Anakinra in children and adults with Still’s disease

Sebastiaan J. Vastert1,*, Yvan Jamilloux2,*, Pierre Quartier3,4,*, Sven Ohlman5, Lisa Osterling Koskinen5, Torbjörn Kullenberg5, Karin Franck-Larsson5, Bruno Fautrel6,* and Fabrizio de Benedetti7,*

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...
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-signaling 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
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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 (≤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 >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 | 9 (7 F/2 M) | 8.4 (4.8) | 4.6 (3.8) | Yes | 78 (7) | 44 (4) | 100 (9) |
| Gattorno et al. 2008 | 22 (11 F/11 M) | 10.3 (4.60) | 3.4 (0.3-10.9) | NR | 55 (12) | 41 (9) | 100 (22) |
| Lequerre et al. 2008 **[63]** | 20 (12 F/8 M) | 12.4 (5.2) | 7.0 (4) | Yes | 95 (19) | 70 (14) | 100 (20) |
| Vastert et al. 2014 | 20 (7 F/13 M) | 7.9 (1.1-15.3) | Newly diagnosed | Yes | 100 (12) | 100 (12) | 100 (12) |
| Kearsley-Fleet et al. 2018 | 22 (15 F/7 M) | Median 6 (IQR 2-13) | Newly diagnosed | Yes | 100 (12) | 100 (12) | 100 (12) |
| ter Haar et al. 2019 **[65]** | 42 (17 F/25 M) | Median 7.1 (IQR 3.9-11.8) | Newy diagnosed | Yes | 100 (12) | 100 (12) | 100 (12) |
| Retrospective uncontrolled studies | | | | | | | |
| Ohlsson et al. 2008 | 7 | Median 8.5 (IQR 5.2-15) | NR | Yes | 86 (6) | 57 (4) | 100 (7) |
| Nigrovic et al. 2011 | 46 (27 F/19 M) | Median 7.6 (IQR 0.75-15.7) | Median 82.4 days (IQR 44-172.5) | NR | 0 | 0 | 67 (31) |
| Pardeo et al. 2015 | 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 | 51 (27 F/24 M) | Median 3.6 (IQR 2.3-8.8) | Median 31.0 months (IQR 9.3-59.1) | NR | 31.4 (16) | 0 | 100 (51) |
| Rossi-Semerano et al. 2015 | 26 | NR | NR | NR | NR | NR | NR |
| Vitale et al. 2016 | 57 treatment courses | NR | NR | NR | NR | NR | NR |
| Saccomanno et al. 2019 | 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 | 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 | NR | 100 (10) |
| Prospective uncontrolled studies | | | | | | | |
| Lequerre et al. 2008 **[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 | 8 (7 F/1 M) | 42 (26-66) | 5.7 (3.7) | Yes | 100 (8) | 75 (6) | 100 (8) |
| Laskari et al. 2011 **[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                          |
| Illou et al. 2013 [77]             | 10                 | NR                                               | NR                                            | Yes                              | NR        | 89 (25)       | 82 (23)                     | 100 (28)                   |
| 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. 2015a [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 0.04-46.4)   | 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. 2016b [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)                                        | 50.33 months (81.67)                          | Yes                              | 75.8 (91) | 20.7 (20)     | 97.8 (137)                 |
| Vercruysse et al. 2019 [35]        | 15                 | NR                                               | Median 1.5 months (IQR 0-14)                  | Yesa                             | NR        | 93 (14)/NR    |                             |

aBased on individual data in publication. bStudy appearing twice in this table. cAnakinra as first-line disease-modifying treatment. dThe study describes 20 patients also included in Vastert et al. 2014 [64]. eAt disease onset. fAt diagnosis. gAll 25 patients were adults but 4 had juvenile onset. hA 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         |
| Lequerre et al. 2008[^63]           | 20                 | 35                        | 6 months                   | ≥ACR50                 |
| Gattorno et al. 2008 [37]           | 22[^5]             | 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                   | ≥ACR50[^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[^70]     | 26                 | 42 (11)                   | Median treatment duration ~17 months | CID                    |
| Pardee et al. 2015 [68]             | 25                 | 56 (14)                   | 6 months                   | CID                    |
| Woener et al. 2015[^69]             | 51                 | 51 (26)                   | At last follow-up (>6 months)| CID                    |
| Vitale et al. 2016[^71]             | 57[^9]             | 88 (50)                   | NR                         | Similar to CID         |
| Kearsley-Fleet et al. 2016[^65]     | 22                 | 25                        | 12 months                  | CID                    |
| ter Haar et al. 2019[^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[^9] | 446[^9]       |                           |                            |                        |

**Still’s disease—adult onset**

| Study                               | Number of patients | Complete responders, % (n) | Time of response            | Definition of response |
|-------------------------------------|--------------------|---------------------------|----------------------------|------------------------|
| Lequerre et al. 2008[^63]           | 15                 | 67 (10)                   | 6 months                   | ≥ACR50                 |
| 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[^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[^70]     | 35                 | 54 (19)                   | Median treatment duration ~15 months | Similar to CID         |
| Sfriso et al. 2016[^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[^81]             | 78                 | 78 (61)                   | NR                        | Similar to CID         |
| Colafrancesco et al. 2017 [82]      | 140                | 81 (114[^i])              | 12 months                  | Unclear                |
| Vercruysse et al. 2019 [35]         | 15                 | 87 (13)                   | NR                        | Unclear                |
| Total number of anakinra-treated patients[^9] | 444[^9]       |                           |                            |                        |

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. Study appears twice in this table. One patient could not be classified in terms of response. Ilowite et al. [61] reports only ≥ACR30 response. Woener 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. Kearsey-Fleet et al. [65] report patients with JIA 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). The study describes 20 patients also included in Vastert et al. [64]. The total number of anakinra-treated patients from the publications is an overestimate since some patients are reported in more than one publication. There is an expected overlap of patients reported in Lequerre et al. [63] and Giampietro et al. [78]. Laskari et al. [75] report that the response was maintained in all but one patient until the latest follow-up (≤12 m). There is an expected overlap of patients reported in Sfriso et al. [81] and Vitale et al. [71]. Including both paediatric and adult patients with JIA diagnosis in Vitale et al. [71]. 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. 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) |
|--------------------------------------------|-------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------|-------------------------------------------------|
| **Still’s disease—paediatric onset**       |                               |                                                                                                                |                                               |                                                 |
| Pascual et al. 2005 [1]                    | 9                             | 9a (100)/NR                                                   | NR                                            | 6/9 (67)b                                      | 3/9 (33)                                      |
| Lequerre et al. 2008 [63]                  | 20                            | 20 (100)/mean 0.50                                            | 9/20 (45)                                     | 10/20 (50)                                    | 0                                           |
| Gattorno et al. 2008 [37]                  | 22                            | 22 (100)/mean 0.79                                            | NR                                            | NR                                             | 3/9 (33)                                      |
| Ohlsson et al. 2008 [66]                   | 7                             | 7 (100)/median 1                                              | ≥3 (≤43)a                                      | ≤3/7 (≤43)a                                    | ≥4/7 (≥57)a                                   |
| Quartier et al. 2011 [82]                  | 22                            | 22 (100)/mean 0.59                                            | 15/22 (68)                                    | NR; mean 0.15a                                 | ≥4/7 (≥57)a                                   |
| Ngovic et al. 2011 [67]                    | 46                            | 31 (67)/mean 0.67                                            | NR                                            | 4/14 (29)a                                    | 6/22 (≥27)                                   |
| Pardeo et al. 2015 [68]                    | 25                            | 14 (56)/median 0.9                                           | NR                                            | NR                                             | 0                                           |
| Saccomanno et al. 2019 [72]                | 62                            | 61 (98)/median 0.5                                            | NR                                            | NR; median 0 in responders and non-respondersa | ≥31/61 (≥51)d                                 |
| **Still’s disease—adult onset**            |                               |                                                                                                                |                                               |                                                 |
| Lequerre et al. 2008 [63]                  | 15                            | 12 (80)/mean 26.8 mg                                         | NR                                            | ≥8/12 (≥67)b                                   | 1/12 (8)                                     |
| Naumann et al. 2010 [74]                   | 8                             | 8 (100)/mean 61.9                                            | NR                                            | 8 (100)b                                      | 2/12 (17)b                                   |
| Nordstrom et al. 2012 [73]                 | 12                            | 12 (100)/mean 22.5                                           | NR; mean dose 10.8 mg reduced                | NR                                             | 0                                           |
| Giampietro et al. 2013 [78]                | 28                            | 28 (100)/mean 34.4                                           | 15/28 (54)                                    | NR                                             | 3/12 (25)                                    |
| Iliou et al. 2013 [77]                     | 10                            | 10 (100)                                                     | NR                                            | NR                                             | ≥9/12 (≥75)b                                  |
| Cavalli et al. 2015 [79]                   | 16                            | 15/16 (94)/mean 21.5                                         | NR                                            | 6/11 (65)b                                    | 5/11 (45)b                                   |
| Dall’Ara et al. 2016 [80]                  | 13a                          | 9/9 (100)/median 25a                                          | NR                                            | 4/9 (44)b                                      | 5/9 (56)b                                    |
| Colafrancesco et al. 2017 [82]             | 140                           | 137 (98)/mean 77.6                                           | NR; mean 5.2                                   | NR; mean 3.4                                   | 34/109 (31)                                  |
| Verbrugse et al. 2019 [35]                 | 15                            | 15 (100) / NR                                                | NR                                            | NR                                             | 0                                           |

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. Two patients stopped GC treatment at the initiation of anakinra (Fig. 4 in the publication). At last follow-up after 2–12 months. aAt last follow-up. Based on the median (range) reported in the publication. At month 12. 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. bAt last follow-up after 1.6–7.3 years. cAt last follow-up after 1-27 months. dAt last follow-up after 6-48 months. Not known if the patients that stopped at week 24 also had been able to stop GCs. Detailed information on GC usage is only available for patients treated with only anakinra. 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.

References

1. Pascual V, Allantaz F, Arce E, Punaro M, Banchereau J. Role of interleukin-1 (IL-1) in the pathogenesis of systemic onset juvenile idiopathic arthritis and clinical response to IL-1 blockade. J Exp Med 2005;201:1479-86.
2. Nirmala N, Brachat A, Feist E et al. Gene-expression analysis of adult-onset Still’s disease and systemic juvenile idiopathic arthritis is consistent with a continuum of a single disease entity. Pediatr Rheumatol Online J 2015;13:50.
3. Kudela H, Drynda S, Lux A, Horneff G, Kekow J. Comparative study of Interleukin-18 (IL-18) serum levels in adult onset Still’s disease (AOSD) and systemic onset juvenile idiopathic arthritis (sJIA) and its use as a biomarker for diagnosis and evaluation of disease activity. BMC Rheumatol 2019;3:4.
4. Cabane J, Michon A, Ziza JM et al. Comparison of long term evolution of adult onset and juvenile onset Still’s disease, both followed up for more than 10 years. Ann Rheum Dis 1990;49:283-5.
5. Tanaka S, Matsumoto Y, Oinushi H et al. [Comparison of clinical features of childhood and adult onset Still’s disease]. Rymuachi 1991;31:511-8.
6. Uppal SS, Pande IR, Kumar A et al. Adult onset Still’s disease in northern India: comparison with juvenile onset Still’s disease. Br J Rheumatol 1995;34:429-34.
7. Luthi F, Zufferey P, Hofer MF, So AK. “Adolescent-onset Still’s disease”: characteristics and outcome in comparison with adult-onset Still’s disease. Clin Exp Rheumatol 2002;20:427–30.
8. Pay S, Turkcapar N, Kalyoncu M et al. A multicenter study of patients with adult-onset Still’s disease compared with systemic juvenile idiopathic arthritis. Clin Rheumatol 2006;25:639–44.
9. Mellins ED, Macaubas C, Grom AA. Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions. Nat Rev Rheumatol 2011;7:416–26.
10. Lee JY, Hsu CK, Liu MF, Chao SC. Evanescent and persistent pruritic eruptions of adult-onset still disease: a clinical and pathologic study of 36 patients. Semin Arthritis Rheum 2012;42:317–26.
11. Gerfaud-Valentin M, Jamilloux Y, Iwaz J, Seve P. Adult-onset Still’s disease. Autoimmun Rev 2014;13:708–22.
12. Jamilloux Y, Gerfaud-Valentin M, Martinon F et al. Pathogenesis of adult-onset Still’s disease: new insights from the juvenile counterpart. Immunol Res 2015;61:53–62.
13. Krozosk S, Benck U, van der Woude FJ, Braun C. Disseminated intravascular coagulation, perimyocarditis and bilateral pleural empyema in adult Still’s disease. Dtsch Med Wochenschr 2004;129:2535–7.
14. Hot A, Toh ML, Coppel B et al. Reactive hemophagocytic syndrome in adult-onset Still’s disease: clinical features and long-term outcome: a case-control study of 8 patients. Medicine (Baltimore) 2010;89:37–46.
15. Gurion R, Lehman TJ, Moorthy LN. Systemic arthritis in children: a review of clinical presentation and treatment. Int J Inflam 2012;2012:271569.
16. Fautrel B, Borget C, Rozenberg S et al. Corticosteroid sparing effect of low dose methotrexate treatment in adult Still’s disease. J Rheumatol 1999;26:373–8.
17. Kotter I, Wacker A, Koch S et al. Anakinra in patients with treatment-resistant adult-onset Still’s disease: four case reports with serial cytokine measurements and a review of the literature. Semin Arthritis Rheum 2007;37:189–97.
18. Raffine B, Botsios C, Dinarello C et al. Adult-onset Still’s disease with myocarditis successfully treated with the interleukin-1 receptor antagonist anakinra. Joint Bone Spine 2011;78:100–1.
19. Hoshino T, Ohta A, Yang D et al. Elevated serum interleukin 6, interferon-gamma, and tumor necrosis factor-alpha levels in patients with adult Still’s disease. J Rheumatol 1998;25:396–8.
20. Kinert EU SPC. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000363/WC500042310.pdf (March 2019, date last accessed).
21. Kinert EU US Prescribing Information. http://www.kineretrx.com/pdf/Full-Prescribing-Information-English.pdf (March 2019, date last accessed).
22. Kinert EU Product Monograph. https://sobi-northamerica.com/sites/sobi-northamerica.com/files/2018-06/Canada.Kinert_PM_EN.pdf(March 2019, date last accessed).
23. Australian Product Information Kinert EU, vA09-0. http://www.guildlink.com.au/gc/ws/ki/pi.cfm?product=fkpkins (March 2019, date last accessed).
24. DeWitt EM, Kimura Y, Beukelman T et al. Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2012;64:1001–10.
25. Kimura Y, DeWitt EM, Beukelman T et al. Adding canakinumab to the Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans for systemic juvenile idiopathic arthritis: comment on the article by DeWitt et al. Arthritis Care Res (Hoboken) 2014;66:1430–1.
26. Ringold S, Weiss PF, Beukelman T et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis.
screening among children receiving biologic medications. Arthritis Rheum 2013;65:2499–512.

27 Pouchot J, Sampalis JS, Beaudet F et al. Adult Still’s disease: manifestations, disease course, and outcome in 62 patients. Medicine (Baltimore) 1991;70:118–36.

28 Hinze CH, Holzinger D, Lainka E et al. Practice and consensus-based strategies in diagnosing and managing systemic juvenile idiopathic arthritis in Germany. Pediatr Rheumatol Online J 2018;16:7.

29 Jamilloux Y, Gerfaud-Valentin M, Henry T, Seve P. et al. Treatment of adult-onset Still’s disease: a review. Ther Clin Risk Manag 2015;11:33–43.

30 Santos MJ, Conde M, Mourao AF et al. 2016 update of the Portuguese recommendations for the use of biological therapies in children and adolescents with juvenile idiopathic arthritis. Acta Reumatol Port 2016;41:194–212.

31 Pouchot J, Arlet JB. Biological treatment in adult-onset Still’s disease. Best Pract Res Clin Rheumatol 2012;26:477–87.

32 ter Haar NM, Dijkhuizen EHP, Swart JF et al. Mechanisms, biomarkers and targets for adult-onset Still’s disease. Nat Rev Rheumatol 2019;doi:10.1002/art.40865.

33 ter Haar NM, Tak T, Mokry M et al. Reversal of sepsis-like features of neutrophils by interleukin-1 blockade in patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheumatol 2018;70:943–56.

34 Feist E, Mitrovic S, Fautrel B. Mechanisms, biomarkers and targets for adult-onset Still’s disease. Nat Rev Rheumatol 2018;14:603–18.

35 Vercruysse F, Barnetche T, Lazaro E et al. Adult-onset Still’s disease biological treatment strategy may depend on the phenotypic dichotomy. Arthritis Res Ther 2019;21:53.

36 Nigrovic PA. Autoimmunity and autoimmunity in systemic juvenile idiopathic arthritis. Proc Natl Acad Sci USA 2015;112:15785–6.

37 Gattorno M, Piccini A, Lasiglie D et al. The pattern of response to anti-interleukin-1 receptor antagonist monotherapy in new-onset systemic juvenile idiopathic arthritis: results from a five year follow-up study. Arthritis Rheumatol 2019;doi:10.1002/art.40865.

38 Gattorno M, Piccini A, Lasiglie D et al. The pattern of response to anti-interleukin-1 receptor antagonist monotherapy in new-onset systemic juvenile idiopathic arthritis. Arthritis Rheumatol 2008;58:1505–15.

39 Ruscitti P, Cipriani P, Di Benedetto P et al. Advances in immunopathogenesis of macrophage activation syndrome during rheumatic inflammatory diseases: toward new therapeutic targets? Expert Rev Clin Immunol 2017;13:1041–7.

40 Vastert S, Prakken B. Update on research and clinical translation on specific clinical areas: from bench to bedside: how insight in immune pathogenesis can lead to precision medicine of severe juvenile idiopathic arthritis. Best Pract Res Clin Rheumatol 2014;28:229–46.

41 Ombrello MJ, Arthur VL, Remmers EF et al. Genetic architecture distinguishes systemic juvenile idiopathic arthritis from other forms of juvenile idiopathic arthritis: clinical and therapeutic implications. Ann Rheum Dis 2017;76:906–13.

42 Martini A, Ravelli A, Avic T et al. Toward new classification criteria for juvenile idiopathic arthritis: first steps, pediatric rheumatology international trials organization international consensus. J Rheumatol 2019;46:190–7.

43 Yamaguchi M, Ohta A, Tsunematsu T et al. Preliminary criteria for classification of adult Still’s disease. J Rheumatol 1992;19:424–30.

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

45 Gohar F, Kessel C, Lavric M, Holzinger D, Foell D. Review of biomarkers in systemic juvenile idiopathic arthritis: helpful tools or just playing tricks? Arthritis Res Ther 2016;18:163.

46 de Jager W, Hoppenreis EP, Wulffraat NM et al. Blood and synovial fluid cytokine signatures in patients with juvenile idiopathic arthritis: a cross-sectional study. Ann Rheum Dis 2007;66:589–98.

47 van den Ham HJ, de Jager W, Bijlsma JW, Prakken BJ, de Boer RJ. Differential cytokine profiles in juvenile idiopathic arthritis subtypes revealed by cluster analysis. Rheumatology (Oxford) 2009;48:899–905.

48 Kim HA, Han JH, Kim WJ et al. TLR4 endogenous ligand S100A8/A9 levels in adult-onset Still’s disease and their association with disease activity and clinical manifestations. Int J Mol Sci 2016;17:1342.

49 Maeno N, Takei S, Nomura Y et al. Highly elevated serum levels of interleukin-18 in systemic juvenile idiopathic arthritis but not in other juvenile idiopathic arthritis subtypes or in Kawasaki disease: comment on the article by Kawashima et al. Arthritis Rheum 2003;49:2539–41; author reply 41–2.

50 Chen DY, Lan JL, Lin FH, Hsieh TY. Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset Still’s disease. J Rheumatol 2004;31:2189–98.

51 Put K, Avau A, Brisse E et al. Cytokines in systemic juvenile idiopathic arthritis and haemophagocytic lymphohistiocytosis: tipping the balance between interleukin-18 and interferon-gamma. Rheumatology (Oxford) 2015;54:1507–17.

52 de Benedetti F, Massa M, Robbioni P et al. Correlation of serum interleukin-6 levels with joint involvement and thrombocytosis in systemic juvenile rheumatoid arthritis. Arthritis Rheum 1991;34:1158–63.

53 De Benedetti F, Massa M, Pignatti P et al. Serum soluble interleukin 6 (IL-6) receptor and IL-6/soluble IL-6 receptor complex in systemic juvenile rheumatoid arthritis. J Clin Invest 1994;93:2114–9.

54 Gerfaud-Valentin M, Maucort-Boulch D, Hot A et al. Adult-onset still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. Medicine (Baltimore) 2014;93:91–9.

55 Uziel Y, Pomeranz A, Brik R et al. Seasonal variation in systemic onset juvenile rheumatoid arthritis in Israel. J Rheumatol 1999;26:1187–9.

56 Fautrel B. Adult-onset Still disease. Best Pract Res Clin Rheumatol 2008;22:773–92.
57. Woo P. Systemic juvenile idiopathic arthritis: diagnosis, management, and outcome. Nat Clin Pract Rheumatol 2006;2:22–34.

58. Guzman J, Oen K, Tucker LB et al. The outcomes of juvenile idiopathic arthritis in children managed with contemporary treatments: results from the ReACCh-Out cohort. Ann Rheum Dis 2015;74:1854–60.

59. Nigrovic PA, Raychaudhuri S, Thompson SD. Review: genetics and the classification of arthritis in adults and children. Arthritis Rheumatol 2018;70:7–17.

60. Hinks A, Bowes J, Cobb J et al. Fine-mapping the MHC locus in juvenile idiopathic arthritis (JIA) reveals genetic heterogeneity corresponding to distinct adult inflammatory arthritis diseases. Ann Rheum Dis 2017;76:765–72.

61. Ilozite N, Porras O, Reiff A et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. Clin Rheumatol 2009;28:129–37.

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

63. Lequerre T, Quartier P, Rosellini D et al. Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. Ann Rheum Dis 2008;67:302–8.

64. Vastert SJ de Jager W, Noordman BJ et al. Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. Arthritis Rheumatol 2014;66:1034–43.

65. Kearsley-Fleet L, Beresford MW, Davies R et al. Short-term outcomes in patients with systemic juvenile idiopathic arthritis treated with either tocilizumab or anakinra. Rheumatology (Oxford) 2018;

66. Ohlsson V, Baildam E, Foster H et al. Anakinra treatment for systemic onset juvenile idiopathic arthritis (SOJIA). Rheumatology (Oxford) 2009;47:535–6.

67. Nigrovic PA, Mannion M, Prince FH et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum 2011;63:545–55.

68. Pardeo M, Pires Marafon D, Insalaco A et al. Anakinra in systemic juvenile idiopathic arthritis: a single-center experience. J Rheumatol 2015;42:1523–7.

69. Woerner A, Uettwiller F, Melki I et al. Biological treatment in systemic juvenile idiopathic arthritis: achievement of inactive disease or clinical remission on a first, second or third biological agent. RMD Open 2015;1:e000036.

70. Rossi-Semerano L, Fautrel B, Wendling D et al. Tolerance and efficacy of off-label anti-interleukin-1 treatments in France: a nationwide survey. Orphanet J Rare Dis 2015;10:19.

71. Vitale A, Insalaco A, Sfriso P et al. A snapshot on the on-label and off-label use of the interleukin-1 inhibitors in Italy among rheumatologists and pediatric rheumatologists: a nationwide multi-center retrospective observational study. Front Pharmacol 2016;7:380.

72. Saccomanno B, Toldati J, Minoia F et al. Predictors of effectiveness of anakinra in systemic juvenile idiopathic arthritis. J Rheumatol 2019;46:416–21.

73. Nordstrom D, Knight A, Luukkainen R et al. Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still’s disease. An open, randomized, multicenter study. J Rheumatol 2012;39:2008–11.

74. Naumann L, Feist E, Natusch A et al. IL1-receptor antagonist anakinra provides long-lasting efficacy in the treatment of refractory adult-onset Still’s disease. Ann Rheum Dis 2010;69:466–7.

75. Laskari K, Tzioufas AG, Moutsopoulos HM. Efficacy and long-term follow-up of IL-1R inhibitor anakinra in adults with Still’s disease: a case-series study. Arthritis Res Ther 2011;13:R91.

76. Riera E, Olive A, Narvaez J et al. Adult onset Still’s disease: review of 41 cases. Clin Exp Rheumatol 2011;29:331–6.

77. Ilou C, Papagoras C, Tsifetaki N, Voulgari PV, Drosos AA. Adult-onset Still’s disease: clinical, serological and therapeutic considerations. Clin Exp Rheumatol 2013;31:47–52.

78. Giampietro C, Ridene M, Lequerre T et al. Anakinra in adult-onset Still’s disease: long-term treatment in patients resistant to conventional therapy. Arthritis Care Res (Hoboken) 2013;65:822–6.

79. Cavalli G, Franchini S, Aiello P et al. Efficacy and safety of biological agents in adult-onset Still’s disease. Scand J Rheumatol 2015;44:309–14.

80. Dalli’Ara F, Frassi M, Tincani A, Airo P. A retrospective study of patients with adult-onset Still’s disease: is peri-carditis a possible predictor for biological disease-modifying anti-rheumatic drugs need? Clin Rheumatol 2016;35:2117–23.

81. Sfriso P, Priori R, Valesini G et al. Adult-onset Still’s disease: an Italian multicentre retrospective observational study of manifestations and treatments in 245 patients. Clin Rheumatol 2016;35:1683–9.

82. Colafrancesco S, Priori R, Valesini G et al. Response to interleukin-1 inhibitors in 140 Italian patients with adult-onset Still’s disease: a multicentre retrospective observational study. Front Pharmacol 2017;8:369.

83. Wallace CA, Giannini EH, Huang B et al. American College of Rheumatology provisional criteria for defining clinical inactive disease in select categories of juvenile idiopathic arthritis. Arthritis Care Res (Hoboken) 2011;63:929–36.

84. Wallace CA, Ruperto N, Giannini E et al.; Childhood Arthritis and Rheumatology Research Alliance; Pediatric Rheumatology International Trials Organization; Pediatric Rheumatology Collaborative Study Group. Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. J Rheumatol 2004;31:2290–4.

85. Giannini EH, Ruperto N, Raveli A et al. Preliminary definition of improvement in juvenile chronic
arthritis patients treated with methotrexate. Ann Rheum Dis 1998;57:38–41.

87 Felson DT, Anderson JJ, Boers M et al. The American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. Arthritis Rheum 1993;36:729–40.

88 Bowyer SL, Roettcher PA, Higgins GC et al. Health status of patients with juvenile rheumatoid arthritis at 1 and 5 years after diagnosis. J Rheumatol 2003;30:394–400.

89 Packham JC, Hall MA. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: functional outcome. Rheumatology (Oxford) 2002;41:1428–35.

90 Mushtaq T, Ahmed SF. The impact of corticosteroids on growth and bone health. Arch Dis Child 2002;87:93–6.

91 Simon D, Fernando C, Czernichow P, Prieur AM. Linear growth and final height in patients with systemic juvenile idiopathic arthritis treated with longterm glucocorticoids. J Rheumatol 2002;29:1296–300.

92 Kondo T, Amano K. Era of steroid sparing in the management of immune-mediated inflammatory diseases. Immunol Med 2018;41:6–11.

93 Bresnihan B, Alvaro-Gracia JM, Cobby M et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. Arthritis Rheum 1998;41:2196–204.

94 Cohen S, Hurd E, Cush J et al. Treatment of rheumatoid arthritis with anakinra, a recombinant human interleukin-1 receptor antagonist, in combination with methotrexate: results of a twenty-four-week, multicenter, randomized, double-blind, placebo-controlled trial. Arthritis Rheum 2002;46:614–24.

95 Cohen SB, Moreland LW, Cush J et al. A multicentre, double blind, randomised, placebo controlled trial of anakinra (Kineret), a recombinant interleukin 1 receptor antagonist, in patients with rheumatoid arthritis treated with background methotrexate. Ann Rheum Dis 2004;63:1062–8.

96 Mertens M, Singh JA. Anakinra for rheumatoid arthritis: a systematic review. J Rheumatol 2009;36:1118–25.

97 den Broeder AA, de Jong E, Fransen MJ et al. Observational study on efficacy, safety, and drug survival of anakinra in rheumatoid arthritis patients in clinical practice. Ann Rheum Dis 2006;65:760–2.

98 Goldbach-Mansky R, Dailey NJ, Canna SW et al. Neonatal-onset multisystem inflammatory disease responsive to interleukin-1β inhibition. N Engl J Med 2006;355:581–92.

99 Kullenberg T, Lofqvist M, Leinonen M, Goldbach-Mansky R, Olivcrona H. Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes. Rheumatology (Oxford) 2016;55:1499–506.

100 Fisher CJ Jr, Dhainaut JF, Opal SM et al. Recombinant human interleukin 1 receptor antagonist in the treatment of patients with sepsis syndrome. Results from a randomized, double-blind, placebo-controlled trial. Phase III rhIL-1ra Sepsis Syndrome Study Group. JAMA 1994;271:1836–43.

101 Fisher CJ Jr, Slotman GJ, Opal SM et al. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. Crit Care Med 1994;22:12–21.

102 Miettunen PM, Narendran A, Jayanthan A, Behrens EM, Cron RQ. Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: case series with 12 patients. Rheumatology (Oxford) 2011;50:417–9.

103 Lovell DJ, Giannini EH, Reiff AO et al. Long-term safety and efficacy of rilonacept in patients with systemic juvenile idiopathic arthritis. Arthritis Rheum 2013;65:2486–96.

104 Feist E, Quartier P, Fautrel B et al. Efficacy and safety of canakinumab in patients with Still’s disease: exposure-response analysis of pooled systemic juvenile idiopathic arthritis data by age groups. Clin Exp Rheumatol 2018;36:668–75.

105 Ruperto N, Brunner HI, Quartier P et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med 2012;367:2396–406.

106 Ruperto N, Brunner HI, Quartier P et al. Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: results from the 5-year long-term extension of the phase III pivotal trials. Ann Rheum Dis 2018;77:1710–9.

107 Ruperto N, Quartier P, Wulffraat N et al. A phase II, multicenter, open-label study evaluating dosing and preliminary safety and efficacy of canakinumab in systemic juvenile idiopathic arthritis with active systemic features. Arthritis Rheum 2012;64:557–67.

108 Mitrovic S, Fautrel B. Complications of adult-onset Still’s disease and their management. Expert Rev Clin Immunol 2018;14:351–65.

109 Quinn MA, Emery P. Potential for altering rheumatoid arthritis outcome. Rheum Dis Clin North Am 2005;31:763–72.

110 Combe B, Landewe R, Daein CI et al. 2016 update of the EULAR recommendations for the management of early arthritis. Ann Rheum Dis 2017;76:948–59.

111 Smolen JS, Landewe R, Bijlsma J et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017;76:960–77.

112 van Nies JA, Tsonaka R, Gaujoux-Viala C, Fautrel B, van der Helm-van Mil AH. Evaluating relationships between symptom duration and persistence of rheumatoid arthritis: does a window of opportunity exist? Results on the Leiden early arthritis clinic and ESPOIR cohorts. Ann Rheum Dis 2015;74:806–12.

113 Nigrovic PA. Review: is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? Arthritis Rheumatol 2014;66:1405–13.

114 Filière de Santé des Maladies Auto-Immunes et Auto-Inflammatoires Rares (FAI2R). Protocole National de Diagnostic et de Soins PNDS 2017: Maladie de STILL de l’adulte et de la forme systémique de l’Arthrite Juvénile Idiopathique ayant évolué jusqu’à l’âge adulte. 2017. https://www.has-sante.fr/portail/jcms/c_2867360/fr/maladie-de-still-de-l-adulte (February 2019, date last accessed).
115 Fantini F, Gerloni V,Gattinara M et al. Remission in juvenile chronic arthritis: a cohort study of 683 consecutive cases with a mean 10 year followup. J Rheumatol 2003;30:579-84.

116 Lomater C, Gerloni V, Gattinara M et al. Systemic onset juvenile idiopathic arthritis: a retrospective study of 80 consecutive patients followed for 10 years. J Rheumatol 2000;27:491-6.

117 Singh-Grewal D, Schneider R, Bayer N, Feldman BM. Predictors of disease course and remission in systemic juvenile idiopathic arthritis: significance of early clinical and laboratory features. Arthritis Rheum 2006;54:1595–601.

118 Russo RA, Katsicas MM. Patients with very early-onset systemic juvenile idiopathic arthritis exhibit more inflammatory features and a worse outcome. J Rheumatol 2013;40:329–34.

119 Svantesson H, Akesson A, Eberhardt K, Elborgh R. Prognosis in juvenile rheumatoid arthritis with systemic onset. A follow-up study. Scand J Rheumatol 1983;12:139–44.

120 Schaller J, Wedgwood RJ. Juvenile rheumatoid arthritis: a review. Pediatrics 1972;50:940–53.

121 Urien S, Bardin C, Bader-Meunier B et al. Anakinra pharmacokinetics in children and adolescents with systemic-onset juvenile idiopathic arthritis and autoinflammatory syndromes. BMC Pharmacol Toxicol 2013;14:40.

122 van Loosdregt J, van Wijk F, Prakken B, Vastert B. Update on research and clinical translation on specific clinical areas from biology to bedside: unpacking the mysteries of juvenile idiopathic arthritis pathogenesis. Best Pract Res Clin Rheumatol 2017;31:460–75.

123 Gabay C, Fautrel B, Rech J et al. Open-label, multicentre, dose-escalating phase II clinical trial on the safety and efficacy of tadeking alfa (IL-18BP) in adult-onset Still’s disease. Ann Rheum Dis 2018;77:840–7.

124 Woo P, Southwood TR, Prieur AM et al. Randomized, placebo-controlled, crossover trial of low-dose oral methotrexate in children with extended oligoarticular or systemic arthritis. Arthritis Rheum 2000;43:1849–57.

125 Lehman TJ. Thalidomide for rheumatic disease: the best of both worlds? Nat Clin Pract Rheumatol 2007;3:308–9.

126 Lehman TJ, Schechter SJ, Sundel RP et al. Thalidomide for severe systemic onset juvenile rheumatoid arthritis: a multicenter study. J Pediatr 2004;145:856–7.

127 Ladhari C, Jorgensen C, Pers YM. Treatment of refractory adult onset Still’s disease with combination anakinra and baricitinib therapy. Rheumatology (Oxford) 2019;58:736–7.

128 Brinkman DM, de Kleer IM, ten Cate R et al. Autologous stem cell transplantation in children with severe progressive systemic or polyarticular juvenile idiopathic arthritis: long-term follow-up of a prospective clinical trial. Arthritis Rheum 2007;56:2410–21.

129 Silva JMF, Ladomenou F, Carpenter B et al. Allogeneic hematopoietic stem cell transplantation for severe, refractory juvenile idiopathic arthritis. Blood Adv 2018;2:777–86.