

The treatment of adult-onset Still's disease with anakinra, a recombinant human IL-1 receptor antagonist: a systematic review of the literature

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ABSTRACT

Adult-onset Still's disease (AOSD) is a rare, inflammatory disease of unknown aetiology, generally affecting young adults and requiring immunosuppressive treatment. In the last few years, biologic disease-modifying anti-rheumatic drugs (bDMARDs) have been successfully used in refractory cases, based on the pathogenic role of inflammatory cytokines in AOSD. Amongst bDMARDs, several observations confirmed the clinical usefulness of anakinra, a recombinant human non-glycosylated IL-1 receptor antagonist, in AOSD. At present, the treatment is still largely empirical and due to the possible fallacious aspects of clinical judgement, in this work, we performed a systematic review of literature (SRL) to summarise the evidence regarding the treatment with anakinra in AOSD, analysing rate of complete remission, corticosteroids (CCSs)-sparing effect, long-term retention rate, and safety. After screening titles, abstracts and analysis of full text, 15 manuscripts were analysed: 1 open randomised multicentre trial with two parallel groups and 14 observational single-arm retrospective studies. Collectively, results of the present SRL suggest the effectiveness of anakinra in the treatment of patients with AOSD. Furthermore, patients with AOSD are likely to achieve a good clinical response with anakinra and these outcomes are associated with a largely favourable safety profile. Furthermore, the majority of patients treated with anakinra may achieve a complete remission, also in monotherapy. Finally, the treatment with anakinra is associated with an important CCSs-sparing effect, and, a large percentage of these patients may stop CCSs, thus reducing predictable

long-term CCSs side effects without the occurrence of new flares.

Introduction

Adult-onset Still's disease (AOSD) is a rare, inflammatory disease of unknown aetiology, affecting young adults, typically characterised by high spiking fevers, arthritis, evanescent salmon-pink rash and multi-visceral involvement (1). According to clinical course, different clinical patterns of AOSD are recognised: i. 30% of patients may evolve toward a monocyclic pattern, characterised by a single episode; ii. 30% a polycyclic pattern, associated with multiple flares, alternating with remissions; iii. 40% a chronic pattern, related to a persistently active disease with polyarthritis (2, 3). Furthermore, patients with AOSD may develop severe complications, mainly macrophage activation syndrome (MAS), burdened by a high mortality rate (4, 5). The treatment of AOSD remains largely empirical, with recommendations mainly obtained from retrospective observational studies (6, 7). Non-steroidal anti-inflammatory drugs (NSAIDs) are rarely effective in controlling the disease, and systemic corticosteroids (CCSs) are, thus, frequently employed (7, 8). In spite of prompt effects, even within a few hours, dependence on CCSs is frequently observed, with flare recurrence during tapering or following discontinuation. Additionally, CCSs expose patients to serious side effects over the long-term, such as osteoporosis and metabolic abnormalities (9). Consequently, different synthetic disease-modifying anti-rheumatic drugs (sDMARDs) have been proposed, like methotrexate (MTX) and cyclosporine A, with controversial results on effec-

tive management of AOSD (10, 11). In fact, a large percentage of patients, treated by these therapies, may experience multiple flares evolving toward a chronic disease course and up to 16% of patients die during the follow up, due to complications of AOSD (12, 13). In the last years, biologic DMARDs (bDMARDs) have been successfully used in refractory cases (14), based on the well-known pathogenic role of inflammatory cytokines in AOSD (15).

Specifically, the activity of IL-1 β has been linked to the pathogenesis of systemic inflammatory diseases characterised by recurrent fevers, leucocytosis, and elevated acute-phase proteins, due to the rapid and sustained resolution of systemic and local inflammation that is observed upon inhibition of IL-1 (16-18). The clinical and molecular analogies of AOSD with these diseases, especially with systemic-onset juvenile idiopathic arthritis (SJIA) (19), provides the rationale of inhibiting IL-1 in these patients (20). Anakinra is a recombinant human non-glycosylated IL-1 receptor antagonist blocking the binding of both IL-1 α and IL-1 β . Several observations showed its efficacy in patients with AOSD refractory to other therapies (6, 7, 14, 21). But so far, several unmet needs concerning the treatment of AOSD as well as the definition of refractory patients and clinical outcomes still need to be fully clarified and many decisions are based on physician clinical judgement, own personal experience and patient's perspective. However, with the rise of modern research methodology, the fallacious aspects of clinical judgement have been increasingly emphasised and due to these limits, in this work, we performed a systematic review of available literature to summarise the evidence regarding the treatment with anakinra in AOSD.

Objectives and methods

Aims of the project

We designed a systematic search of available literature with regard to the use of anakinra in patients with AOSD, assessing i. rate of complete remission; ii. CCSs-sparing effect; iii. long-term retention rate; iv. safety.

Search design

A scientific committee composed by expert rheumatologists (RG and LC) and bibliographic fellows (PR and JS) established research questions, temporal limits, online databases, and methodology to be applied to the systematic literature review. Medline via PubMed, Web of Science, and Cochrane library were searched up to 30th April 2019.

Search strategy

The search strategy combined indexed and free-text terms for AOSD, interventions and outcomes of interest in Medline via PubMed, Web of Science, and Cochrane library. The main search was conducted in Medline via Pubmed using the following string of research terms: (“adult onset Still’s disease” OR “adult onset stills disease” OR “adult onset Still disease” OR “Still’s disease” or “stills disease” or “still disease” or “Still’s Disease, Adult-Onset” OR “adult onset Still*”) AND (“anakinra” OR “Interleukin 1 Receptor Antagonist Protein” OR “Kineret”). The search strategy was updated to be fitted with Web of Science and Cochrane Library. Furthermore, the main keywords were used in different combinations in order to improve the sensitivity of the search strategy. The bibliography of relevant articles was also hand-searched for other possible suitable studies.

Eligibility criteria

To be included in the systematic review of literature (SRL), studies had to meet the following inclusion criteria: study design: randomised controlled trial, observational cohort studies or case series recruiting ≥ 6 patients, as reported in previous meta-analysis (14); population: studies enrolling patients with AOSD; intervention: anakinra; comparison: assessment of the rate of response after a minimum follow-up > 4 weeks (since the majority of studies was characterised by a single arm); outcome: i. complete remission; ii. CCSs-sparing effect; iii. long-term retention rate; iv. safety. Complete remission was defined according to pre-specified definition explicitly defined before the study entry. CCSs-sparing effect was defined as the ability of anakinra to re-

duce and/or discontinue the intake of systemic CCSs. The drug retention rate (DRR) was defined as the proportion of patients maintaining the therapy with anakinra in the long-term. Safety endpoints included the count of all reported adverse events (AEs), the number of patients with treatment-related AEs either systemic or local and serious AEs, defined according to WHO International Classification for Patients Safety. Briefly, a serious AE was defined as an AE responsible for any fatal event, life-threatening event, prolonged hospitalisation, persistent or marked disability or incapacity, or was considered as an important medical event. Additionally, infections were considered serious if they met criteria for a serious AE or required intravenous antibiotics.

One fellow (PR) independently screened titles and abstracts of retrieved records for inclusion in the systematic review, as shown in Figure 1. Concerning limitations, only full-text versions published in English language were considered. Congress abstracts, reviews, editorials, case reports and pre-clinical studies were excluded for the purpose of this work. Manuscripts, retrieved by literature search, reporting insufficient data according to selected PICO strategy were also excluded from the review.

Study identification and data extraction

After screening and selection, data extraction was performed by fellows (PR and JS) and independently verified by expert rheumatologists (RG and LC). In the studies, in which patients underwent sequential treatment with bDMARDs, the treatment category was codified considering the bDMARD to which the patient was exposed for a longer period. Finally, the results of the analysis of literature was summarised and presented to an expanded working group with other authors (CC, SC, LD, DI, FI, GL, and PS) and further inputs were evaluated. Conflicting results were analysed by discussion until reaching an agreement in the working group.

Quality assessment

Quality assessment was performed by two independent reviewers (RG and

PR) using the Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group proposed by the National Heart, Lung, and Blood Institute - US Department of Health & Human Services (<https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiopvascular-risk-reduction/tools/before-after>). After scoring each item an overall rate (good, fair or poor) was assigned by each reviewer. Disagreements among the reviewers were resolved by discussion with a until reaching a final consensus.

Reporting method

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines was followed for preparing the present manuscript [<http://www.prisma-statement.org/>].

Results

Results from the analysis of databases

As detailed in Figure 1, the analysis of databases retrieved 347 manuscripts (Medline via Pubmed: n. 152; Web of Science: n. 188; Cochrane Library: n. 7); after screening titles and abstracts (removing duplicates, preclinical studies, manuscripts with not English language, congress abstracts, letters to the editor without original data, case reports, reviews, manuscripts with wrong population, manuscripts out of topic), 23 manuscripts were assessed for eligibility by analysis of full-texts and 15 manuscripts were, finally, included in the SRL. Amongst selected manuscripts, 1 open randomised multicentre trial with two parallel groups (22) and 14 observational single-arm retrospective studies (23-36) were retrieved. The overall rate of evidence retrieved by SRL is poor due to the majority of single-arm poor quality studies.

The rate of complete pre-specified remission following anakinra was investigated in 13 manuscripts (22-34), whereas its CCSs-sparing effect in 9 manuscripts (22-29, 32, 35), as shown in Table I. The DRR of anakinra in AOSD was evaluated in 1 study (36). Finally, AEs and serious AEs, following anakinra, were assessed in the 12 manuscripts (22-24, 26-33, 35, 36).

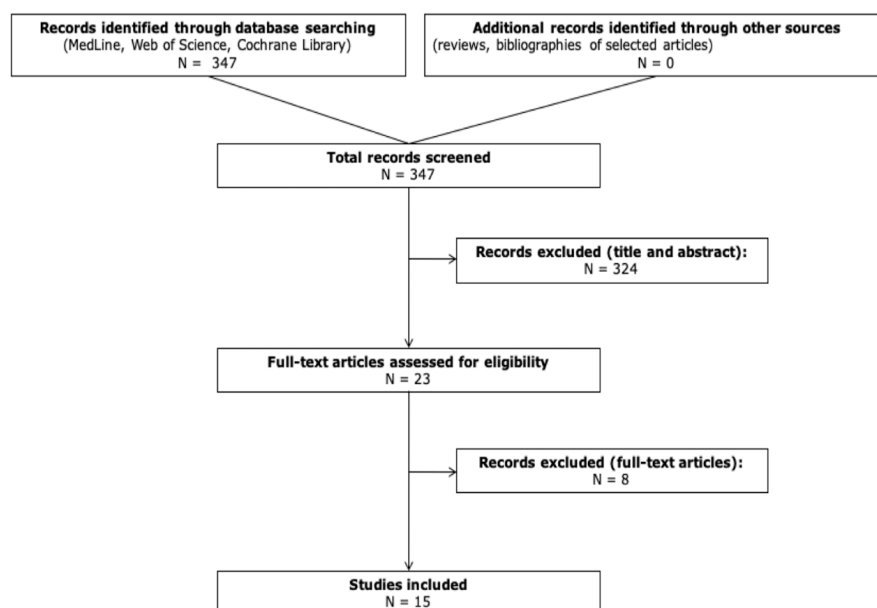


Fig. 1. The process of studies selection. The analysis of databases retrieved 347 manuscripts; after screening titles and abstracts, 23 manuscripts were assessed for eligibility by analysis of full-texts and 15 manuscripts were included in the SRL.

Assessing remission, CCSs-sparing effect, and safety of anakinra in a clinical trial on AOSD

In a randomised multicentre trial (22), the efficacy of anakinra *versus* sDMARD in refractory patients with AOSD, affected by active disease despite the therapy with prednisolone ≥ 10 mg/day with or without concomitant sDMARD, was assessed in a 24-week study. The primary endpoint was the achievement of remission after 8 weeks, defined as disappearance of fever ($\leq 37^{\circ}\text{C}$ body temperature) in the absence of NSAIDs 24 hours before to measurement, normalisation of CRP and ferritin, and no swollen and tender joint. In the study, 22 patients were enrolled and randomised to anakinra [n=12; females 6; mean age (SD): 39 years (18); median disease duration (range): 14 months (2–240)] or sDMARD [n=10; females 5; mean age (SD): 39 (17); median disease duration (range): 19 (3–204)]. Analysing the results, after 8 and 24 weeks, 7 out of 12 and 6 out of 12 receiving anakinra and 5 out of 10 and 2 out of 10 receiving sDMARDs achieved the primary endpoint, respectively. During an open-label extension (OLE) of 28 weeks, 7 out of 14 patients treated with anakinra and 2 out of 3 patients treated with sDMARDs maintained the remission. In both groups of patients, by week

24, dosages of CCSs were significantly reduced by mean 10.8 and 10.5 mg, respectively, and 3 patients treated with anakinra discontinued CCSs, compared with none of patients treated with sDMARDs. Finally, assessing the safety, 3 patients experienced serious AEs, including the worsening of AOSD due to lack of efficacy, 1 on anakinra and in 2 on sDMARDs. Seven patients out of 12 receiving anakinra reported injection site reactions (ISRs), although no of them withdrew from the study because this AE (22).

Assessing remission in observational studies of anakinra on AOSD

The effectiveness of anakinra was investigated in a retrospective French study (23), in which the complete clinical response was defined as the resolution of systemic symptoms and an improvement of ACR score by 70%. Patients [n=15; females 11; mean age (SD): 38.1 years (12.8); mean disease duration (SD): 7.8 years (6.4)] were evaluated during a mean follow-up (range) of 17.5 (11–27) months. Concerning the effectiveness, 11 patients responded to anakinra: 9 out of 11 patients achieved a complete response at 3 months; 10 out of 11 patients, at 6 months; and 9 out of 11 patients, at the last follow-up (23). The long-term effectiveness of anakinra

Table I. Rate of complete remission and CCSs-sparing effect after treatment with anakinra in AOSD.

First Author	Year	Type of Study	Classificative criteria	Number of patients	Complete remission	Type of CCS	Daily Dosage Pre*	Daily Dosage Post*	Percentage of CCSs discontinuation n (%)
Lequerre T. (23)	2008	Retrospective study	Yamaguchi	15	11 (60%)	Prednisone/Prednisolone	26.8±20.1 mg	8.6±7.6 mg	2 (18%)
Laskari K. (26)	2011	Retrospective study	Yamaguchi	25	20 (80%)	Methylprednisolone	18 (0-48) mg	0 (0-8) mg	12 (48%)
Iliou C. (31)	2012	Retrospective study	Yamaguchi, Fautrel, Cush	10	10 (100%)	NR	NR	NR	NR
Giampietro C. (24)	2013	Retrospective study	Yamaguchi, Fautrel	28	16 (57%)	Prednisone	34.4±21.9 mg	9.7±7.9 mg	NR
Ortiz-Sanjuan F. (35)	2015	Retrospective study	Yamaguchi	41	NR	Prednisone	20 (11.3-47.5) mg	5 (0-10) mg	NR
Gerfaund-Valentin V. (30)	2014	Retrospective study	Yamaguchi	6	5 (83%)	NR	NR	NR	NR
Cavalli G. (27)	2015	Retrospective study	Yamaguchi	16	14 (87%)	Prednisone	22.34±18.40 mg	2.50±2.89 mg	7 (43%)
Rossi-Semeraro L. (32)	2016	Retrospective study	NR	35	19 (54%)	NR	NR	NR	NR
Vitale A. (32)	2016	Retrospective study	NR	78	61 (78%)	NR	NR	NR	NR
Sfriso P. (34)	2016	Retrospective study	Yamaguchi	35	26 (74%)	NR	NR	NR	NR
Dall'Ara F. (29)	2016	Retrospective study	Yamaguchi	11	11 (100%)	Prednisone	30.45±21.35 mg	1.81±2.26 mg	5 (55%)
Colafrancesco S. (28)	2017	Retrospective study	Yamaguchi	140	114 (81.5%)	Prednisone	77.6±86.3 mg	3.4±4.8 mg	43 (44%)
Vercruysee F. (25)	2019	Retrospective study	Yamaguchi, Fautrel	15	13 (86.7%)	NR	NR	NR	5 (33.3%)

*data are reported as mean ± SD or median (range) according to the results reported in each study of daily intake of CCSs. CCSs: corticosteroids; NR: not reported; AOSD: Adult-onset Still's disease; SD: standard deviation.

inra was assessed in a further French retrospective study, defining the remission as the disappearance of all clinical and laboratory features (24). The study included patients [n=28; females 19; mean age (SD): 40.3 years (11.8); mean disease duration (SD): 9.3 years (5.7)] who were followed-up for a mean of 23 months. All patients were refractory to NSAIDs, CCSs, and sDMARDs. Fourteen failed to 1 or more bDMARDs (11 etanercept, 9 infliximab, 3 adalimumab, and 2 rituximab). All patients responded to anakinra and, at the last follow-up, 16 patients were still being treated with anakinra, 12 were in complete remission. In 3 patients, the complete remission induced the discontinuation of anakinra. Six patients tapered the dosage of anakinra, with sustained remission in 2 and relapse in the others. Furthermore, a dosage reduction and discontinuation of MTX was possible in 3 and 2 patients, respectively, without an observed relapse (24). In a more recent French retrospective study, patients were stratified as having two distinct disease patterns, systemic form or chronic articular form, and remission was considered with the disappearance of all initial symptoms and the normalisation of laboratory abnormalities (25). The study included 15 patients treated with anakinra, 5 as a first-line treatment, 4 as a second-line, 5 as a third-line, and 1 as a fourth-line. Of them, 13 patients achieved the remission at the end of

follow-up. Additionally, the authors reported that the systemic form and the absence of arthritis could be predictive of good response to anakinra (25). The effectiveness of anakinra was also assessed in a retrospective Greek experience (26), in which the remission was defined as the complete disappearance of all disease-related symptoms, except for joint erosion. Patients (n=25; 12 females; median age: 32 years; median disease duration 7 months) were treated with anakinra, 16 in combination therapy, anakinra and sDMARD, and 9 in monotherapy, respectively. In 21 patients, the disease activity resolved completely within a few days (median time 0.2 months), and response was maintained until the last visit in all but one patient. A complete response of all symptoms of the disease occurred subsequently within a median of 3 months in 80% of patients. Comparing monotherapy and combination therapy, no difference was retrieved in good clinical response. During the follow-up [median time (range): 15 months (1.5-71)], in patients achieving the remission, 7 patients spaced infusions and 8 patients discontinued anakinra, without a flare of disease (26). The effectiveness of anakinra in inducing the remission was investigated in a retrospective Italian study (27), in which the remission was defined as the disappearance of articular and systemic manifestations of AOSD with

normalisation of laboratory inflammatory markers, and concomitant reduction of CCSs dosages of at least 50%, from the baseline, for at least 2 months. Anakinra was administered as first-line bDMARD in 16 patients, and was collectively used in all patients (20 treatment courses), considering all the bDMARDs assessed in the study, resulting in 16 out of 20 responses. The response to anakinra was promptly observed, within days of treatment initiation. Analysing the results of the study, assigning the treatment category according to the drug to which the patient was exposed for a longer period, 14 out of 16 patients achieved the complete remission. Anakinra was maintained as monotherapy in 5 patients, 2 patients of them achieved a sustained complete remission leading to the discontinuation of sDMARD. Furthermore, discontinuation or tapering of MTX was reported in 9 patients receiving anakinra. Similarly, cyclosporine A was discontinued in 4 patients receiving anakinra and achieving the remission (27). In a more recent Italian retrospective study (28), response was considered complete, leading to the remission, with the disappearance of all clinical manifestations of disease and normalisation of laboratory inflammatory markers. This is the largest cohort available in literature of patients with AOSD who were treated with anakinra [n=140; 93 females; mean age (SD): 37.4 years

(16.1)]. Concerning the clinical response, anakinra primary and secondary inefficacy, after 12 months of treatment, was 15 out of 140 (10.7%) and 11 out of 140 (7.8%), respectively. At the same time-point, 97 out of 140 patients (69.2%) were still receiving anakinra. Considering the last observation of patients, the authors reported that 69 out of 140 patients (49.3%) were still being treated with anakinra, and 71 (50.7%) had discontinued anakinra, after a mean duration (SD) of treatment of 35.7 (36.1) months. The remission led to the discontinuation of anakinra in 20 out of 71 cases (28.1%). Anakinra was employed as second-line bDMARD in 29 out of 140 (20.7%), in those patients, anakinra showed effectiveness in improving clinical manifestations and in normalising inflammatory laboratory markers. Methotrexate (MTX) was the most frequent sDMARD used before treatment with anakinra [91 out of 140 (75.8%)]. The percentage of patients receiving sDMARDs decreased at the end of follow up (baseline: 85.7% vs end of follow-up: 50.7%). In addition, the clinical response did not differ when patients were stratified and analysed according to age, gender, disease pattern, monotherapy or combination therapy (28).

Finally, the rate of remission of treatment with anakinra was investigated in further studies retrieved by the SRL, non-primarily designed to assess the rate of remission (29-34). In these works, mainly aimed at describing clinical features and prognostic factors, a large percentage of patients treated with anakinra achieved the remission, as shown in Table I.

The CCSs-sparing effect of anakinra in observational studies on AOSD

The CCSs-sparing effect of anakinra was investigated in 9 manuscripts (22-29, 32, 35), included in the present report, as shown in Table I. Of these studies, 8 also investigated the complete remission. The study, which is not included in the previous section, is a retrospective Spanish study [n=41; females 28; mean age (SD): 34.4 years (14)] (35). The authors showed that anakinra led to a rapid clinical re-

Table II. AEs and serious AEs during treatment with anakinra.

First Author	Year	Type of Study	Number of patients	AEs n (%)	Serious AEs n (%)
Lequerre T. (23)	2008	Retrospective study	15	4 (26.7%)	0 (0%)
Laskari K. (26)	2011	Retrospective study	25	12 (48%)	3 (12%)
Iliou C. (31)	2012	Retrospective study	10	NR	0 (0%)
Giampietro C. (24)	2013	Retrospective study	28	2 (7.1%)	0 (0%)
Gerfaund-Valentin V. (30)	2014	Retrospective study	6	1 (16.7%)	0 (0%)
Ortiz-Sanjuan F. (35)	2015	Retrospective study	41	15 (36.6%)	3 (7.3%)
Cavalli G. (27)	2015	Retrospective study	16	4 (25%)	0 (0%)
Rossi-Semeraro L. (32)	2016	Retrospective study	35	NR	3 (8.6%)
Vitale A. (33)	2016	Retrospective study	78	NR	4 (5.1%)
Dall'Ara F. (29)	2016	Retrospective study	13	1	0 (0%)
Colafrancesco S. (28)	2017	Retrospective study	140	44 (31.4%)	3 (2.1%)

AEs: adverse events; NR: not reported; AOSD: Adult-onset Still's disease.

sponse. Paralleling with clinical improvement, a significant CCSs-sparing effect of anakinra was reported when baseline dosages of CCSs were compared with those after 12 months of the study [baseline: median 20 (11.3–47.5) mg vs. end of follow-up: median 5 (0–10) mg] (35). Similarly, in other observational studies (23, 24, 26-29), a significant decrease of CCSs dosage was observed in patients treated with anakinra. Interestingly, it has been reported that a percentage of patients, about 40% (18%–48%), discontinued CCSs without experiencing a flare of disease (22, 23, 25-29).

The long-term retention rate of anakinra in an observational study on AOSD

As far as the DRR of anakinra in AOSD is concerned, we found only 1 study reporting long-term DRR (36). Patients enrolled in the present study are almost overlapping with those previously presented in another retrospective study on efficacy and safety of anakinra in AOSD (28). Patients (48 males, 93 females) were treated with anakinra for a mean period (SD) of 35.9 (36.0) months were enrolled. [n= 141; females 93; mean age (SD): 37.3 (16.9) years] and assessed for DRR. The authors described an overall DRR of 44.6% at 60-month and 30.5% at 120-month assessments, respectively. After excluding patients, who discontinued anakinra due to prolonged remission, anakinra DRR resulted to be 55.2% and 39.5% at 60-month and 120-month assessments, respectively (36).

The safety of anakinra in observational studies on AOSD

The presence of AEs and serious AEs, including mortality were reported in the 12 manuscripts, the majority of selected studies assessing the efficacy (22-24, 26-33, 35, 36). Table III summarises safety profile for the selected studies. AEs were reported in 91 out of 296 patients (30.74%) whereas serious AEs were described in 17 out of 419 patients (4.05%). Table IV details the AEs reported by each study. The majority of AEs consisted in 54 ISRs and 13 generalised skin rashes. The remaining AEs were represented mainly by infections (n= 20), whereas serious infections had been reported in 10 patients: pneumonia (n=7), osteomyelitis of a phalanx (n=1), varicella zoster virus reactivation (n=1), gluteal abscess (n=1). Three patients developed a severe urticarial reaction after the first months of treatment (1 patient at 1.5 months and 2 others at 3 months) (26). Among studies recording serious AEs, 4 cases of death were reported (33).

Discussion

During AOSD, CCSs are largely used as first-line therapy, but so far, around 60% of patients develop a chronic pattern, and a significant percentage of these patients may die for visceral complications of the disease and/or developing MAS. At present, CCSs seem to be able to control only a minority of the patients, thus suggesting the need of additional therapies (37-39). Due to the important pathogenic role of IL-1 β in AOSD (15, 18), in this SRL, we analysed the clinical usefulness of anakin-

Table III. Description of AEs and serious AEs during treatment with anakinra.

First Author	Year	Number of patients	AEs	Serious AEs
Lequerre T. (23)	2008	15	4 infections*	0
Laskari K. (26)	2011	25	5 ISRs, 7 infections**	3 severe urticarial reactions
Iliou C. (31)	2012	10	NR	0
Giampietro C. (24)	2013	28	2 ISRs	0
Gerfaund-Valentin V. (30)	2014	6	1 ISRs	0
Ortiz-Sanjuan F. (35)	2015	41	8 ISRs, 2 urinary tract infections, 1 VZVs, 3 mild leukopenia, 1 myopathy with elevation of muscle enzymes	1 phalanx osteomyelitis, 1 respiratory tract infection by <i>P. Aeruginosa</i> , 1 gluteal muscle abscess
Cavalli G. (27)	2015	16	2 ISRs, 2 VZVs	0
Rossi-Semeraro L. (32)	2016	35	minor ISRs (number not detailed)	1 pneumonia, 1 VZV, 1 MAS and infection
Vitale A. (33)	2016	78	NR	4°
Dall'Ara F. (29)	2016	13	1 cutaneous rash	0
Colafrancesco S. (28)	2017	140	28 ISRs, 12 generalised skin rash, 3 urinary tract infections, 1 dental abscess	3 pneumonia

*1 bronchitis, 1 hepatitis A, 1 VZV, 1 cutaneous infection after a piercing.

**1 tracheobronchitis, 1 H1N1 of upper respiratory tract, 1 gastroenteritis, 1 soft tissues abscess, 3 lower urinary tract infections.

° 2 pneumonia, 1 myocarditis, 1 MAS.

ISRs: injection site reactions; VZV: varicella zoster virus reactivation; MAS: macrophage activation syndrome; NR: not reported; AOSD: Adult-onset Still's disease.

ra, an IL-1 inhibitor, in the treatment of these patients.

Analysing the clinical response, there is evidence that about 75% (50-100%) of patients treated with anakinra with AOSD may achieve remission. A dramatic improvement is usually observed in all disease-related manifestations within the first month of treatment with anakinra, from a few hours after the first injection up to two months of treatment. This is usually followed by normalisation of inflammatory laboratory markers, within the first three months, from one week to two months (23-26). Of importance, in this systematic review of the literature, the analysed data suggest the use of anakinra in order to achieve a good clinical response especially in those patients with a higher risk of mortality characterized by multiple drug resistances and long-term duration. Furthermore, the results did not show any difference in the achievement of remission, between patients treated with or without combination

therapy, highlighting the effectiveness of anakinra as monotherapy. The DRR, defined as the proportion of patients who maintain the same drug in a given time period, is another tool for evaluating effectiveness and safety of specific therapies. The only study investigating long-term anakinra retention rate showed a good overall DRR with an estimated probability of 55% to maintain the treatment in a 5-year period. Interestingly, the authors did not detect significant differences between monotherapy and combination therapy with sDMARDs and between naïve patients to bDMARD and those previously exposed to other bDMARDs (36).

Analysing the data derived from the SJIA, the juvenile counterpart of AOSD, we may observe a high rate of remission by early administration of anakinra, within the first two months of the disease (40, 41). Furthermore, a large percentage of these early-treated patients, achieved a long-term drug-free remission (40, 41). This finding is

likely to suggest the presence of a “window of opportunity”, when it could be possible to modify the natural history of the disease. We may speculate that similarly to the paediatric disease, also in the adult form, an early treatment with anakinra may modify the natural course of the disease. In fact, during the early phases of inflammatory diseases, if appropriate treatment is administered, the acute inflammatory process could be switched off, thus reaching an “immunological remission” and avoiding the development of a chronic inflammatory process (42). In fact, the early intervention with bDMARDs may induce larger and sustained long-term improvements, than delayed administration (43, 44). The early suppression of the inflammatory process by anakinra could induce a significant reduction of the economic burden of the disease, estimated around \$30000 for each hospitalisation (45), and probably also decreasing the indirect costs, which are still not fully evaluated. Due to these elevated costs, searching for the most cost-effective therapeutic strategy is an unmet need. Additionally, when compared with CCSs and sDMARDs, the higher cost of treatment with anakinra would be balanced by the higher rate of expected remission, decreasing the rate of patients developing the chronic pattern of the disease, the recurrence of hospitalisation, and the life-threatening complications (46, 47). In fact, although this outcome was not specifically investigated for the purposes of the present SRL, few cases of MAS were reported in the selected studies when compared with available literature (48-50). In patients with AOSD treated with anakinra, the rate of MAS seems to be different compared with patients with SJIA enrolled in clinical trial and treated by different IL-1 inhibitors including canakinumab, a human monoclonal anti-IL-1 β antibody, and rilonacept, a dimeric fusion protein. Despite a clinical benefit reported in SJIA clinical trials, the occurrence of MAS was higher than in studies with anakinra and mainly reported after infectious episodes (51, 52). Although these data could suggest dissimilar effects on MAS by different IL-1 inhibitors (53, 54), further studies are necessary to entirely clarify this issue.

We also investigated the CCSs-sparing effect of anakinra in AOSD. Although CCSs play a pivotal role in the treatment of AOSD (6-8), CCSs-treated patients experience a significant risk of predictable AEs, such as Cushingoid changes, osteoporosis, glaucoma and metabolic abnormalities, which contribute to the development of atherosclerosis and, consequently, to cardiovascular events (55). The results of the SRL showed a reduction of daily intake CCSs, with the noteworthy consequence of reducing the predictable side effects related to the chronic intake of CCSs, in patients treated with anakinra. Interestingly, a large percentage of these patients, about 40% (18–48%), discontinued CCSs, without occurrence of new flares.

Even though it is well-known that immunosuppressive treatment is associated with the development of AEs (56), such as opportunistic infections, the results of the present systematic literature review showed a favourable safety profile of anakinra. More in detail, among patients experiencing AEs, the most frequent treatment-related AEs was ISRs, followed by generalised skin rash, developed in 59.3% and 14.28% of cases, respectively. Non-cutaneous AEs were mainly represented by infections. In line with previous data suggesting an optimal tuberculosis-safety profile of IL-1 inhibitors in different rheumatologic conditions (57), no cases of tuberculosis reactivation were reported. The 4 recorded deaths were related to the poor clinical conditions and co-existing comorbidities more than a direct consequence of treatment with anakinra, confirming data showing that AOSD is characterised by a high mortality rate, especially in case of multi-organ involvement (12, 49). Furthermore, no malignancies were reported in the patients treated with anakinra, as previously suggested (58).

The results of the present systematic literature review are affected by different limitations, mainly related to the poor methodological quality of the included studies. The retrospective studies provide less reliable results than possible randomised controlled trials, specifically designed and powered to assess

the efficacy. On the other hand, we have to take into account that AOSD is a rare disease and organising a randomised clinical trial is quite challenging. Furthermore, since it was not clearly specified in texts, the analysis of overlapping cohorts of patients could not be entirely excluded. Moreover, considering the low quality of the retrieved evidence, there was a very low possibility of manuscripts with negative results, thus our findings could be burdened by a publication bias. This would be a common concern when dealing rare disease, like AOSD, that we tried to mitigate by a comprehensive review of available literature and by reporting our findings according to PRISMA guidelines. In addition, unfortunately, validated scores of disease activity, definitions of refractory patients as well as of remission, are still missing and each study used individual and empirical definitions of these features. Thus, we codified the complete remission according to the definitions reported in each study, and for this reason, the results should be cautiously generalised. Furthermore, in selected manuscripts, although the assessment of patients achieving the remission was reported at the end of follow-up, the time needed to reach the remission and the time of remission maintenance could not be fully derived, although the clinical relevance of these features. Taking together all these issues, future studies, specifically designed and adequately powered, are needed to entirely elucidate the role of anakinra in the management of AOSD, further stratifying the therapeutic strategy according to the different clinical expressions and the effectiveness over time.

Conclusions

In conclusion, after the first observation of an IL-1 inhibitor in SJIA (59), multiple lines of evidence suggest the efficacy of IL-1 inhibition in AOSD and the results of the present SRL suggest the clinical usefulness of anakinra in the treatment of those patients. We observed that patients with AOSD are likely to achieve a clinical response with anakinra and these results are associated with a largely favourable safety profile. There is evidence that about

75% of patients treated with anakinra may achieve a complete remission, also in monotherapy. Furthermore, the treatment with anakinra is associated with a CCSs-sparing effect, and, it is noteworthy, that about 40% of these patients may completely discontinue CCSs, without the occurrence of new flares. Further properly designed studies, using standardised efficacy and safety endpoints and assessing also the dosage and schedule of anakinra, are warranted to shed light in this emerging topic.

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