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Expert consensus on the treatment of patients with adult-onset still's disease with the goal of achieving an early and long-term remission

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ABSTRACT

We performed a comprehensive systematic targeted literature review and used the Delphi method to formulate expert consensus statements to guide the treatment of adult-onset Still's disease (AOSD) to achieve an early and long-term remission. Seven candidate statements were generated and reached consensus in the first round of voting by the panel of experts. We postulate: (i) In patients with AOSD with predominant arthritis at onset who achieved no disease control with glucocorticoids (GCs), the use of methotrexate can be considered, whereas the use of cyclosporin A and low-dose GCs should not (Statements 1–3); (ii) In patients with AOSD with poor prognostic factors at diagnosis, an IL-1 inhibitor (IL-1i) in addition to GCs should be taken into consideration as early as possible (Statement 4); (iii) A switch to an IL-6 inhibitor (IL-6i) may be considered in patients with AOSD with prevalent joint involvement, who are unresponsive or intolerant to IL-1i (Statement 5); (iv) Drug tapering or discontinuation may be considered in patients who achieved a sustained clinical and laboratory remission with IL-1i (Statement 6); (v) In patients with AOSD who failed to attain a good clinical response with an IL-1i, switching to an IL-6i may be considered in alternative to a different IL-1i. TNF-inhibitors may be considered as a further choice in patients with a prominent joint involvement (Statement 7). These statements will help clinicians in treatment decision making in patients with AOSD.

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1. Introduction

Adult-onset Still's disease (AOSD) is a rare systemic auto-inflammatory disorder of unknown aetiology with an estimated prevalence of 0.16–0.4/100,000 [1]. The disease affects multiple organs and systems and has a variable clinical presentation [1]. The most prevalent clinical signs and symptoms include high spiking fever, arthritis, and transient salmon pink maculopapular rash. Other clinical features encountered comprise sore throat, hepatomegaly, splenomegaly, lymphadenopathy and serositis [2]. Several life-threatening complications may occur in AOSD such as disseminated intravascular coagulation and reactive haemophagocytic syndrome (including macrophage activation syndrome (MAS) [3]), alone or with acute respiratory distress syndrome, myocarditis, liver failure, or less frequently thrombotic thrombocytopenic purpura, haemolytic uraemic syndrome, aseptic meningoencephalitis, neuropathy and status epilepticus [4].

To-date, the diagnosis of AOSD still remains difficult, which can lead to diagnostic delays even of several years [5]. The differential diagnosis of AOSD requires the exclusion of infections, cancer, other rheumatologic disorders, and adverse drug reactions [6,7]. The disease is categorised into three patterns of natural history including monocyclic disease course, polycyclic disease course with flares and remissions, or persistently active chronic disease course. Moreover, systemic and chronic articular disease phenotypes may exist [2]. Given the substantial overlap of clinical manifestations, laboratory features, response to treatment and, possibly, genetic background, AOSD and systemic juvenile idiopathic arthritis (SJIA) may be considered a disease continuum [8].

Similarly to the lack of reliable diagnostic criteria, with the exception of the Japanese recommendations [9], there are no international evidence-based guidelines to inform therapeutic approaches and the treatment for AOSD is empirical [2,5]. Because of the rarity of the disease and for ethical reasons, prospective randomised double-blind clinical trials in AOSD are difficult to perform. Hence, most evidence comes from case reports, case series and relatively small observational studies.

First line treatment option consists of glucocorticoids (GCs). Nonsteroidal anti-inflammatory drugs (NSAIDs), e.g., indomethacin, are used in the diagnostic phase and rarely elicit clinical response, whereas GCs at the dose of 0.5–1 mg/kg induce clinical response in ~60% of patients [2]. High dose GCs (> 40 mg, daily) seem to be more effective at inducing remission and result in less relapses than lower doses; the clinical response to GCs can be rapid. GC tapering should start 4–6 weeks later, when clinical signs and laboratory results improve. However, up to 45% of patients become GC dependent [2].

Conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs) usually constitute the second line of treatment with methotrexate (MTX) being most commonly administered to patients with AOSD [2]. It was reported that MTX intake may lower the need for GC in patients with GC dependency, an effect known as "steroid sparing" [10]. In cases who fail to respond to MTX, other csDMARDs can be considered [2]. For example, cyclosporin A (CyA) has also been used in few studies, usually in more severe patients [11,12].

Biological DMARDs have been increasingly given to patients with disease refractory to GC and MTX. They mostly include anti-interleukin (IL)-1, -IL-6, −tumour necrosis factor (TNF) α, thus targeting some molecules that have been implicated in the pathogenesis of AOSD [13]. More recently, treatment with anti-interferon (IFN)- γ or Janus kinase inhibitors has been proposed but is rarely used [5]. Achieving remission is an important therapeutic target as one study showed that male sex, diagnosis delayed by >6 months, failure to achieve remission after initial treatment, and wrist/elbow arthritis were related to a chronic disease course [14].

We performed a systematic targeted literature review with the scope of formulating expert consensus statements using the Delphi method to guide the treatment of AOSD to achieve an early and long-term remission.

2. Materials and methods

2.1. Study design

In December 2021, the authors (i.e., the Scientific Board), major Italian experts of AOSD, decided to elaborate an expert consensus on the treatment of AOSD using the mini estimate-discuss-estimate (EDE) Delphi method.

The kick-off meeting, held in May 2022, aimed at identifying the clinical questions for the bibliographic research (to be performed with the use of PICO approach) through an interactive discussion between the members of the scientific board. The members of the scientific board, together with a small group of experts of systematic literature reviews (responsible for gathering the bibliography necessary for the preparation of the statements), and a Delphi methodologist participated in the meeting. Between May and October 2022, the members of the Scientific Board worked independently on the formulation of the statements.

During the second meeting of the Scientific Board in October 2022, statements relating to the therapeutic approach to AOSD were finalised on the basis of selected bibliography. In preparation for this meeting, each member of the Scientific Board provided their proposal for the statements to the methodologist, who harmonised the statements for discussion during the meeting. The Scientific Board also established a minimum acceptable level of consensus needed for the approval of each statement.

In November–December 2022, the statements were delivered electronically to a pool of 47 Italian experts (i.e., the Expert Panel) of the AOSD, who voted anonymously to express their level of agreement with the proposed statements. Supporting literature was provided. All statements reached the consensus so a second round of voting was not necessary.

During the final meeting in January 2023, the results of the survey were presented and discussed by the Scientific Board members. Project's timeline is shown in Fig. 1.

2.1.1. Voting system

Expert Panel members were asked to express their level of agreement/disagreement with candidate statements on a scale from 1 to 9 (where scores 1–3 were considered a disagreement, scores 4–6 – neither an agreement nor a disagreement, and scores 7–9 – an agreement). Expert Panel Members were asked to add a brief comment to support the score given. A statement had to achieve a median score of 7 or more for the consensus to be reached. In the case of a lack of consensus on a given statement, the wording of that statement was modified and voted again.

2.2. Literature search

Seven PICO literature searches were performed using the PICO framework as detailed in the Supplementary Material. Medline via PubMed, Embase and Cochrane databases were interrogated. Prisma diagram is shown in Fig. 2.

3. Results

The consensus was met for all statements upon first voting and is shown in Table 1.

In the successive sections of the results, each statement will be discussed in detail in the light of the available literature.

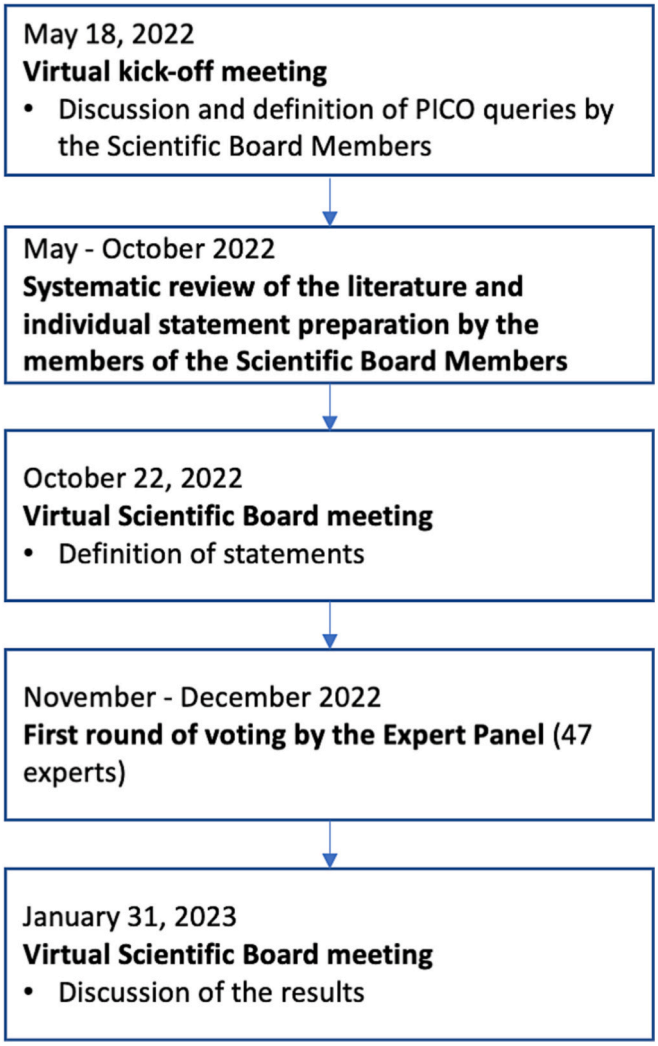

Fig. 1. Project timeline.

3.1. AOSD with predominant arthritis at onset not controllable by glucocorticoids alone (Statement 1: In AOSD patients with predominant arthritis at onset who have not achieved disease control with GC alone, the addition of methotrexate (MTX) may be taken into consideration (as an alternative to GC alone), to increase response rate and achieve GC sparing effects)

Statement 1 refers to the management of patients with AOSD at presentation with predominant arthritis who failed to respond to GC alone. In such cases, the available literature supports the notion that MTX at the dose of 7.5–17.5 mg/week may be considered.

Of the 46 abstracts screened, five relevant case series were selected [15–19]. None of the series conducted a direct comparison between GC and GC + MTX; MTX was given to patients who were refractory to GCs in four series [15–18].

According to the literature, systemic GC therapy led to remission in approximately 65% of patients, showing greater efficacy in resolving systemic symptoms. The majority of patients with AOSD were treated with at least one csDMARD, with MTX being the most commonly used. MTX was found to be effective for disease control in systemic and chronic articular AOSD, particularly in 40–70% of patients with steroid dependent AOSD. Zeng et al. were the first to add MTX to GC. Sixty-one patients with AOSD were treated with prednisone (49%) or methylprednisone (44.3%). MTX was used as add-on treatment in 77% of patients; however, no outcome data were reported in this study [19]. A year later, Franchini et al. reported retrospective data on 45 patients with AOSD treated with GCs and MTX. Prednisone was given in 56 efficacy trials at the dose of 0.5 to 1.7 mg/kg. MTX was additionally given in 22 efficacy trials at the dose of 25 mg/week. An "efficacy trial" was defined as a therapeutic regimen unchanged for at least 1 month in a given patient. The response rate obtained with prednisone alone was 35% and 78% for patients with chronic articular disease and systemic disease, respectively; for MTX, the same numbers equalled 64% and 88%, respectively. Although no direct comparison was performed between prednisone alone and prednisone + MTX, lower effectiveness of prednisone alone was observed in patients with chronic articular disease [16]. Similarly, Riera at al prescribed MTX as an add-on therapy in 20/41 (49%) of patients treated with prednisone at a dose of 0.5–1 mg/kg because of lack of response to GCs (mainly in patients with articular disease) or to reduce its dose. The response rate of 37.5% for CG alone and 65% for MTX was seen [18]. Kim et al., instead, treated 92.5% of their 54 patients with GC monotherapy (prednisone at the dose of 0.5–1 mg/kg) and prescribed add-on MTX in 27/54 (50%) of them. GC requirements were lower in patients treated with MTX; however, seven patients were refractory to treatment with MTX. Eighty % of patients treated with MTX had poor prognostic factors [17]. Most recently, Arcila Duran reported a series of 24 patients with AOSD. Twenty-three patients (96%) were treated with GC; MTX was given as an add-on in 13/24 (54%) because of a partial response to GC; however, no outcome data are provided [15].

The statement received a median score of 8 from the Expert Panel.

3.2. AOSD with systemic manifestations at onset (Statement 2: In AOSD patients with systemic manifestations at onset, CyA in addition to GC should not be taken into consideration (as an alternative to GC alone), to allow a clinical response)

Statement 2 refers to the management of AOSD with systemic manifestations at onset. In such cases, the available literature does not support the use of CyA.

Out of 56 abstracts screened, four relevant case series were selected [16,18,20,21]. None of the series provided a direct comparison between GC and GC + CyA. In three of them, CyA was given to patients who were refractory to GC in monotherapy [16,18,20].

Of the six patients treated by Marchesoni et al., four obtained complete remission and two showed an improvement but no remission. In all six cases, low-dose (< 5 mg/kg/day) CyA was used as an add-on to NSAIDs, GCs or both. Four out of six patients experienced adverse effects related to CyA [20]. In Singh's series, 5/14 patients received CyA, one as a first line monotherapy, one as a first line immunosuppressive treatment, and others as an add-on to GCs in patients who were resistant to MTX of chloroquine. The authors reported improvements in joint symptoms, reduction of ESR and increase of haemoglobin levels in 4/5 patients treated with CyA within 3 months of starting the treatment [21]. In the study by Franchini and colleagues, CyA was an add-on in 12 efficacy trials. The response rate for patients with chronic articular disease and systemic disease in CyA trials was 100% and 70%, respectively; however, the number of patients who responded is unknown [16]. Riera at al used CyA as an add-on to GC monotherapy in one patient who obtained no remission [18].

Statement 2 received a median score of 7 from the Expert Panel.

3.3. AOSD at onset (Statement 3: In patients with AOSD at onset, low dose GC should not be taken into consideration (as an alternative to high dose GC), to achieve clinical remission)

Statement 3 refers to the management of AOSD at onset. In patients with AOSD at onset, the available literature does not support the use of low dose GC.

For the purpose of this statement, we have adopted the definition or low- versus high-dose GC proposed by the First European Workshop on

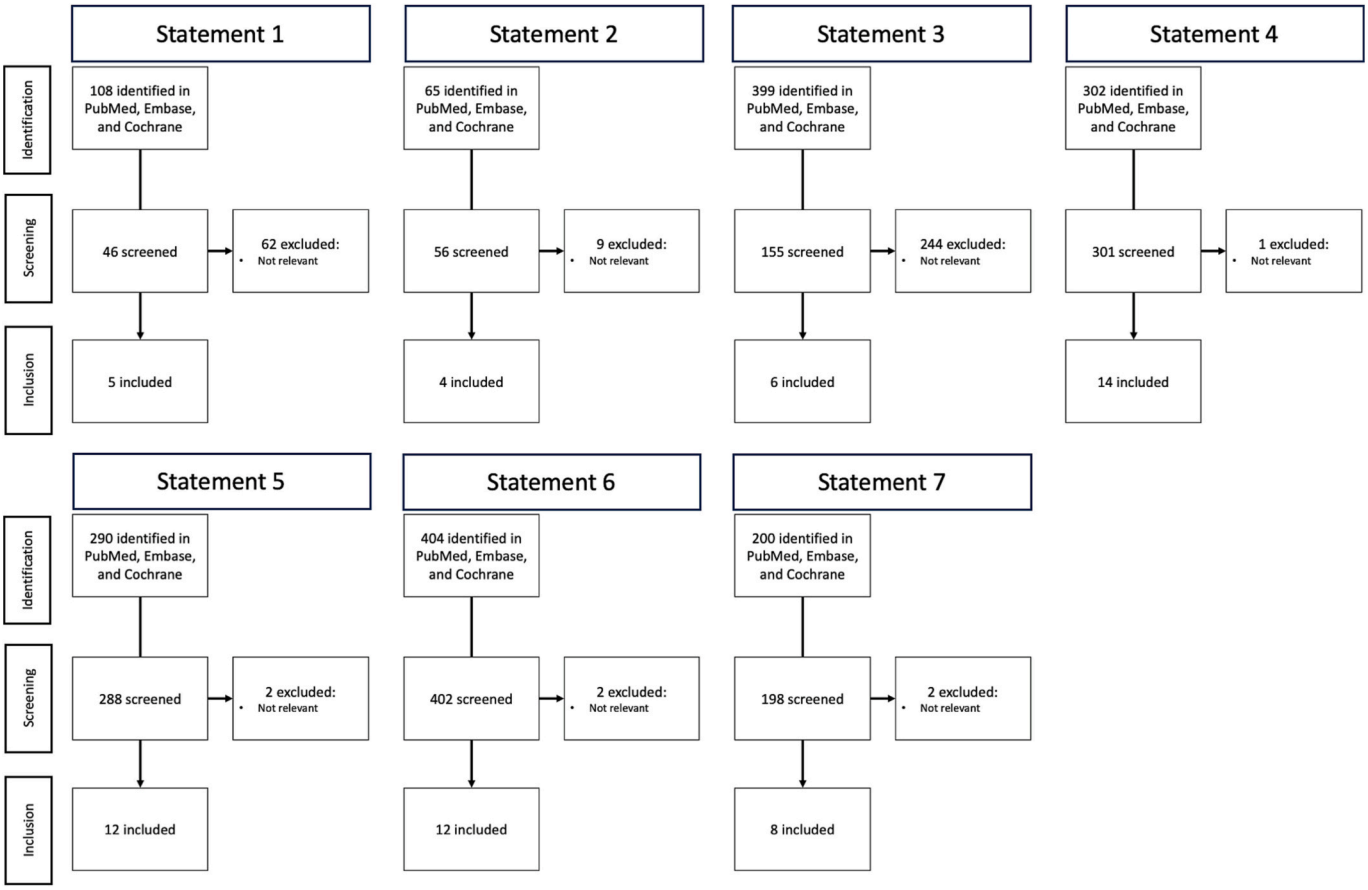

Fig. 2. Prisma diagram for literature searches performed.

Table 1
Consensus statements and agreement level.

Statement	Median vote
1. In AOSD patients with predominant arthritis at onset who have not achieved disease control with GC alone, the addition of MTX may be taken into consideration (as an alternative to GC alone), to increase response rate and achieve GC sparing effects.	8
2. In AOSD patients with systemic manifestations at onset, CyA in addition to GC should not be taken into consideration (as an alternative to GC alone), to allow a clinical response.	7
3. In patients with AOSD at onset, low dose GC should not be taken into consideration (as an alternative to GC high dose), to achieve clinical remission.	7
4. In AOSD patients with poor prognostic factors at onset, IL-1 inhibitors in addition to GC should be taken early into consideration in case of unsatisfactory clinical response (as an alternative to GC alone), to increase response rate and achieve GC sparing effects.	9
5. In AOSD patients with prevalent joint involvement who are unresponsive or intolerant to an IL-1 inhibitor, switching to an IL-6 inhibitor may be taken into consideration (as an alternative to a different IL-1 inhibitor), in terms of increased response/tolerability.	8
6. In AOSD patients failing to attain a good clinical response with an IL-1 inhibitor, switching to an IL-6 inhibitor may be taken into consideration (as an alternative to a different IL-1 inhibitor). TNF-inhibitors may be considered as further choice in patients with a prominent joint involvement.	7
7. In AOSD patients achieving a sustained clinical and laboratory remission with IL-1 inhibitors, a drug tapering/discontinuation may be taken into consideration (as an alternative to unchanging the IL-1 inhibitor schedule), in terms of response maintenance/tolerability improvement.	8

Glucocorticoid Therapy held under the auspices of the EULAR Standing Committee on International Clinical Studies including Therapeutic Trials. In this document, low dose of GC has been defined as $\leq$7.5 mg prednisone equivalent a day, whereas, pulse therapy is described as a dose of $\geq$250 mg prednisone equivalent a day for one or a few days [22].

Of the 155 abstracts screened, six relevant case series in which patients were treated with GCs were selected [15–19,23]. None of the studies treated patients with low-dose GCs and, therefore, provided no data on a comparison between high- and low-dose GCs.

Zeng et al., Franchini et al., Riera et al., Kim et al. and Arcila Duran et al. treated patients with doses of 0.5–1 mg/kg [15,16,18,19]. In Kondo's series, all 71 patients were treated with GCs at onset at a daily dose of 0.82 $\pm$ 0.23 mg/kg and 34 patients received a pulse therapy at week 0. Forty-two patients (59%) responded within 4 weeks, albeit a relapse was encountered in 18/42 (42.8%) of these patients during the follow-up lasting from 4 to 52 weeks. A total of 29/71 (40.8%) of patients had a poor response (relapse or no remission) at 4 weeks and received a second pulse or immunosuppressive drugs. The study provided no comparison between pulse and oral GS therapy [23].

Similarly to Statement 2, Statement 3 received a median score of 7 from the Expert Panel.

3.4. AOSD with poor prognostic factors at onset

(Statement 4: In AOSD patients with poor prognostic factors at onset, IL-1 inhibitors in addition to GC should be taken early into consideration in case of unsatisfactory clinical response (as an alternative to GC alone), to increase response rate and achieve GC sparing effects.)

Statement 4 refers to the management of patients with AOSD with poor prognostic factors at onset. There is evidence that in such patients, inhibitors of IL1 as add-on to GC should be considered early in patients

with an unsatisfactory response to GC alone.

Three aspects of this Statement require an explanation. These: are poor prognostic factors, unsatisfactory clinical response and acting early. Several studies looked at prognostic factors in AOSD. Zeng at al reported that pleuritis, interstitial pneumonia, elevated ferritin levels, and failure of fever to subside after 3 days of prednisolone at 1 mg/kg/day were unfavourable prognostic factors for patients with AOSD [19]. A more recent study of 100 patients by Ruscitti et al. showed a prognostic value of a high systemic score and of the presence of AOSD-related complications (such as AOSD-related MAS, kidney failure requiring dialysis or myocarditis) at the time of diagnosis. A systemic score ≥ 7.0 and AOSD-related complications at onset were significantly associated with mortality [24]. In addition, a systemic score ≥ 7.0 was associated with the occurrence of parenchymal lung disease, another negative prognostic factor in patients with AOSD [25].

Instead, in a large Chinese cohort study that included almost 500 patients with AOSD, age at onset $\geq$50, hepatomegaly, infection, and MAS were prognostic factors for AOSD mortality [26]. Regarding the unsatisfactory clinical response, in AOSD it includes either lack of remission with high-dose GC, i.e., AOSD refractory to GCs, or steroid dependence, i.e., the impossibility to lower the dose because of symptoms or laboratory findings that do not justify the reduction. The word "early" is the key word in this statement and is to be intended as "as soon as possible" as a unique time interval from the disease onset is not reported in the examined studies.

Of the 301 abstracts screened, 14 studies relevant to this issue were selected.

In the refractory disease setting, Lequerre et al. analysed retrospectively 15 patients with AOSD treated with anakinra, an IL-1 inhibitor, and found that 11/15 of them achieved at least a 50% improvement for all disease markers (mean follow-up: 17.5 (11–27) months). Steroids had been stopped in two cases and their dose was decreased by 45% to 95% in 12 patients [27]. Nordstrom et al. randomised patients with refractory AOSD on GC 1:1 to anakinra or csDMARDs (CyA, MTX, azathioprine, sulfasalazine, or leflunomide). Six out of 12 patients randomised to anakinra achieved complete remission compared to 2/10 in the csDMARD patient group. GCs could be reduced in both groups of patients; however, three patients treated with anakinra compared to no patients treated with csMARDs discontinued oral GCs [28]. Similarly, all but one of the 13 patients treated with anakinra due to refractory disease in a Turkish study obtained remission. In all but one GCs were discontinued during the first 6 months of follow-up, whilst two patients died because of active disease [29]. Of note, although treatment with anakinra was associated with rapid and maintained clinical and laboratory improvement in refractory AOSD, joint manifestations seemed to be more refractory than systemic manifestations [30]. Last but not least, anakinra was well tolerated. Campochiaro et al. studied the drug retention rates and reasons for drug discontinuation for anakinra that was given to 41 patients with AOSD concomitantly with GC in all patients and with csDMARDs during some treatment courses. At 24 months, anakinra had a discontinuation rate of 53.1%. The reasons behind stopping the treatment were inefficacy in 24%, adverse events in 10% and other in 2% [31].

Regarding the treatment of patients with AOSD and complications, Lenert et al. showed that patients with MAS may benefit from a triple therapy consisting of GC, CyA and anakinra. In a series of seven patients with MAS and active AOSD treated with systemic GCs, and in addition, anakinra in five patients and CyA in three patients. All seven patients survived and had a better outcome than 48 published cases [32]. The usefulness of anakinra in adult patients with non-malignancy associated secondary haemophagocytic lymphohistiocytosis, of which MAS is a form, was also suggested by Sammut at al who showed that anakinra may be effective in improving the clinical outcomes. In particular, a rapid reduction of ferritin levels was noted [33]. High dose anakinra also was given to a woman with myocarditis that occurred as a complication of AOSD leading to a complete resolution of myocarditis and remission [34].

In an early study of another anti-IL1 drug, all four patients treated with canakinumab reached ACR70 response criteria at 6 and 12 months [35]. In a subsequent real-world experience study, canakinumab was given to nine patients with AOSD. In this study, canakinumab showed prompt and remarkable effectiveness in controlling AOSD activity regardless of the phenotype of the disease (systemic versus chronic articular), with a significant glucocorticoid-sparing effect and an excellent safety profile. [36]. A striking and rapid clinical response (a substantial decrease of modified Pouchot score and a normalisation of acute phase reactants) and a significant steroid sparing effect was observed after 3 months of treatment in another series of 13 patients of which six received canakinumab as first line bDMARD [37]. Similarly, high rates of sustained remission were observed in a large real-life cohort of 50 adult patients with refractory Still's disease treated with canakinumab in Greece. Complete remission was obtained in almost 78% of patients, partial in 20% and only one patient was refractory to this treatment modality [38]. Importantly, real-life data from 15 patients confirmed also that canakinumab was effective both as first-line therapy and after other bDMARDs failure, including in patients who had previously failed IL-1 inhibition through anakinra [37]. Moreover, one study suggested that clinical and therapeutic outcomes with anakinra were independent of whether the treatment was started early (at 6 months) or late (at 12 months) since the disease onset [39].

Statement 4 received a median score of 9 from the Expert Panel.

3.5. AOSD with prevalent joint involvement unresponsive/intolerant to an IL-1 inhibitor (Statement 5: In AOSD patients with prevalent joint involvement who are unresponsive or intolerant to an IL-1 inhibitor, switching to an IL-6 inhibitor may be taken into consideration (as an alternative to a different IL-1 inhibitor), in terms of increased response/tolerability)

Statement 5 refers to the management of patients with AOSD with prevalent joint disease unresponsive or intolerant to IL-1-inhibition. There is evidence that in such patients, inhibitors of IL-6 as an alternative to a different IL-1 inhibitor may be considered to increase response rates and tolerability, although their use in such a scenario remains an off-label approach.

Of the 288 abstracts screened, 12 studies relevant to this subject were selected. Six studies demonstrated the effectiveness of tocilizumab, an anti-IL6 agent, in patients with AOSD who failed conventional and biologic treatments [40–45]. In the Spanish series of 32 patients with refractory AOSD, tocilizumab yielded an early and long-lasting clinical and laboratory improvement, even in cases that were refractory to other biologic agents. Joint manifestations were more refractory to treatment than systemic manifestations and after a median of ~18 months of follow up, joint manifestations disappeared in 80.6% of patients, whilst fever and rash in over 94% [43]. In a Korean study, 90% of the 20 patients with AOSD refractory to conventional therapy and other biologics had a clinical and laboratory improvement following the therapy with tocilizumab [41]. Tocilizumab treatment was linked to rapid and sustained clinical improvement in most patients with refractory AOD and seemed more effective than anakinra in the Palmou et al. multicentre study of 75 patients. Whereas none of the 34 patients treated with tocilizumab had to discontinue treatment due to drug inefficacy, the treatment with anakinra was stopped in 11/41 (26.8%) for this reason. Adverse effects leading to discontinuation were seen in two patients treated with tocilizumab and four with anakinra [44]. In the Israeli experience of 15 patients with AOSD, tocilizumab at 8 mg/kg was extremely efficacious in treating adult patients with refractory AOSD. After 6 months of treatment and at the end of follow-up, the number of tender and swollen joints, the erythrocyte sedimentation rate and CRP levels, as well as the prednisone dosage decreased significantly [40]. The study by Toz et al. suggested that anakinra and tocilizumab seemed to be better treatment choices than TNF-inhibitors in terms of remission rate

and time to remission in patients refractory to conventional treatments. The regression analysis indicated that the use of tocilizumab or anakinra as first biologic was associated with a better response independently of the disease course type (polycyclic versus chronic) [45]. The results of the prospective single-centre, single-arm, cohort, pilot study of tocilizumab as monotherapy in Japan showed that such monotherapy can be an alternative strategy in patients with AOSD [42]. The study enrolled seven patients with AOSD. At month 7, the improvement rate of fever, arthralgia and eruption were 100%, 85.7% and 85.7%, respectively. Two patients discontinued the treatment due to inefficacy or adverse effects, while remaining five completed the treatment and had no symptoms at 7 months. After stopping, 4/5 patients had no flare-up signs for 5 months [42]. In another case series of eight patients with AOSD treated with tocilizumab administered intravenously (6–8 mg/kg every 3–4 weeks) or subcutaneously (162 mg weekly), one patient had a relapse, one had to discontinue due to a serious infection, whilst 5 remained in stable remission [46].

The evidence of the usefulness of anti-IL6 treatment in articular forms of AOSD comes from two studies [47,48]. Based on data from 16 patients, Kougkas et al. suggested that inhibition of TNF and IL-6 with tocilizumab was the preferred option for the chronic articular form. Patients with chronic articular form of the disease remained on bDMARD until the end of the follow up [47]. Similarly, in a multicentre exploratory retrospective study by Vercruysse et al., clinical response depended on disease phenotype. The presence of arthritis and a chronic articular phenotype were associated with a substantial response to tocilizumab with $p = 0.0009$ (OR 36 [2.6–1703]). At the same time, the systemic form and the absence of arthritis were associated with a substantial response to anakinra with $p = 0.0009$ (OR 36 [2.6–1703]) and $p = 0.017$ (OR 10 [1.22–92.6]), respectively [48].

Available metanalyses confirm the results of individual studies [49,50]. A metanalysis of 19 published studies by Ruscitti et al. suggested that patients with AOSD may experience a clinical response and/or a complete remission when treated with biologic drugs including IL-1 and IL-6 inhibitors [49]. Data concerning tocilizumab in an evidence-based review showed that 124/163 (76%) patients pooled from 40 studies that reported on the efficacy and safety of this anti-IL6 molecule achieved remission [50].

Statement 5 received a median score of 8 from the Expert Panel.

3.6. AOSD failing to attain a good clinical response with an IL-1 inhibitor (Statement 6 in AOSD patients failing to attain a good clinical response with an IL-1 inhibitor, switching to an IL-6 inhibitor may be taken into consideration (as an alternative to a different IL-1 inhibitor). TNF-inhibitors may be considered as further choice in patients with a prominent joint involvement)

Statement 6 refers to the management of patients with AOSD who failed to attain a good clinical response with IL-1-inhibition. There is evidence that in such patients, inhibitors of IL-6 as an alternative to a different IL-1 inhibitor may be considered and that in patients with prominent joint involvement, TNF-inhibitors may also be considered as a further choice. It has to be noted that the use of anti-IL-6 and TNF-inhibitors in AOSD is for the time being an off-label approach as mentioned above.

Of the 402 abstracts screened, 12 relevant studies were selected.

In the multicentre retrospective open-label study of 34 patients with AOSD treated with tocilizumab, a rapid and maintained improvement in clinical and laboratory parameters was seen also in patients who were refractory to a previous biological therapy with IL-1 inhibitor, anakinra, but also to other bDMARDs such as etanercept, adalimumab, rituximab, infliximab or abatacept [43]. In another retrospective study of 20 patients, biologic agent first administered was ineffective warranting a switch to a different bDMARD in eight patients, whilst in three of them a third agent was needed. Anakinra was the first-line biologic in 16 patients. Four patients (one with systemic disease and three with chronic articular disease) did not respond to anakinra. Three of them eventually responded to tocilizumab and one responded to adalimumab. Etanercept was ineffective in all four patients who received it as a first-line biologic and in two who received it as a second choice of treatment [51]. In the Italian series, biologics (anakinra in 53.4%, anti-TNFα in 46.6% of patients) were shown to be effective in 48/58 (82.7%) patients from a retrospective cohort of 245 patients with AOSD. Second- and third-line biologics were used in 19 and 5 patients, respectively and included anti-TNFα, anakinra and other therapeutic agents [52].

Both primary and secondary unresponsiveness to anti-IL1 agents have been described. In the multicentre, retrospective observational study, 140 patients with AOSD were treated with anakinra. Primary and secondary inefficacy after 12 months was seen in 15/140 (10.7%) and 11/140 (7.8%) patients, respectively. Four patients were switched to canakinumab. A good response was noted for both biologics at 3 months of treatment [53]. In Vercruysse et al. study, a total of 15 patients were treated with anakinra: five as a first-line treatment, four as a second-line treatment, five as a third-line treatment, and one as a fourth-line treatment. Thirteen (86.7%) patients were responders, whilst the two non-responders received it as a third-line treatment; one of the two later responded to tocilizumab and was able to stop treatment [48]. Ruscitti et al. reported that 32/45 (72.7%) patients in their cohort were treated with bDMARDs due to the inefficacy of the previous therapeutic strategies. The most common first-line bDMARD was anakinra, which was used in 15 (46.9%) patients. Complete remission was achieved in 21 (65.6%) of all patients treated with first-line bDMARD, whereas 11 (34.4%) patients required treatment with a second-line bDMARD and 2 (6.2%) with a third-line bDMARD [54]. In another series of nine patients with AOSD, a switch from anakirna to canakinumab was performed in five patients because of secondary inefficacy (1 case) or adverse effects (3 cases) or disease exacerbation despite long-term use of anakirna. The results suggested that good clinical response can be obtained in this setting [36]. One out of 50 patients from the Laskari cohort had a disease primarily resistant to canakinumab [38]. Inefficacy was one of the reasons of drug discontinuation in the drug retention study by Campochiaro et al. It was the highest for TNF inhibitors (65%) and the lowest for tocilizumab (14%); the discontinuation rate due to inefficacy of anakinra was 24% [31].

Statement 6 received a median score of 7 from the Expert Panel.

3.7. AOSD in sustained clinical and laboratory remission with IL-1 inhibitors (Statement 7: In AOSD patients achieving a sustained clinical and laboratory remission with IL-1 inhibitors, a drug tapering/discontinuation may be taken into consideration (as an alternative to unchanging the IL-1 inhibitor schedule), in terms of response maintenance/tolerability improvement)

Statement 7 refers to the management of patients with a sustained clinical and laboratory remission with IL-1-inhibition.

Of the 198 abstracts screened, 8 relevant studies were selected.

In the study by Giampietro et al., drug discontinuation thanks to the achievement of complete remission was possible in three (11%) of 28 patients included in the nationwide survey. The dose was tapered in further six and resulted in sustained remission in two patients and relapse in the others [55]. In another study, 140 patients were treated with anakinra [53]. After 12 months of treatment, 71/140 (50.7%) of patients discontinued the treatment. Importantly, 20/140 (14.2%) achieved clinical and laboratory parameter remission with anakinra that was sustained over time and led to treatment discontinuation [53]. In a subsequent study that enrolled an almost overlapping cohort, Vitale et al. observed the same anakinra withdrawal rate due to long-lasting remission of 14.2% in patients who were treated with anakinra for a mean period of 35.6 ± 35.4 months. Seventeen out of 20 patients withdrawing anakinra as a result of long-term remission had suffered from active AOSD for at least 12 months [56]. In the study by Vercruysse et al., eight patients (29.6%; 3/13 anakinra responders and 5/15

tocilizumab responders) managed to stop their biological treatment without relapse at the last known follow-up visit, the timing of which ranged from 6 to >24 months after the discontinuation of the biologics [48]. Laskari et al. attempted treatment de-escalation or complete discontinuation in 15/39 (38.5%) and 21/39 (53.8%) complete responders to canakinumab, respectively, by increasing the interval between the injection, lowering the dose or both. The patients were in remission for a median of 10 months (range 1–62) before treatment reduction. Complete discontinuation was tried in 19 patients in remission for a median of 14 months (range 0–54). Treatment de-escalation led to relapse in one patient out of 15 and treatment discontinuation relapse in 11/21 (52%) patients [38].

Drug tapering/discontinuation can be done by diminishing the dose or extending the interval between drug administration, this statement makes no recommendations regarding the best way to perform it. A phase 3b/4 open-label, randomised study in SJIA assessed the efficacy and safety of canakinumab tapering through dose or dose frequency reduction [57]. Patients had to be in clinical remission for at least 24 weeks prior to tapering. One third of these patients discontinued canakinumab and remained in remission for 24 weeks. The proportion of patients in clinical remission for 24 weeks with a reduced dose of canakinumab was 27 of 38 (71% of patients [97.5% CI 52–86%]), whilst the proportion of patients in clinical remission with the prolonged dose interval regimen was 31 of 37 patients (84% of patients [97.5% CI 66–95%] [57].

In most available studies, drug tapering/discontinuation was attempted after 6 or 12 months of treatment. The panel agreed that such an action should be done after a period of remission lasting 1 year (i.e., 1 year without GCs), although, at present there are no studies to support this timing. For example, a different timing of tapering was undertaken by Ter Haar et al. [58]. In this report, patients with SJIA were treated with anakinra as a first line monotherapy after unsatisfactory response to NSAIDs. In patients with inactive disease following the treatment with this anti-IL1, anakinra was tapered after 3 months and subsequently stopped. Approximately half of the cohort had recurrent disease following the first attempt of stopping anakinra [58].

Statement 7 received a median score of 8 from the Expert Panel.

4. Discussion

In this study, we deployed the Delphi method to formulate expert consensus statements to guide the treatment of AOSD to achieve an early and long-term remission. Our intention was to include all scenarios encountered in the treatment of patients with AOSD: patients at presentation and those with refractory disease.

The Delphi process generated seven candidate statements. All seven statements met consensus during the first round of voting confirming high quality of work that went into their formulation. Statement 4 received the highest median score of 9 from the Expert Panel suggesting that the evidence concerning the use of anti-IL1 agents in patients with poor prognostic factors is the most convincing. Statement 5 and Statement 7 had a median score of 8 and Statement 2, Statement 3, and Statement 6–7. The voting of Statement 2 and Statement 3 may have suffered from a misunderstanding of the fact that they were formulated as a negation (“should not”). This is apparent from the detailed comments inserted into the voting form (e.g., “I consider other therapeutic options” in reference to Statement 2 or “Cortisone has always proved to be effective in rapidly treating systemic manifestations for which it should be started at high doses early perhaps with the introduction of a therapy that allows us to reduce it more rapidly in order to reduce hospitalisation” in relation to Statement 3). Such a misunderstanding could explain a lower level of consensus for these two statements compared to statements 1, 4, 5 and 7. At the same time, a relatively low level of consensus reached by Statement 6 may be due to the fact that more data are needed in support of switching from anti-IL1 to anti-IL6 or TNF-inhibitor. This was reflected in some the comments from the Expert Panel members in the voting form (e.g., “TNF is an inflammatory cytokine, but I would not consider it a principal target in pathogenesis of the disease.” or “There are no data to support the use of those biologicals”).

Based on the literature review and the statements formulated, we propose a treatment algorithm presented in Fig. 3. It is clear that many patients first resort to NSAIDs at presentation, as they can be self-administered. This happens mainly when systemic manifestations are mild or self-limiting and is effective in ~20% of patients [59]. Patients are later given GC and/or csDMARDs, albeit up to one third of patients with AOSD results refractory [59]. In the series of Kondo, initial treatment outcome to GCs was assessed at 4 weeks. Poor response was defined as administration of two or more rounds of GC pulses or any other immunosuppressives within 4 weeks due to failure to achieve remission or due to relapse after an initial remission [23]. Biological agents have been developed to tackle the pathophysiology of chronic inflammation, and in particular to contrast the increase in blood serum of cytokines including IL-1, IL-6, IL-18, IL-17 and TNFα [60]. At present, biologics are used in patients who failed other therapies. Anti-IL-1 therapies (anakinra, canakinumab and rilonacept) are first line biologic treatment for AOSD. To-date, IL-1 inhibition remains the gold standard in systemic and refractory AOSD [59]. A recent study of 26 patients with AOSD (that came out after the systematic literature review for this paper was completed) suggests that canakinumab can be effective in both systemic and chronic articular form of AOSD [61], while a Turkish study, missed by the initial literature search, showed that only 1/14 patients with refractory AOSD was primarily unresponsive to anakinra [62]. Tocilizumab, administered both intravenously and subcutaneously, can also be used [42,46,63]. A very recent systematic review of studies in which patients with AOSD were treated with bDMARDs further highlighted their safety and usefulness in reducing the dose of GCs. The authors concluded calling for larger controlled studies and for standardisation of the response criteria [64].

It is important to note that Statements 5 and 7 use the verb “may” in their wording denoting an option and not an imperative recommendation. Indeed, in patients with AOSD who failed to attain a good clinical response with an IL-1 inhibitor, switching to an IL-6 inhibitor may be considered, but another anti-IL-1 can be just as effective as shown by the paper cited above [61]. Moreover, Vitale et al. showed that canakinumab works also in the articular form of AOSD, whilst Colafrancesco et al. concluded that based on available efficacy data, the failure to respond upon one IL-1 inhibitor did not preclude achieving a response with another [8,61]. Also in the Turkish series, patients refractory to other treatments including anakinra responded to canakinumab [65]. Future studies will provide more definite data on the use of the available armamentarium against AOSD. However, one can envisage that whilst more studies will become available on biologics, we doubt that more good quality data will be generated for the sDMARDs, such as CyA.

Given that satisfactory results have been obtained with many of the new drugs, future studies may need to explore further patients’ preferences. One study suggested that patients with AOSD may prefer canakinumab because of feeling less pain at the site of injection and being satisfied with administration frequency [66].

The most appropriate management of AOSD is still work in progress. In the future artificial intelligence will be employed to establish novel biomarkers to inform therapeutic decisions and tailor the treatment to the precise pathophysiology of each patient [67].

The current study has several limitations. It was hard to draw conclusions from the available literature as reports included in this systematic review are very heterogenous and provide data that cannot be directly compared. Many of the studies included here are conference abstracts and, therefore, not much detail can be extracted from them. Also, a small number of relevant papers seems to have been missed by the systematic literature search performed at the beginning of the study. One such paper is a study that directly compared high versus low GC dosage confirming the superiority of high dose GCs [68]. Finally, a second voting of selected statements after minimal rephrasing may have

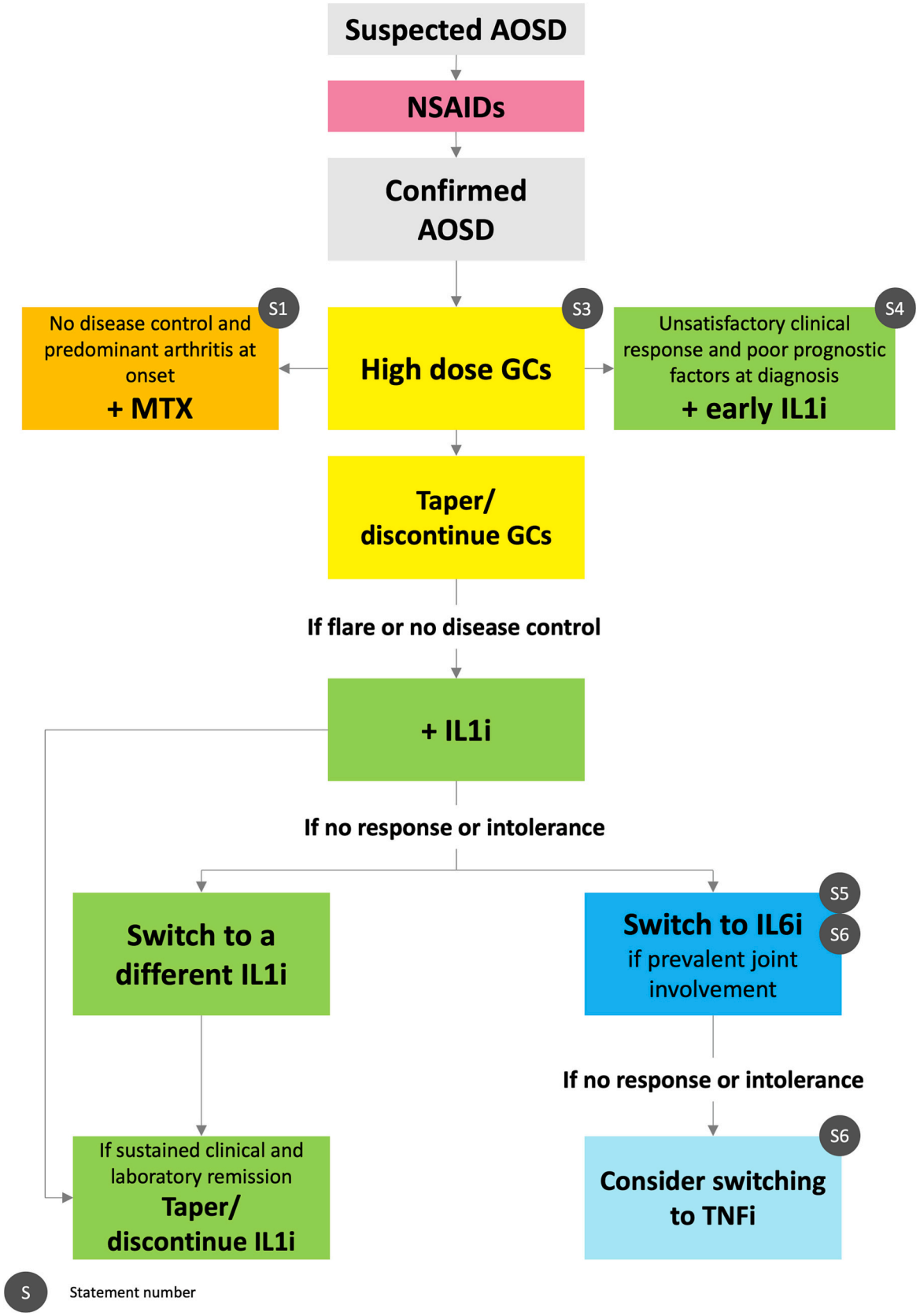

Fig. 3. Treatment algorithm for adult-onset Still's disease. AOSD, adult-onset Still's disease; CyA, cyclosporin A; GC, glucocorticoid; IL1i, interleukin 1 inhibitor; IL6i, interleukin 6 inhibitor; TNFi, tumour necrosis factor inhibitor.

been useful to gauge the stability of the Expert Panel's opinions that added up to this consensus.

5. Conclusions

The statements provided in this paper represent an expert consensus of Italian experts on the treatment of AOSD with the goal of achieving early and long-term remission based on current knowledge. Future updates will be needed when more data become available. We believe that the application of these statements in clinical practice will improve the prognosis of patients with AOSD and their quality of life.

Declaration of Competing Interest

RP received fees from Novartis; RC received speaker's and paid consultation fees from Abbvie, BMS, Lilly. Pfizer, Galapagos, Novartis, MSD. Janssen, Fresenius-Kabi, Sandoz, UCB. The remaining authors have nothing to declare.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2023.103400.

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