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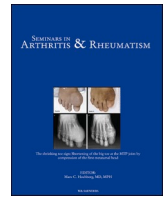
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Systematic review on the use of biologics in adult-onset still's disease[☆]

Bruno Fautrel^a, Jacoby Patterson^b, Catherine Bowe^{b,*}, Mick Arber^b, Julie Glanville^b, Stuart Mealing^b, Viviam Canon-Garcia^c, Laura Fagerhed^c, Hilde Rabijns^c, Roberto Giacomelli^d

^a Sorbonne Université, INSERM UMRS 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, AP-HP, Hôpital Pitié Salpêtrière, Département de Rhumatologie, F75013 Paris, France

^b York Health Economics Consortium, Enterprise House, Innovation Way, University of York, Heslington, York YO10 5NQ, UK

^c Novartis Pharma, Basel, Switzerland

^d Clinical Unit of Rheumatology and Clinical Immunology, University of Rome "Campus Biomedico", School of Medicine, 00128 Rome, Italy

ABSTRACT

This systematic review (SR) describes the efficacy and safety of biologic disease modifying anti-rheumatic drugs (bDMARDs) for patients with adult-onset Still's disease (AOSD). Three randomised controlled trials (RCTs), one retrospective case series of multiple interventions, and 17 case series of single interventions met the inclusion criteria for this SR. Comparisons of biologic therapy in AOSD were only available against conventional DMARDs in one RCT and against placebo in two RCTs. There was a lack of common assessment criteria, meaning treatment efficacy across studies could not be compared. Uncontrolled retrospective case series suggested that bDMARDs have an effect for patients with AOSD, but these studies did not provide comparative data to show whether bDMARDs were more effective than other interventions or, whether any bDMARD was more effective than another bDMARD. However, there was evidence that bDMARDs could reduce steroid dose. Safety data from all included studies showed that bDMARDs appear to be a safe alternative to conventional DMARDs. This SR has highlighted the need for larger comparative studies in AOSD and has shown the need to standardize the definition of therapeutic response in AOSD. This would allow comparisons between studies in order to gain clarity on which bDMARDs may be more effective treatments for AOSD.

Introduction

Systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD) are rare autoinflammatory disorders of unknown etiology [1]. Both sJIA and AOSD display significant systemic inflammation and are associated with inappropriate activation of the innate immune system [1]. Current evidence suggests that pro-inflammatory cytokines, particularly interleukin (IL)-1, IL-6, IL-18, tumor necrosis factor (TNF), and interferon (INF)- γ , are closely associated with various clinical manifestations of sJIA/AOSD [2–4].

Although the clinical manifestations and laboratory findings are similar, AOSD and sJIA have been previously viewed as separate diagnostic entities. Currently, it is generally accepted that sJIA and AOSD represent a disease continuum with different ages of onset, known together as Still's disease [2,3,5,6]. The sJIA population has been studied far more extensively than the AOSD population, due to the lower prevalence of AOSD and lack of standardised classification criteria [7]. However, the European Medicines Agency (EMA) and Scottish Medicines Consortium (SMC) recently accepted that the outcomes from trials in the sJIA population can be generalised to AOSD [8,9].

Two different AOSD phenotypes have been described: the systemic predominant form (characterised by the dominance of fever, evanescent rash, weight loss and other systemic manifestations) and the joint predominant form (characterised by progressive joint damage and increasing functional limitations) [10–13]. Some patients with systemic AOSD only experience one episode of the disease (monophasic AOSD), while those with intermittent (or polyphasic) AOSD experience multiple episodes separated by periods of remission, and some people have persistent (chronic) AOSD where symptoms are continuous [14]. This systematic review includes patients with all forms of AOSD.

Recently, to dissect the clinical heterogeneity of AOSD, four different subsets were identified combining the manifestations at the beginning of symptom onset with possible diverse outcomes over time [15]. The first subset was identified by the highest levels of ferritin, seen in younger patients, characterised by fever, skin rash and arthritis. The second subset was identified by the highest CRP levels in addition to fever, arthritis and liver involvement. The third subset was characterised by the highest levels of systemic score, in addition to fever, splenomegaly and occurrence of life-threatening complications. Accordingly, this disease subset was considered the most severe. The fourth subset was

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* Corresponding author at: York Health Economics Consortium, Enterprise House, Innovation Way, University of York, Heslington, York YO10 5NQ, UK.

E-mail address: Catherine.bowe@york.ac.uk (C. Bowe).

characterised by the lowest levels of ferritin and CRP. These patients typically had fever and arthritis. The different clinical features of these four subsets indicates dissimilar underlying pathogenic mechanisms (at least partially) [15]. According to principles of the precision medicine, future management of AOSD may be tailored to these specific disease subsets.

Currently, there are no clear and specific predictors of AOSD evolution, and the therapeutic strategy does not differ depending on disease expression [16]. However, a retrospective study based on national survey data from French hospitals, has shown that Janus kinase inhibitors (JAKis) may be a therapeutic option for patients with incomplete remission who depend on medium to high dose corticosteroids (CS) [17]. Tadekinig alfa, an IL-18 inhibitor, has also been associated with early signs of efficacy in AOSD patients, based on a phase 2 study [18]. However, most patients in this trial had chronic arthritic AOSD (83%), while only 8.7% had the systemic form of AOSD (indicated by fever at baseline). Therefore, the efficacy of tadekinig alfa in systemic AOSD patients remains unknown [18].

The non-specific and heterogenous clinical presentation, the lack of specific diagnostic biomarker, and the rarity of AOSD often result in a significant delay in diagnosis. Furthermore, at the time of writing, international guidelines specific to AOSD were not yet available.

AOSD treatment

Prior to first-line treatment, non-steroidal anti-inflammatory drugs (NSAIDs) are often offered to patients awaiting diagnosis. Once a diagnosis is made, CS, particularly glucocorticoids, are commonly used as first-line treatment for AOSD and are effective in controlling disease for around 60% to 65% of patients, with efficacy typically greater in patients with systemic disease [13,19-24]. The initial response to glucocorticoids is generally good, although even high-dose glucocorticoids sometimes fail to induce remission. However, glucocorticoid toxicity causes iatrogenic problems and decreasing glucocorticoids frequently leads to relapse. Furthermore, steroid dependence, which occurs in 42% to 45% of cases [24,25], carries a high risk of medium- and long-term CS-induced side effects, which increase the human burden of the disease and can potentially lead to life-threatening complications [26,27]. In one cohort study [24], 75% of CS-treated patients experienced adverse effects, including Cushing syndrome, osteoporosis, diabetes, hypertension and psychiatric disorders.

Historically, conventional synthetic (cs) disease modifying anti-rheumatic drugs (DMARDs) were considered in combination with glucocorticoids for patients with inadequate response to CS or for their steroid-sparing effect in patients with dependence on high dose CS [28-30]. Methotrexate is the DMARD most frequently used in AOSD [31] and was found by two studies to provide effective disease control in 40% to 70% of steroid-dependent and steroid-resistant AOSD [31,32]. If methotrexate fails to control the disease, other csDMARDs, e.g. ciclosporin, azathioprine, tacrolimus, have been proposed in case series of limited sample size [33]. However, for at least 30% to 40% of patients, AOSD cannot be controlled by these traditional approaches. In the last 15 years, successful use of biologic agents in the treatment of other chronic rheumatic diseases, coupled with evidence that cytokine inhibitors could interfere with the inflammatory response in AOSD, led to the use of biologics in the treatment of refractory AOSD [13].

Biologic treatment in AOSD

Given the activation of IL-1, IL-6 and TNF in AOSD, anti-cytokine biologics such as inhibitors of TNF, IL-1, or IL-6 have been used to treat patients who are refractory to conventional treatment and patients who have systemic complications [24,34-37]. However, several experts, notably in paediatrics, have proposed to use them rapidly after disease onset using the rationale of a therapeutic window of opportunity in sJIA and AOSD as it has been shown in other immune-mediated

inflammatory diseases [38]. Biologic DMARDs (bDMARDs) offer a more target-specific mechanism of action than csDMARDs and have emerged as an important therapeutic alternative in patients with AOSD. In a multicentre, retrospective study in Italy, the physician's prescribing motivations for bDMARDs were inadequate response to CS and/or csDMARDs, the CS-sparing effect and occurrence of macrophage activation syndrome (MAS) [39].

There are currently two bDMARDs licensed for the treatment of AOSD by the FDA and EMA (canakinumab, an IL-1 inhibitor, and anakinra, an IL-1 receptor antagonist). Tocilizumab, an IL-6 inhibitor, is approved only for sJIA. These three biologics can be used as monotherapy or in combination with csDMARD. Biologics with other modes of actions such as abatacept (T-cell blocker) and anti-TNFs have not been approved for the treatment of AOSD [1,40-42]. However, other molecules such as tadekinig alpha and Janus kinases (JAK) inhibitors have been investigated in open-label clinical trials or case series [43,44].

In 2017, a SR and meta-analysis (MA) suggested that AOSD patients may experience clinical response and/or complete remission when treated with biologic drugs [1]. However, the data used in the MA were limited, and because new treatment options have become available, there was a need for a new SR to explore the evidence regarding current biologic treatment of AOSD. The objective of this SR was to evaluate the clinical efficacy and safety of biologics, including remission, treatment response, dosing, duration of treatment, burden of disease and health-related quality of life (HRQoL) outcomes, for the treatment of AOSD.

Methods

This SR was undertaken according to the principles of systematic reviewing embodied in the Cochrane handbook [45] and guidance published by the centre for Reviews and Dissemination (CRD) [46]. The protocol was registered on the PROSPERO database (CRD42021240142) [47]. Full details of the eligibility criteria are presented in Table 1.

Searches

A MEDLINE (OvidSP) search strategy was designed to identify studies of the eligible drugs in patients with AOSD (Supplementary Figure S1). This strategy was translated appropriately for multiple databases and information resources (Supplementary Table S1). Reflecting the eligibility criteria, the strategy was restricted to studies published in English. The strategy was not restricted by date. Full details of the strategies for all sources searched are presented in Supplementary Figures S1 to S12.

Reference lists of any included studies and retrieved relevant SRs published in the last five years were checked for any eligible studies that might have been missed by the database searches. SRs were not data extracted.

Study selection

Results of the searches were downloaded in a tagged format, loaded into EndNote bibliographic software [48] and deduplicated using several algorithms.

A single reviewer assessed the search results according to their relevance in providing information on the review and removed the obviously irrelevant records such as those about ineligible diseases or interventions. Titles and abstracts were assessed for relevance against the protocol by double independent reviewer selection (Catherine Bowe [CB] and Jacoby Patterson [JP]) with disagreements adjudicated by a third reviewer (Julie Glanville [JMG]). The full texts of potentially relevant papers were assessed for relevance in the same way.

Where results for one study were reported in more than one document, all related documents were identified and grouped together to ensure that data for participants in individual studies were only reported

Table 1
Summary of the review eligibility criteria.

Population	Inclusion	<ul style="list-style-type: none"> • AOSD (any severity, any co-morbidity, and any disease course)
	Exclusion	<ul style="list-style-type: none"> • Studies with combined indications (e.g. sJIA and AOSD, where AOSD was not analysed as a separate subgroup) • Studies in which some patients are under 16 years and results were not separate • Studies that included patients with no AOSD diagnosis
Intervention	Inclusion	<ul style="list-style-type: none"> • Infliximab, adalimumab, etanercept, certolizumab pegol, golimumab (TNF inhibitors) • Anakinra, canakinumab, rilonacept (anti-IL-1 drugs) • Tocilizumab (IL-6 receptor antagonist drug) • Rituximab (anti-CD20 drug) • Abatacept (co-stimulation inhibitor drug) <p>Any combination therapies that included at least one of the treatments listed above. This included:</p> <ul style="list-style-type: none"> • Studies of a single drug investigating different dosages of that drug • Studies investigating drug switches • Studies investigating the delivery of one drug by different administration routes (i.e. oral vs. injection) • Studies combining an intervention of interest (listed above) with another intervention • Studies varying the personnel delivering the treatments of interest • Studies were only eligible if the treatment dosage was pre-defined
	Exclusion	<ul style="list-style-type: none"> • Any intervention not listed in the inclusion criteria*
Comparator	Inclusion	<ul style="list-style-type: none"> • Any comparator (including drugs listed above, or any other drugs) • No comparator • Placebo
	Exclusion	<ul style="list-style-type: none"> • None
Outcomes		<p>Primary efficacy outcomes:</p> <ul style="list-style-type: none"> • Number of patients with a clinical response in each arm after a minimum follow-up >12 weeks** • Number of patients with complete remission in each arm** <p>Secondary outcomes:</p> <ul style="list-style-type: none"> • Duration of follow-up • Duration of response to treatment • Time on treatment • Quality of life • Dosage/reduction/withdrawal of steroids • Drug-free remission (as defined by study authors) • Burden of disease: <ul style="list-style-type: none"> ◦ Absenteeism ◦ Presenteeism ◦ Number of health care/hospital visits <p>Safety outcomes:</p> <ul style="list-style-type: none"> • Overall rates of severe adverse events (as defined by the study authors) • Overall rates of treatment-related adverse events
Study design	Inclusion	<ul style="list-style-type: none"> • RCTs • Prospective comparative studies: • Prospective single arm studies • Retrospective studies • SRs published in the last five years for reference checking only
	Exclusion	<ul style="list-style-type: none"> • Case reports • Non-systematic reviews • Any study enrolling fewer than 10 patients
Limits	Inclusion	<ul style="list-style-type: none"> • Full publication or conference abstract that reports study results • Conference abstracts will be limited to abstracts published from 2019 to date
	Exclusion	<ul style="list-style-type: none"> • Letters to the editor, comments and other publications that do not report study results • Studies not published in English

* JAK inhibitors were not excluded from the search. However, no studies mentioning JAK inhibitors met the eligibility criteria for this review.

** As defined in the Ruscitti study [44] clinical response or complete remission was collected if the study had pre-specified criteria explicitly before the study entry (criteria of remission and partial remission according to reported definitions in each study).

Abbreviations: AOSD - adult-onset Still's disease; CRP - C-reactive protein; IL - interleukin; RCT - randomised controlled trial; sJIA - systemic juvenile idiopathic arthritis; SR - systematic review; TNF - tumor necrosis factor.

once. The number of records included and removed at each selection stage was recorded in a PRISMA flow diagram (Fig. 1).

Data extraction

One researcher (CB or JP) extracted data from the eligible studies and a second researcher (CB or JP) checked all the data points. Any discrepancies were resolved through discussion or by consulting a third reviewer (JMG).

The efficacy outcomes of primary interest to the SR were the number of patients with a clinical response after a minimum follow-up >12 weeks or the number of patients with complete remission. Secondary outcomes of interest are reported in Supplementary Section S1. For each outcome, data were collected at all time points reported. The subgroups for which data were collected (where reported) are listed in Supplementary Section S1.

Quality assessment

One reviewer assessed the quality of each included study, and a second reviewer checked this assessment. Case control studies, case series, and cohort studies were assessed using the relevant tools from the Joanna Briggs Institute [49], while RCTs were assessed using the Cochrane Risk of Bias tool [50].

Feasibility of indirect comparisons

An assessment of the feasibility of indirect quantitative comparisons using RCT data was conducted, in which RCTs included in the review were qualitatively assessed for similarity of study design, patient characteristics, treatments administered, consistency of outcomes across studies, and whether a connected network was possible between the comparisons of interest for each outcome.

Results of the SR

Studies identified and selected

The searches were conducted between 03 March 2021 and 11 March 2021 and identified a total of 2062 records. Following deduplication, 1537 records were screened based on the title and abstract, of which 1411 records were excluded. 126 records were assessed at full text review, 85 of which were excluded. 21 studies, reported in 41 documents, were eligible for inclusion. Fig. 1 illustrates the record selection process. Lists of included and excluded papers (with reasons for exclusion) can be found in Supplementary Tables S2 and S3.

Characteristics of the included studies

Of the 21 included studies, three were parallel group RCTs [7,27,51], one was a retrospective case series of multiple interventions [10], and the remaining 17 were retrospective case series of single interventions [33,36,52-66]. Of the three RCTs, one study compared tocilizumab vs. placebo [27]; one compared canakinumab vs. placebo [7]; and one compared anakinra vs. a DMARD (methotrexate or azathioprine or leflunomide or cyclosporin A or sulfasalazine) [51]. The retrospective case series of multiple interventions reported on patients treated with anakinra or tocilizumab [10]. Interventions included in the

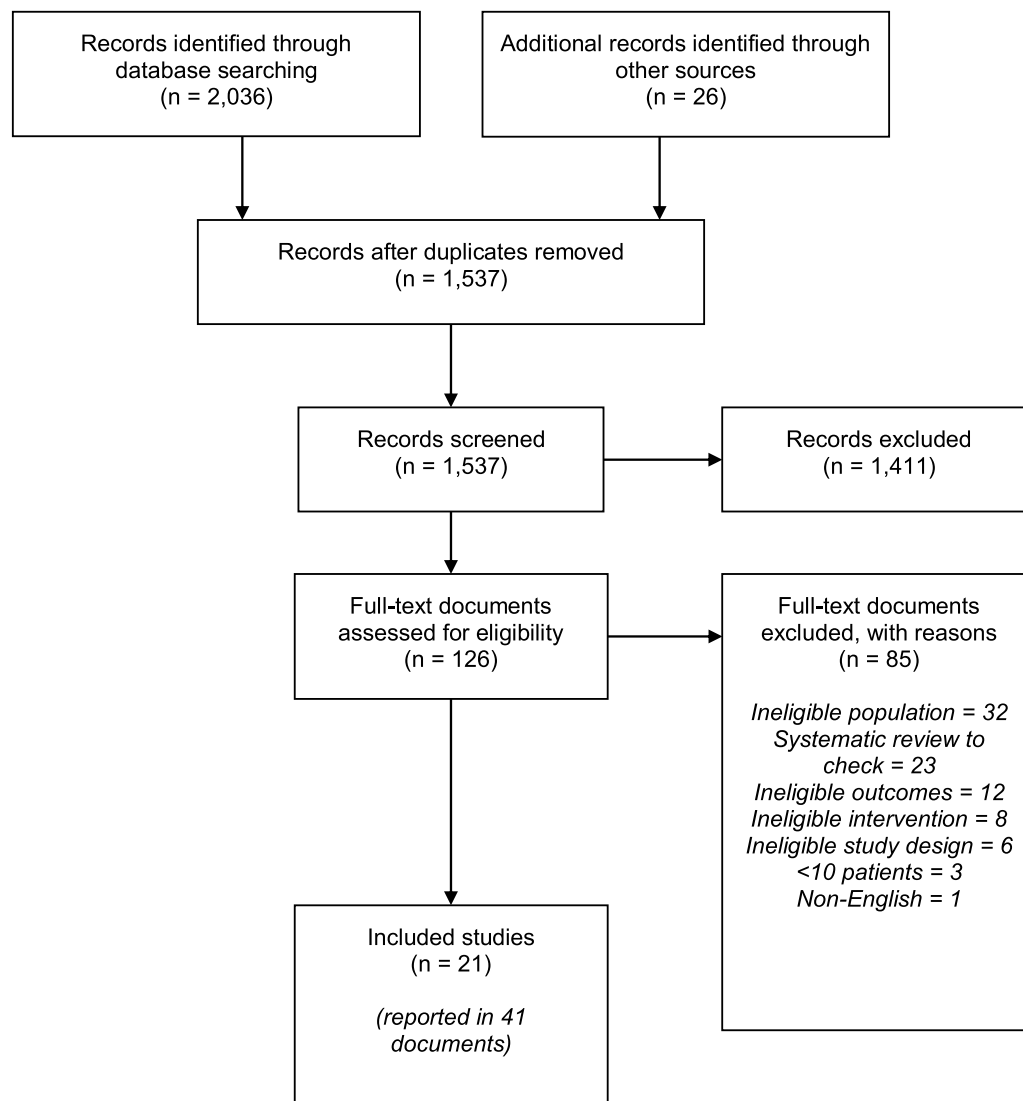


Fig. 1. PRISMA flow diagram.

retrospective single intervention case series were anakinra [53,55,57, 58,62], canakinumab [52,65,66], infliximab [56] and tocilizumab [33, 36,54,59-61,63,64].

An overview of the study and population characteristics is presented in Table 2, with full details in Supplementary Tables S4 to S5b.

Four studies were judged to have a low risk of bias [27,36,54,59], fourteen studies had an unclear risk of bias [7,33,51-53,55-58,60-63, 66], and the remaining three studies had a high risk of bias [10,64,65]. Full details are presented in Supplementary Tables 6a to 6c.

Clinical results

Primary outcomes of interest (number of patients with a clinical response after a minimum follow-up >12 weeks or the number of patients with complete remission) are reported below, while the results for secondary outcomes of interest are reported in Supplementary Section S3.

Disease activity

Measurement of disease activity differed across the included studies. Nine studies [7,27,51-54,56,57,63] reported “response” and/or “treatment failure”, using a variety of different definitions and measured at

timepoints from four weeks [51] to 102 months [53]. Eighteen studies [7,10,33,36,52-60,62-66] reported “remission”, although definitions of remission varied across studies and were reported at timepoints ranging from 12 weeks [7,53,54] to 102 months [53]. One study reported “complete response / remission” [57].

“Response” and “treatment failure”

Data for response outcomes as reported by the three RCTs are shown in Tables 3 and 4, with full details in Supplementary Table S7. In the Kedor 2020 RCT, response was classified using various methods and was reported for the comparison of canakinumab 4 mg/kg body weight monthly vs. placebo at 12 weeks [7]. In the intention to treat (ITT) population, none of the response rates were significantly different from placebo (all $p > 0.05$). For the primary response outcome (see definition in Table 4), 66.7% experienced response in the canakinumab group vs. 41.2% in the placebo group ($p = 0.18$) [7]. For the per protocol (PP) population, two patients randomised to placebo who received canakinumab in error at week 4 were excluded. In this population, treatment with canakinumab resulted in higher response rates compared with placebo regarding ACR30 response (61.1% vs. 20.0%; $p = 0.03$), modified ACR30 (55.6% vs. 13.3%; $p = 0.03$), ACR50 response (50.0% vs. 6.7%; $p = 0.01$), ACR70 response (27.8% vs. 0.0%; $p = 0.05$), and low

Table 2
Overview of study characteristics.

	RCTs [6,24,48]	Retrospective case series of multiple interventions [9]	Case series of single interventions [30, 33,49-63]
Sample size	• 22 [48] to 36 patients [6]	• 15 patients received anakinra and 17 received tocilizumab	• 10 [55,57] to 141 patients [52]
Age (years)	• 39 [48] to 55.5 years [24]	• NR	• 16 [58,59,63] to 81 years [56]
Gender (% male)	• 23.5% (bDMARD arm) and 44.4% (placebo arm) [6] • 23.1% (in both arms) [24] • 50% (in both arms) [48]	• NR	• 18% [53] to 62% [49]
Disease activity outcomes	• Response: Proportion of patients with a reduction in disease activity score (ΔDAS28 (ESR) > 1.2) [6] • DAS28 (ESR and CRP) [6] • Systemic feature score [24]** • Normal SJC and TJC [48] • Fever episodes [6] • Physician global assessment of disease activity [6] • Pain [6] • VAS score [24]	• NR	• EULAR remission (DAS28) • Clinical manifestations of AOSD • Fever • Patient global health • Remission • Drug-free remission • Relapse • ESR • PG-VAS scores
Therapeutic response outcomes	• ACR 20/30/50/70/90 [6,24] • Modified ACR30* [6] • Full response: Body temperature ≤ 37 °C, CRP ≤ 10 mg/l, and ferritin ≤ 200 µg/l female, ≤ 275 µg/l male, and normal SJC and TJC [48]	• Number of patients experiencing effective / partially effective / ineffective treatment • Number of patients who stopped biological treatment without relapse	• ACR20 • Complete/partial/failure response • Substantial decrease of modified Pouchot score • Primary inefficacy • Secondary inefficacy
Function outcomes	• Limitation of motion [6]	• NR	• NR
Other outcomes	• NR	• NR	• Number of AOSD patients treated at medical institutions • Effectiveness • Drug retention rate • NR
HRQoL outcomes	• SF-36 [6,48]	• NR	• NR
Safety outcomes	• AEs [24,48]	• NR	• Discontinuation due to AE • AEs
Steroid use outcomes	• Glucocorticoid dose [24] • Reduction or cessation of steroids [48]	• Whether the choice of bDMARD influenced the likelihood of steroid discontinuation	• Reduction in steroid dose • Reduction or cessation of prednisone • Change in steroid dose

Table 2 (continued)

	RCTs [6,24,48]	Retrospective case series of multiple interventions [9]	Case series of single interventions [30, 33,49-63]
Data collection timepoints (primary outcome)	• 4 weeks [24] • 8 weeks [48] • 12 weeks [6]	• NR	Varied from 2 weeks [30] to 9 years [50]
Duration of treatment	• 12 [6,24] to 24 weeks [48]	• NR	• <1 [64] to 102 months [50]
Date and location(s)	• Germany (2012–2018) [6] • Japan (2014–2016) [24] • Centres in Finland, Norway and Sweden (2005–2010) [48]	• Until 2018 in France (start date unclear)	• From 1985 to 2020 • In Japan [33,57, 61], Italy [49–52], France [53,54], Greece [55,63], Turkey [56,62], Spain [58,59], Korea [60], and China [30]

* A modified ACR variable (requiring ACR30 response in addition to no intermittent fever in the preceding week and no more than one out of seven variables worsening by more than 30%) [6].

** The systemic feature score consists of five clinical (fever, rash, lymphadenopathy, hepatosplenomegaly and serositis) and five laboratory assessments (erythrocyte sedimentation rate, CRP, leucocyte count, hemoglobin level and platelet count) [65].

Abbreviations: ACR - American College of Rheumatology; AE - adverse event; ANK - anakinra; AOSD - adult-onset Still's disease; cDMARD - conventional disease modifying anti-rheumatic drug; CNK - canakinumab; CRI - Club Rhumatismes et Inflammation; CRP - C-reactive protein; DAS - disease activity score; DMARD - disease-modifying anti-rheumatic drug; ESR - erythrocyte sedimentation rate; EULAR - European league against arthritis and rheumatism; HRQoL - Health related quality of life; IL - interleukin; IQR - interquartile range; MTX - methotrexate; NA - not applicable; NR - not reported; PG-VAS - Patient-reported global visual analogue scale; QoL - quality of life; RCT - randomised controlled trial; SD - standard deviation; SJC - swollen joint counts; TCZ - tocilizumab; TJC - tender joint counts; TNF - tumor necrosis factor; VAS - visual analogue scale.

disease activity DAS28(CRP) <3.2 score (50.0% vs. 13.3%; $p = 0.03$) [7].

The Kaneko 2018 RCT reported no significant differences in response rates (ACR20/50/70) between tocilizumab 8 mg/kg every two weeks vs. placebo in the full analysis set, which included patients who received at least one dose of the study medication, at 4 and 12 weeks [27]. For the primary outcome (ACR50 response at 4 weeks), 61.5% experienced response in the tocilizumab group vs. 30.8% in the placebo group ($p = 0.238$) [27].

In the Nordstrom 2012 RCT [51], comparing anakinra vs. a DMARD (methotrexate or azathioprine or leflunomide or cyclosporine A or sulfasalazine), no significant differences between groups were reported for full response (see definition in Table 4) at 4 weeks (anakinra: 50.0% vs. DMARD: 30.0%), 8 weeks (anakinra: 58.3% vs. DMARD: 50.0%) or 24 weeks (anakinra: 50.0% vs. DMARD: 20.0%). No p values were reported for these comparisons. This RCT [51] also reported lack of efficacy, defined as worsening of AOSD, in 8.3% of patients on anakinra and 20% of patients on DMARDs.

Treatment response was not reported in the retrospective case series of multiple interventions.

In the case series, definitions of response varied between studies (full definitions used by each study can be found in Supplementary Table S7) but did not include patients with complete remission. 'Good responses' at 12 months were achieved with tocilizumab with rates between 9.1% [54] and 64.3% [63] and with anakinra at a rate of 60.0% [57]. 'Partial responses' were achieved with tocilizumab with rates between 31.8% at 6 months and 14.3% at 12 months [63]; with anakinra with rates between 10% [53] and 34.3% [57]; with infliximab at a rate of 63.6%

Table 3
Clinical response at week 12: ACR20, ACR50 and ACR70.

RCT	Intervention	n	Number (%) with event	Difference between groups and odds ratio (95% CI)
ACR20 response				
UMIN000012987; Kaneko [24]	Tocilizumab 8 mg/kg every 2 weeks	13 (FAS)	8 (61.5)	$p = 0.238$
	Placebo	13 (FAS)	4 (30.8)	
CONSIDER; Kedor [6]	Canakinumab 4 mg/kg monthly	18 (ITT)	11 (61.1)	19.9% (−15.0 to 51.3); OR: NR $p = 0.32$
	Placebo	17 (ITT)	7 (41.2)	
ACR50 response				
UMIN000012987; Kaneko [24]	Tocilizumab 8 mg/kg every 2 weeks	13 (FAS)	8 (61.5)	$p = 0.238$
	Placebo	13 (FAS)	4 (30.8)	
CONSIDER; Kedor [6]	Canakinumab 4 mg/kg monthly	18 (ITT)	9 (50)	32.4% (−0.7 to 60.5); OR 4.06 (0.95 to 17.42) $p = 0.08$
	Placebo	17 (ITT)	3 (17.6)	
	Canakinumab 4 mg/kg monthly	18 (PP)	9 (50)	$p = 0.01$
	Placebo	15 (PP)	1 (6.7)	
ACR70 response				
UMIN000012987; Kaneko [24]	Tocilizumab 8 mg/kg every 2 weeks	13 (FAS)	6 (46.2)	$p = 0.238$
	Placebo	13 (FAS)	4 (30.8)	
CONSIDER; Kedor [6]	Canakinumab 4 mg/kg monthly	18 (ITT)	5 (27.8)	19.9% (−15.0 to 51.3); OR: NR $p = 0.32$
	Placebo	17 (ITT)	2 (11.8)	

Abbreviations: ACR - American College of Rheumatology; CI - confidence interval; FAS - full analysis set; ITT - intention to treat; kg - kilograms; mg - milligrams; OR - odds ratio; PP - per protocol; RCT - randomised controlled trial.

Table 4
Clinical response rates: Definitions other than ACR.

Outcome definition	Timepoint	Intervention	n	Number (%) with event	Difference between groups and odds ratio (95% CI)
NCT01033656; Nordstrom [48]					
“Full response”: Defined as body temperature $\leq 37^\circ\text{C}$, CRP ≤ 10 mg/l, and ferritin ≤ 200 $\mu\text{g/l}$ female, ≤ 275 $\mu\text{g/l}$ male, and normal SJC and TJC.	4 weeks	Anakinra 100 mg/day	12 (ITT)	6 (50)	P value NR but no significant difference
	4 weeks	DMARD: Methotrexate or azathioprine or leflunomide or cyclosporine A or sulfasalazine*	10 (ITT)	3 (30)	
	8 weeks	Anakinra 100 mg/day	12 (ITT)	7 (58.3)	P value NR but no significant difference
	8 weeks	DMARD: Methotrexate or azathioprine or leflunomide or cyclosporine A or sulfasalazine*	10 (ITT)	5 (50)	
	24 weeks	Anakinra 100 mg/day	12 (ITT)	6 (50)	P value NR but no significant difference
	24 weeks	DMARD: Methotrexate or azathioprine or leflunomide or cyclosporine A or sulfasalazine*	10 (ITT)	2 (20)	
CONSIDER; Kedor [6]					
“Primary response”: Proportion of patients with a clinically relevant reduction of the articular manifestation measured by change in disease activity score ($\Delta\text{DAS28(ESR)} > 1.2$).	12 weeks	Canakinumab 4 mg/kg monthly	18 (ITT)	12 (66.7)	25.5% (−10.3% to 55.9%); OR 2.86 (0.72 to 11.31) $p = 0.18$
	12 weeks	Placebo	17 (ITT)	7 (41.2)	

* DMARDs assessed in NCT01033656 were Anakinra 100 mg/day; Methotrexate 10–25 mg weekly oral/subcutaneous/intramuscular; Azathioprine 1–3 mg/kg/day oral; Leflunomide 20 mg/day oral; Cyclosporine A 2.5–5 mg/kg/day divided into 2 oral doses; Sulfasalazine 1000–2000 mg/day oral

Abbreviations: ACR - American College of Rheumatology; CI - confidence interval; CRP - C-reactive protein; DAS - disease activity score; DMARD - disease-modifying anti-rheumatic drug; ESR - erythrocyte sedimentation rate; ITT - intention to treat; kg - kilograms; mg - milligrams; NR - not reported; OR - odds ratio; PDN - prednisone; SJC - swollen joint count; TJC - tender joint count.

[56]; and with canakinumab at a rate of 50.0% [52]. In the three studies that reported ‘treatment failure’ or ‘no response’, a minority of patients did not achieve a response with anakinra, with rates between 8.6% [57] and 20.0% [53]. Full details are presented in Supplementary Table S7

“Remission”

For remission as reported in the RCTs (Table 5; full details in Supplementary Table S8), no significant differences were reported between canakinumab 4 mg/kg body weight monthly vs. placebo in the ITT population at 12 weeks [7]. For the PP population, there was a

Table 5
Reported remission rates at 12 weeks.

Outcome definition	Intervention and number analysed	Number (%) with event, and difference between groups and odds ratio (95% CI) (where reported / applicable)
CONSIDER; Kedor [6]		
Remission represented by a DAS28 (CRP) score < 2.6	Canakinumab 4 mg/kg monthly: $N = 18$ (ITT)	7 (38.9)
	Placebo: $N = 17$ (ITT)	2 (11.8) 27.1% (95% CI: −4.6 to 54.6) $p = 0.12$
Remission represented by a DAS28 (ESR) score < 2.6	Canakinumab 4 mg/kg monthly: $N = 18$ (ITT)	6 (33.3)
	Placebo: $N = 17$ (ITT)	2 (11.8) 21.6% (95% CI: −8.1 to 49.9) $p = 0.23$
Extended remission*	Canakinumab 4 mg/kg monthly: $N = 18$ (ITT)	5 (27.8)
	Placebo: $N = 17$ (ITT)	2 (11.8) 16.0% (95% CI: −12.6 to 43.4) $p = 0.40$

* Defined as any of Yamaguchi’s primary classification criteria for AOSD which included fever attacks at 39°C for more than a week, arthralgia, salmon red, maculate, urticarial or maculo-papular rash and leukocytosis (white blood cells increase) of $> 10,000/\text{mm}^3$ with $> 80\%$ neutrophils

Abbreviations: AOSD - adult-onset Still’s disease; CI - confidence interval; CRP - C-reactive protein; DAS28 - Disease Activity Score in 28 joints; ESR - erythrocyte sedimentation rate; ITT - intention to treat; OR - odds ratio.

significant difference in favor of canakinumab for DAS28 (CRP) remission (38.9% vs. 0.0%; $p = 0.01$), DAS28 (ESR) remission (33.3% vs. 0.0%; $p = 0.02$), and extended remission (27.8% vs. 0.0%; $p = 0.05$). Remission was not reported in the other two RCTs.

In the retrospective case series of multiple interventions, remission rates were 86.7% for anakinra and 82.4% for tocilizumab in the ITT population [10]. As noted in Supplementary Table S6b, anakinra was used in an earlier patient cohort as it was launched onto the market in an earlier year than tocilizumab. Anakinra was also used much earlier in the disease course (median 1.5 months after diagnosis vs. 17 months for tocilizumab). Those patients receiving tocilizumab had a median of two prior pharmacotherapies vs. one for those receiving anakinra.

In the case series of single interventions, remission was defined in various ways across the studies, but three main definitions were used:

- Resolution of clinical symptoms
- Resolution of clinical symptoms plus resolution of laboratory abnormalities
- Drug-free remission, i.e. being able to stop the biological agent or all treatments

Of the studies reporting resolution of clinical symptoms, 36.4% of patients treated with infliximab experienced remission (timepoint not reported) [56], and of those treated with tocilizumab [54], 45.5% were in remission at 3 months, 63.6% at 6 months and 81.8% at 12 months.

Of the studies requiring resolution of laboratory values as well as clinical symptoms, remission rates with tocilizumab varied from 22.2% (at the last medical examination) [36] to 100% at 32 weeks [33]. Remission rates with anakinra varied from 54.3% at a median of 461 days [57] to 100% (time point not reported) [58]. Remission rates with canakinumab varied from 50.0% at a median of 9 months [52] to 77.0% (time point not reported) [66].

Of the studies reporting drug-free remission, the proportions of patients able to stop biologic therapies ranged from 2.4% at 12 months [62] to 14.2% at a median of 23 months [55] from the onset of treatment with anakinra. Drug-free remission for tocilizumab ranged from 14.3% at a mean observation duration of 26.4 months [64] to [65] 72.7% at 18 months (including 12 months of active treatment followed by 6 months where treatment was discontinued) [54]. For canakinumab, the proportion of patients able to stop treatment was 9.1% at a mean of 42.2 months [65].

Summary of secondary outcomes

Steroid reduction for tocilizumab patients was reported by one RCT (Kaneko 2018 [27]) to be “significantly more” ($p = 0.017$) than patients receiving placebo, and two case series of single interventions reported that the proportion of tocilizumab patients able to stop steroids was 25.0% at 48 weeks [33] to 72.7% at 12 months [54].

For anakinra, a second RCT (Nordstrom 2012 [51]) found no significant difference ($p = 0.22$) at 24 weeks in numbers of patients stopping steroids on anakinra or DMARDs. Two case series of single interventions reported that the proportion of anakinra patients able to stop steroids was 42.1% at 12 months [55] and 13.3% at the latest follow up (12 to 27 months) [57].

One case series reported the proportion of canakinumab patients able to stop steroids to be 23.1% at 12 months [52].

Full data on steroid reduction and withdrawal can be found in Supplementary Section S3.1. The available data on HRQoL and burden of disease were minimal (see Supplementary Section S3.2 and S3.3).

Safety results

None of the three RCTs reported the statistical difference between arms for the number of patients experiencing AEs.

In the Kedor 2020 RCT [7], 80% of canakinumab-treated patients

experienced at least one AE vs. 66.7% with placebo. There were two serious adverse events (SAEs) in the canakinumab group (increased liver enzymes and patellofemoral pain syndrome leading to hospitalization) vs. none in the placebo group, and no patients died in either group [7]. One case series assessing canakinumab (Ugurlu [65]) reported 9.1% discontinuation due to AEs, and Tomelleri [52] reported 23.1% discontinuation.

In the Kaneko 2018 RCT [27], 84.6% of the patients receiving tocilizumab experienced at least one AE vs. 57.1% of patients receiving placebo. No participants in either group experienced a SAE [27]. Of the tocilizumab case series, Nishina [60] reported no discontinuations due to AEs for patients treated with tocilizumab, but Ortiz-Sanjuan [61] reported 6% discontinuation due to AEs. Song [63] reported 4.5% discontinuation with tocilizumab treatment, and Asanuma [36] reported 55.6% discontinuation due to AEs for patients in the tocilizumab induction phase.

Safety data were not reported by the retrospective case series of multiple interventions (Vercruysse 2019) comparing tocilizumab and anakinra.

In the Nordstrom 2012 RCT [51], injection site reactions were reported for the anakinra group, but data for the DMARD group were not reported. No participants in either group withdrew from the study due to injection site reactions. Three SAEs were reported (one in the anakinra group and two in the DMARD group); all three were a worsening of AOSD, i.e. lack of efficacy [51]. For single-intervention case series assessing patients treated with anakinra, 12.2% discontinued due to AEs in the Ortiz-Sanjuan [62] study, while 8.6% discontinued in the Rossi-Semarano [57] study and 13.3% discontinued anakinra in the pre-2005 group due to AEs [67]. 18% of patients in the Vitale [55] study discontinued anakinra due to AEs.

Finally, Fautrel [56] reported 9.1% discontinuation due to AEs for patients treated with TNF inhibitors.

Across all interventions, adverse events that were cited as causes of discontinuation of treatment included infection [36,52,55,61,62,65] and allergy [36,55]. One study reported that there were no severe AEs [54], two studies reported no SAEs [33,63], and one reported no “major” AEs (i.e. life-threatening, fatal or requiring hospitalization) [58].

Results for sub-groups of interest

Outcome data were not available for all subgroups of interest to the review (see Supplementary Section S1 for a full list of subgroups). Only Vitale (2020) reported any data by phenotype. In this study there was no significant difference in drug retention rate between those with the systemic form and those with the chronic articular form. No other study reported results by phenotype.

Subgroup data for remission rates in ‘responders’ were reported in the retrospective case series of multiple interventions, and AE rates for responders were reported in the Kedor 2020 RCT. However, these analyses were limited by the small sample size and no statistical comparison was reported. The data are presented in Supplementary Table S9.

Subgroup analysis regarding the likelihood of steroid withdrawal with biologics by line of therapy was reported in the retrospective case series of multiple interventions. One case series study also performed a subgroup analysis by line of therapy for differences in anakinra effectiveness, drug retention rate and prednisone dose. No statistically significant difference was found in any of these analyses by line of therapy [10,55]. The data for these outcomes are shown in Supplementary Table S10.

No studies reported efficacy outcome data by biomarker sub-groups; therefore, therapy choice cannot be informed by biomarkers.

Feasibility assessment of indirect comparisons

Three RCTs were included in the SR. The feasibility assessment considered the homogeneity of these three trials in respect of their

methods, populations, locations and dates, and treatments and outcomes assessed. For all but one outcome (response as measured by ACR20 [68]), data were only available from one RCT per outcome. Two RCTs [7,27] reported ACR20 at 12 weeks, the end of the randomised treatment period in both trials. However, due to differences in placebo (administered subcutaneously in one trial and intravenously in the other) and assumptions around the similarity of trial populations, quantitative analysis of this outcome was not conducted. We did not consider any of the case series studies for the feasibility assessment because of the high risk of bias and lack of generalisability inherent in these study designs.

Discussion

AOSD is a rare and often long-term condition, and treatments are required that can offer long-term control of symptoms and prevent the need for steroids. This SR confirms and updates the findings of existing reviews [1,40] which found that RCTs of bDMARD therapies in AOSD are few and of small size, with the available observational studies being of poor quality and difficult to compare. This is due in part to the rarity of AOSD, its heterogeneous clinical manifestations, the absence of a composite outcome measure to detect disease activity accurately, and the use of varying definitions of response [40]. In addition to a lack of comparable clinical evidence, burden of illness was not reported in any of the comparative studies identified by this review, and the only burden of illness data came from two retrospective case series, discussed in Supplementary Section S2 [59,60].

This review found that response rates and remission were defined differently in the various studies, and were measured at different time points, making comparisons difficult (see Table 2 for the full list of response measures). This limits the comparability and the generalization of the results. The three RCTs concluded that tocilizumab was not superior to placebo [27], anakinra was not statistically different to methotrexate [51], and canakinumab was not statistically superior to placebo in the ITT analysis [7]. In 2022, Sota et al. [69] assessed the efficacy and safety of tocilizumab using real world data from 31 patients with refractory AOSD enrolled in the international Autoinflammatory Disease Alliance (AIDA) registry. It was found that clinical manifestations of AOSD, as measured through Pouchot score, significantly decreased throughout the study period from baseline. However, no differences were observed between the six-month evaluation and the last follow-up. All laboratory parameters (including CRP, ESR and serum ferritin) significantly decreased from baseline to the last follow-up and mean CS daily dose was also significantly reduced from baseline [69].

Results from the case series studies are too varied to suggest a trend in efficacy. Therefore, the heterogeneity of the case series studies means they cannot be used to support any of the efficacy outcomes. Steroid sparing effects of biologics were reported in the Kaneko 2018 RCT [27], the retrospective case series of multiple interventions [10], and in 12 of the 17 retrospective case series of single interventions [33,52-55,57-63]. This is an important parameter to consider because steroid dependency is frequently observed in AOSD, and the use of steroids can lead to serious side effects over the long term [70].

There were no serious safety concerns reported for any biologic treatment. In all three RCTs, AEs were common in both groups, but serious adverse events were uncommon. Withdrawal due to AEs in general was not reported in any RCT, although the Nordstrom 2012 RCT [51] reported that no patients in either arm withdrew specifically due to injection site reactions. Based on the real-world data from Sota et al. [69], two patients discontinued treatment with tocilizumab due to AEs (cardiac tamponade and pneumonia). It was not stated whether these were related to tocilizumab treatment [69].

In the retrospective case series of single interventions, discontinuation due to AEs was low (<6%) [60,61,63] for patients treated with tocilizumab, although a much greater percentage of patients receiving tocilizumab as induction therapy withdrew due to AE (55.6%) [36].

Discontinuation due to AEs were also low for patients receiving TNF inhibitors (<10%) [56], while withdrawal due to AEs varied for patients receiving anakinra (between 9% and 18%) [55,57,62,67] and for patients receiving canakinumab (between 9% and 23%) [52,65]. Patients switched between biologic therapies due to lack of efficacy, adverse events, lack of (anakinra) availability in the region, or to avoid daily injections [52,60,66]. The safety of biologics for AOSD has been acknowledged in other studies, which report that biologics are safe to use in the long-term management of AOSD and are generally associated with mild to moderate skin rash and infections rather than life-threatening complications [53,71,72]. However, previous reviews have cautioned that larger studies are required to confirm the safety of emerging bDMARDs, particularly with regards to macrophage activation syndrome [73].

This systematic review was conducted using rigorous methods, with a well-defined question, and searches developed to identify relevant evidence across a number of suitable databases. Study selection was undertaken by double independent reviewers, and the range of eligible study designs was broad. Peer reviewed tools were used to assess the risk of bias of the included studies. One key limitation of the review was the restriction to English-language studies only.

There are few studies available for each intervention and comparator, and many of the studies were small case series. This has limited the possibility of assessing publication bias or of providing a strong evidence base for any of the interventions. Even within the treatment groups, there was considerable heterogeneity between studies, including a variety of definitions of response and timepoints (which were in some cases not clearly stated) and study designs (RCTs and retrospective studies). This means that bDMARD treatments cannot be directly compared using the existing evidence base, nor can the results of the existing studies be generalised to the full AOSD population. The previous SR of biologics in AOSD also found high levels of heterogeneity across studies [1]. Comparing results between studies was difficult not only due to the small cohorts and differences in study design (retrospective or RCT), but also because the outcome criteria were different. A lack of validated diagnostic criteria or a clear definition means that clinical response and remission were defined differently across studies. However, the European League Against Rheumatism (EULAR) currently has a project underway to define a disease activity score for AOSD, referred to as the DAVID project (CLI113). EULAR is also developing recommendations for the diagnosis and management of sJIA and AOSD (QoC011) [74].

Another limitation of the current data on bDMARDs for AOSD was the short follow-up period in the RCTs and most case series. The longest follow-up period in the RCTs was at 52 weeks in the UMIN000012987 trial [27]. Among the retrospective case series, the Vitale 2020 [55] cohort were followed up for 120 months, which allowed for analysis of loss of anakinra efficacy (17.5% after 10 years). Two further case series reported follow-up of 31 months [65] and a range of between 3 and 102 months [53]. However, the majority of the remaining 14 case series reported follow-up at under 3 years [33,52,54,57,59-64]. Four case series [36,56,58,66] did not report the timepoint of outcome assessment. Information regarding the long-term use of bDMARDs is therefore lacking, meaning there is uncertainty on the efficacy of bDMARDs in treating long-term chronic AOSD.

Conclusion

While this SR has identified numerous retrospective uncontrolled case series, this study design is generally considered to be prone to bias and does not offer comparative information. The results from this SR, and that of the previous SR on biologics [75], highlight the need for further large high-quality RCTs that would ideally be required to assess these drugs in this patient population, although this is challenging in a rare condition. Data relating to the long-term duration of treatment, drug survival (the rate and duration of adherence to biologics), quality

of life outcomes, and burden of illness are also lacking for AOSD. Furthermore, there are no validated clinical or lab predictors that can be used to identify patients who will develop polycyclic or chronic disease. While real-world data have indicated there is no difference between tocilizumab efficacy for chronic and polycyclic AOSD, further investigation into the efficacy of other bDARDS according to the polycyclic and chronic disease subtypes is required [69]. Additionally, there is presently no information on the efficacy of bDMARDs in the four specific AOSD subsets defined by Ruscitti et al. [15]. Determining whether certain bDAMRDS are more efficacious in some AOSD subsets would allow tailored treatment of AOSD in the future. Modeling-based approaches, the use of real-world evidence such as registries, collaborations between hospitals, and better methods of data collection are all additional options that may help to better develop the evidence base for treatments for AOSD.

Declarations of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2022.152139.

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