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CLINICAL SCIENCE

Efficacy and safety of therapies for Still's disease and macrophage activation syndrome (MAS): a systematic review informing the EULAR/PReS guidelines for the management of Still's disease

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ABSTRACT

Objectives To analyse the efficacy and safety of treatments for Still's disease and macrophage activation syndrome (MAS).

Methods Medline, Embase and Cochrane Library were searched for clinical trials (randomised, randomised controlled trial (RCT), controlled and clinical controlled trial (CCT)), observational studies (retrospective, longitudinal observational retrospective (LOR), prospective and longitudinal observational prospective (LOP)) and systematic reviews (SRs), in which the populations studied were patients with Still's disease and MAS. The intervention was any pharmacological treatment (approved or under evaluation) versus any comparator drug or placebo, and as outcomes, any relevant efficacy and safety event. The risk of bias (RoB) was assessed with the Cochrane RoB and AMSTAR-2 (Assessing the Methodological Quality of Systematic Reviews-2, version 2) for SRs.

Results 128 full texts were included: 25 RCTs, 1 CCT, 11 SRs published after 2013 and 91 LOP/LOR studies. In Still's disease, interleukin (IL)-1 inhibitors (IL-1i) and IL-6R inhibitors (IL-6i) were the most studied drugs. Two meta-analyses on RCTs showed an OR, to achieve an ARC50 response rate, of 6.02 (95% CI 2.24 to 21.36) and 8.08 (95% CI 1.89 to 34.57) for IL-1i and IL-6Ri, respectively. Retrospective studies showed that early initiation of IL-1i or IL-6i was associated with high rates of clinically inactive disease. In MAS, GCs were employed in all patients, often associated with ciclosporin and/or anakinra. Rates of complete response were reported, with a range from 53% to 100%. Emapalumab was the only drug tested in a CCT, with a complete response of 93%.

Conclusion IL-1i and IL-6Ri show the highest level of efficacy in the treatment of Still's disease. For MAS, IL-1 and interferon-γ inhibition appear to be effective on a background of high-dose glucocorticoids.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Systemic juvenile idiopathic arthritis (sJIA) and adult-onset Still's disease (AOSD) are the adult and child counterparts of a unique autoinflammatory disease for which no consensual therapeutic strategy has been defined yet. There was a need to systematically review the new evidence on the efficacy and safety of the therapies for sJIA/AOSD and macrophage activation syndrome (MAS), to inform an ongoing task force aiming to propose EULAR/Paediatric Rheumatology European Society (PReS) joint recommendations for the diagnosis and management of sJIA and AOSD.

WHAT THIS STUDY ADDS

⇒ Interleukin-1 inhibitors (IL-1i) and IL-6Ri show the highest level of evidence in terms of efficacy, safety and an acceptable risk-benefit ratio for the treatment of sJIA and AOSD. Studies on methotrexate, ciclosporin A and tumour necrosis factor inhibitors showed marginal efficacy. In MAS, some immunomodulating agents (particularly IL-1 and interferon-γ inhibitors) appear to be effective on a background of high-dose glucocorticoids.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ IL-1 and IL-6R inhibitors show the most interesting risk-benefit ratio compared with all alternatives in Still's disease. In MAS, despite the scarcity of data, high-dose glucocorticoids combined with IL-1 or IFN-γ inhibition appear presently to be the best available strategy. Data derived from this systematic review informed the EULAR/PReS task force to determine the optimal therapeutic strategy to manage people living with sJIA/AOSD and MAS.

INTRODUCTION

Adult-onset Still's disease (AOSD) and systemic juvenile idiopathic arthritis (sJIA) are the adult and child counterparts of the disease described by George Frederic Still. Still's disease is a rare non-familial systemic inflammatory disorder,[1 2] often classified among autoinflammatory diseases.[3] Patients with Still's disease are at high risk of developing a potentially life-threatening complications, including macrophage activation syndrome (MAS).[4]

A vast body of evidence points, particularly in the initial phase, to excessive activation of innate immunity that leads to overproduction of the

proinflammatory mediators like interleukin (IL)-1β, IL-6, IL-18 and S100 proteins.[5–7] The therapeutic approach in both sJIA and AOSD historically relies on non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (GCs). GCs have been used as anchor therapy for decades, with major safety concerns when employed at high doses and for long periods.[1] Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) were subsequently proposed, particularly to treat GC-dependent disease, with methotrexate (MTX) and ciclosporin A (CsA) being the most widely used.[8] Recently, the identification of the key roles of IL-1 and IL-6 led to the use of bDMARDs targeting these cytokines. This has transformed the approach to patients with Still's disease,[9] being associated with significantly improved outcomes and the reduction, if not elimination, of GC use.[2 10 11]

MAS is a hyperinflammatory condition.[4] It is characterised typically by fever, cytopenia and hyperferritinaemia associated with variable multiorgan involvement, including spleen, liver dysfunction and neurological abnormalities. Viral infections are the main triggers of MAS in sJIA and AOSD.[8 12] Early immunomodulation treatment is associated with a reduction in mortality, both in adults and children. Although GCs are the cornerstone for the treatment of MAS, additional immunosuppressive and biologic treatments are more and more often used.

The current systematic review (SR) aimed to gather scientific evidence on the efficacy and safety of treatments for sJIA/AOSD and MAS.

METHODS

Search strategy and inclusion criteria

The protocol for this SR was registered in PROSPERO (CRD42022374273 and CRD42024534021). An online literature search was conducted on Medline, Embase and the Cochrane Database of Systematic Reviews CENTRAL. The search strategy included synonyms for MeSH/Emtree and free terms for 'adult-onset Still's disease', 'systemic juvenile idiopathic arthritis' and 'macrophage activation syndrome' along with eligible drugs, without language restrictions. The detailed search strategy is presented in online supplemental file (SF)1. The research question was formulated according to the population, intervention, comparator and outcome format.[13] For treatment in Still's disease, the included population were patients with sJIA and AOSD. Interventions considered were: (1) GCs (prednisone, methylprednisolone and dexamethasone); (2) NSAIDs; (3) csDMARDs: MTX, CsA, leflunomide (LEF), azathioprine (AZA), sulfasalazine (SSZ) and hydroxychloroquine (HCQ); (4) bDMARDs: anakinra (ANK), canakinumab (CAM), rilonacept (RIL), tocilizumab (TCZ), sarilumab, siltuximab, etanercept (ETA), adalimumab (ADA), infliximab (IFX), secukinumab, ixekizumab, certolizumab pegol and golimumab; (5) targeted synthetic (ts) DMARDs: Janus-Kinases inhibitors (JAKi): ruxolitinib (RUX), tofacitinib (TOF), baricitinib (BAR), filgotinib and upadacitinib; (6) intravenous immunoglobulins (IVIGs); (7) colchicine; (8) thalidomide; (9) IL-18 binding protein (BP): tadekinig-alpha; (10) emapalumab; and (11) etoposide (VP-16). All doses, formulations, regimens (eg, on-demand or continuous), duration and any combination were evaluated. Comparators were defined as any other active drug or placebo. The outcomes of interest were all relevant efficacy and safety information. The details of the eligibility criteria are shown in online supplemental file SF2.

Study selection, data extraction and risk of bias (RoB) assessment

The results of the original searches were downloaded in Research Information Systems format and uploaded to the Rayyan software.[14] After the removal of duplicates, the titles and abstracts, without restriction dates, were independently examined by two reviewers (SB and ADM). In cases of disagreement about the eligibility of certain studies, a consensus was reached through discussion between the two reviewers and the methodologist (LC). The number of records included and removed at each selection stage is reported in the PRISMA flowcharts[15] (figure 1A and B). The RoB of randomised controlled trials (RCTs), clinical controlled trial (CCTs) and longitudinal observational prospective (LOP)/

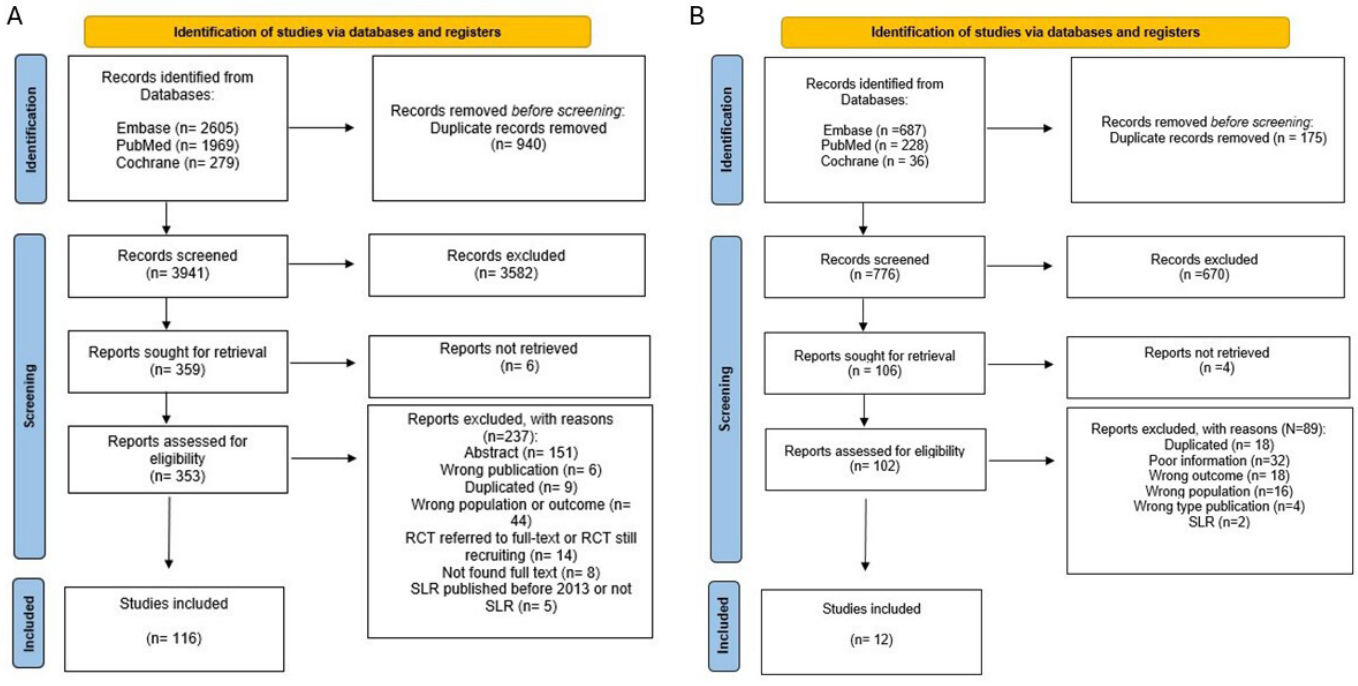

Figure 1 Preferred Reporting Items for Systematic reviews and Meta-Analyses flowchart.

longitudinal observational retrospective (LOR) studies, was assessed with V.2 of the Cochrane RoB-2,[16] and the overall risk was defined (online supplemental file SF3A, SF3B). AMSTAR-2[17] was employed to assess the quality of SRs.

Data synthesis and statistical analysis

The synthesis of the results was done qualitatively, and the results of the studies were described by drug and outcome. To perform meta-analyses, considering the heterogeneity of the designs and outcomes involved, we made the following choices: (1) withdrawal design trials were excluded because they did not allow a comparison of the efficacy between active treatment and placebo, (2) as all IL-1i trials had a randomised placebo phase of 4-week duration, we chose to use 4 weeks as the time of assessment also for the IL-6i trials; (3) since setting the time of assessment at 4 weeks implied a short period of treatment, we chose to use a relatively low, although clinically meaningful, level of response (American College of Rheumatology (ACR)50) as the outcome. Notably, in all trials, the predefined primary outcome was ACR30 or adapted-ACR30. We performed a pooled analysis of the safety of IL-1i or IL-6i from articles reporting safety data in RCT, in their long-term extension (LTE) phases and registries. None of the LOR/LOP provided information from which exposure could be derived, and therefore, these were excluded. Placebo data were not included as (1) placebo data from randomised withdrawal trials could not be considered because of the carry-over effect of the active drug administered during the lead-in open-label phase that precedes the randomised withdrawal phase and (2) the very few data with very limited exposure to placebo in classical randomised trials were deemed not informative. No meta-analysis was performed for MAS treatment.

RESULTS

For sJIA/AOSD, of the 3941 screened records, 353 full-text documents were downloaded, and 116 were included. The main characteristics of the studies are presented in online supplemental file SF4, divided by drug and design. A hierarchical approach based on the level of evidence was used, starting from SRs and RCTs to observational studies and case series. It should be noted that for MAS, some studies performed before the development of the 2016 MAS criteria[18] were included[19–22] because, from an analysis of the articles, we could establish that the patients satisfied the criteria.

Outcome measures

Since there is no consensus tool to assess disease activity or treatment responses, different efficacy outcome measures have been used. In sJIA RCTs, the adapted JIA American College of Rheumatology (aJIA-ACR 30/50/70/90) response criteria were often adopted. The response is achieved when the patient reaches a percentage of improvement from baseline greater than or equal to 30/50/70/90 in a minimum of three out of six core variables (physician's global assessment of disease activity (PhGA), patient or parent's assessment of overall well-being (Pt/PrGA), the number of joints with active arthritis, the number of joints with limited range of motion, the Childhood Health Assessment Questionnaire and the erythrocyte sedimentation rate (ESR)), with no more than one of the remaining variables worsening by greater than 30% from baseline.[23] These criteria, developed for JIA in general, were adapted to sJIA by adding, to the level of ACR response, the absence of fever (defined as a temperature ≤38°C in the preceding 7 days).[24] In sJIA, clinical inactive disease (CID) was often used: CID is defined as the absence of clinical manifestations of sJIA (arthritis, fever, rash, serositis, splenomegaly, lymphadenopathy and morning stiffness) with normal levels of inflammatory markers (ESR and C reactive protein (CRP)) at a single time point visit. Maintenance of CID for 6 months has been defined as clinical remission on medication (CRM).[25]

In AOSD, the efficacy outcome measures were more heterogeneous across studies. In RCTs, the proportion of patients who achieved a clinical response was defined by the ACR response (20/30/50/70/90) developed for rheumatoid arthritis.[26] Similarly to sJIA, an adapted ACR response (an ACR response level without fever in the previous week) has also been used in AOSD. In AOSD, other endpoints included the proportion of patients with a significant reduction of articular manifestations (Disease Activity Score-28 (DAS28)-CRP/ESR) or the EULAR response criteria. In AOSD, 'complete response' was also used, defined as the absence of clinical features, including fever, skin rash, arthralgia, arthritis, lymphadenopathy, hepatosplenomegaly and normalisation of laboratory values, including complete blood count, ESR, CRP, ferritin, lactate dehydrogenase and transaminases.

To achieve homogeneity in the evaluation of efficacy reported in the studies selected for this SR, we chose to consider a 'complete response', as used in AOSD studies, equivalent to CID in sJIA studies and, for simplicity, is reported as CID. A long-lasting, complete response to medication was considered equivalent to CRM and is reported as such. All other measures of response are reported separately from tables 1–4 and in the online supplemental files. In terms of outcomes for MAS, we evaluated the achievement of complete response, defined as resolution of symptoms and normalisation of laboratory parameters, GCs sparing effect, mortality and serious and non-serious severe adverse events (table 5).

Safety outcomes are based on the number of adverse events (AEs) and serious adverse events (SAEs) and are reported as such. When possible, rates per 100/patients-year (PY) were reported.

sJIA and AOSD treatments

Non-steroidal anti-inflammatory drugs

Although NSAIDs are used in most patients, we did not identify studies specifically assessing the efficacy of NSAIDs in sJIA or AOSD. In AOSD, remission with NSAIDs was not achieved in the vast majority; most patients reported side effects.[8 27 28]

Glucocorticoids

Data from the studies with GCs are shown in table 1. In the single available RCT, patients with sJIA were randomly assigned to receive two GC schedules for 6 months: oral prednisone (1 mg/kg/day) or pulse intravenous methylprednisolone (mPDN) for 3 days at 5 mg/kg/day and an additional 3 days at 2.5 mg/kg/day, followed by oral prednisone (1 mg/kg/day). Fever and joint scores, as defined by the authors, decreased after 6 and 12 months without a difference between the two schedules.[29] In another study,[30] 18 patients with sJIA were treated with mPDN pulses: 55% experienced improvement in systemic features and three achieved CRM. Side effects related to prolonged use of GCs were observed in five patients (acne, hirsutism, striae rubrae and overweight), two avascular necrosis of the hip and one requiring hip replacement.[29 30] In a recent LOR, two GC schedules in naive AOSD were compared: high (0.8–1 mg/kg/day) versus low-dose prednisone (0.2–0.3 mg/kg/day). At 6 months, 33/73 (45%) achieved CID, 25/38 (64.7%) in the high-dose regimen and 8/35 (22.8%) in the low-dose regimen.[31]

Table 1 Studies reporting the efficacy and/or safety of GCs, csDMARDs, MTX and CsA colchicine and IVIG in sJIA and AOSD

	First author	Study design	Patients (N)	Intervention	Concomitant treatment	CID (%)	Other outcomes (%)	AE *	SAE*	Risk†
GCs	Picco[29]	RCT	sJIA (12)	MPDN intravenous 5 mg/kg/day for 3 days, then 2.5 mg/kg/days for 3 days, then PDN per os (1 mg/kg/day) for 6 months	NSAIDs	na	11/12 (92%) ‡	5	na	
			sJIA (10)	PDN 1 mg/kg/day for 6 months	NSAIDs	na	9/10 (90%)			
	Adebajo[30]	LOR	sJIA (18)	MPDN pulses (8 one pulse, 7 two pulses and 4 three pulses)	Other GCs, NSAIDs and csDMARDs		10 (55%)§ CRM: 3 (16%) for 24 months	na	Two avascular necrosis hip and hip replacement	
	Ruscitti[31]	LOP	AOSD (80) 50% on low dose (LD); 50% on high dose regimen (HD)	HD: PDN 0.8–1 mg/kg/day LD: PDN 0.2–0.3 mg/kg/day	na	Overall: 33/73 (45%) HD 25/38 (65%) LD 8/35 (23%)	na	(7%)	5 (6%) MAS: 1 (2%) on HD and 4 (10%) on LD	
MTX	Fujii[36]	LOR	AOSD (13)	MTX 5–20 mg/week for 4 months	GCs	8/13 (61%)	na	5/13 (38%) patients		
	Al-Sewairy[37]	LOR	sJIA (18)	MTX 2.5–15 mg/week for 18 months	GCs	na	16 (89%) ¶ CRM: 7 (39%) at 12 M	na	na	
	Woo[39]	RCT	sJIA (45)	MTX PO 15–20 mg/m^2	GCs and NSAIDs	na	ACR30 (25%)	57	One pneumonitis	
			sJIA (44)	PBO	GCs and NSAIDs	Na	ACR30 (16%)	63	Two pneumonitis	
	Fautrel[38]	LOR	AOSD (26)	MTX 10 mg/week for 8–136 months	GCs	18 (69%)	na	14	One AA amyloidosis and severe neutropenia (died) seven GCs related	
Multiple csDMARDs interventions and CsA	Mitamura[41]	LOR	AOSD (34)	CsA 7 (21%) 125 mg/day to 200 mg/day for 12.4 months (1–31) MTX 10 (29%) 5–8 mg/week	GCs, 13 (38%): CYC, FK506, AZA, Gold, D-PEN, SSZ, colchicine and mizoribine	6/7 (86%) on CsA 1/10 (10%) on MTX	na	0	On CsA: one brain nocardiosis, pericarditis, interstitial pneumonia,one lung nocardiosis and one MAS+DIC	
	Franchini[28]	LOR	AOSD (45)	MTX 22 courses (49) up to 25/mg week for 56 months CsA 12 courses (27) up to 250 mg/day for 56 months	GCs NSAIDs, AZA, SSZ	16/22** (73%) MTX 9/12 (75%) CsA 3/4 (75%) AZA	na	na	na	
CsA	Pal[40]	LOP	sJIA (15)	CsA 3.1 mg/kg/day for 12 months	GCs, MTX	M2: 13/15 (86.6%) †† At 5 years: 11 (73%)	na	2	0	

Continued

Table 1 Continued

	First author	Study design	Patients (N)	Intervention	Concomitant treatment	CID (%)	Other outcomes (%)	AE *	SAE*	Risk†
Colchicine	Myachikova‡‡[32]	LOR	AOSD (20) with serositis	Colchicine 1 mg/day	NSAIDs and GCs	13 (65%)	na	6	0	
IVIGs	Silverman[33]	RCT	sJIA (14)	IVIG 1.5 g/kg (maximum 75 g) every 2 weeks for 2 months, then monthly for 4 months	NSAIDs and GCs	na	7/14 (50%)§§ 7/14 (50%)¶¶ 14/47 (30%)***	10	0	
			sJIA (17)	PBO	NSAIDs and GCs	na	4/15 (27%)§§ 7/14 (50%)¶¶ 22/48 (46%)***	0	0	
	Uziel[34]	LOR	sJIA (27)	IVIG 1 g/kg/day for 2 days, then 1.5 g/kg/day 1 day (2–102 months)	NSAIDs, GCs, MTX (six patients)	4/25 (16%)†††		0	One septic meningitis, one MPGN, one SLE and one necrotising vasculitis	
	Gerfaud-Valentin[35]	LOR	AOSD (23)	IVIG (dose not specified)	na	na	4/23 (17%)‡‡‡		One acute renal failure	
	Néel[132]	LOR	AOSD (6)	IVIG 2 g/kg/day	GCs	na	1/6 (17%)§§§	na	na	

*AE only number is reported (% of patients). For SAE, individual SAEs are listed. Infection events are also listed.
†RoB was calculated with RoB-2 tool; red=high, yellow=intermediate and green=low.
‡The outcome of efficacy is expressed as 'decrease in fever and disease activity score'.
§Normalisation of systemic features.
¶The response to MTX was evaluated in all patients and was defined as a reduction of 50% or more in the number of joints with active arthritis and control of all systemic features; the response was defined as 'clinical improvement'.
**22 refers to the total drug courses.
††Classified as responders off CsA and GCs;.
‡‡Colchicine in this study was employed for the specific manifestation of pericarditis in AOSD. Remission in this study was defined if persistent apyrexia, absence of rash, absence of articular syndrome and sore throat, pericardial effusion less than 7 mm according to transthoracic echocardiography, absence of chest pain, CRP level less than 5 mg/L, normalisation of aminotransferases, leucocyte count and ferritin level.
§§Better, much better according to Physician Global Assessment.
¶¶Clinically important improvement in severity score (articular).
***Improvement on the total number of laboratory tests executed. Improvement is expressed as: 'at least 25% improvement or normalisation in haemoglobin, albumin and platelet count and ESR'.
†††Remission expressed as 'no active joints'.
‡‡‡IVIG 'controlled the disease'.
§§§In this study, IVIG were used in second line in ICU patients and the outcome is defined as 'efficacy'.
ACR, American College of Rheumatology; AE, adverse events; ALT, alanine aminotransferase; AOSD, adult-onset Still's disease; AP, alkaline phosphatase; AZA, azathioprine; CID, clinical inactive disease; CRM, clinical remission on medication; CRP, C reactive protein; CsA, ciclosporin A; csDMARDs, conventional synthetic disease-modifying antirheumatic drug; CYC, cyclophosphamide; DIC, disseminated intravascular coagulation; D-PEN, D-penicillamine; ESR, erythrocyte sedimentation rate; FK506, tacrolimus; GCs, glucocorticoids; ICU, intensive care unit; IVIG, intravenous immunoglobulins; LOP, longitudinal observational prospective; LOR, longitudinal observational retrospective; M, months; MAS, macrophage activation syndrome; MPDN, methylprednisolone; MPGN, membranoproliferative glomerulonephritis; MTX, methotrexate; NSAIDs, non-steroidal anti-inflammatory drugs; PBO, placebo; PDN, prednisone; PO, per os; RCT, randomised controlled trial; RoB, risk of bias; SAE, severe adverse events; sJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; SSZ, sulfasalazine.

Table 2 Randomised and clinical controlled trials reporting the efficacy of IL-1 inhibitors (anakinra, canakinumab and rilonacept) in sJIA and AOSD

First author	Study design	Patients (N)	Intervention	CID (%)	Other outcomes (%)	Risk*
Quartier[45]	Double-blind randomised placebo-controlled	sJIA (12)	ANK	na	M1: ACRPed 70 5 (42%)	
		sJIA (12)	PBO	na	M1: ACRPed 70 0	
	LTE	sJIA (22)	ANK	5/16 (31%)*	na	
Nordstrom[46]	Open-label randomised	AOSD (12)	ANK	M6: 6/12 (50%)	na	
		AOSD (10)	csDMARDs	M6: 2/10 (20%)	na	
	LTE	AOSD (17)	ANK	M12: 7/14 (50%)	na	
Ruperto† [52]	Double-blind randomised single dose	sJIA (43)	CAM	M1: 13 (30%)	M1: ACR70 29/43 (67%) ACR90 20/43 (47%)	
		sJIA (41)	PBO	M1: 0	M1 aACR70 1/41 (2%) aACR90 1/41 (2%)	
Ruperto[52]	Open-label lead-in phase	sJIA (177)	CAM	55/176 (31)	aACR70 113/175 (65%) aACR90 90/175 (51%)	
	Randomised withdrawal	sJIA (50)	CAM	31/50 (62)	aACR70 41/50 (82%) aACR90 38/50 (76%)	
		sJIA (50)	PBO	17/50 (34)	aACR70 31/50 (62%) aACR90 28/50 (56%)	
Ruperto[53]	LTE from NCT00886769, NCT00889863, NCT00426218 and NCT00891046 open-label single arm	sJIA (144)	CAM	M6: 58/177 (33) M24: 69/177 (40)	M6: aJIA-ACR 70 116 (65%) aJIA-ACR 90 92 (52%) At 3 years: aJIA-ACR 70 95 (54%) aJIA-ACR 90 87 (50%) CRM: 33/177 (19%) at 6M	
Nishimura[54]	Open label-single arm	sJIA (19)	CAM	M11: 9/12 (75)	M11: ACRPed70 16 (100%) ACRPed90 12/14 (87%)	
Quartier[55]		sJIA (98)	CAM	na	M6: CRM: 49/98 (50%)	
Lovell[65]	Randomised double blind	sJIA (17)	RIL	na	M1: ACR 70 3/17 (18%)	
		sJIA (7)	PBO	na	M1: ACR 70 1/7 (14%)	
	LTE	sJIA (23)	RIL	2/23 (8%)	M12: ACR70 19 (83%)	
Ilowite[66]	Randomised double blind	sJIA (36)	RIL	M3: 4/33 (12%) M6: 11/55 (20%)	M1: ACRPed70 14/35 (40%) M3: ACRPed70 23/33 (70%)	
		sJIA (35)	PBO	na‡	M1: ACRPed70 4/33 (12%)	
Kedor[60]	Double-blind randomised	AOSD (18)	CAM	M3: 5/18 (33%)	M3: ACR70 5 (28%) ACR90 2 (11%) DAS28-ESR<2.6 5 (33%)§ DAS28-CRP 12 (67%)	
		AOSD (17)	PBO	M3: 2/17 (12%)	M3: ACR70 2 (12%) ACR90 1 (6%) DAS28-ESR<2.6 1 (12%)§ DAS28-CRP 7 (41%)	
	LTE	AOSD (23)	CAM	4/23 (17%) at M5	na	

The RoB was assessed with the Rob2 tool. Red=high, yellow=intermediate and green=low.
*In the long-term open-label phase, 16 patients reached month 12; among seven responders, five of them had inactive disease.
†The principal outcome of Trial-1 was the proportion of patients who achieved adapted ACR30 response; the open-label phase determined if at least 25% of patients treated with GCs were able to have their dose tapered; in the withdrawal phase (Trial-2) the objective was to show that the time to flare was longer with CAM than placebo. In Trial-2, patients were also evaluated for higher levels of improvement including adapted JIA-ACR50.
‡The PBO group received RIL after the 4-week double-blind phase, therefore CID is not available for the initial PBO group.
§Data are referred to as per-protocol population.
ACR, American College of Rheumatology; ANK, anakinra; AOSD, adult-onset Still's disease; CAM, canakinumab; CID, clinical inactive disease; CRM, clinical remission on medications; CRP, C reactive protein; csDMARDs, conventional synthetic disease antirheumatic modifying drugs; DAS, disease activity score; ESR, erythrocyte sedimentation rate; LTE, long-term extension; M, month; na, not available; OLE, open-label extension; PBO, placebo; RIL, rilonacept; sJIA, systemic juvenile idiopathic arthritis.

Table 3 Randomised and clinical controlled trials reporting the efficacy of IL-6 inhibitors in sJIA and AOSD

First author	Study design	Patients (N)	Intervention	CID (%)	Other outcomes (%)	Risk *
Woo[96]	Open-label	sJIA (18)	TCZ 2 mg/kg/2 weeks cohort I 6 (33%); 4 mg/kg/2 weeks cohort II 6 (33%); 8 mg/kg/2 weeks cohort III 6 (33%)	na	2.5M: ACR70 3 (17%)(overall three cohorts)	
Yokota[133]	Escalating dose	sJIA (11)	TCZ in escalating mode	na	LACF: At 2 mg/kg: ACR 70 1/11 (9 %) At 4 mg/kg: ACR 70 4/8 (50%) At 8 mg/kg: ACR 70 3/3 (100%)	
Yokota[80]	Open label lead-in	sJIA (56)	TCZ intravenous	na	LACF: ACRPed70 38 (68%)	
	Double-blind randomised	sJIA (20)	TCZ intravenous	na	M3: ACRPed70 15 (75%)	
		sJIA (23)	PBO	na	M3: ACRPed70 3 (13%)	
	Extension phase	sJIA (50)	TCZ intravenous	na	M11: ACRPed70 43/48 (90%)	
De Benedetti[24]	Double-blind randomised	sJIA (75)	TCZ intravenous	na	M3: ACR70 53 (71%) ACR90 28 (37%)	
		sJIA (37)	PBO	na	M3: ACR70 3 (8%) ACR90 2 (5%)	
	Open-label	sJIA (112)	TCZ intravenous	36/112 (32%)	M12: ACR90 66/112 (59%)	
Yokota[81]	LTE from NCT00144599 NCT 00144612	sJIA (67)	TCZ intravenous	na	38.6M: JIA-ACR 70 46/61 (75%) JIA-ACR 90 37/61 (61%)	
Mallalieu[82]	Open-label single arm	sJIA (11)	TCZ intravenous	na	JADAS-71 reduction 5/11 (45%	
Ruperto[84]	Open-label single arm	sJIA (51)	TCZ subcutaneous	35/51 (69%)	na	
Kaneko[83]	Double-blind randomised	AOSD (13)	TCZ intravenous	na	M3: ACR70 6/13 (46%)	
		AOSD (14)	PBO	na	M3: ACR70 4/13 (31%)	
	LTE	AOSD (26)	TCZ intravenous	na	M12: ACR70 8/13 (61%)	

*The RoB was assessed with the RoB2 tool. Red=high, yellow=intermediate, green=low and blue=not assessable.
ACR, American College of Rheumatology; AOSD, adult-onset Still's disease; CID, clinical inactive disease; JADAS, Juvenile Arthritis Disease Activity Score; LACF, last observation carried forward; LTE, long term extension; M, month; na, not available; PBO, placebo; RoB, risk of bias; sJIA, systemic juvenile idiopathic arthritis; TCZ, tocilizumab.

Colchicine

A recently published LOR[32] described the use of colchicine to treat pericarditis in 20 subjects with AOSD. Colchicine (1 mg/day, in association with NSAIDs and GCs) led to CID in 13/20 (65%) of the patients. Colchicine controlled serositis and reduced articular manifestations and systemic features; side effects were unremarkable.

Intravenous immunoglobulins

IVIG use has been reported in sJIA/AOSD (table 1). In a placebo-controlled trial in sJIA, IVIG (in association with GCs and/or NSAIDs), used at a dose of 1.5 g/kg/2 weeks for 2 months and then monthly for 4 months, yielded improvement in arthritis and PhGA in 50% of the patients. CID data are not available.[33] In a LOR, CID was achieved by 4 out of 25 patients with sJIA (16%) (IVIG 1 g/kg/day for 2 days, then 1.5 g/kg/day 1 day for 2–102 months).[34] In one LOR, IVIG led to 'controlled' disease in 17% of the 23 patients with AOSD included.[35] AEs included one case each of septic meningitis, membranoproliferative glomerulonephritis, lupus, necrotising vasculitis and acute renal failure.[34 35]

Conventional synthetic DMARDs

csDMARDs have been used either after inadequate response to GCs or concomitantly to bDMARDs (table 1). Studies with MTX exhibited heterogeneous results. However, the MTX dose ranged from 2.5 mg to 20 mg/week, and this could partially explain the heterogeneity of the response rates.[36–38] In the only randomised placebo-controlled trial, performed in sJIA,[39] an improvement in PhGA and Pt/PrGA was reported. The overall response, defined by JIA-ACR30, was not statistically different between the MTX-treated and the placebo groups (25% vs 16%). Non-serious AEs included, essentially, transaminitis and gastrointestinal symptoms.

Ciclosporin (CsA) was assessed in one LOP and two LORs in combination with other csDMARDs.[28 40 41] In the LOP,[40] 13/15 (87%) patients resistant to or dependent on GCs treated with CsA achieved CID after 2 months. As mentioned above, CsA was also used in combination with other csDMARDs (table 1). Hirsutism and transient hypertension were observed as AEs, as well as one severe event of nocardiosis and one MAS.[40 41]

Biologic DMARDs

Treatment with bDMARDS has initially been proposed for patients with sJIA or AOSD who did not respond adequately to GCs or csDMARDs.[42]

IL-1 inhibition

Anakinra

ANK is a recombinant, non-glycosylated form of the human IL-1 receptor antagonist (IL-1Ra) that binds to the IL-1 receptor, preventing its activation by both IL-1β and IL-1α.[43] ANK is currently approved for sJIA/AOSD by the EMA. ANK has been evaluated in two SRs,[11 44] two RCTs[45 46] (table 2) and 28 LOP/LOR studies (online supplemental file SF5).

Table 4 Early versus late treatment strategy with IL-1 inhibitors and IL-6 inhibitors

	Intervention	First author	Study design	Patients (N)	Concomitant treatment	Time from disease onset to treatment start in months (IQR)	Time of assessment	CID (%)	Other outcomes
Early treatment	**IL-1 inhibitors**	Nigrovic[48]	LOR	sJIA (46)	DMARDs, GCs and DMARDs+GCs	2.8 (1.5–4.8)	M1	27 (59%)*	na
		Kimura[70]	LOP	sJIA (12)	GCs	1 (median)	M9	5 (42%)	na
		ter Haar[73]	LOP	sJIA (42)	GCs	1 (0.6–2)	M1, M3 and M12	23 (55%) 35 (83%) 32 (76%)	na
	IL-6 inhibitors	Kimura[70]	LOP	sJIA (10)	GCs	1.8 (median)	M9	6 (60%)	na
		Roszkiewicz[98]	LOR	sJIA (10)	GCs, MTX and CsA	5.5 (median)	M3	10 (100%)	na
Comparison of early versus late treatment	**IL-1 inhibitors**	Pardeo[68]	LOR	sJIA (56)	DMARDs and GCs	Early <3	M6	35/37 (92%)	na
						Late ≥3	M6	7/19 (37%)	
		Horneff[71]	LOR	sJIA (20)	GCs	Early <12	M24†	na	JADAS<1 (80%)
				sJIA (37)	GCs	Late ≥12	M24	na	JADAS<1 (38%)
	IL-6 inhibitors	Horneff[71]	LOR	sJIA (24)	GCs	Early <12	M24	na	JADAS<1 (75%)
				sJIA (47)	GCs	Late ≥12	M24	na	JADAS<1 (44%)
		Pacharapakornpong[97]	LOR	sJIA (43)	GCs and DMARDs	Early 1 (4)	M12	6/11 (54%)	ACR70 (94%)
						Late 7.5 (23)		0/12	ACR70 (50%)
Late treatment	**IL-1 inhibitors**	Quartier[45]	RCT and LTE	sJIA (22)	0	4.2 (3.33 SD) years minimum 6M	M12	5 (16%)	na
		Ruperto[52]	RCT and LTE	sJIA (177)	GCs, MTX and NSAIDs	2.1 (0.8–4.3) years minimum 2M	M7	55 (31%)	na
		De Benedetti[24]	RCT and LTE	sJIA (112)	GCs and MTX	5.2±4 years minimum 6M	M12	36 (32%)	na

*In this study, the response was defined as complete if no or minimal residual symptoms, with no requirement for supplemental agents to maintain clinical remission and normal laboratory findings.
†Estimated as last time observation.
ACR, American College of Rheumatology; ANK, anakinra; CID, clinical inactive disease; DMARDs, disease-modifying antirheumatic drugs; GC, glucocorticoids; IL, interleukin; JADAS, juvenile arthritis disease activity score; LOP, longitudinal observational prospective; LOR, longitudinal observational retrospective; LTE, long-term extension; MTX, methotrexate; na, not available; NSAIDs, non-steroidal anti-inflammatory drugs; RCT, randomised controlled trial; sJIA, systemic juvenile idiopathic arthritis.

Two pooled analyses in AOSD, with 8[11] and 15 longitudinal studies,[44] respectively, showed that CID rates ranged from 57% to 84%. Only two RCTs evaluated the efficacy of ANK.[45 46] In a double-blind RCT on 24 patients with sJIA, ANK (2 mg/kg/day, maximum 100 mg/day) was compared with placebo. At 1 month, the ACR70 response was 42% in the ANK group and 0% in the placebo group. In the LTE phase, 31% of the patients achieved CID at 12 months.[45] In an open-label RCT comparing 12 patients with AOSD treated with ANK and 10 treated with csDMARDs, CID rates at month 6 were 50% and 20%, respectively.[46] It should be noted that both trials have a small sample size. Several longitudinal studies (24) reported the efficacy of ANK in sJIA/AOSD, with CID rates ranging from 50% to 100% (online supplemental file SF5).

A pooled analysis of eight studies investigated the tapering and discontinuation of GCs under ANK,[47] yielding a mean reduction of 22.4 mg of prednisone equivalent per day and a discontinuation rate of 35%.

ANK is generally administered subcutaneously. Although the intravenous route is not approved, it was evaluated, often at doses higher than the standard 2 mg/kg/day, for the treatment of sJIA or AOSD with or without MAS, with positive efficacy outcomes and no safety concerns.[48–50]

Canakinumab

CAM is a fully human monoclonal antibody against IL-1β, approved for sJIA in 2013, and for AOSD in 2020. CAM was evaluated in six CCTs and four longitudinal studies (table 2, online supplemental file SF6). In a pooled analysis conducted in AOSD,[51] CID was achieved in 69% of the 99 patients. In an RCT in sJIA,[52] comparing CAM with placebo, CID was achieved by 30% of the CAM-treated patients and by none of the placebo-treated patients, at 1 month (the rates of the adapted JIA-ACR70 (aJIA-ACR70) responses were 67% and 2%, respectively). In a withdrawal design trial in sJIA, the CID rate was 31% during the open-label lead-in phase[52] (aJIA-ACR70 and aJIA-ACR90 responses were 65% and 51%, respectively). In the LTE phase,[53] 40% achieved CID at 24 months and 50% acheived an aJIA-ACR90 response at 3 years. In another open-label study in sJIA,[54] the CID and JIA-ACR90 rates at week 48 were 75% and 87%, respectively. In another study in sJIA, 50% achieved CID at 6 months.[55]

A subgroup analysis performed on the trial data[52] revealed similar response rates in patients with or without fever at baseline: CID was 49% and 44% at month 6, respectively.[56] A pooled analysis of 301 patients from four trials on sJIA or AOSD[52 57 58] showed comparable efficacy across three age groups (2 to <12

Table 5 Studies reporting the efficacy of the treatments employed in MAS

First author	Study design	Number of patients with sJIA (N)	Intervention	Concomitant treatment	Previous treatment	Outcome measure (complete response)	R*
Miettunen[113]	LOP	8	ANK	GCs, CsA and IVIG†	GCs, CsA, TNFi†, IVIg† and VP-16	8 (100)	
Phadke[110]	LOR	10	ANK	GCs, VP-16 and ruxolitinib	na	9 (90)	
Demir[114]	LOP	11	ANK	na	na	7 (64)	
Fingerhutovà[115]	LOR	15	ANK	na	na	8 (53)	
Kostik[109]	LOR	8	CAM	GCs and CsA	ANK, TCZ† and IVIG†	7 (88)	
Mouy[19]	LOR	12	CsA	GCs	NSAIDs†, MTX†, SSZ†, AZA† and IVIG†	9 (75)	
De Benedetti[108]	CCT	14	Emapalumab	GCs, CsA, ANK and IVIG†	na	13 (93)	
Silva[22]	LOR	7	GCs, CsA, PE and IVIG†	None	NSAIDs, aspirin, GCs, MTX and SSZ	4 (57)	
Kounami[20]	LOR	9	GCs, CsA, VP-16, PE and IVIG†	None	NSAIDs, aspirin, GCs, MTX and mizoribine	5 (56)	
Zeng[111]	LOR	13	GCs, CsA, VP-16, PE and VCR†	None	na	10 (77)	
Lin[21]	LOR	9	GCs, CsA and IVIG†	None	na	9 (100)	
Horne[112]	LOP	5	GCs, ANK, VP-16, IVIG† and RTX†	None	GCs, HCQ, MTX, CsA, ANK and TCZ	5 (100)	

*Risk of bias: red=high, yellow=intermediate and green=low.
†Drugs not considered in the SR.
ANK, anakinra; AZA, azathioprine; CAM, canakinumab; CCT, clinical controlled trial; CID, clinical inactive disease; CsA, cyclosporin A; GCs, glucocorticoids; IVIG, Intravenous immunoglobulin; LOP, longitudinal observational prospective; LOR, longitudinal observational retrospective; MAS, macrophage activation syndrome; MTX, metotrexate; na, not available; NR, no response; NSAIDs, non-steroidal anti-inflammatory drugs; PE, plasma exchange; PR, partial response; RTX, rituximab; sJIA, systemic juvenile idiopathic Arthritis; SSZ, sulfasalazin; TAC, tacrolimus; TCZ, tocilizumab; TNF, tumour necrosis factor; VCR, vincristine; VP-16, etoposide.

years; 12 to <16 years and ≥16 years) with an ACR70 response, at month 3, of 58%, 66% and 72%, respectively.[59] In a double-blind placebo-controlled trial in AOSD (n=36), responses in the canakinumab group were numerically superior to those in the placebo group: CID 33% versus 12%, ACR90 11% versus 6% and EULAR DAS-28-CRP response 67% versus 41%.[60] Several longitudinal studies have reported the efficacy and safety of CAM in sJIA. Overall, most of the studies showed CID rates ranging from 40% to 94%[61–64] (online supplemental file SF6).

Rilonacept

RIL is a fully human dimeric fusion protein that incorporates the extracellular domains of the IL-1 receptor, currently not approved for sJIA or AOSD. RIL has been evaluated in two RCTs in patients with sJIA (table 2). In a classical RCT, 18% of the patients treated achieved an ACR70 response at 4 weeks, compared with 14% in the placebo group. In the 12-month extension, 83% achieved an ACR70 response.[65] In another RCT, 40% of RIL-treated patients achieved JIA-ACR70 at 1 month, compared with 12% in the placebo group. GC dose reduction was significantly higher in the RIL group: mean reduction of −0.21 mg/kg/day and −0.16 mg/kg/day in the RIL and placebo groups, respectively.[66]

IL-1 inhibitors safety

The most common AEs with ANK were injection site reactions (ISR) reported with variable frequencies. Several episodes of MAS were observed.[48 64 67–76] The Pharmachild registry, a comprehensive source of information, collected safety data from 306 patients with sJIAs[75] showing an overall incidence rate (IR) of AEs of 39.5/100 PY, with infections being the most frequently reported (IR 10.2/100 PY). The IR of SAEs was 11.0/100 PY, with serious infections (IR 2.6/100 PY) and MAS (IR 2.2/100 PY) being the most frequently reported. Although infections with targeted biologicals are always a concern, the rate of infections during ANK appears low and is not related to the dose. Notably, high-dose (48 mg/kg/day) of intravenous ANK was tested in patients with severe sepsis and safety concerns were not reported.[77] The most frequent AEs reported with CAM were infections, gastrointestinal disorders, skin/subcutaneous disorders and cytopenia. The main SAE included MAS.[52–54 60–62 64] A MAS rate of 2.8/100 PY was calculated based on data from two clinical trials (a total of 324 patients). This rate includes patients with definitive or probable MAS as defined by an independent adjudication committee.[78] A drug reaction with eosinophilia and systemic symptoms and one deep vein thrombosis were reported.[53 60] Other SAEs included four sJIA flares, one varicella infection and one pulmonary fibrosis; two MAS occurred during rilonacept[65] (online supplemental file SF7).

Meta-analysis with IL-1i

A meta-analysis was performed by combining RCT with the three IL-1i (figure 2A). All were performed in sJIA. One sJIA trial was excluded as it was a withdrawal design.[52] The meta-analysis of the four studies combined the ACR50 results at week 4 from baseline; the trial performed in AOSD[60] did not provide data at 4 weeks and therefore was excluded. Treatment with IL-1i was associated with an OR of 6.92 (95% CI 2.24 to 21.36) for ACR50 compared with placebo, with moderate to high heterogeneity (I^2 69%, p=0.022).

IL-6 inhibition

Tocilizumab (TCZ), the IL-6i, has been tested in sJIA/AOSD, and the efficacy and safety have been reported in 8 RCTs, 1 SR and 26 LOR/LOP (table 3, online supplemental file SF8).

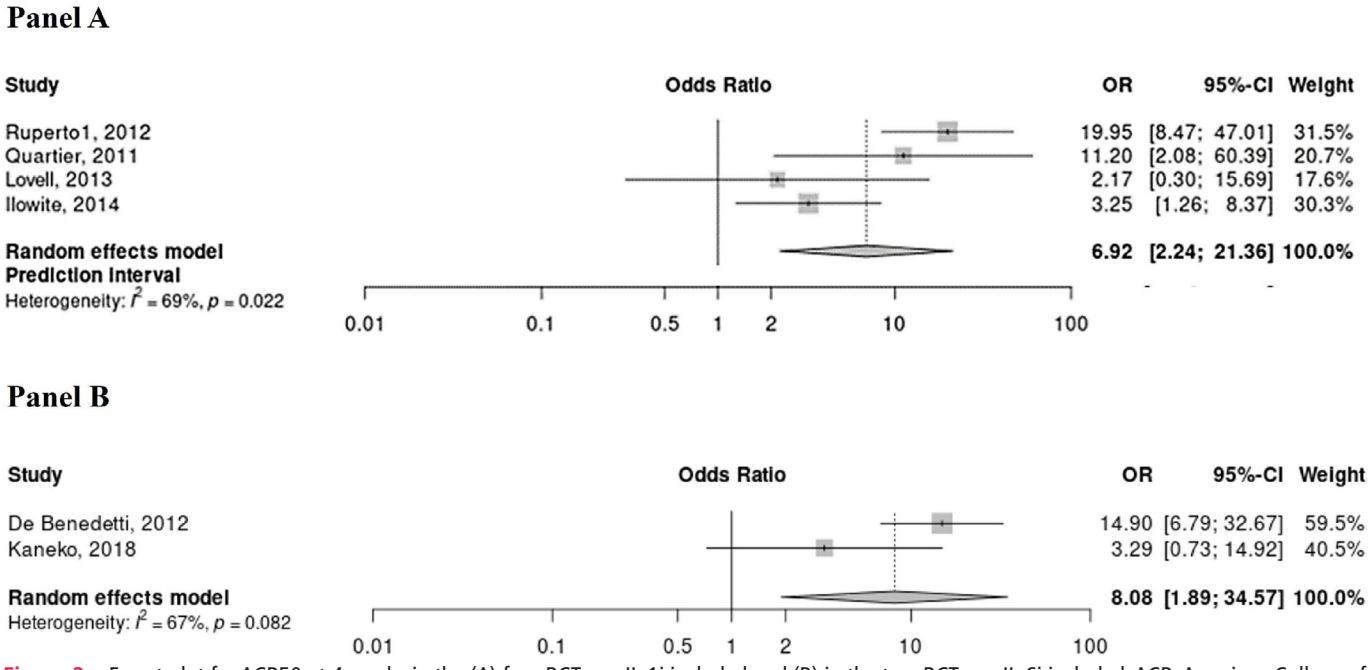

Figure 2 Forest plot for ACR50 at 4 weeks in the (A) four RCTs on IL-1i included and (B) in the two RCTs on IL-6i included. ACR, American College of Rheumatology; IL, interleukin; RCT, randomised controlled trial.

A pooled analysis that included 10 retrospective series with 113 patients with AOSD reported that 77% achieved CID. Additionally, clinically relevant GC tapering was observed, with a discontinuation rate of 41%.[79] In a randomised withdrawal-design trial in sJIA, aJIA-ACR70 response was achieved by 68% of the patients during the open-label phase and maintained at 3 months in 75% of those randomised to TCZ, compared with 13% randomised to placebo.[80] In the extension phase, a JIA-ACR70 response was achieved by 90%.[81] In an RCT in sJIA, aJIA-ACR70 was achieved at 3 months by 71% of the patients receiving TCZ compared with 8% receiving placebo. At the end of the open-label extension (2 years), CID was achieved by 32% of the patients.[24] A small open-label single-arm trial reported a mean change in JADAS-71 of −13.9 (−2.7 to −10.1) from baseline to week 12 in the 5/11 patients who completed the trial.[82] In AOSD, a numerically higher rate of ACR70 response (46% vs 31%) in patients receiving TCZ compared with placebo at 3 months was observed. In the LTE, the ACR70 response rate reached 61% in 1 year.[83] In the BIKER registry at 6 months, a JADAS-10 (median (IQR)) reduction was observed: from 16.9 (8.1–24.8) to 1.5 (0.2–3.8).[71] Subcutaneous TCZ, which was tested and approved after the intravenous formulation, showed comparable efficacy and a comparable safety profile in an open-label trial conducted in sJIA.[84] Longitudinal studies in sJIA and AOSD showed CID rates ranging from 35% to 100% (online supplemental file SF8).

IL-6i safety

Infections were the most common events reported in almost all studies (online supplemental file SF9). A large retrospective cohort (417 patients with sJIA) reporting data after 1-year of follow-up showed a rate of AEs and SAEs of 224.3/100 PYs and 54.5/100 PYs, respectively. Serious infections had a rate of 18.2/100 PY.[85] A MAS rate of 1.8/100 PY was calculated based on data from two clinical trials and one postmarketing surveillance programme (a total of 627 patients). These rates include patients with definitive or probable MAS as defined by an independent adjudication committee.[24 86 87] MAS was also reported in longitudinal studies[52 70 71 82 88–94] and in two RTCs.[24 82] Subcutaneous administration was associated with ISR[80 83 89 92 95] and skin reactions,[24 71 81 83 84 90 96] while other studies reported infusion reactions (table 6).[64 70 71 85 91 94]

Meta-analysis with IL-6i

The meta-analysis was performed by combining one trial in AOSD and one in sJIA (figure 2B). The withdrawal-design trial in sJIA was excluded.[80] The meta-analysis showed that TCZ was associated with an OR=8.08 (95% CI: 1.89 to 34.57) for ACR50 compared with placebo at week 4 with moderate to high heterogeneity (I^2 67%, p=0.082).

Early treatment with IL-1i or IL-6i: the window of opportunity

No trial formally compared early versus late treatment. Several LOPs and LORs, all performed in sJIA, reported on the response to early treatment and some compared early versus late treatment with IL-1i or IL-6i (table 4). Early treatment, ranging between <3 and <12 months from disease onset, was associated with CID or JADAS remission rates ranging from 60% to >90%.[48 70 71 73 97 98] In contrast, late treatment, that is, started more than 12 months after the onset of the disease, led to rates of CID or JADAS remission ranging from 37% to 45%.[48 68 70 71 73 97 98] These response rates to late treatment are consistent with the CID rates observed in the trials with ANK, CAM or TCZ that recruited patients with long-lasting disease, respectively, of 13%, 31% and 32% (mean disease duration of 4.2, 2.1 and 5.2 years, respectively).[24 45 52] Even though these studies on early treatment provide rates of CID that are rather homogenous in a large number of patients (n>200), it should be acknowledged that there is no formal trial and that the data are derived from heterogenous sources (eg, registries, case series and prospective cohorts).

IL-18i

Tadekinig-alpha, a recombinant human IL-18-binding protein, has been tested in a multicentre open-label dose-escalating trial

Table 6 Pooled analysis of the safety of IL-1 and IL-6 inhibition in systemic juvenile idiopathic arthritis and adult-onset Still's disease

Intervention		SAE	Infectious AE	Infectious SAE	Grades 3–4 neutropenia	Abnormal liver function tests	Macrophage activation syndrome	Infusion reactions	Injection site reactions
		Number of patient-years rate/100 patient-year (95% CI)							
IL-6 inhibition	TCZ	1141 36.5 (33.1 to 40.2)	855 104.6 (97.9 to 111.8)	1083 12.9 (10.9 to 15.3)	688 6.7 (4.9 to 8.9)	687 10.3 (8.1 to 13.0)	1141 2.7 (1.8 to 3.9)	1094 4.8 (3.6 to 6.2)	NA
IL-1 inhibition	ALL	1447 22.6 (20.2 to 25.2)	1447 94.5 (89.5 to 99.6)	1399 4.1 (3.1 to 5.3)	1447 1.9 (1.3 to 2.8)	1399 2.6 (1.8 to 3.6)	1447 3.2 (2.3 to 4.2)	NA	604 9.4 (7.1 to 12.2)
IL-1 inhibition	ANK	739 10.4 (8.2 to 13.0)	739 18.1 (15.2 to 21.5)	739 3.2 (2.1 to 4.8)	739 0.9 (0.4 to 2.0)	739 0.9 (0.4 to 2.0)	739 2.2 (2.4 to 3.5)	NA	526 9.9 (7.4 to 13.0)
IL-1 inhibition	CAM	605 38.9 (34.0 to 44.1)	605 190.2 (179.3 to 201.4)	605 4.8 (3.2 to 6.9)	605 3.3 (2.2 to 5.1)	605 4.6 (3.1 to 6.7)	605 4.8 (3.2 to 6.9)	NA	31 16.2 (5.2 to 37.6)
IL-1 inhibition	RIL	103 14.6 (8.2 to 24.0)	103 80.6 (64.2 to 99.9)	103 3.9 (1.1 to 9.9)	103 1.0 (0.3 to 5.4)	103 1.9 (2.4 to 7.0)	103 2.9 (0.6 to 8.5)	NA	48 29.2 (16.0 to 48.9)

AE, adverse events; ANK, anakinra; CAM, canakinumab; IL, interleukin; NA, not applicable; RIL, rilonacept; SAE, serious adverse events.

in 23 patients with AOSD.[99] Most of the patients escalated to the high dose (160 mg subcutaneously three times per week). At 3 months, 44% achieved a reduction of CRP >70% or normal CRP and a joint count reduction of ≥20%. ISR (13 patients) and infections (11 patients) were common. In terms of SAE, one optic neuropathy was reported (online supplemental file SF11).

Tumour necrosis factor inhibitors (TNFi)

TNFi was the first bDMARD used in sJIA/AOSD, as it became available before IL-1i or IL-6i. No RCT evaluated TNFi in sJIA/AOSD. Most of the longitudinal studies appraised ETA (online supplemental file SF10). In the only open-label trial in AOSD, CID was not reported; an ACR70 response was achieved by 28% of the 12 patients.[100] In LOR/LOP studies in patients with sJIA, CID was reported with a rate ranging from 6% to 31% with the two largest cohorts (45 and 143 patients, respectively) reporting CID rates with ETA of 31% and 25%[71 101] (online supplemental file SF10). In AOSD, studies had a small sample size. ETA-, IFX- and ADA-treated patients were often pooled in the same report. Overall, in studies of AOSD patients, CID was reported at rates ranging from 6% to 47%. In a LOR study, CID was achieved by 47% of the AOSD-treated with ETA, IFX or ADA, with somewhat better responses in patients with chronic articular patterns (56%) compared with those with a systemic polycyclic pattern (33%).[35]

Safety data on TNFi in sJIA are mostly provided by the BIKER registry.[71 102] During ETA, a case of Crohn's disease, one demyelination, four serious infections, one malignancy, two MAS, one uveitis and one vasculitis were reported. Eighteen non-severe infections were observed in 13 patients.[64 71 103 104] Two deaths occurred during the ETA, one after MAS and one due to septic shock.[71] Two MASs were reported.[104] Other reported SAEs included one optic neuritis, one lupus rash, one cardiac failure and one severe pneumonia during ETA, one abscess,[103] one Crohn's disease, one pulmonary restrictive syndrome and one antineutrophil cytoplasmic antibody-associated glomerulonephritis during IFX.[64]

Pooled analysis comparing TNFi, IL-1i and IL-6i

A formal comparison of the efficacy of TNFi compared with IL-1i or IL-6i is not possible given the absence of trials with TNFi. To provide an estimate of the efficacy of cytokine-targeted therapies in sJIA and AOSD, we performed a pooled analysis of the response rate (ACR70 or CID) in the longitudinal studies available with IL-6i, IL-1i or TNFi. These analyses yielded an estimated response rate of 59% (95% CI 51 to 68) for IL-1i, 55% (95% CI 45 to 65) for IL-6i and 26% (95% CI 17 to 35) for TNFi (figure 3A–C).

Targeted synthetic DMARDs—JAKi

The use of JAKi in sJIA and AOSD has not been evaluated in RCTs. The only available SR provides an overview of the studies in which different JAKi (tofacitinib, ruxolitinib and baricitinib) were used in patients with sJIA/AOSD[105] (online supplemental file SF11). GCs and NSAIDs were allowed as concomitant treatments. CID was obtained in 11/26 (42%) of the patients. In the same SR, data from four sJIA children were reported: CID was achieved by two (50%) patients, while the two remaining achieved a partial response. Regarding AEs, pneumonia was frequent.

Other therapeutic approaches

Thalidomide

We included two longitudinal studies[106 107]; in the LOP study, thalidomide was administered to 13 sJIA children for 6 months, leading to a sustained response and adequate disease control in 85% of the patients. Of the 22 patients in the LOR study, 73% were fever-free and 73% showed an improvement in arthritis at 12 months. AEs were short-lived paraesthesia,[106] transient elevations of aminotransferase and somnolence. The well-known safety profile is, however, always a concern with this agent.

MAS treatments

The information about treatments and efficacy is summarised in table 5, online supplemental file SF13. Online supplemental file

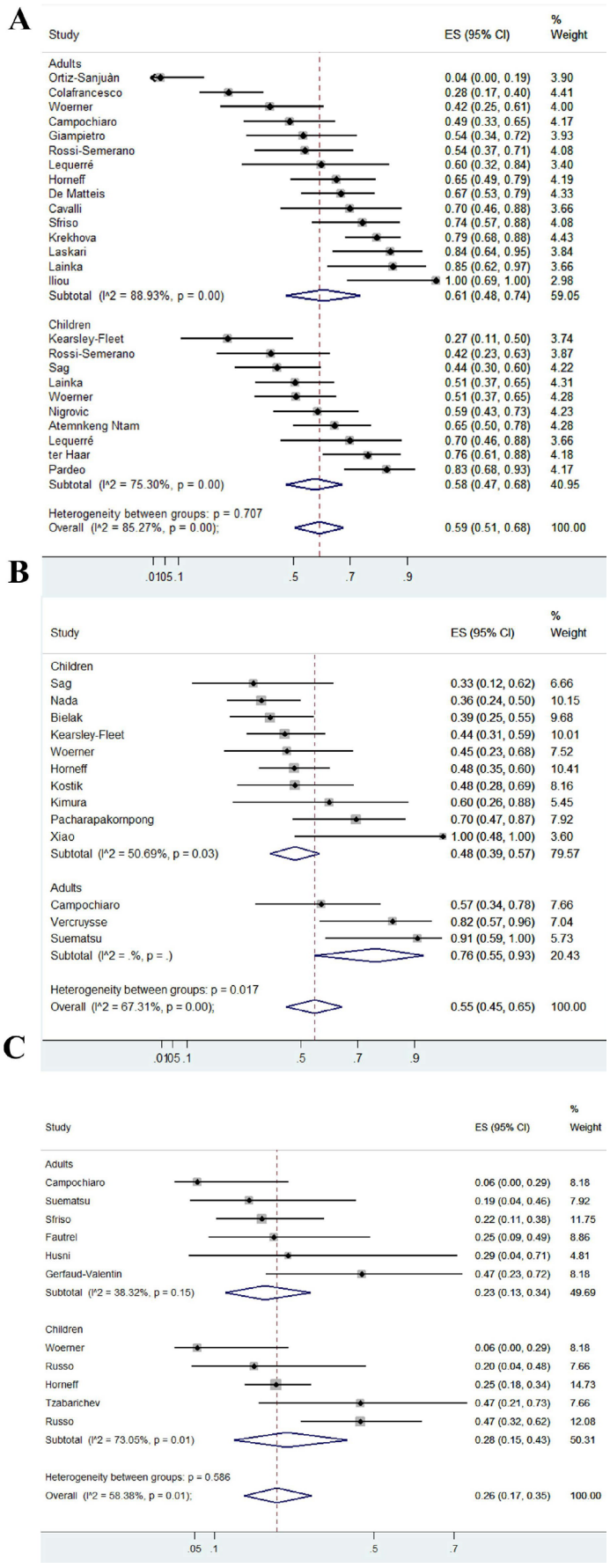

Figure 3 Pooled analysis of the efficacy (ACR70 or CID) of LOR and LOP studies available for (A) IL-1 inhibitors, (B) IL-6 inhibitors and (C) TNF inhibitors. ACR, American College of Rheumatology; CID, clinical inactive disease; IL, interleukin; LOR, longitudinal observational retrospective; LOP, longitudinal observational prospective; TNF, tumour necrosis factor.

SF14 shows the efficacy of JAKi and IL-18 inhibitors reported in single case reports that could not be included in the analysis because they were described in less than five patients.

Glucocorticoids

Information about GCs was present in 10 articles.[19–22 108–113] The most used GCs were methylprednisolone (dose from 3 to 30 mg/kg/day), prednisone (dose from 0.4 to 3 mg/kg/day) and dexamethasone (dose not reported). The duration of therapy was not specified. In all patients, GCs were associated with other treatments: 32 patients received CsA, 10 received etoposide, 17 received ANK, 8 received CAM, 1 received ruxolitinib, 14 received emapalumab and 7 received plasma exchange (PE). The efficacy and safety observed in these studies are reported for each treatment associated with GCs.

Ciclosporin A

Eight articles were reported on CsA associated with GCs[19–22 108–110 113] in 38 patients. CsA was administered intravenously or orally; the dose ranged from 2 to 8 mg/kg/day[19 20 22] with an unspecified duration. Efficacy and safety of CsA were reported in nine patients with MAS: six patients achieved a complete response and three achieved a partial response (symptom resolution with persistence of abnormal laboratory parameters). Moreover, the use of CsA led to GCs sparing in all cases.[19] The other studies described the use of CsA in combination with other treatments (table 5): in two patients with etoposide,[20 111] in 11 with ANK,[108 113] in three with CAM,[109] in eight with emapalumab[108] and in three patients with PE.[20 22] One event of an increase in creatinine[19] and one event of mild hypertension[20] were reported.

Etoposide

Data on 10 patients with MAS secondary to sJIA treated with etoposide, always associated with GCs, were available.[20 110–112] The efficacy of etoposide was evaluated in five patients; all achieved complete responses; notably, a low-dose regimen was used.[112] In other patients, etoposide was associated with other drugs and the efficacy described resulted from the combination of treatments (table 5). One event of neutropenic sepsis was reported.[112]

Anakinra

Data on 51 patients with MAS in sJIA treated with ANK were available.[108 110 112–115] It is not clear how many patients were receiving also treatment with CsA. In 44 cases, the efficacy of ANK was evaluable.[110 112 114 115] Therapy with ANK led to a complete response in 32/44 patients (73%), a partial response in 9/44 patients (21%) and no response in 2/44 patients (5%). In the remaining seven cases, the efficacy was related to the combinations of different treatments (table 5). Regarding safety, one event of a moderate increase in transaminases was reported.[110]

Canakinumab

One LOR study described the use of CAM in eight patients with MAS in sJIA[109] (dose range 4–25 mg/kg/4 weeks subcutaneously, with unspecified duration). All patients received GCs (high doses of methylprednisolone and/or prednisone) and three patients received CsA (unspecified dose and duration). Seven patients (87.5%) achieved a complete response, while one patient presented a partial response. Safety was not reported.

JAK inhibitors

Based on the search parameters set, we found a deceased patient with MAS treated with ruxolitinib associated with methylprednisolone, dexamethasone, etoposide and ANK.[108] There are a few reports of patients receiving JAKi treatment in the literature.[116–125] Although these reports did not meet the eligibility criteria, we reported the cases in online supplemental file SF14.

Emapalumab

A CCT described the efficacy and safety of emapalumab in 14 patients (13 with sJIA and 1 with AOSD) with MAS who had failed high-dose GCs.[108] The initial dose of emapalumab was 6 mg/kg, followed by 3 mg/kg every 3 days until day 15 and subsequently twice a week until day 28. Emapalumab was administered together with high-dose methylprednisolone. 13 of the 14 patients (93%) achieved a complete response, and one patient had a partial response. Emapalumab treatment led to a rapid GC dose reduction in all cases, with withdrawal in five patients. AEs were mainly related to viral infections; one CMV reactivation (SAE) and four CMV positivities were reported.

Plasma exchange (PE)

Patients with MAS secondary to sJIA were treated with PE associated with other treatments; the efficacy was evaluated based on the combination of therapies. No adverse events were described.[20 22 111]

DISCUSSION

Treatment of sJIA/AOSD has historically been based on NSAIDs and GCs. GCs are effective. However, their use at high or intermediate doses in the medium to long term is associated with severe, well-known side effects. Therefore, physicians are obliged to limit their use. In the past, csDMARDs have been employed to spare GCs. No formal trials with csDMARDs have been performed, except for a randomised crossover design trial with MTX in sJIA. Despite the primary outcome being set at a low level of efficacy, the JIA-ACR30 response, was not met, showing no significant difference with the placebo. CsDMARDs, particularly MTX, are often used in patients with persistent joint involvement. However, this SR did not find evidence to support MTX use. CsA has also been used, but no formal trial has been performed. In less-resourced countries, csDMARDs are a potential approach. In this regard, the efficacy of thalidomide in severe patients with sJIA has been reported in longitudinal studies.[107] Careful attention should be given to birth control measures.

The approach to sJIA/AOSD treatment has changed dramatically after the introduction of IL-1i and IL-6i, which followed translational research, performed essentially in sJIA on the pathogenic role of excessive IL-1 and IL-6 production.[5 126 127] Because sJIA and AOSD are rare, the number of RCTs with IL-1 or IL-6 inhibitors is small, as is their sample size. Additionally, to limit placebo exposure and sample size, some trials in sJIA were withdrawal-design studies. These studies cannot be evaluated in formal meta-analyses because the carry-over effect of the active drug administered during the open-label run-in phase hampers the interpretation of efficacy and safety data. Despite these limitations, the meta-analyses conducted in our SR showed efficacy over the placebo of IL-1i and IL-6i. It should be noted that, to include data that allowed for appropriate comparisons, these meta-analyses were conducted on data obtained after 4 weeks of treatment, a relatively short time, and using ACR50, a clinically meaningful, although rather low-level, response. A longer time of treatment during the extension phase of the trials,

indeed, showed that most of the patients achieved high-level responses, such as CID, and withdrew GC therapy. TNFi was the first bDMARDS used in sJIA/AOSD, as they became available well before IL-1i or IL-6i. TNFi were not tested in formal trials. However, a large body of real-world evidence provides information. This is also true for IL-1i and IL-6i, for which a wealth of data has been made available in LOR/LOP. In rare diseases, such as sJIA/AOSD, the number of RCTs is usually limited, often only one performed for authorisation purposes. Data from real life and registries provide additional clinically relevant data on both efficacy and safety. To gain information on the efficacy in the real world of the bDMARDs used in sJIA/AOSD, we performed a pooled analysis of the efficacy in LOR/LOP, using high-level responses (CID or ACR70) as the outcome. As mentioned above, these high-level responses were achieved by a significant number of patients in the formal trials, but even more so in real-life use, providing evidence that these are indeed achievable objectives for most of the patients. Although a formal comparison cannot be performed, TNFi use was associated with a markedly lower proportion of high-level responses than those receiving IL-1 or IL-6i.

Real-world data also provide the rationale for early initiation of IL-1 or IL-6i in patients with a new onset of sJIA/AOSD. The randomised trials recruited patients with long disease duration, who had failed most, if not all, of the previously available treatments. We performed a pooled analysis to investigate the high-level response rate, CID or JADAS remission, in patients who received early treatment. This analysis performed from real-world data included >200 patients and showed that starting the treatment early during the disease course provides high rates of high-level response in a short time frame (a few months), associated, for most of the patients, with rapid tapering and withdrawal of GCs. Many of these data were generated using the short-acting IL-1i anakinra. These observations are consistent with the hypothesis of a window of opportunity that foresees an early phase of the disease characterised by innate immunity involvement, including increased IL-1β production and a later chronic phase characterised by the involvement of adaptive immunity.[128]

Due to the small number of trials mentioned above and their small size, the safety data from trials are limited. A pooled analysis of the safety data provided by clinical trials, their open-label extension phase, and the registries allowed the collection of data from more than 1000 PY of exposure to IL-1i or IL-6i in sJIA/AOSD. SAEs were more frequent in patients receiving IL-6i. This was also evident when infectious SAEs were considered. The lowest rate of infectious AEs was observed with anakinra, the IL-1i with a short half-life, which is often the bDMARD of choice early in the disease course. Grades 3 and 4 neutropenia were also more frequent with IL-6 inhibition. This is a well-known pharmacodynamic effect of IL-6i that is not associated with an increased risk of infections.[129] MAS was observed during treatment, with comparable rates among the IL-1i or IL-6i.

One limitation of the presently available evidence is that RCTs with rigorous design and a reasonable sample size report data only on the efficacy of IL-1i and IL-6i. LOR and LOP studies on TNFα-i showed marginal efficacy and therefore RCTs were not performed. For novel approaches, such as JAKi and IL-18i, clinical trials are underway or are being planned for the near future.

Regarding MAS, our SR yielded information concerning the treatment of MAS, mainly in sJIA. Response is often achieved through the association of multiple therapies. Despite high-dose GCs being accepted as the pillar of the treatment for MAS, no formal trial has been performed. In an international survey that collected data from 362 patients with MAS in sJIA, 97.7% of the patients received GCs, supporting the conclusion that in practice, GCs are used in all patients.[130] On the other hand, high-dose GCs alone cannot control hyperinflammation in a significant proportion of patients and a variety of different treatments have been used. It should be noted that only one CCT has been performed and its results were published only recently.[108] In the absence of high-quality data and consensus guidelines concerning MAS treatments, the choice of treatment and their dosing regimen are variable, depending on the clinical severity, the previous treatments that failed and the expertise of the centres. Although in the above-mentioned survey,[130] CsA was the second most frequently used drug after high-dose GCs, our SR found only one LOR study with CsA. A few studies with ANK in MAS have been published. Efficacy appears to be promising,with complete response rates ranging from 50% to 100%. In these studies, ANK has been used often, but not always, as a second-line treatment. Moreover, variable dosing regimens and different routes of administration (intravenous vs subcutaneous) have been used, making it impossible to draw conclusions on the most efficacious dose. The only available CCT has been performed using emapalumab in patients who have failed high-dose GCs.[108] In this high-risk population, emapalumab yielded a high rate of complete response (>90%) associated with a marked reduction in GC dose. JAKi has been proposed in the treatment of MAS, mainly in chronic-relapsing MAS that is not responsive to other therapies (online supplemental file SF14). The use of JAKi in patients with MAS is supported by the evidence of strong express ion of genes associated with type I IFN and IFNγ signalling and the high percentage of activated T cells. Type I IFN and IL15 augment the percentage of activated T cells, which in turn produce high levels of IFN-γ.[131] One single case treated with IL-18 inhibition has been reported[125] (online supplemental file SF14). A comparison of the safety of the different drugs is not possible due to the scarcity of data and their use in different treatment combinations.

Regarding MAS treatment, while high-dose GCs remain the mainstay of treatment, our SR suggests that therapies aimed at targeting IL-1 and IFN-γ appear to be effective on a background of high-dose GCs. Given the rarity of the condition (ie, MAS that did not respond to high-dose GCs) and the severity of the condition with a potentially rapidly evolving course with mortality risk, placebo-controlled or head-to-head trials are not feasible. Therefore, in addition to CCT, data from multicentre, ideally prospective, registries may indeed provide guidance to clinicians in the treatment of this difficult-to-manage complication of Still's disease.

The results of this SR informed the task force of the EULAR/PReS recommendations for the diagnosis and management of sJIA/AOSD and MAS.

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Contributors SB performed the SR. ADM and SM participated in the interpretation of the systematic review results. LC was the methodologist supervising the

systematic review. BF and FDB were the two convenors (guarantors) of the recommendation production process.

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