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Anakinra in children and adults with Still's disease

Sebastiaan J. Vastert[1,*], Yvan Jamilloux[2,*], Pierre Quartier[3,4,*], Sven Ohlman[5], Lisa Osterling Koskinen[5], Torbjörn Kullenberg[5], Karin Franck-Larsson[5], Bruno Fautrel[6,*] and Fabrizio de Benedetti[7,*]

Abstract

Systemic juvenile idiopathic arthritis and adult-onset Still's disease are rare autoinflammatory disorders with common features, supporting the recognition of these being one disease—Still's disease—with different ages of onset. Anakinra was recently approved by the European Medicines Agency for Still's disease. In this review we discuss the reasoning for considering Still's disease as one disease and present anakinra efficacy and safety based on the available literature. The analysis of 27 studies showed that response to anakinra in Still's disease was remarkable, with clinically inactive disease or the equivalent reported for 23–100% of patients. Glucocorticoid reduction and/or stoppage was reported universally across the studies. In studies on paediatric patients where anakinra was used early or as first-line treatment, clinically inactive disease and successful anakinra tapering/stopping occurred in >50% of patients. Overall, current data support targeted therapy with anakinra in Still's disease since it improves clinical outcome, especially if initiated early in the disease course.

Key words: adult-onset Still's disease (AOSD), anakinra, IL-1, IL-1 receptor antagonist (IL-1Ra), systemic juvenile idiopathic arthritis (sJIA), Still's disease

Rheumatology key messages

- sJIA and AOSD represent the same disease continuum with different ages of onset.
- Anakinra treatment for Still's disease generates high response rates and possibilities for glucocorticoid sparing.
- Early treatment and achievement of early remission are important to improve clinical outcome in sJIA and AOSD.

Introduction

Systemic JIA (sJIA) and adult-onset Still's disease (AOSD) are rare autoinflammatory disorders of unknown aetiology. Typical clinical manifestations include daily spiking fevers, arthritis and evanescent rash. Both diseases display significant systemic inflammation and are associated with inappropriate activation of the innate immune system and excessive secretion of the pro-inflammatory cytokines IL-1, IL-6 and IL-18 [1–3]. Most patients are currently treated by paediatric rheumatologists (sJIA), internal medicine specialists or adult rheumatologists (AOSD). Although the clinical manifestations and laboratory findings are similar, AOSD and sJIA have traditionally been viewed as separate diagnostic entities. Because of the growing recognition that sJIA and AOSD represent a disease continuum with different ages of onset, we will refer to these entities as Still's disease in this review [2, 4–12].

The current treatment strategy for Still's disease typically includes NSAIDs to relieve symptoms during the differential diagnostic process while reaching a final diagnosis. Glucocorticoids (GCs) are commonly used as first-line treatment once a diagnosis is made [13–15] and DMARDs are often considered in combination with GCs [16]. Biologic DMARDs (bDMARD) offer a more target-specific mechanism of action than regular DMARDs and have, for this reason, emerged as an important therapeutic alternative in patients with Still's disease of all ages. The IL-6 inhibitor tocilizumab is

[1]Department of Pediatric Rheumatology and Laboratory of Translational Immunology, University Medical Centre Utrecht, Utrecht, The Netherlands, [2]Department of Internal Medicine Hospices Civils de Lyon, Croix-Rousse Hospital, Lyon, France, [3]Pediatric Immunology-Hematology and Rheumatology Unit, RAISE Rare Disease Reference Centre, IMAGINE Institute, Necker Hospital, Assistance Publique Hôpitaux de Paris, Paris, France, [4]Université Paris-Descartes, Paris, France, [5]Sobi, Stockholm, Sweden, [6]Department of Rheumatology, AP-HP Pitié-Salpêtrière Hospital, Paris, France and [7]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù, Rome, Italy

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*Sebastiaan J. Vastert, Yvan Jamilloux, Pierre Quartier, Bruno Fautrel and Fabrizio de Benedetti contributed equally to this study.

Correspondence to: Pierre Quartier, Pediatric Immunology-Hematology and Rheumatology Unit (UIHR), Necker Hospital, 149 rue de Sevres, 75743 Paris cedex 15, France.
E-mail: pierre.quartier@aphp.fr

approved for treatment of sJIA in the US and European Union (EU) [12, 17–19], and the IL-1β inhibitor canakinumab is approved in the US for sJIA and in the EU for Still's disease.

The IL-1 receptor antagonist (IL-1Ra) anakinra, which blocks both IL-1α and IL-1β biologic activity, has been previously approved for the treatment of RA and different forms of cryopyrin-associated periodic syndrome in the US, Canada, Europe and Australia [20–23], as well as for sJIA in Australia, and has recently been approved for Still's disease by the European Medicines Agency (EMA). Anakinra is also included in several treatment recommendations, guidelines and strategy documents for sJIA and AOSD, both in the US and Europe [24–31]. The recent approval in the EU was based on a limited number of patients in a company-sponsored study, extensive safety information in different indications as well as results from a large number of academic studies available in the scientific literature. It should be noted that in this case the vast majority of efficacy data for anakinra in Still's disease was generated from academic studies rather than from company-sponsored studies. In this review we explore the reasoning why Still's disease is now considered one disease, we summarize some of the key results supporting the use of anakinra for Still's disease and discuss the data pointing to the importance of early treatment.

sJIA and AOSD are one disease: Still's disease

The growing acceptance that sJIA and AOSD represent one disease continuum with different ages of onset is based on a number of shared clinical, genetic and laboratory features as well as a strikingly similar response to IL-1 and IL-6 inhibitors.

Although large clinical cohort studies comparing sJIA and AOSD symptoms are lacking, there are numerous reports suggesting that, at least for the cardinal features —(spiking) fevers, arthritis/arthralgia, skin manifestations and leucocytosis/neutrophilia—sJIA and AOSD cohorts show clear similarities [12, 29, 32–34]. Also, the overall disease course and prognosis have been reported to be similar for sJIA and AOSD [4, 7, 8]. For both sJIA and AOSD, a phenotypic dichotomy has been recognized, with a more systemic inflammatory phenotype (often early in the disease course) and a more articular chronic phenotype [35–37]. Additional clinical similarities include a clear predisposition to develop macrophage activation syndrome (MAS) in both sJIA and AOSD [38].

Given the marked activation of the innate immune system, at least during the initial phase of the disease, as well as the pathogenic role played by IL-1 and IL-6, both sJIA and AOSD are now considered complex, polygenic autoinflammatory diseases [32, 34, 39]. At a molecular or genetic level, there is ample evidence that IL-1 plays a major role in both sJIA and AOSD [1, 40]. Pascual *et al.* [1] demonstrated that peripheral blood mononuclear cells of healthy subjects incubated with serum from patients with sJIA secrete large amounts of IL-1β following strong induction of the transcription of innate immunity genes, including IL-1. In agreement with this, it has been shown that a similar set of innate immunity genes were upregulated in most patients with AOSD, including several members of the IL-1-signalling pathways (e.g. *IL-1β, IL-1RAP, IL-1RN, IL-1R1* and *IL-1R2*) [2]. The same study also showed a significant overlap for the set of downregulated genes in sJIA after IL-1β inhibition with canakinumab and the set of upregulated genes in active AOSD [2]. These gene expression analyses are consistent with and further support the concept of a disease continuum.

In paediatric rheumatology, sJIA is still classified under the umbrella of JIA, although it is becoming increasingly accepted that it should be considered as a separate clinical entity. Genome-wide association studies have confirmed this genetic distinction of sJIA from other forms of JIA [41]. Along these lines, a revision of the classification criteria for JIA has recently been proposed, with important suggested changes in the classification criteria for sJIA [42]. sJIA is thereby set apart in the sense that it is characterized by severe systemic inflammation, while the presence of arthritis is no longer considered necessary, which is similar to the commonly used diagnostic criteria in adults, the Yamaguchi criteria [43]. Of note is that the standardized medical dictionary for regulatory activities (MedDRA), used to facilitate sharing of regulatory information internationally, is already classifying sJIA and AOSD as Still's disease.

There are also striking similarities between sJIA and AOSD when it comes to laboratory features at disease onset. Hyperferritinaemia and elevated levels of both CRP and ESR are common in most patients. Moreover, both sJIA and AOSD are characterized by elevations of IL-1, IL-6, IL-18 and S100 proteins [44, 45], some of which have been considered biomarkers. Due to a very short half-life in plasma, IL-1β is poorly detectable in peripheral blood and does not constitute a reliable biomarker. Nevertheless, when measured, IL-1β concentrations appear significantly higher in patients with active sJIA [46, 47] or AOSD [17, 48] compared with patients with inactive disease or healthy controls. IL-18 has repeatedly been found to be elevated in peripheral blood of patients with sJIA and AOSD [3, 49, 50], distinguishing them from many other rheumatic diseases. For this reason, IL-18 has been regarded as a potential biomarker, mostly with regard to its association with macrophage activation. Levels of IL-6, downstream from IL-1 in the inflammation cascade, have been found to be elevated in patients with sJIA and AOSD compared with healthy controls [12, 50, 51]. IL-6 levels correlate with disease activity, fever spikes, number of active joints and elevated CRP and platelet counts [52, 53]. In addition, IL-6 may contribute to hyperferritinaemia along with elevation of CRP and other acute-phase reactants synthesized by the liver [19].

Despite the similarities, there are also reported differences between sJIA and AOSD. The gender ratio is ~1 for sJIA, while women are more likely to be affected by AOSD (70% *vs* 30%) [27, 54]. Seasonality has been described for both conditions but appears higher for sJIA, pointing to a potential infectious trigger in children to a greater extent, possibly due to the relatively high exposure to antigens in

combination with an immature immune system [9, 55]. Conversely, the low incidence of AOSD in the elderly may be explained by immune system senescence or by greater protection against infectious agents by memory cells. Sore throat is reported more often in adults, a difference that may be due to less frequent self-reporting from children [12]. A study comparing clinical features of sJIA and AOSD patients reported no differences in the cardinal features. A higher frequency of sore throat and myalgia was found in AOSD compared with sJIA; this could possibly be explained by reporter bias in the different cohorts of different ages. Arthritis had similar frequencies, with differences only in the distribution; involvement of lower limb joints was more frequent in sJIA [8].

As already mentioned, there is some scarcity in outcome studies from both sJIA and AOSD cohorts over time. Studies from the pre-biologicals era, where treatment regimens for both sJIA and AOSD were generally based on high-dose corticosteroids (often combined with MTX maintenance therapy), report ongoing or refractory disease in ~40% of patients [56, 57]. The outcome has improved significantly for both sJIA and AOSD with the use of targeted treatment over the past decade [35, 58].

In conclusion we, as well as others, have suggested positioning sJIA and AOSD as equivalent parts of the same disease continuum. From clinical practice and a research point of view, and for optimization of treatment paradigms, there is a clear need and growing support for harmonization of paediatric and adult classification criteria, which is supported by recent research data [59, 60].

Review of available data on anakinra treatment in Still's disease

Literature search

A literature search in Embase and MEDLINE with 13 March 2019 as a cut-off was performed to collect all literature on anakinra and Still's disease (including both sJIA and AOSD). The search strategy was disease and treatment specific, but sufficiently broad to minimize the risk of missing relevant published studies. Relevant literature was selected manually based on publications in English in a peer-reviewed journal and the presence of efficacy data from a minimum of five individual patients with Still's disease treated with anakinra. See supplementary material, section Literature Search, Supplementary Fig. S1 and Supplementary Table S1, available at *Rheumatology* online, for additional details on the literature search.

Patient characteristics when starting anakinra treatment

Based on the literature search and the criteria mentioned above, 27 studies were selected to be included in this review (Table 1). The studies include patients with Still's disease across all age groups with various symptoms and degrees of disease severity. Most patients had received prior therapy with GCs, MTX and other DMARDs before initiation of anakinra. Anakinra was often used in a subset of refractory patients who did not respond well to MTX and would otherwise have required unacceptably high doses of GCs for long-term therapy. In a few studies, anakinra was given as first-line therapy [33, 64, 67].

Response rate to anakinra treatment

Several definitions of treatment response have been used in Still's disease, hampering the comparison of outcomes across different clinical studies. In paediatric patients, clinically inactive disease (CID) has been regularly used as an efficacy outcome measure. CID is defined as no active arthritis, no systemic features, no uveitis, normal ESR ($\leqslant$20 mm/h) and physician global assessment indicating no disease activity [83, 84]. Alternatively, the ACR Pedi criteria have been used, with the ACR Pedi 50 being the most relevant clinically [85, 86]. In adult patients, responses are either based on ACR response criteria developed for RA [87] or qualitatively defined as complete or partial responses depending on the full resolution of any inflammatory signs of the disease or the persistence of only one or two of them [78]. The lack of consensus, as well as the substantial heterogeneity of studied patient populations (previously untreated patients, patients treated with DMARDs and/or bDMARDs, patients in controlled interventional trials or in observational studies, etc.), provide a likely explanation for the variations observed when assessing the response rates to anakinra in the publications from the literature search.

Table 2 presents the response rates observed in 27 studies for which information was available. A total of 446 patients with sJIA were included across studies, although this number is probably an overestimation since some patients are most likely reported in more than one publication. A clinically meaningful response to anakinra, i.e. either an ACR Pedi 50 response or CID, was reached in 23–88% of the patients. It is important to point out that there is substantial heterogeneity between the studies in terms of patient population, i.e. disease duration and treatment history. There were also differences in the timing of when outcome measures were assessed. For some studies it was 4–12 weeks, identifying high rates of rapid response to anakinra; for other studies, response rates were provided at $\geqslant$6 months, reflecting treatment maintenance. For AOSD, 15 studies included ~444 patients, with the same issues regarding patient and time point heterogeneity. Overall, the response rates ranged from 50% to 100% after a follow-up of 3–>12 months. A substantial part of the patients who did not reach a clinically significant response or CID did experience some clinical improvement with anakinra. Primary failure, i.e. absence of any response, was observed in a few patients across the studies.

Based on these data, IL-1 pathway blocking by anakinra seems to provide a dramatic, rapid and sustained response in a substantial proportion of Still's patients regardless of age. The lack of response is rare, at least at the early stage of the disease, and should lead to reconsideration of the Still's disease diagnosis.

Table 1 Characteristics of patients with Still's disease at the start of anakinra treatment

Study	Number of patients	Age at anakinra start, years, mean (s.d. or range)	Disease duration, years, mean (s.d. or range)	Refractory to previous treatment	MTX, % (*n*)	Anti-TNF, % (*n*)	Glucocorticoid treatment, % (*n*)
Still's disease—paediatric onset							
Prospective randomized double-blind placebo-controlled studies							
Ilowite *et al*. 2009 [61]	15	NR	NR	NR	NR	NR	NR
Quartier *et al*. 2011 [62]	12 (7 F/5 M) anakinra	9.5 (5.19)	4.2 (3.33)	Yes, GC	67 (8)	42 (5)	100 (12)
	12 (8 F/4 M) placebo	7.5 (3.73)	3.2 (1.95)		92 (11)	67 (8)	100 (12)
Prospective uncontrolled studies							
Pascual *et al*. 2005 [1]	9 (7 F/2 M)	8.4 (4.8)	4.6 (3.8)	Yes	78 (7)	44 (4)	100 (9)
Gattorno *et al*. 2008 [37]	22 (11 F/11 M)	10.3 (4.60)	3.4 (0.3–10.9)	NR	55 (12)[a]	41 (9)[a]	100 (22)[a]
Lequerré *et al*. 2008[b] [63]	20 (12 F/8 M)	12.4 (5.2)	7.0 (4)	Yes	95 (19)	70 (14)	100 (20)
Vastert *et al*. 2014 [64]	20 (7 F/13 M)	7.9 (1.1–15.3)	Newly diagnosed	Yes, NSAIDs[c]	0	0	0
Kearsley-Fleet *et al*. 2018 [65]	22 (15 F/7 M)	Median 6 (IQR 2–13)	Median 1 (IQR 0–1) (*n* = 21)	NR	86 (19)	9 (2)	59 (13)
ter Haar *et al*. 2019[d] [33]	42 (17 F/25 M)	Median 7.1 (IQR 3.9–11.8)	Newly diagnosed	Yes, NSAIDs[c]	0	0	0
Retrospective uncontrolled studies							
Ohlsson *et al*. 2008 [66]	7	Median 8.5 (IQR 5.2–15)	NR	Yes	86 (6)	57 (4)	100 (7)
Nigrovic *et al*. 2011 [67]	46 (27 F/19 M)	Median 7.6 (IQR 0.75–15.7)[e]	Median 82.4 days (IQR 44–172.5)	NR[c]	0	0	67 (31)
Pardeo *et al*. 2015 [68]	25 (12 F/13 M)	Median 7.3 (IQR 4.8–10.8)	Median 4.9 months (IQR 1.6–24.5)	Yes	24 (6)	24 (6)	56 (14)
Woerner *et al*. 2015 [69]	51 (27 F/24 M)	Median 3.6 (IQR 2.3–6.8)[f]	Median 31.0 months (IQR 9.3–59.1)	NR	31.4 (16)	0	100 (51)
Rossi-Semerano *et al*. 2015[b] [70]	26	NR	NR	NR	NR	NR	NR
Vitale *et al*. 2016[b] [71]	57 treatment courses	NR	NR	NR	NR	NR	NR
Saccomanno *et al*. 2019 [72]	62 (30 F/32 M)	Median 9.7 (IQR 4.1–13.1)	Median 1.4 (IQR 0.4–5.5)	NR	61 (38)	37 (23)	98 (61)
Still's disease—adult onset							
Prospective randomized active-controlled open-label study							
Nordstrom *et al*. 2012 [73]	12 (6 F/6 M) anakinra	39 (18)	Median 14 months (IQR 2–240)	Yes	NR	NR	100 (12)
	10 (5F/5M) DMARD	39 (17)	Median 19 months (IQR 3–204)		NR	NR	100 (10)
Prospective uncontrolled studies							
Lequerré *et al*. 2008[b] [63]	15 (11 F/4 M)	38.1 (12.8)	7.8 (6.4)	Yes	100 (15)	67 (10)	80 (12)
Naumann *et al*. 2010 [74]	8 (7 F/1 M)	42 (26–66)	5.7 (3.7)	Yes	100 (8)	75 (6)	100 (8)
Laskari *et al*. 2011[g] [75]	25 (12 F/13 M)	Median 32 (IQR 18–71)	Median 7 months (IQR 1–228)	Yes	16 (4)	16 (4)	68 (17)

(continued)

Table 1 Continued

Study	Number of patients	Age at anakinra start, years, mean (s.d. or range)	Disease duration, years, mean (s.d. or range)	Refractory to previous treatment	MTX, % (*n*)	Anti-TNF, % (*n*)	Glucocorticoid treatment, % (*n*)
Retrospective uncontrolled studies							
Riera *et al*. 2011 [76]	5	NR	NR	Yes	NR	60 (3)	NR
Iliou *et al*. 2013 [77]	10	NR	NR	Yes	NR	NR	100 (10)
Giampietro *et al*. 2013 [78]	28 (19 F/9 M)	40.3 (23–72)	9.3 (1–22)	Yes	89 (25)	82 (23)	100 (28)
Gerfaud-Valentin *et al*. 2014 [54]	6	NR	NR	Yes	NR	NR	NR
Cavalli *et al*. 2015 [79]	20 (11 F/9 M)	41	9	Yes	75 (15)	20 (4)	95 (19)
Rossi-Semerano *et al*. 2015[b] [70]	35 (23 F/12 M)	Median 40.9 (IQR 22.4, total range 21.4–79.4)	Median 4.4 (IQR 7.4, total range 0.04–46.9)	NR	NR	NR	NR
Dall'Ara *et al*. 2016 [80]	13 (9 F/4 M)	32.8 (17–59)	NR	Yes	92 (12)	15 (2)	100 (13)
Vitale *et al*. 2016[b] [71]	78 treatment courses	NR	NR	NR	NR	NR	NR
Sfriso *et al*. 2016 [81]	35	NR	NR	NR	NR	NR	NR
Colafrancesco *et al*. 2017 [82]	140 (93 F/47 M)	35.4 (17)[d]	50.33 months (81.67)	Yes	75.8 (91)	20.7 (20) or less[h]	97.8 (137)
Vercruysse *et al*. 2019 [35]	15	NR	Median 1.5 months (IQR 0–14)	Yes[c]	NR	NR	93 (14)/NR

[a]Based on individual data in publication. [b]Study appearing twice in this table. [c]Anakinra as first-line disease-modifying treatment. [d]The study describes 20 patients also included in Vastert *et al.* 2014 [64]. [e]At disease onset. [f]At diagnosis. [g]All 25 patients were adults but 4 had juvenile onset. [h]A total of 20.7% of the patients had previous bDMARDs (including anti-TNF). F: female; M: male; NR: not reported.

TABLE 2 Overview of complete response rate for anakinra treatment in Still's disease

Study	Number of patients	Complete responders, % (*n*)	Time of response	Definition of response
Still's disease—paediatric onset				
Pascual *et al*. 2005 [1]	9	78 (7)	Mean follow-up 6.6 months	Similar to CID
Lequerré *et al*. 2008[a] [63]	20	35	6 months	⩾ACRpedi 50
Gattorno *et al*. 2008 [37]	22[b]	45 (10)	Mean follow-up ∼16 months	Similar to CID
Ohlsson *et al*. 2008 [66]	7	86 (6)	Median follow-up 12 months	Similar to CID
Ilowite *et al*. 2009 [61]	15	73[c]	3 months	⩾ACRpedi 30[c]
Quartier *et al*. 2011 [62]	22	23 (5/22)	12 months	CID
Nigrovic *et al*. 2011 [67]	46	59 (27)	Median follow-up 14.5 months	Similar to CID
Vastert *et al*. 2014 [64]	20	85 (17)	12 months	CID
Rossi-Semerano *et al*. 2015[a] [70]	26	42 (11)	Median treatment duration ∼17 months	CID
Pardeo *et al*. 2015 [68]	25	56 (14)	6 months	CID
Woerner *et al*. 2015[e] [69]	51	51 (26)	At last follow-up (⩾6 months)	CID
Vitale *et al*. 2016[a] [71]	57[n]	88 (50)	NR	Similar to CID
Kearsley-Fleet *et al*. 2018[e] [65]	22	25	12 months	CID
ter Haar *et al*. 2019[f] [33]	42	76 (32)	12 months	CID
Saccomanno *et al*. 2019 [72]	62	39 (24)	12 months	Similar to CID
Total number of anakinra-treated patients[g]	446[g]			
Still's disease—adult onset				
Lequerré *et al*. 2008[a,h] [63]	15	67 (10)	6 months	⩾ACR 50
Naumann *et al*. 2010 [74]	8	100 (8)	⩾6 months	Unclear
Riera *et al*. 2011 [76]	5	100 (5)	⩾12 months	Unclear
Laskari *et al*. 2011[m] [75]	25	84 (21)	Median 0.2 months[i]	Similar to CID
Nordstrom *et al*. 2012 [73]	12	50 (6)	∼6 months	Similar to CID
Giampietro *et al*. 2013 [78]	28	57 (16)	At last follow-up (mean 23 months)	Similar to CID
Iliou *et al*. 2013 [77]	10	100 (10)	NR	Similar to CID
Gerfaud-Valentin *et al*. 2014 [54]	6	83 (5)	12 months	Similar to CID
Cavalli *et al*. 2015 [79]	20	70 (14)	⩾3 months	Similar to CID
Rossi-Semerano *et al*. 2015[a] [70]	35	54 (19)	Median treatment duration ∼15 months	Similar to CID
Sfriso *et al*. 2016[j] [81]	34	76 (26)	NR	Similar to CID
Dall'Ara *et al*. 2016 [80]	13	92 (12)	⩾6 months	Similar to CID
Vitale *et al*. 2016[a,j,k] [71]	78	78 (61)	NR	Similar to CID
Colafrancesco *et al*. 2017 [82]	140	81 (114)[l]	12 months	Unclear
Vercruysse *et al*. 2019 [35]	15	87 (13)	NR	Unclear
Total number of anakinra-treated patients[g]	444[g]			

Studies report response or remission. Remission is interpreted as complete response. The study by Quartier *et al.* [62] included a 1 month randomized period comparing anakinra with placebo. A higher proportion of anakinra-treated patients had an ACR30 response compared with placebo ($P = 0.003$). Among 22 patients exposed to anakinra, one non-responder was diagnosed afterwards with Crohn's disease. The study by Nordstrom *et al.* [73] had a 24 week open-label randomized period comparing anakinra with DMARDs. At week 24, 6/12 (50%) on anakinra were in remission *vs* 2/10 (20%) on DMARDs. This difference did not reach statistical significance. [a]Study appears twice in this table. [b]One patient could not be classified in terms of response. [c]Ilowite *et al.* [61] reports only ⩾ACR30 response. [d]Woerner *et al.* [69] describe a retrospective study on a nationwide register in France. For this reason we expect a possible overlap with any other patient data from France (January 2005–June 2012) also appearing in this table. [e]Kearsley-Fleet *et al.* [65] report patients with sJIA within the UK Biologics for Children with Rheumatic Diseases study (2010 and 2016). For this reason we expect a possible overlap with any other patient data from the UK (2010–2016). [f]The study describes 20 patients also included in Vastert *et al.* [64]. [g]The total number of anakinra-treated patients from the publications is an overestimate since some patients are reported in more than one publication. [h]There is an expected overlap of patients reported in Lequerré *et al.* [63] and Giampietro *et al.* [78]. [i]Laskari *et al.* [75] report that the response was maintained in all but one patient until the latest follow-up (⩽12 m). [j]There is an expected overlap of patients reported in Sfriso *et al.* [81] and Vitale *et al.* [71]. [k]Including both paediatric and adult patients with sJIA diagnosis in Vitale *et al.* [71]. [l]Primary and secondary inefficacy was reported [15/140 (10.7%) and 11/140 (7.8%), respectively] and the number provided in the table represents estimated efficacy as interpreted by the authors of this review. [m]All 25 patients were adults but 4 had juvenile onset. NR: not reported.

GC-sparing effect of anakinra

Historically, first-line treatment for Still's disease has been based on NSAIDs and systemic GCs. The disease usually responds very satisfactorily to GCs but does so at doses that are unacceptable in the medium and long term because of the well-known side effects. Until recently, treatment with bDMARDs was limited to patients with Still's disease refractory to or dependent on high-dose GCs, and these agents were likely to be introduced after several months or years of GC therapy, thereby exposing patients to substantial GC side effects [63, 66, 74, 78, 79, 88, 89].

In sJIA, prolonged high-dose GC treatment often leads to growth impairment and defective accrual of bone mass [90], which correlates with the duration of treatment [91]. In a study on AOSD [54], almost half of the cohort developed GC-dependent disease and 75% of the patients had GC-related side effects, such as Cushing syndrome, osteoporosis, aseptic osteonecrosis, GC-induced diabetes, high blood pressure, cataract, psychiatric disorders and infectious diseases. Long-term treatment might also cause side effects such as gastric ulcers, especially when used in combination with NSAIDs. It is therefore of great importance to minimize GC treatment [67] or, ideally, to avoid initiation of GC treatment [33, 64, 92]. Indeed, tapering and discontinuation of GCs is a treatment objective for clinicians managing patients with Still's disease in real life, as well as a relevant outcome in all clinical trials in Still's disease.

The analysis of GC use after the introduction of anakinra was reported in most publications found in the literature search and is summarized in Table 3, illustrating both dose reductions and discontinuation of GCs. In the eight studies on patients with sJIA, GC tapering was achieved in 29–67% of patients and discontinuation in 5–71% of patients. In the AOSD studies, GC reduction and/or discontinuation was reported in a majority of patients in eight of nine studies and in 33% in the remaining study. In a study by Laskari *et al.* [75] that reported combined data from sJIA and AOSD patients, 12/22 (55%) were able to discontinue GCs and the median GC daily dose decreased from 22.5 to 8.75 mg/day. In none of the studies was a structured decision on tapering or stopping GC treatment applied, but instead relied on the physician's and the patient's decision. Hence the change in GC use might not correctly reflect the actual steroid-sparing potential.

In a single-centre prospective cohort, anakinra was initiated before DMARDs, GCs or other bDMARD in 20 paediatric patients with Still's disease who failed to respond to NSAIDs [64]. At year 1, 13/20 (65%) patients had achieved CID on anakinra treatment alone. In six patients GCs had been added, and in the remaining patient MTX was added due to incomplete response to anakinra. In summary, 70% of the patients did not have to use GCs within the first year of anakinra treatment [64].

Safety

The safety profile of anakinra is well established since its first market authorization in the USA in 2001. The safety profile is based on studies in RA [93–97], cryopyrin-associated periodic syndrome [98, 99] and Still's disease [61, 62, 73], as well as on high-dose i.v. infusion studies (up to 2 mg/kg/h) in sepsis [100, 101]. No new clinically relevant adverse drug reactions have emerged compared with the already known safety profile of anakinra. The most common and consistently reported treatment-related adverse drug reactions associated with s.c. injections of anakinra are injection-site reactions, the majority being mild to moderate. The injection-site reactions typically appear within 2 weeks of therapy initiation and disappear within 4–6 weeks [20] during continued anakinra treatment.

Liver-related adverse events have been associated with anakinra. These events are more frequent in patients with Still's disease and patients with predisposing factors, such as a history of increased liver enzymes. Events of MAS are described in patients treated with anakinra for Still's disease, but a causal relationship between anakinra and MAS has not been established. It should be noted that anakinra also has been reported as an effective treatment for MAS [20, 96, 102].

Other IL-1 inhibitors in Still's disease

Reported clinical trials and case series of patients treated with other IL-1 inhibitors, i.e. canakinumab and rilonacept, in Still's disease support the efficacy of IL-1 inhibition. In addition, these data do not suggest new or different safety issues [61, 103–107].

The importance of early treatment in Still's disease

The therapeutic strategies that are recommended and implemented nowadays in both sJIA and AOSD have two main objectives: to achieve rapid and complete remission and prevent disease complications, specifically life-threatening manifestations such as MAS, as well as organ damage, mainly joint erosion and amyloidosis; and to limit or avoid side effects of GCs and other immunomodulating agents [34, 108]. This strategy is common to many other systemic immune-mediated inflammatory disorders.

In RA, the notion of a therapeutic window of opportunity and the benefit of early therapeutic intervention have been clearly established [109] and initiation of DMARDs within 3 months after disease onset is associated with a higher response rate and better disease outcome [110–112]. This concept of a therapeutic window and benefits of early intervention has also been suggested for sJIA [64, 113] but has not been explored for patients with AOSD to the same extent. As indicated above, the major remaining unmet need in the treatment of Still's disease today is to avoid GC side effects. In recent years, guidelines have proposed to move more quickly from GCs to bDMARDs targeting IL-1 or IL-6, introducing them as soon as the disease diagnosis is set, and in combination (or not) with GCs, or within the very first weeks of the disease if GC tapering results in disease relapse [34, 114].

The early inflammatory cascade of sJIA appears to be characterized by features and symptoms of innate

Table 3 Glucocorticoid-sparing effect in patients with Still's disease treated with anakinra

Study	Number of patients on anakinra	Glucocorticoid use at anakinra start, *n* (%)/mean or median dose (mg/kg in children, mg in adults)	Glucocorticoid reduction, *n* (%) of patients		Glucocorticoids discontinuation, *n* (%) of patients	
			⩽month 6	At any time	⩽month 6	At any time
Still's disease—paediatric onset						
Pascual *et al*. 2005 [1]	9	9[a] (100)/NR	NR	6/9 (67)[b]	3/9 (33)	3/9 (33)[b]
Lequerré *et al*. 2008 [63]	20	20 (100)/mean 0.50	9/20 (45)	10/20 (50)	0	1/20 (5)
Gattorno *et al*. 2008 [37]	22	22 (100)/mean 0.79	NR	NR	⩾10/22 (⩾45)	11/22 (50)[c]
Ohlsson *et al*. 2008 [66]	7	7 (100)/median 1	⩽3 (⩽43)[d]	⩽3/7 (⩽43)[d]	⩾4/7 (57)[d]	⩾4/7 (⩾57)[d]
Quartier *et al*. 2011 [62]	22	22 (100)/mean 0.59	15/22 (68)	NR; mean 0.15[e]	⩾1/22 (⩾4.5)	⩾6/22 (⩾27)
Nigrovic *et al*. 2011 [67]	46	31 (67)/mean 0.67	NR	NR	⩾15/31 (48)[f]	⩾15/31 (48)[f]
Pardeo *et al*. 2015 [68]	25	14 (56)/median 0.9	NR	4/14 (29)[g]	NR	10/14 (71)[g]
Saccomanno *et al*. 2019 [72]	62	61 (98)/median 0.5	NR	NR; median 0 in responders and non-responders[d]	NR	⩾31/61 (⩾51)[d]
Still's disease—adult onset						
Lequerré *et al*. 2008 [63]	15	12 (80)/mean 26.8 mg	NR	⩾8/12 (⩾67)[h]	1/12 (8)	2/12 (17)[h]
Naumann *et al*. 2010 [74]	8	8 (100)/mean 61.9	NR	8 (100)[i]	NR	0[i]
Nordstrom *et al*. 2012 [73]	12	12 (100)/mean 22.5	NR; mean dose 10.8 mg reduced	NR	3/12 (25)	⩾9/12 (⩾75)[j]
Giampietro *et al*. 2013 [78]	28	28 (100)/mean 34.4	15/28 (54)	NR	NR	NR
Iliou *et al*. 2013 [77]	10	10 (100)	NR	10/10 (100)	NR	NR
Cavalli *et al*. 2015 [79]	16	15/16 (94)/mean 21.5	NR	6/11 (55)[j]	NR	5/11 (45)[j]
Dall'Ara *et al*. 2016 [80]	13[k]	9/9 (100)/median 25[k]	NR	4/9 (44)[k]	NR	5/9 (56)[k]
Colafrancesco *et al*. 2017 [82]	140	137 (98)/mean 77.6	NR; mean 5.2	NR; mean 3.4	34/109 (31)	⩾44/137 (⩾32)[l]
Vercruysse *et al*. 2019 [35]	15	15 (100) / NR	NR	NR	0	5/15 (33)

Doses given in prednisolone equivalents and for oral GCs only. In the study by Quartier *et al.* [62], GC tapering was not allowed during the 1 month randomized part of the study. In the study by Nordstrom *et al.* [73], for the first 24 weeks the comparator group consisted of 10 patients who were treated with conventional DMARDs. In this group the mean GC dose was 18.5 mg at the study start and was reduced by a mean of 10.5 mg. None of the DMARD patients were able to discontinue GCs, compared with three in the anakinra group. [a]Two patients stopped GC treatment at the initiation of anakinra (Fig. 4 in the publication). [b]At last follow-up after 2–12 months. [c]At last follow-up. [d]Based on the median (range) reported in the publication. [e]At month 12. [f]At month 4. Fig. 2 in original article illustrates that 30% of the total study population was off GCs. This equals 13 patients. If the 31 patients starting on GCs were still in the study, this equals 13/31 = 42% who were still treated with GCs at month 4, which is thus an estimation by the authors of this article. [g]At last follow-up after 1.6–7.3 years. [h]At last follow-up after 1–27 months. [i]At last follow-up after 6–48 months. [j]Not known if the three patients that stopped at week 24 also had been able to stop GCs. [k]Detailed information on GC usage is only available for patients treated with only anakinra. [l]Unknown follow-up time. NR: not reported.

immune activation. The adaptive immune system appears to be involved in later phases of the disease. Data from historical cohorts demonstrate that ~50% of patients with sJIA have a chronic disease course often characterized by severe arthritis [115–120]. In line with this, several studies have suggested and observed that early intervention with IL-1 blockade may be very beneficial, as it seems more effective than in later phases of the disease [33, 64, 67, 68]. These studies support the window of opportunity in which autoinflammatory or innate immune features dominate in the early phase and autoimmune or adaptive features develop later in the disease course. It should be noted that a single-centre prospective cohort study [33, 64] using anakinra as first-line therapy in sJIA as an early targeted approach may represent a paradigm shift compared with the still widely used 'step-up' therapy (first NSAIDs, then GCs, combined with MTX, and only in resistant or GC-dependent patients, stepping up to IL-1 or IL-6 blockade). The presumed benefit of the step-up approach is that only a small number of patients is exposed to the potential risks of costly bDMARDs. This prospective cohort showed that anakinra, when used early in the disease course and as first-line disease-modifying therapy, has high response rates (up to 75% of CID in the first year of treatment). More importantly, it shows that anakinra can be tapered and withdrawn without relapse of disease in >50% of patients [33, 64], suggesting that early interference with innate immunity through IL-1 blockade might affect the natural history of the disease. In addition, the 5-year follow-up data of this prospective cohort also show significantly lower use of GCs (both reduced percentage of children ever exposed to GCs and lower doses) than other published cohorts [33]. This lower use of GCs translates to low incidences of GC-related long-term side effects and likely influences the patient-reported outcomes of this cohort, which are remarkably good [33].

Remaining challenges

Even if new treatment options have improved the clinical outcome in Still's disease, there is a need to better understand why not all patients respond to targeted treatments such as IL-1 or IL-6 inhibitors. This could be linked to disease heterogeneity, since Still's disease might be a syndrome rather than a homogeneous entity, with some patients developing persistent disease with diffuse polyarthritis. It could also be linked to the proposed 'window of opportunity', in which case some patients might over time switch from a pure autoinflammatory disease to a more complex less IL-1-dependent disease. There is still a lack of biomarkers able to indicate which pathophysiological pathway should be the main target in a given patient at a given stage of the disease.

In addition, in patients who do not respond adequately to a first bDMARD, it is important to check compliance, particularly in teenage patients who do their s.c. injections themselves. Treatment dosage should also be considered. For anakinra, clinical and pharmacokinetic data indicate that low-weight (<30 kg) children with Still's disease usually require dosages >2 mg/kg/day to achieve optimal clinical response [62, 121].

In patients who respond to anakinra, it remains a challenge to decide when to taper and/or stop treatment. Also in this context, validated biomarkers for disease activity to help guide treatment decisions are needed [122].

Patients who fail to respond to a first bDMARD or several biologic treatments deserve a case-by-case discussion with an expert team. These patients may respond to a second, third or fourth bDMARD, and a significant proportion of them may eventually achieve inactive disease, in most cases on anti-IL-1 or -IL-6 treatment [69]. Moreover initial experiences with IL-18 inhibition have been reported [123]. MTX, which is not the first-choice DMARD for Still's disease [124], is often combined with a bDMARD in patients with no active systemic features but persistent arthritis. It should be considered, however, that the only randomized trial of MTX in sJIA failed to show significant improvement over placebo [124]. Some difficult-to-treat patients deserve more experimental approaches, such as thalidomide, which requires special attention regarding the risks for thrombosis, peripheral neuropathy and teratogenicity [125, 126] or Janus kinase inhibitors [127]. In a few cases, intensive immunosuppression followed by either autologous [128] or, to minimize the risk of relapse, allogeneic haematopoietic stem cell transplantation may be considered as a last resort to control the disease [129].

We conclude that there is a strong scientific rationale for considering Still's disease as a single entity, regardless of the age of onset, and thereby also call for a harmonization of paediatric and adult classification. Further, a harmonization of the response criteria would aid the evaluation and comparison of different treatment options. Abundant information in the scientific literature support the use of targeted therapy with anakinra for treating Still's disease since it provides the possibility of avoiding or minimizing treatment with GCs and allows for improved clinical outcome, with some data supporting very favourable outcome if treatment is initiated early in the disease course.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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