

## Review

## Current and emerging biological therapy in adult-onset Still's disease

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## Abstract

Adult-onset Still's disease (AOSD) is a rare, but characteristic non-familial, multi-genic systemic auto-inflammatory disorder, characterized by high spiking fever, salmon-like evanescent skin rash, polyarthritides, sore throat, hyperferritinemia and leucocytosis. The hallmark of AOSD is a cytokine storm triggered by dysregulation of inflammation. Nowadays, with advances in anti-cytokine biologic agents, the treatment of AOSD is no longer limited to NSAIDs, glucocorticoids or conventional synthetic DMARDs. In this review, we focussed on the roles of these cytokines in the pathogenesis of AOSD and summarized the current and emerging biological therapy.

**Key words:** adult-onset Still's disease, cytokine storm, biological therapy

## Rheumatology key messages

- The hallmark of AOSD is a cytokine storm triggered by dysregulation of inflammation.
- Biologics targeting the cytokines and some other biologics have been tested in AOSD patients.

## Introduction

Adult-onset Still's disease (AOSD) is a rare, non-familial, multi-genic auto-inflammatory disorder with multisystem involved. The incidence is estimated between 0.16 and 0.4/100 000 persons in different ethnic groups [1–3]. Patients with AOSD often suffer from high spiking fever, salmon-like evanescent skin rash, polyarthritides, sore throat, hyperferritinemia and leucocytosis. More importantly, the mortality is high due to severe life-threatening complications, including macrophage activation syndrome (MAS) and fulminant hepatitis [4,5]. In 1897, Sir George Still reported for the first time 22 children whose symptoms were similar to systemic onset of JIA (SOJIA) [6]. In 1971, Bywaters analysed 14 adult patients with similar clinical manifestations to SOJIA

and named this independent disease as AOSD [7]. Due to heterogeneous clinical features and rarity of randomized controlled studies of this disease, therapy is usually empirical. Nowadays, rheumatologists still face a great challenge in therapy of AOSD despite a large swathe of new drugs. Herein, the most recent progress in the biological treatment of AOSD is reviewed.

## Pathogenesis

Based on the different clinical courses, AOSD can be classified into three distinct patterns, including a monocyclic course, a polycyclic course and a chronic course. To better make a therapeutic strategy, AOSD phenotype can be dichotomized in systemic form and chronic articular form instead of these three patterns [5, 8,9]. The hallmark of AOSD pathogenesis is cytokine storm, characterized by excessive production of IL-1 $\beta$ , IL-18, IL-6, IL-10, IFN- $\gamma$ , TNF and other cytokines [10]. No single definition of cytokine storm in AOSD is widely accepted nowadays; we define the cytokine storm in AOSD as a persisting and chronic self-sustaining cytokine and cellular stimulation, of which the dominant cytokines can be changed due to different clinical phenotypes. IL-1 $\beta$ , IL-18, IFN- $\gamma$ , IL-4 and IL-10 are believed to be more

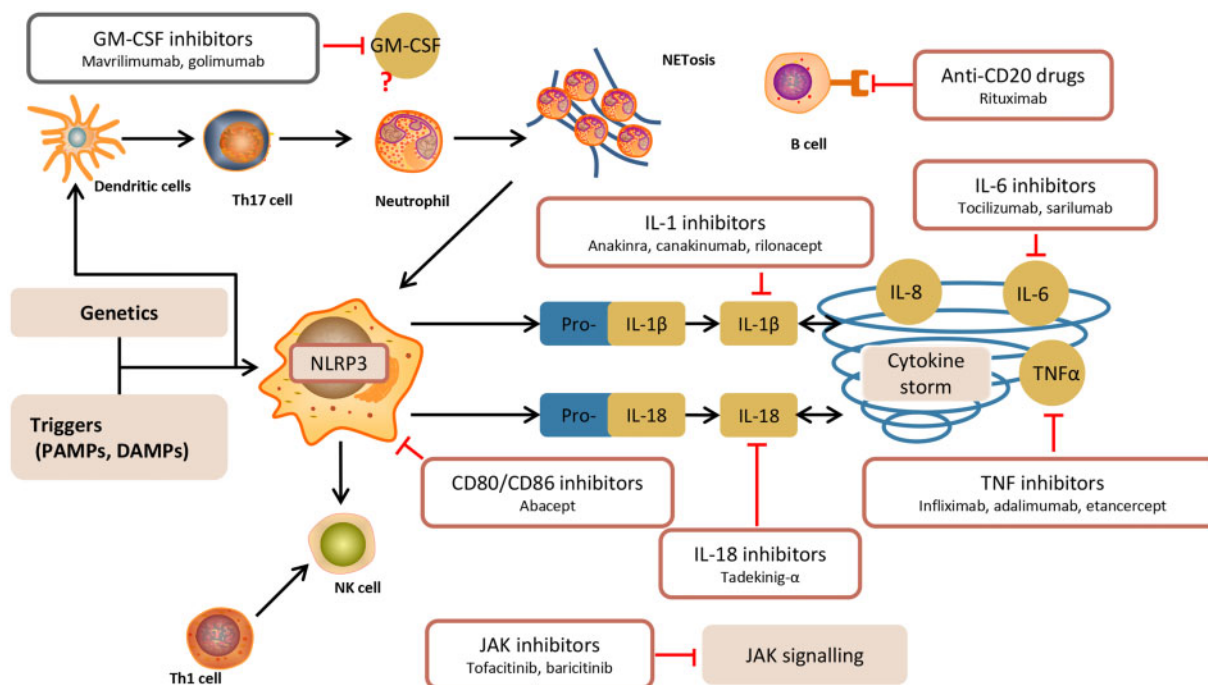
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**Fig. 1** Pathogenesis and targeted therapy of adult-onset Still's disease

Genetics and triggers including PAMPs and DAMPs start the initiation of inflammation in AOSD. NLRP3 inflammasomes in macrophages are activated. Then NLRP3 inflammasomes facilitate caspase-1 activation, leading to the formation bioactive IL-1 $\beta$  and IL-18. After that, several pro-inflammatory cytokines induced by IL-1 $\beta$  and IL-18, including IL-6, IL-8, IL-17 and tumour necrosis factor TNF, as well as IL-1 $\beta$  and IL-18 themselves, generate the burst of a cytokine storm. Besides, neutrophils, Th17 cells, Th1 cells and NK cells also contribute to the burst of the cytokine storm. Targeted therapy for the treatment of AOSD is at IL-1 $\beta$  or IL-1R with anakinra, canakinumab or rilonacept, at IL-18 with tadekinig alfa, at IL-6R with tocilizumab or sarilumab, and at TNF- $\alpha$  or TNFR2 with infliximab, adalimumab or etanercept, at CD20 with rituximab, at CD80/CD86 with abacept, at JAK with tofacitinib or baricitinib or at GM-CSF or GM-CSFR with mavrilimumab or golimumab. AOSD: adult-onset Still's disease; DAMP: damage-associated molecular pattern; NK: natural killer; NLRP3: NACHT, LRR and PYD domains-containing protein 3; PAMP: pathogen-associated molecular pattern.

associated with systemic form, whereas IL-6, TNF, IL-17 and IL-23 are more associated with chronic arthritic form [11–13]. Secreted by hyperactivated neutrophils and macrophages, these inflammatory mediators further activate other immune cells (such as helper T (Th)1 and Th17 cells), leading to uncontrollable inflammatory cascade [14–17]. There is accumulating evidence that infectious triggers can initiate a complicated inflammatory cascade in AOSD with certain genetic susceptibility (Fig. 1).

### A cytokine storm

Inappropriate activation of the innate immune cells (mainly macrophage and neutrophil) is recognized as the first line of formation of cytokine storm in AOSD. Both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), including S100 proteins, soluble CD163, high mobility group box-1, advanced glycation end products, macrophage inhibitory factor (MIF) and neutrophil extracellular traps (NETs) can activate macrophages and neutrophils via specific Toll-like receptors

(TLRs), then NACHT, LRR and PYD domains-containing protein 3 (NLRP3) inflammasome are excessively activated [5, 18–21]. Thus, the activity of caspase-1 is upregulated, leading to forming bioactive IL-1 $\beta$  and IL-18 [20]. After that, innate and adaptive immune cells are intensely activated, leading to exuberant production of pro-inflammatory cytokines induced by IL-1 $\beta$  and IL-18, including IL-6, IL-8, IL-17, IFN- $\gamma$ , TNF, as well as IL-1 $\beta$  and IL-18 themselves, gush forth and course on like a veritable cascade [14–17].

Other innate immune cells, natural killer (NK) cells, are also found to play a role in the facilitation of inflammatory cascade. Cytolytic function of NK cells plays a cardinal role in immune responses to destroy pathogens and maintain lymphoid and myeloid immune homeostasis. Deficiency of cytotoxicity will lead to persistent activation of lymphocytes and macrophages [22,23]. Though the cytolytic function of NK cells is decreased in AOSD, the ability to secrete IFN- $\gamma$  is enhanced due to upregulation of IL-12 and IL-15 receptors on NK cells, and then IFN- $\gamma$  acts as an accomplice of the macrophage activation [24–26].

T cells also contribute to the pathogenesis of AOSD. Increased levels of circulating Th1 cells and Th17 cells, and decreased levels of circulating CD4<sup>+</sup>CD25<sup>high</sup> Treg cells were found in active AOSD patients [27–29]. Th1 cells produce IFN- $\gamma$ , regulating the recruitment of macrophages, and Th17 cells produce IL-17, which may induce the production of IL-6 and IL-8 [30,31].

Aside from amplified inflammatory cascade, it's hypothesized that deficient resolution of inflammation also plays a role in the cytokine storm of AOSD. The typical anti-inflammatory cytokines IL-10 and IL-37 are increased in active AOSD, which may partly quell the abnormal inflammation response [32,33]. IL-10 may inhibit the activation of inflammasome in macrophage, suppress neutrophil migration and control the production of IL-1 $\beta$ , IL-6 and TNF [34–36]. IL-37 may inhibit the production of IL-1 $\beta$ , IL-6 and TNF, just like IL-10 [33, 37]. Moreover, IL-10 and IL-37 can induce the polarization of anti-inflammatory macrophages, which help with resolving the exaggerated inflammatory response [38,39].

## Genetic background

No evidence has shown that family aggregation has appeared in the occurrence of AOSD, but previous studies have revealed an association between genetic susceptibility and gene polymorphisms of the HLA, including HLA-Bw35, -B17, -B18, -B35, -DR2, -DR4, -DR5, -DQ1, DRw6, -DRB1 and -DQB1 [40–44]. A genome-wide association study was conducted for the first time to systematically screen genetic factors influencing susceptibility to AOSD in a Chinese multicentre cohort, consisting of 264 AOSD cases and 2420 controls. This finding identified that both HLA class I and II regions are susceptibility loci for AOSD [45]. Polymorphisms in the non-HLA regions encoding IL-6, IL-18, serum amyloid A, MIF and MEFV also contribute to the susceptibility of AOSD patients [46–50]. Recently, functional leucocyte immunoglobulin-like receptor A3 (LILRA3) has been reported to be a novel genetic susceptibility factor for AOSD [51].

## Infectious triggers

There is a popular belief that infection trigger is the main driver of inflammatory response of AOSD. The outbreak of COVID-19, a novel virus-induced severe respiratory disease with high mortality rate has brought attention to the pathogenetic role of viral infections as inflammatory triggers in cytokine storm. The similarities of clinical manifestations between viral infections and AOSD – such as acute-onset, high spiking fever and sore throat – have often been remarked on [10]. Unlike the classical cytokine storm with systemic inflammatory response, the cytokine storm triggered by SARS-CoV-2 infection leads to organ-specific dysfunction, characterized by intra-pulmonary macrophage activation and thrombotic lesions formation. The cytokine panel between severe COVID-19 and active AOSD is different, as our previous

study reports [10, 52]. Some studies have found the presence of anti-viral antibody and viral DNA in active AOSD patients. Besides viral infections, bacterial infections have been reported to be accompanied by the onset of AOSD, due to the potential to initiate inflammatory response by TLRs activation [5, 19, 53–58].

## Treatment

In the past, the treatment of AOSD was a tough task with limited therapeutic options to nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, or conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs). Glucocorticoids remain the mainstay treatment of AOSD, and DMARDs are often required in some patients with poor response to glucocorticoids. Around 17–32% of AOSD patients are resistant to both first-line corticosteroids and second-line DMARDs in some observational studies, and this group of patients are uniformly called 'refractory AOSDs' [59–63]. Nowadays, with the success of targeted biological treatments in rheumatic diseases, the management of AOSD has been revolutionized, especially in the refractory forms (Fig. 2).

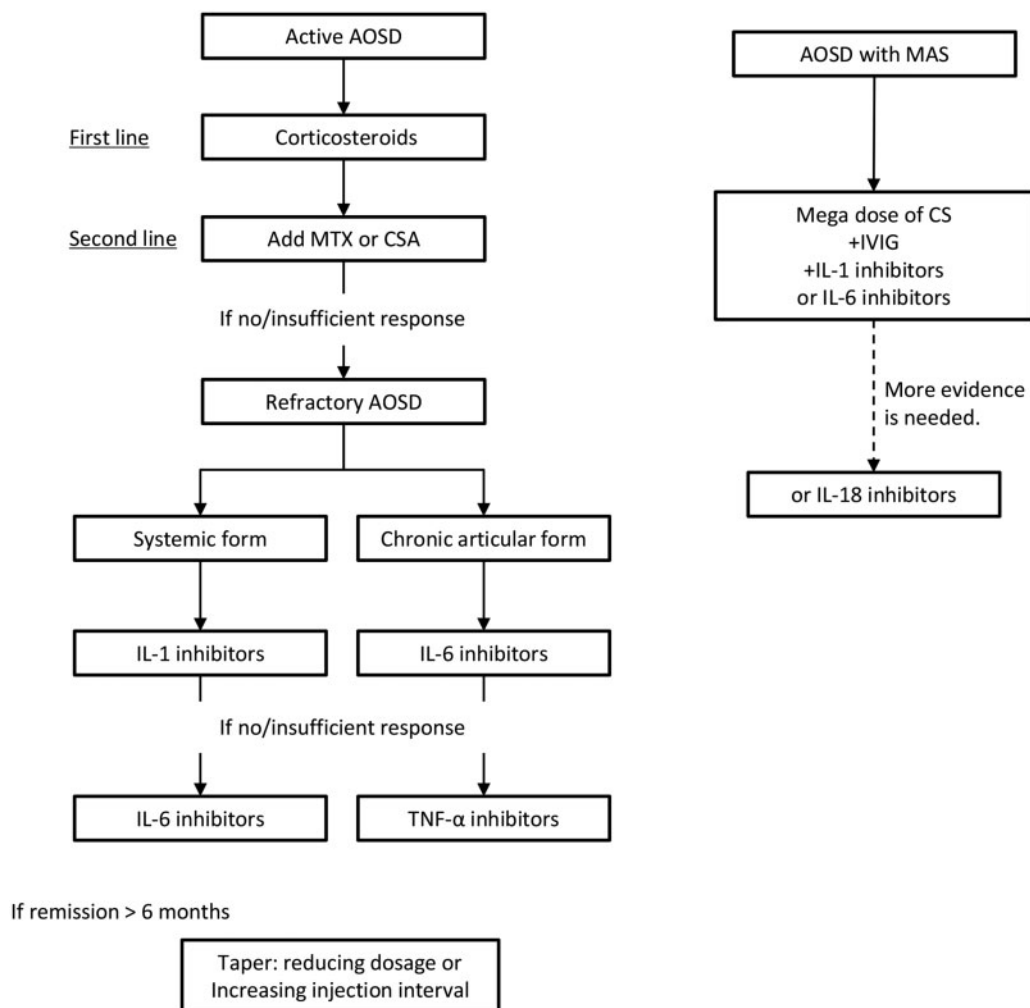
## IL-1 $\beta$ and its inhibitors

IL-1 $\beta$  is the most frequently studied and well characterized member of the IL-1 superfamily. Secreted mostly by myeloid cells, IL-1 $\beta$  activates granulocytes, Th17 cells and innate lymphoid cells (ILC)3, leading to tissue inflammation and injury. The pathogenic role of IL-1 $\beta$  has been involved in rheumatic and auto-inflammatory diseases, including RA, gout, cryopyrin-associated periodic syndromes, SOJIA and AOSD [64,65].

Activation of IL-1 $\beta$  is mediated by inflammasome-dependent means in monocytes/macrophages and inflammasome-independent means in neutrophils. After engagement of pattern recognition receptors (PRRs), transcription of *IL1B* mRNA is induced and translated to a biologically inert precursor, pro-IL-1 $\beta$ . Pro-IL-1 $\beta$  is stored in the cytosol of activated monocytes/macrophages and gains its biological activity after the cleavage of its amino-terminal pro-peptide with caspase-1 depending on the assembly of inflammasome complexes [65]. Then, mature IL-1 $\beta$  will be released into extracellular space and bind to IL-1 receptor 1 (IL-1R1) on target cells. The intracellular signalling molecules of IL-1 $\beta$  will be provoked, including myeloid differentiation factor 88, IL-1 receptor-associated kinase 4 (IRAK4) and TNF receptor-associated factor 6, resulting in activation of nuclear factor  $\kappa$ B (NF- $\kappa$ B) and p38, as well as c-Jun-N-terminal kinase, extracellular signal-regulated kinase and mitogen-activated protein kinases [65].

This signalling activated by IL-1 $\beta$  will lead to the production of various pro-inflammatory mediators, including IL-6, IL-8, TNF and many chemokines, followed by the attraction of macrophages, neutrophils and ILC3 capable of secreting IL-17 and IL-22. Besides, IL-1 $\beta$  is also a key cytokine to promote adaptive immunity. IL-1 $\beta$  supports the differentiation of CD4<sup>+</sup> T cells into pro-

Fig. 2 Therapeutic algorithm for adult-onset Still's disease



CS: corticosteroids; CSA: ciclosporin A.

inflammatory T cell populations, including Th1 and Th17 cells, and it can induce expansion and differentiation of antigen-specific CD8<sup>+</sup> T cells as well [66,67].

As a potent pro-inflammatory mediator, IL-1 $\beta$  plays a fundamental role in the initiation and amplification of cytokine storm in AOSD. Increased levels of NLRP3 inflammasome, caspase-1 and IL-1 $\beta$  have been found in peripheral blood mononuclear cells (PBMCs) of AOSD patients, and NLRP3 inhibitor decreased the protein expressions of NLRP3 and IL-1 $\beta$  in PBMCs from AOSD patients [20]. As the role of IL-1 $\beta$  in the pathogenesis of AOSD is gradually unveiled, therapeutic inhibition of IL-1 $\beta$  has already become an established target in AOSD. Three IL-1-targeted biologics (anakinra, canakinumab and rilonacept) have been approved so far [68].

### Anakinra

Anakinra, a recombinant human IL-1 receptor antagonist, reduces the activity of IL-1 $\alpha$  and IL-1 $\beta$  by competing

their IL-1 receptor [69]. Anakinra have been proven effective and well-tolerated in some case series (Table 1). Based on data from clinical trials, anakinra has been approved for a licence extension to treat both SOJIA and AOSD by the European Medicines Agency.

The only randomized study was carried out among 22 patients with refractory AOSD aiming to evaluate the efficacy of anakinra vs DMARDs. More patients with anakinra treatment achieved remission than patients with DMARDs treatment [71]. A large number of retrospective observational studies have confirmed the efficacy of anakinra in treating AOSD. The largest retrospective observational study of IL-1 inhibitors in AOSD patients in Italy reported that anakinra was effective in improving all clinical and serological manifestations, and Pouchot's score was found to be significantly reduced at all time points [78]. A meta-analysis including nine clinical studies suggested the potential of anakinra to reduce and even stop concomitant glucocorticoids without AOSD flares [79]. However, a randomized, multicentre, phase

**TABLE 1** Major clinical studies on the efficacy and safety of IL-1 inhibitors in adult-onset Still's disease

Drugs	Author, year (refs)	Patient number	Treatment and dosage	Overall response	Follow-up duration (months)	Severe adverse events	Study character
Anakinra	Naumann L, 2010 [70]	8	ANK 100 mg/day (8)	Sustained remission: 8 (100%) Concomitant glucocorticoids to low doses: 8 (100%)	<12 (2) ≥12 (4)	0	Retrospective observational study
	Nordström D, 2012 [71]	12	ANK 100 mg/day (12)	Remission at 8 weeks: 7 (58.3%) Remission at 24 weeks: 6 (50%) Discontinued corticosteroids use: 3 (25%)	<12 (12)	Worsening of AOSD (lack of efficacy) (1)	Open randomized multicentre study
	Lequerré T, 2008 [72]	15	ANK 100 mg/day (15)	Complete remission: 9 (60%) Partial remission: 2 (13.3%) No response: 2 (13.3%) Intolerance: 2 (13.3%) Stopped steroids use: 2 (13.3%)	<12 (6) ≥12 (9)	Varicella (1) Cutaneous infection (1)	Retrospective observational study
	Laskari K, 2011 [73]	25	ANK 100 mg/day (25)	Complete clinical response: 21 (84%) Partial clinical response: 3 (12%) No clinical response: 1 (4%) Stopped steroids use: 12 (48%)	<12 (7) ≥12 (18)	Severe urticarial reaction (3) Infection (7)	Retrospective case series
	Giampietro C, 2013 [74]	28	ANK 100 mg/day (28)	Complete remission: 16 (57.1%) Partial remission: 8 (28.6%) Loss of efficacy: 4 (14.3%)	>12	0	Retrospective case series
	Cavalli G, 2015 [60]	20	ANK 100 mg/day (20)	Complete response: 14 (70%) Partial response: 2 (10%) No response: 4 (20%) Decreased corticosteroids use: 8 (40%)	<12 (6) >12 (14)	Varicella-zoster virus reactivation (2)	Retrospective multicentre case series
	Ortiz-Sanjuán F, 2015 [158]	41	ANK 100 mg/day (41)	Improvement of symptoms: arthritis 87.8% to 41.5% skin rash 58.5% to 7.3% fever 78% to 14.6% lymphadenopathy 26.8% to 4.9%	<12 (14) ≥12 (27)	Severe cutaneous rash (2) Infection (2)	Retrospective open-label multicentre study
	Colafrancesco S, 2017 [72]	140	ANK 100 mg/day (127) ANK 200 mg/day (3) ANK 150 mg/day (1) ANK 50 mg/day (1) ANK 100 mg/2 days (8)	Significantly reduced Pouchot's score [mean score 5.5 (± 1.9), range 2-10, at baseline vs 1.1 (± 1.4), range 0-7, after 3 months; P < 0.0001] Complete remission: 20 (14.2%) Primary inefficacy after 12 months: 15 (10.7%) Secondary inefficacy after 12 months: 11 (7.8%) steroid therapy: from 97.8% to 55.6% after 12 months (P < 0.001)	<12 (43) ≥12 (97)	severe skin reactions (18) infection (7)	Multicentre retrospective observational study

(continued)



TABLE 1 Continued

Drugs	Author, year (refs)	Patient number	Treatment and dosage	Overall response	Follow-up duration (months)	Severe adverse events	Study character
Canakinumab	Néel S, 2018 [159]	5	ANK 100 mg/day (5)	Response: 4 (80%)	NA	NA	Retrospective multicentre case series
	Colafrancesco S, 2017 [72]	4	CAN 150 mg/8 weeks (4)	Complete remission: 1 (25%) Partial remission: 2 (50%) Loss of efficacy: 1 (25%)	<12 (1) 12 (3)	0	Multicentre retrospective observational study
	Feist E, 2018 [160]	29	CAN 150 mg/4 weeks (29)	ACR ≥ 70 responses at day 15; 19 (65.5%) Improvements at day 85: 13/18 (72.2%)	<12	MAS (3) Pyrexia (1) Cytomegalovirus infection (2)	Pooled analyses
	Kedor C, 2020 [76]	35	CAN 4 mg/kg/4 weeks (19) (maximum 300 mg) Placebo (17)	In the intention-to-treat analysis, reduction of the DAS28 (ESR) of >1.2: 66.7% (CAN) vs 41.2% (PBO) (P = 0.18) In the per-protocol analysis, significantly higher ACR 30%: 61% (CAN) vs 20% (PBO) (P = 0.033) Significantly higher ACR 50%: 50% (CAN) vs 6.7% (PBO) (P = 0.009) Significantly higher ACR 70%: 28% (CAN) vs 0% (PBO) (P = 0.049)	<12	Increased liver enzymes (1) Patellofemoral pain syndrome (1) Deep vein thrombosis (1) Hypotonia (1)	Phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial

ANK, anakinra; CAN, canakinumab; MAS, macrophage activating syndrome; NA, not available; PBO, placebo.

study for evaluating the efficacy and safety of anakinra in treating AOSD has been terminated due to a lack of included patients (ClinicalTrials.gov Identifier: NCT03265132). Overall, anakinra seems to be not only effective in improving clinical and laboratory manifestations, but also likely to reduce the dosage of glucocorticoids.

### Canakinumab

Canakinumab is a human monoclonal antibody against IL-1 $\beta$  [80]. Although only a handful of clinical trials with canakinumab were conducted on AOSD patients, canakinumab was approved by the EMA and Food and Drug Administration (FDA) for both SOJIA and AOSD in 2016 on the basis of the concept of the Still's disease continuum [81]. A randomized, phase II study recruited 35 AOSD patients. Although the difference between the canakinumab group and the placebo group was not statistically significant due to the lower number of included patients, a higher response rate was observed in the canakinumab group [82]. The clinical symptoms and laboratory findings can be improved after the use of canakinumab in some trials (Table 1) [19, 78].

### Rilonacept

Rilonacept (also known as IL-1 Trap), an IL-1 $\alpha$  and  $\beta$  inhibitor, has an ability to ameliorate clinic manifestations and achieve a prolonged remission in refractory AOSD patients [83,84]. Experience with rilonacept has shown its effectiveness to both arthritic and systemic symptoms of refractory AOSD patients [84–86]. In a 24-month follow-up study, five refractory AOSD patients were treated with rilonacept; three of the five patients had meaningful clinical improvements [87]. Rilonacept is mostly used in patients with unsatisfied response to anakinra. Moreover, rilonacept is well-tolerated and has demonstrated efficacy in a randomized, placebo-controlled study of active SOJIA [88]. However, rilonacept hasn't been licenced for use in AOSD either in Europe or the USA. In summary, treatment with IL-1 inhibitors leads to complete or partial remission in most AOSD patients.

### IL-6 and its inhibitors

Although IL-6 is mostly regarded as a pro-inflammatory cytokine, it is considered to be pleiotropic due to its protective and regenerative functions on the grounds of different patterns of signalling [89]. IL-6 can be produced by neutrophils and monocytes/macrophages. The membrane-bound mIL-6R $\alpha$  binds IL-6, and mIL-6R $\alpha$  interacts with gp130 and thereby provokes signal transduction through the signal transducer and activator of transcription 3 (STAT3) and NF- $\kappa$ B pathway [90,91]. IL-6 can feed back in the control of neutrophil and monocyte responses. It is also a survival factor for lymphocytes [89,90, 92]. Moreover, IL-6 can drive polarization of

CD4<sup>+</sup> T cells towards Th17 cells [93,94]. It can lead to some pro-inflammatory effects, including typical manifestations of active AOSD, such as fever, arthritis, skin rash and elevated CRP. Not surprisingly, IL-6 level is significantly increased in both serum and cutaneous lesions of active AOSD patients. The clinical application experience of two IL-6 inhibitors (tocilizumab and sarilumab) have been achieved in AOSD.

### Tocilizumab

Tocilizumab is a humanized anti-IL-6 receptor antibody that binds to both membrane-bound and soluble form of the IL-6 receptor. Iwamoto *et al.* used tocilizumab for the first time in a refractory AOSD patients in 2002 with promising results [95]. Many previous reports have suggested that tocilizumab is effective in treating AOSD of both systemic and chronic articular forms (Table 2) [96, 98,99, 101–110]. In a pilot study in China, a combination of tocilizumab with DMARDs or glucocorticoids can partially improve clinical and laboratory manifestations of refractory AOSD patients and contribute to withdrawal of glucocorticoids [110]. The first randomized, phase III study included 27 patients with AOSD refractory to glucocorticoids in Japan. An improvement of clinical manifestation and a remarkable steroid-sparing effect was observed in most patients. Serious adverse events in the tocilizumab group included infections, exacerbation of AOSD, drug eruption, anaphylactic shock and aseptic necrosis in the hips. The study suggests that tocilizumab is effective and well-tolerated [102]. Moreover, some case reports have indicated that tocilizumab is effective for the treatment of AOSD-related systemic complications, including MAS, pulmonary arterial hypertension and thrombotic thrombocytopenic purpura [111–114].

### Sarilumab

Sarilumab is an IL-6 receptor inhibitor. To our knowledge, the use of sarilumab in AOSD has been reported only once. The case report observed that sarilumab ameliorated clinical manifestations and spared corticoid in a 25-year-old male patient with cortico-dependent AOSD [115]. A *post hoc* analysis of the ASCERTAIN EXTEND (NCT01146652) trial suggests that switching tocilizumab non-responders to sarilumab may have favourable efficacy outcomes by investigating outcomes for tocilizumab non-responders completing ASCERTAIN (NCT01768572) who switched to sarilumab [116].

### TNF- $\alpha$ and its inhibitors

TNF- $\alpha$ , a member of the TNF superfamily, is mainly produced by activated macrophages and lymphocytes [117]. After binding to two receptors, TNFRI and TNFRII, it can thereby lead to a variety of cellular and molecular behaviours and events [118]. TNF- $\alpha$  is a two-edged sword with the ability of promoting and inhibiting inflammatory response. On one hand, TNF- $\alpha$  can regulate

TABLE 2 Major clinical studies on the efficacy and safety of tocilizumab in adult-onset Still's disease

Author, year (Refs)	Patient number	Dosage of tocilizumab	Overall response	Mean follow-up (months)	Severe adverse events	Study character
Puéchal X, 2011 [96]	14	8 mg/kg/4 weeks (9) 8 mg/kg/2 weeks (4) 8 mg/kg/3 weeks (1) 8 mg/kg/month (1)	EULAR remission at 6 months: 8 (57.1%) resolved systemic symptoms: 6/7 (85.7%) Corticosteroid dosage $\leq$ 10 mg/day: 7 (50%) Remission without further flares: 10 (90.9%) Stopped steroids use: 2 (18.2%) EULAR (DAS28 < 2.6) remission at 6 months: 7 (63.6%) EULAR (DAS28 < 2.6) remission at 12 months: 9 (81.8%)	<12	0	Retrospective observational study
Suematsu R, 2012 [97]	11	8 mg/kg/month (11)	Discontinued corticosteroid use: 8 (72.7%) Improvement of arthralgia: 13 (86.7%) Improvement of systemic symptoms: 15 (100%) Discontinued prednisone use: 9 (60%) Improvement of arthritis 97.1% to 32.4% Improvement of skin rash 58.8% to 5.9% Improvement of fever 58.8% to 5.9% Improvement of lymphadenopathy 29.4% to 0% The median dosage of prednisone was also reduced.	>12	0	Retrospective multicentre observational study
Cipriani P, 2013 [98]	11	8 mg/kg/4 weeks (11)	Improvement of fever 58.8% to 5.9% Improvement of lymphadenopathy 29.4% to 0% The median dosage of prednisone was also reduced.	>12	0	Multicentre retrospective open label study
Elkayam O, 2014 [99]	15	8 mg/kg/4 weeks (12) 8 mg/kg/2 weeks (3)	Remission without further flares: 7 (100%) Stopped corticosteroid use: 1 (14.3%) Improvement of systemic symptoms: 10 (100%) Improvement of arthralgia: 8 (80%) The median dose of glucocorticoids had been significantly reduced.	>12	MAS (2)	Retrospective case series
Ortiz-Sanjuán F, 2014 [100]	34	8 mg/kg/4 weeks (22) 4 mg/kg/4 weeks (2) 8 mg/kg/2 weeks (10)	Good response at 6 months (modified Pouchot's score decrease >2): 11 (50%) Good response at 12 months: 9 (64.3%) After 6 months of follow-up, remission rates of fever: 6 (75%) remission rates of arthritis: 8 (100%) remission rates of rashes: 6 (75%)	>12	0	Retrospective case series
Bannal E, 2014 [101]	7	8 mg/kg/2 weeks (6) 8 mg/kg/4 weeks (1)	Good response at 6 months (modified Pouchot's score decrease >2): 11 (50%) Good response at 12 months: 9 (64.3%) After 6 months of follow-up, remission rates of fever: 6 (75%) remission rates of arthritis: 8 (100%) remission rates of rashes: 6 (75%)	<12	0	Multicentre retrospective case series
Nishina N, 2015 [92]	10	8 mg/kg/2 weeks (6) 8 mg/kg/4 weeks (4)	After 6 months of follow-up, remission rates of fever: 6 (75%) remission rates of arthritis: 8 (100%) remission rates of rashes: 6 (75%)	<12	Hepatic dysfunction and coagulation function deterioration (1) Serious infection (3) Anaphylactic shock (1)	Multicentre prospective open label study
Song ST, 2016 [93]	22	8 mg/kg/4-5 weeks (18) 6 mg/kg/4 weeks (2) 4 mg/kg/4 weeks (2)	ACR50 response at week 12: 61.5% (TCZ) vs 30.8% (PBO) (P = 0.238) ACR70 response at week 12: 46.2% (TCZ) vs 30.8% (PBO) (P = 0.688) Decrease in systemic feature score from baseline at week 12: -4.1 (TCZ) vs -2.3 (PBO) (P = 0.003) Decrease in dose of prednisolone from baseline at week 12: 46.2% (TCZ) vs 21.0% (PBO) (P = 0.017)	<12	0	Randomized, double-blind, placebo-controlled phase III trial
Li T, 2017 [103]	8	8 mg/kg/4 weeks (5) (maximum 400 mg) 4 mg/kg/4 weeks (4)				
Kaneko Y, 2018 [91]	27	8 mg/kg/2 weeks (13), placebo (13) for 12 weeks, after then open study with 8 mg/kg/2 weeks until 52 weeks.				

MAS, macrophage activating syndrome; PBO, placebo; TCZ, tocilizumab.



leucocyte activation, maturation, cytokine and chemokine release, production of reactive oxygen species, and facilitate inflammatory response. On the other, it's an immunosuppressive mediator capable of inhibiting the development of autoimmune diseases and tumorigenesis [119]. TNF- $\alpha$  level is significantly elevated in serum and synovial membranes of patients with either systemic or chronic AOSD [43, 120]. Two classes of TNF- $\alpha$  blockers have a place currently in managing rheumatic disease: the monoclonal anti-TNF antibodies, such as infliximab and adalimumab, and the soluble TNF receptor, etanercept. The anti-TNF agents, infliximab, adalimumab and etanercept have been approved by the FDA for the treatment of RA. TNF inhibitors were the first bDMARDs in treating SOJIA, but the experience is limited in treating AOSD.

In 2001, infliximab was first used in three patients with chronic and active AOSD. It showed a prolonged efficacy in the treatment of relapse of refractory AOSD patients [121]. Remarkable improvements of clinical manifestations and normalization of laboratory indices were observed in all six AOSD patients with severe disease activity after infliximab treatment [122]. In an observational study of 20 AOSD patients, ten patients were treated with infliximab, five treated with etanercept and five with both drugs. With treatment with infliximab, four patients achieved complete remission and nine achieved partial remission [123].

In an open-label study, 12 AOSD patients with active arthritis refractory to DMARDs were enrolled to receive etanercept and showed improvement in arthritis without adverse event [124]. However, in an observational study of 20 cases, most patients achieved partial response (7/10) with etanercept treatment, while only one patient achieved complete remission (1/10) [123]. The safety and efficacy of adalimumab in AOSD remains uncertain, because it is limited by small sample sizes and lack of relevant trials [125,126].

## IL-18 and its inhibitors

Similar to IL-1 $\beta$ , IL-18 is a pro-inflammatory cytokine belonging to the IL-1 superfamily, and it is secreted by monocytes, macrophages and dendritic cells [100]. After cleavage of the precursor (pro-IL-18) by caspase-1, IL-18 become an active form [65]. The mature IL-18 binds to the IL-18 receptor  $\alpha$  (IL-18R $\alpha$ ) and IL-18 receptor  $\beta$  (IL-18R $\beta$ ) and leads to activation of downstream pro-inflammatory signals in effector cells. IL-18 activity is tightly regulated by natural IL-18 binding protein (IL-18BP), which precludes IL-18 from binding to its cognate receptors [127].

The circulating level of unbound IL-18 (free IL-18) is elevated in patients with AOSD during the active and inactive phase of AOSD compared with other inflammatory situations, such as RA, SLE, AS and PsA. A higher level of free IL-18 is found in patients with active disease compared with inactive disease, indicating that IL-18 is a potential biomarker for evaluation

disease activity of AOSD [128,129]. An extremely high level of IL-18 is also found in AOSD patients with MAS [130]. Due to its critical role in AOSD pathogenesis, IL-18 inhibitor, tadekinig alfa, has emerged as a potential therapeutic strategy for AOSD, and may have a particular indication in the forms of AOSD associated with MAS.

## Tadekinig alfa

Tadekinig alfa is a recombinant human IL-18 binding protein. Recently, a phase II, open-label clinical trial recruited 23 refractory AOSD patients with fever or CRP levels  $\geq 10$  mg/l. Patients received 80 mg ( $n=10$ ) or 160 mg ( $n=13$ ) tadekinig alfa three times per week. One patient receiving 160 mg tadekinig alfa dropped out due to an injection site reaction. One (toxic optic neuropathy) of three serious adverse events was possibly related to the use of tadekinig alfa. At week 3, the response rate of either group is 50%, and all non-responders receiving 80 mg tadekinig alfa were up-titrated to 160 mg and still achieved no clinical response, indicating a favourable efficacy of 80 mg tadekinig alfa in AOSD patients [131]. Two AOSD patients were reported to have achieved favourable outcomes after tadekinig alfa treatment. The levels of free IL-18 in serum dropped to almost undetectable levels within 2 h after injection and continued low up to 48 h [132].

## Janus kinase inhibitors

The cytoplasmic domain of both type I and type II cytokine receptors binds to the Janus kinases (JAKs), including TYK2, JAK1, JAK2 and JAK3 [133]. After binding their receptors, several cytokines lead to further induction of inflammatory gene expression via JAK pathways, which amplify the loop of inflammatory signalling. Due to their prominent effects on cytokine production and modulation of immune response, JAK inhibitors have been a promising therapeutic strategy in the treatment of inflammatory diseases such as RA, SLE and SpA [134]. JAK inhibitors impede the effect of IL-6, IL-10, IFN- $\gamma$ , IFN- $\alpha$  and GM-CSF, which are strongly implicated in the AOSD pathogenesis.

## Tofacitinib

Tofacitinib (formerly CP-690550), a JAK1/JAK3 inhibitor, is renowned for the first time as the first JAK inhibitor tested in the clinic [135]. In 2019, tofacitinib was tested in 14 patients with refractory AOSD for the first time from a single centre in China. Seven AOSD patients achieved complete remission with decrement of concomitant glucocorticoids, six patients achieved partial remission and one relapsed when the prednisone dose was reduced. It suggests that tofacitinib may be an alternative in treating AOSD, particularly in those with arthritic form [136].

## Baricitinib

Baricitinib (formerly designated INCB028050), a JAK1/JAK2 inhibitor, has shown its good efficacy and tolerability in active refractory RA [137]. The efficiency of baricitinib has been reported in a corticosteroid-dependent refractory AOSD patient for the first time in 2019 [138].

In conclusion, JAK inhibitors appear to be effective in AOSD due to cytokine inhibition, thus warranting further clinical trials. Nowadays, more selective JAK inhibitors are developed and will provide more therapeutic options for the treatment of AOSD.

## Other biologic agents

### Abatacept

Abatacept is a CTLA4 Ig fusion protein that blocks the interaction between CD28 and CD80/86, thus down-regulates T-cell activation, a potential pathogenetic role in AOSD. Furthermore, abatacept reduces the production of pro-inflammatory cytokines, including IFN- $\gamma$  and IL-17 [139]. Some case reports have shown a successful use of abatacept in treating refractory AOSD, who were unresponsive to traditional DMARDs, anakinra and adalimumab [140,141]. Disruption CD28 co-stimulatory signalling by abatacept has specific immune-suppressive effect on T cells, making it a promising therapeutic strategy for AOSD, but more practices are still needed [140,141].

### Rituximab

The role of B cells in AOSD remains to be determined. It's possible that treatment targeting B cells might inhibit pro-inflammatory cytokine release mediated by T cell. Rituximab, a chimeric anti-CD20 monoclonal antibody can inhibit the activation of T cells and the production of pro-inflammatory cytokines [142]. It has been approved for treatment of RA. However, only a few case reports have highlighted the potential efficacy of rituximab in refractory AOSD patients [85, 143,144].

### Future treatment perspectives

GM-CSF can up-regulate neutrophil properties, including survival, adhesion and trafficking, oxidative burst, phagocytosis, and formation of NETs [145–149]. As increased neutrophil count and NETs are key characteristics of AOSD [150,151], it will be of interest to see if treatment targeting GM-CSF or its receptor will be a new, highly effective way. GM-CSF binds to GM-CSF receptor  $\alpha$  (GM-CSFR $\alpha$ ), and then macrophage and neutrophil are enhanced in number and function in inflammatory lesions, resulting in excessive secretion of pro-inflammatory cytokines, including IL-1 $\beta$ , IL-6, IL-12, IL-23 and TNF [152–154]. There is increasing evidence that GM-CSF deletion/depletion has indicated encouraging efficacy and safety profiles in many inflammatory and autoimmune diseases, including RA, axial spondylarthritis and plaque psoriasis.

Mavrilimumab (formerly known as CAM-3001) is an IgG4 mAb that blocks GM-CSFR $\alpha$  directly, and otilimab (formerly known as MOR-103) is an IgG1 mAb that binds to GM-CSF and prevents its interaction with GM-CSFR $\alpha$ . In a phase Ib/Ia clinical trial, otilimab has preliminary evidence of clinical efficacy, and has a good safety and tolerability in patients with active RA [155]. In 2 phase IIb studies and an open-label extension study with a total of 442 RA patients, 65% of patients achieved remission with Disease Activity Score in 28 joints using the CRP level (DAS28-CRP) <3.2, demonstrating the sustained efficacy of mavrilimumab [156]. In a 24-week, randomized phase IIb study, mavrilimumab and golimumab (anti-TNF) were demonstrated to be well-tolerated and had similar efficacy in RA patients who had an inadequate response to other previous treatments [157]. In a prospective cohort study in patients with severe COVID-19 pneumonia and hyperinflammation, mavrilimumab improved clinical outcomes in resolution of inflammation and mortality [158]. Mavrilimumab quenches downstream production of myriad pro-inflammatory mediators mediated by granulocytes and macrophages, indicating a potential efficacy in the treatment of AOSD.

## Conclusions

A cytokine storm evoked mainly by macrophages and neutrophils is the hallmark of AOSD pathogenesis. As the role of cytokines in the pathogenesis of AOSD is gradually unveiled, new windows are opened for effective experimental treatments, especially for refractory cases. IL-1-targeted biologics and IL-6-targeted biologics are the major therapeutic agents in treating refractory AOSD now. New biologics against IL-18, TNF- $\alpha$  and GM-CSF and JAK inhibitors may become promising therapeutic options for AOSD. Because the incidence of AOSD is quite low, large collaborative projects are required to confirm the efficiency and safety of emerging biologics.

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