrawal trials*). Nos résultats, issus des études observationnelles, suggèrent aussi que la survenue des EI graves est variable au cours du temps. La méta-régression indique une corrélation inverse significative entre le temps de suivi et le nombre d'évènements, suggérant que plus d'EI graves surviennent dans les étapes initiales d'un traitement par biothérapie. Les catégories d'AJI et la qualité des cohortes étudiées, sont significativement associées aux variations du taux d'incidence des infections graves. Une limite à considérer est l'absence de standardisation pour la notification des EI graves dans les ECR, ainsi que dans les études observationnelles. Ainsi, l'analyse des hospitalisations de cause non-infectieuse chez les patients avec AJI n'a pas été possible. Bien que les infections graves soient plus fréquentes en comparaison aux cancers et décès, cela ne représente pas la majorité des EI graves sous biothérapie. Toutes les biothérapies disponibles n'ont pas été évaluées par des études observationnelles de sécurité. Ainsi, une seule cohorte de patients avec AJI sous rituximab (47), et une autre sous canakinumab (48), ont été publiées. Cet élément pointe la nécessité de poursuivre les efforts de recherche, dans la sécurité des biothérapies, dans le cadre de l'AJI. De plus, la sécurité des biothérapies est actuellement difficile à connaître car, le suivi à long-terme n'est pas atteint pour la plupart des biothérapies utilisées dans la rhumatologie pédiatrique.

A ce jour, peu d'études interventionnelles de pratique sont en cours dans le domaine de la rhumatologie pédiatrique. Elles existent principalement pour les catégories polyarticulaires de l'AJI (12,49). Nous considérons que l'innocuité des biothérapies est un élément central dans

l'étude de la prise en charge des patients à l'âge pédiatrique. Des études comparant la sécurité des différentes thérapeutiques seraient intéressantes à réaliser afin de connaître les patients à risque de survenue d'un évènement grave. D'autre part, les biothérapies ne sont pas accessibles de façon égale dans tous les pays dans le monde. La majorité des patients, des études observationnelles et interventionnelles étaient issus des pays européens et nord-américains. Ainsi, ces résultats ne sont pas transposables dans d'autres populations où la génétique, la couverture de soins, et les facteurs d'exposition infectieux, sont différents. Il serait, à ce titre, intéressant d'étudier l'effet du traitement par biothérapies dans les populations pédiatriques de pays à revenus bas et intermédiaires (50).

5. Conclusion

La connaissance de la balance bénéfice-risque des biothérapies, est cruciale au moment d'adopter une thérapeutique pour un patient donné, car elle représente un traitement immunosuppresseur s'utilisant à long-terme. Le bénéfice net des biothérapies n'est probablement pas constant dans le temps.

La modélisation du bénéfice net, avec les données publiées dans les ECR, a suggéré que les plans expérimentaux utilisés (ERC en bras parallèle versus ERC de retrait) et les catégories d'AJI, influencent les résultats finaux. La majorité des biothérapies montrent un profil bénéfique favorable dans le court terme. Dans l'analyse des études observationnelles de registres et de données de la vie réelle, nous avons constaté que la survenue des EI graves avait une relation inverse avec le temps d'exposition et l'utilisation d'un traitement immunosuppresseur concomitant.

Les registres et les cohortes de suivi de patients sous traitement par biothérapie font partie des outils de pharmacovigilance, et indiquent que les EI graves sont peu nombreux voire rares. Cependant, ils sont présents dans toutes les biothérapies disponibles. Le suivi actuel dans la majorité de cohortes n'est pas optimal, inferieur habituellement à 5 ans.

Le risque associé à la médication est un élément central dans l'évaluation du bénéfice net. Les biothérapies sont des médicaments suspensifs, jouant un rôle dans la réponse immunitaire, s'utilisant au long cours sur une population en phase de croissance. Les conséquences à long terme nécessitent d'être explorées davantage. La standardisation des données d'efficacité et de sécurité dans les ECR, ainsi que pour les cohortes et les registres de suivi des patients, est un enjeu crucial pour assurer la comparabilité des résultats.

6 : Bibliographie

1. Davies R, Gaynor D, Hyrich KL, Pain CE. Efficacy of biologic therapy across individual juvenile idiopathic arthritis subtypes: A systematic review. Semin Arthritis Rheum. 2017;46(5):584–93.

2. Brunner HI, Rider LG, Kingsbury DJ, Co D, Schneider R, Goldmuntz E, et al. Pediatric Rheumatology Collaborative Study Group - over four decades of pivotal clinical drug research in pediatric rheumatology. Pediatr Rheumatol Online J. 2018 Jul 11;16(1):45.

3. Bettiol A, Silvestri E, Di Scala G, Amedei A, Becatti M, Fiorillo C, et al. The right place of interleukin-1 inhibitors in the treatment of Behçet's syndrome: a systematic review. Rheumatol Int. 2019 Jun;39(6):971–90.

4. Bettiol A, Lopalco G, Emmi G, Cantarini L, Urban ML, Vitale A, et al. Unveiling the Efficacy, Safety, and Tolerability of Anti-Interleukin-1 Treatment in Monogenic and Multifactorial Autoinflammatory Diseases. Int J Mol Sci. 2019 Apr 17;20(8).

5. Ardoin SP, Daly RP, Merzoug L, Tse K, Ardalan K, Arkin L, et al. Research priorities in childhood-onset lupus: results of a multidisciplinary prioritization exercise. Pediatr Rheumatol Online J. 2019 Jul 1;17(1):32.

6. Joseph PD, Craig JC, Caldwell PHY. Clinical trials in children. Br J Clin Pharmacol. 2015 Mar;79(3):357–69.

7. Food and Drug Administration, HHS. International Conference on Harmonisation; guidance on E11 clinical investigation of medicinal products in the pediatric population; availability. Notice. Fed Regist. 2000 Dec 15;65(242):78493–4.

8. Ruperto N, Vesely R, Saint-Raymond A, Martini A, Paediatric Rheumatology International Trials Organisation (PRINTO). Impact of the European paediatric legislation in paediatric rheumatology: past, present and future. Ann Rheum Dis. 2013 Dec;72(12):1893–6.

9. Monti S, Grosso V, Todoerti M, Caporali R. Randomized controlled trials and real-world data: differences and similarities to untangle literature data. Rheumatol Oxf Engl. 2018 01;57(57 Suppl 7):vii54–8.

10. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in Children with Polyarticular Juvenile Rheumatoid Arthritis. N Engl J Med. 2000 Mar 16;342(11):763–9.

11. Smith JA, Thompson DJS, Whitcup SM, Suhler E, Clarke G, Smith S, et al. A randomized, placebo-controlled, double-masked clinical trial of etanercept for the treatment of uveitis associated with juvenile idiopathic arthritis. Arthritis Rheum. 2005 Feb 15;53(1):18–23.

12. Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, et al. Trial of Early Aggressive Therapy in Polyarticular Juvenile Idiopathic Arthritis. Arthritis Rheum. 2012 Jun;64(6):2012–21.

13. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without Methotrexate in Juvenile Rheumatoid Arthritis. N Engl J Med. 2008;359(8):810–20.

14. Horneff G, Fitter S, Foeldvari I, Minden K, Kuemmerle-Deschner J, Tzaribacev N, et al. Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement. Arthritis Res Ther. 2012 Oct 24;14(5):R230.

15. Burgos-Vargas R, Tse SML, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A Randomized, Double-Blind, Placebo-Controlled Multicenter Study of Adalimumab in Pediatric Patients With Enthesitis-Related Arthritis. Arthritis Care Res. 2015 Nov;67(11):1503–12.

16. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2007;56(9):3096–106.

17. Tynjälä P, Vähäsalo P, Tarkiainen M, Kröger L, Aalto K, Malin M, et al. Aggressive combination drug therapy in very early polyarticular juvenile idiopathic arthritis (ACUTE-JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011 Sep;70(9):1605–12.

18. Brunner HI, Ruperto N, Tzaribachev N, Horneff G, Chasnyk VG, Panaviene V, et al. Subcutaneous golimumab for children with active polyarticular-course juvenile idiopathic arthritis: results of a multicentre, double-blind, randomised-withdrawal trial. Ann Rheum Dis. 2018 Jan;77(1):21–9.

19. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011 May;70(5):747–54.

20. Ilowite N, Porras O, Reiff A, Rudge S, Punaro M, Martin A, et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. Clin Rheumatol. 2009 Feb;28(2):129–37.

21. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two Randomized Trials of Canakinumab in Systemic Juvenile Idiopathic Arthritis. N Engl J Med. 2012 décembre;367(25):2396–406.

22. Lovell DJ, Giannini EH, Reiff AO, Kimura Y, Li S, Hashkes PJ, et al. Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. Arthritis Rheum. 2013 Sep;65(9):2486–96.

23. Ilowite NT, Prather K, Lokhnygina Y, Schanberg LE, Elder M, Milojevic D, et al. Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. Arthritis Rheumatol Hoboken NJ. 2014 Sep;66(9):2570–9.

24. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015 Jun;74(6):1110–7.

25. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet Lond Engl. 2008 Mar 22;371(9617):998–1006.

26. Ruperto N, Lovell DJ, Quartier P, Paz E, Rubio-Pérez N, Silva CA, et al. Long-term safety and efficacy of abatacept in children with juvenile idiopathic arthritis. Arthritis Rheum. 2010;62(6):1792–1802.

27. Tudur Smith C, Williamson PR, Beresford MW. Methodology of clinical trials for rare diseases. Best Pract Res Clin Rheumatol. 2014 Apr;28(2):247–62.

28. Varnier GC, Ciurtin C. Paediatric and adolescent rheumatic diseases: measures of disease activity. Br J Hosp Med Lond Engl 2005. 2019 Jun 2;80(6):338–42.

29. Horneff G, Minden K, Foeldvari I, Onken N, Windschall D, Hospach A, et al. [Current news from the BIKER register]. Z Rheumatol. 2014 Dec;73(10):897–906.

30. Prince FHM, Ferket IS, Kamphuis S, Armbrust W, Ten Cate R, Hoppenreijs EP

a. H, et al. Development of a web-based register for the Dutch national study on biologicals in JIA: www.ABC-register.nl. Rheumatol Oxf Engl. 2008 Sep;47(9):1413–6.

31. Beukelman T, Kimura Y, Ilowite NT, Mieszkalski K, Natter MD, Burrell G, et al. The new Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry: design, rationale, and characteristics of patients enrolled in the first 12 months. Pediatr Rheumatol Online J. 2017 Apr 17;15(1):30.

32. Hinze C, Gohar F, Foell D. Management of juvenile idiopathic arthritis: hitting the target. Nat Rev Rheumatol. 2015 May;11(5):290–300.

33. Rodriguez-Smith J, Brunner HI. Update on the treatment and outcome of systemic lupus erythematous in children. Curr Opin Rheumatol. 2019 Sep;31(5):464–70.

34. Boers M, Brooks P, Fries JF, Simon LS, Strand V, Tugwell P. A first step to assess harm and benefit in clinical trials in one scale. J Clin Epidemiol. 2010 Jun;63(6):627–32.

35. Vanoni F, Minoia F, Malattia C. Biologics in juvenile idiopathic arthritis: a narrative review. Eur J Pediatr. 2017 Sep;176(9):1147–53.

36. Bartelds GM, Wijbrandts CA, Nurmohamed MT, Stapel S, Lems WF, Aarden L, et al. Anti-infliximab and anti-adalimumab antibodies in relation to response to adalimumab in infliximab switchers and anti-tumour necrosis factor naive patients: a cohort study. Ann Rheum Dis. 2010 May 1;69(5):817–21.

37. Horneff G. Biologic-associated infections in pediatric rheumatology. Curr Rheumatol Rep. 2015 Nov;17(11):66.

38. Crépin S, Villeneuve C, Merle L. Quality of serious adverse events reporting to academic sponsors of clinical trials: far from optimal. Pharmacoepidemiol Drug Saf. 2016;25(6):719–24.

39. Schroll JB, Maund E, Gøtzsche PC. Challenges in coding adverse events in clinical trials: a systematic review. PloS One. 2012;7(7):e41174.

40. Mayo-Wilson E, Fusco N, Li T, Hong H, Canner JK, Dickersin K, et al. Harms are assessed inconsistently and reported inadequately Part 2: nonsystematic adverse events. J Clin Epidemiol. 2019 Sep;113:11–9.

41. Berard RA, Laxer RM. Learning the hard way: clinical trials in juvenile

idiopathic arthritis. Ann Rheum Dis. 2018;77(1):1–2.

42. Morley G. Adverse event reporting: A brief overview of MedDRA. Med Writ. 2014 Jun 1;23(2):113–6.

43. Schroll JB, Maund E, Gøtzsche PC. Challenges in coding adverse events in clinical trials: a systematic review. PloS One. 2012;7(7):e41174.

44. Otten MH, Anink J, Spronk S, van Suijlekom-Smit LWA. Efficacy of biological agents in juvenile idiopathic arthritis: a systematic review using indirect comparisons. Ann Rheum Dis. 2013 Nov;72(11):1806–12.

45. Tarp S, Amarilyo G, Foeldvari I, Christensen R, Woo JMP, Cohen N, et al. Efficacy and safety of biological agents for systemic juvenile idiopathic arthritis: a systematic review and meta-analysis of randomized trials. Rheumatol Oxf Engl. 2016 Apr;55(4):669–79.

46. Giancane G, Alongi A, Ravelli A. Update on the pathogenesis and treatment of juvenile idiopathic arthritis. Curr Opin Rheumatol. 2017 Sep;29(5):523–9.

47. Alexeeva EI, Valieva SI, Bzarova TM, Semikina EL, Isaeva KB, Lisitsyn AO, et al. Efficacy and safety of repeat courses of rituximab treatment in patients with severe refractory juvenile idiopathic arthritis. Clin Rheumatol. 2011 Sep;30(9):1163–72.

48. Horneff G, Ruperto N, Brunner H, Quartier P, Constantin T, Alexeeva E, et al. Long term efficacy and safety of canakinumab in children with systemic juvenile idiopathic arthritis with and without fever. Pediatr Rheumatol Online J. 2015 Sep 28;13(Suppl 1):O83.

49. Tynjälä P, Vähäsalo P, Tarkiainen M, Kröger L, Aalto K, Malin M, et al. Aggressive Combination Drug Therapy in Very Early Polyarticular Juvenile Idiopathic Arthritis (ACUTE–JIA): a multicentre randomised open-label clinical trial. Ann Rheum Dis. 2011 Sep 1;70(9):1605–12.

50. Ravelli A, Consolaro A, Horneff G, Laxer RM, Lovell DJ, Wulffraat NM, et al. Treating juvenile idiopathic arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2018 Jun;77(6):819–28.