Current treatment in macrophage activation syndrome worldwide: a systematic literature review to inform the METAPHOR project

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Short running title: Current treatment of MAS

ABSTRACT

Objective. To assess current treatment in macrophage activation syndrome (MAS) worldwide and to highlight any areas of major heterogeneity of practice.

Methods. A systematic literature search was performed in both Embase and PubMed databases. Paper screening was done by two independent teams based on agreed criteria. Data extraction was standardized following the PICO framework. A panel of experts assessed paper validity, using the Joanna Briggs Institute appraisal tools and category of evidence (CoE) according to EULAR procedure.

Results. Fifty-seven papers were finally included (80% retrospective case-series), describing 1148 patients with MAS: 889 systemic juvenile idiopathic arthritis (sJIA), 137 systemic lupus erythematosus (SLE), 69 Kawasaki disease (KD) and 53 other rheumatologic conditions. Fourteen and 11 studies specified data on MAS associated to SLE and KD, respectively. All papers mentioned glucocorticoids (GCs), mostly methylprednisolone and prednisolone (90%); dexamethasone was used in 7% of patients. Ciclosporin was reported in a wide range of patients according to different cohorts. Anakinra was used in 179 MAS patients, with a favourable outcome in 83% of sJIA-MAS. Etoposide was described by 11 studies, mainly as part of HLH-94/04 protocol. Emapalumab was the only medication tested in a clinical trial in 14 sJIA-MAS, with 93% of MAS remission. Ruxolitinib was the most reported JAK-inhibitor in MAS.

Conclusion. High-dose GCs together with IL-1 and IFNγ inhibitors have shown efficacy in MAS, especially in sJIA-associated MAS. However, global level of evidence on MAS treatment, especially in other conditions, is still poor and requires standardized studies to be confirmed.

Keywords: macrophage activation syndrome, haemophagocytic syndromes, haemophagocytic lymphohistiocytosis, treatment

Key messages:

- High-dose GCs together with IL-1 and IFNγ inhibitors have shown efficacy in sJIA-associated MAS.
- Current level of evidence on MAS treatment, especially in condition other than sJIA, is still poor.
- MAS treatment is still extremely variable, with potential significant discrepancies across different centres and countries.

INTRODUCTION

Macrophage activation syndrome (MAS) is an hyperinflammatory life-threatening condition, part of the wide spectrum of hemophagocytic lymphohistiocytosis (HLH). The term MAS refers to a secondary form of HLH that complicates the course of rheumatological conditions. MAS is characterized by a marked hyperferritinemia, cytopenia, liver insufficiency with coagulopathy, neurological manifestations, and a high risk of rapid progression to multiorgan failure. Despite great improvement in diagnosis and management[1-9], MAS still represents a major challenge in clinical practice.

MAS treatment remains largely empiric and based on expert consensus. Although promising data are emerging, results from large cohorts and standardized trials are still required for most medications used to treat MAS. Multinational data on sJIA-associated MAS highlighted several disparities in its management in relation to geographic location of the treating centre and subspecialty of the caring physicians[10]. Recently, the first international recommendations for the early-stage management of HLH/MAS have been published[11]. Despite their milestone relevance, these guidelines focus on the initial management of the spectrum of haemophagocytic syndromes, and did not specifically address the treatment of MAS. Furthermore, there is a particular lack of evidence on therapeutic approach to MAS associated with rheumatologic conditions other than sJIA. It is thus conceivable that a wide heterogeneity in the management of MAS exists, due to differences in treatment strategies, access to medications and involvement of different specialists.

The METAPHOR project was conceived to provide an overview of current real-life therapeutic approaches to MAS in different clinical settings worldwide by means of a web-survey involving the paediatric rheumatology community part of the Pediatric Rheumatology European Society (PReS) and the Pediatric Rheumatology International Trial Organization (PRINTO) and the

paediatric haematologists from the Histiocyte Society. In this context, a systematic literature review (SLR) to explore available data on MAS treatment was performed.

METHODS

The SLR was conducted following the EULAR standardised operating procedures[12]. A multinational panel of experts in the field of MAS was involved. The PICO (Patient-Intervention-Comparison-Outcome) framework was adopted to structure the research (see **Supplementary Data S1** and **Supplementary Table S1, available at *Rheumatology* online**). Acknowledging the concomitant international effort of the EULAR/PRES task force for sJIA and adult-onset Still disease, which includes a SLR on the treatment of sJIA-associated MAS (De Matteis et al, *submitted*), we decided to particularly address MAS in conditions other than sJIA. On June 30th, 2022 the literature search was performed both in PubMed and Embase databases, and then updated on June 30th, 2023. Search strings were designed under the supervision of an expert librarian (see **Supplementary text**). Main inclusion criteria were: original articles, English language, studies reporting data regarding treatment of patients with MAS, population's age <18-years-old and papers with more than 3 cases reported. Exclusion criteria are detailed in **Figure 1**. In light of the scarcity of available data on specific conditions or medication, and only after discussion in our core team, we did exceptionally include a case-report, if this was deemed relevant for the analysis. Papers were checked for duplicates and then screened, using Rayyan software (Cambridge, USA). A first title and abstract screening was performed, and then selected papers were evaluated through a full-text read.

To establish the quality and the category of evidence of included papers, two members of the Expert Panel evaluated each manuscript independently. The Joanna Briggs Institute critical appraisal tools were used to assess the validity score[13], identifying three validity levels (low-

moderate-high), and the category of evidence (CoE) was attributed as per EULAR standardized operating procedures[12].

RESULTS

A total of 6588 papers were identified through the first search. After the deletion of duplicates and the title/abstract selection, 560 articles underwent full text screening and finally 57 studies fulfilled the eligibility criteria (**Figure 1**). Twenty-three papers reported sJIA cohorts, 4 SLE cohorts, 8 KD cohorts, while in 22 studies the described population was mixed. Thirty-six were single-centre retrospective case series, 10 multicentre retrospective case series, 2 single-centre retrospective cohorts, 1 multicentre prospective cohort, only 1 was a standardized single arm open label clinical trial; 7 case reports were included for the relevancy of the medication or the condition reported. Three additional studies about JAK-inhibitors (JAK-i)[14-16] were considered, despite reporting data about mixed HLH cohorts; data from those studies only contributed to the JAK-i evidence review. Most papers (84%) were found to have low or moderate validity, and almost all (96%) were classified with a CoE of 3 or 4. **Supplementary Table S2, available at *Rheumatology* online,** reports all the information available on papers included in the SLR.

Data from a total of 1148 patients with MAS were finally evaluated: 889 sJIA, 137 SLE, 69 KD and 53 other rheumatological conditions, including 8 juvenile dermatomyositis, 7 mixed connective tissue disease, 6 vasculitis, 2 antiphospholipid syndrome, 2 spondyloarthritis, 2 undefined connective tissue disease, 2 polyarticular JIA, 1 undefined arthritis, 1 rheumatic fever, 1 enthesitis-arthritis (ERA), 1 Kikuchi disease, 1 Sjogren disease, 1 sarcoidosis, 1 cryopyrin associated periodic syndrome, 1 mevalonate-kinase deficiency (MKD), 1 Crohn disease, and 15 unspecified rheumatic disorders.

Glucocorticoids

All studies mentioned the use of GCs and information were available for 1054 MAS patients (829 sJIA, 91 SLE, 66 KD, 68 other rheumatologic conditions). Among the 300 patients in which this information was assessable, most patients (86%, 258/300) received GCs as a co-medication, while 42/300 (14%) were successfully treated with GCs as monotherapy. Methylprednisolone (MPN) or prednisolone were the mostly used GC (90%), followed by dexamethasone (DEX, 7%). DEX was used in 15%, 10%, and 6% of patients with MAS in the contect of KD, SLE, and sJIA, respectively.

MPN dose ranged from 2 mg/kg/day to 30 mg/kg/day, with high-dose MPN pulses (10-30 mg/kg/day) reported in almost 60% of studies. Interestingly, a tapering regimen of MPN pulses was suggested by Loganathan et al. for severe MAS complicating sJIA in a resource limited setting[17]. DEX dose ranged from 4mg/m^2/day to 10-15 mg/m^2/day. Two Japanese studies[18,19] reported the successful use of dexamethasone palmitate (DEX-P), a liposomal incorporated formulation, in 24 sJIA-MAS patients (17 naïve and 7 refractory to MPN/prednisolone +/- CsA).

Ciclosporin

Fifty studies mentioned the use of CsA in 611 MAS patients (483 sJIA, 34 SLE, 10 KD, 84 other rheumatological diseases). In the largest multinational cohort of sJIA-MAS[20], CsA was the medication most frequently prescribed besides GCs (61% of patients). Only 10 studies reported details about the route and the dose of administration: CsA was given intravenously (iv) in 29 patients and orally in 12, with dose ranging from 0.8 to 8 mg/kg/day. Trough levels were mentioned only in 3 studies[21-23] and ranged between 78 and 480 ng/ml.

Globally, outcome in patients treated with CsA was assessable for 186 patients (138 sJIA, 9 SLE, 8 KD, 31 other rheumatic diseases): in 6 patients (3%) a poor outcome (4 deaths, 2 severe neurological adverse events) was reported. Posterior reversible encephalopathy syndrome (PRES) was mentioned in 1 sJIA-MAS patient, who was receiving co-treatment with GCs, IVIG and

etoposide[24]. Five sJIA-MAS patients were successfully treated with CsA without modification of the background GC therapy[22,25].

Etoposide

Details on etoposide were available from 11 studies, for a total of 120 patients (78 SJIA, 14 SLE, 14 KD, 14 other rheumatic diseases); outcome data were available for 17 sJIA, 7 SLE, 14 KD and 4 other rheumatic diseases. Seven patients (17%) died. Neutropenia was the main adverse event reported; in 3 patients, severe bone marrow suppression with sepsis was reported.

Dose of etoposide ranged from 50 to 150 mg/m^2 weekly-biweekly. Of note, two studies reported the use of low dose etoposide (50-100 mg/m^2/week for 4-11 weeks)[26,27], in 7 patients with MAS (5 sJIA and 2 SLE). All sJIA patients were refractory to high-dose GCs and CsA, 3/5 also to anakinra (2.7-15 mg/kg/day), and all achieved MAS remission after etoposide. The two patients with SLE had failed oral prednisone: both survived with MAS remission, but one developed long-term CNS sequela.

Anakinra

A total of 179 patients received anakinra for MAS (147 sJIA, 12 SLE, 1 KD, 19 other rheumatologic disorders), reported in 19 studies all published after 2011. Outcome data were available for 82 sJIA, 10 SLE, 1 KD, 12 other rheumatological conditions, and for 3 sHLH treated with iv anakinra continuous infusion (**Table 1**). A complete response was reported in 68 patients with sJIA-MAS (83%); 8 patients presented an incomplete (10%) and 3 (4%) a lack of response to anakinra, 2 had a recurrency of MAS, and 2 (2%) died. Patients with SLE-MAS treated with anakinra had a favourable outcome in 6/10 (60%), with 4 reported deaths (40%).

In the included studies, anakinra was used with a wide dosing range (2 – 48 mg/kg/day). The highest dose was used as continuous iv infusion in 2 patients: one patient with MAS secondary

to SLE/MCTD was treated for 72 hours without any other medication, but eventually died from multiorgan failure[28]. The second patient was a 9 year-old girl with severe sHLH and neurological involvement without a known trigger, refractory to MPN pulss and IVIG and anakinra (12 mg/kg/day); given her worsening conditions, anakinra was steeply increased to 2 mg/kg/hr (48 mg/kg/day) with a positive outcome[29]. The use of high-dose anakinra (at least 5 mg/kg/day) was specified in 6 studies[26,28-32] for 27 patients, and 93% of them were reported after 2020.

Concomitant medications in patients treated with anakinra were assessable only for 67 episodes of MAS. High-dose anakinra was reported mainly together with GCs and CsA (85% and 37%, respectively), followed by etoposide (15%). Anakinra was used as monotherapy in 6 patients (5 sJIA and 1 SLE/MTCD)[28]: all patients with sJIA achieved MAS remission (dosing range of 2.9 – 6.2 mg/kg/day), while the patient with SLE/MTCD died despite being treated with high-doses (48 mg/kg/day iv). Data on MAS patients treated with anakinra as single medication on the background of GCs were available from two studies[28,30] reporting 15 episodes of MAS: all the 10 episodes with assessable outcome data achieved MAS remission.

Emapalumab

The first and only clinical trial in MAS assessed the role of emapalumab (anti-IFNγ monoclonal antibody) on sJIA-associated MAS refractory to high-dose GCs[31]. In this single-arm, open label trial, 14 sJIA-MAS were included: 8 were refractory also to CsA and 7 to anakinra. By week 8, MAS remission was achieved in 13/14 patients (93%), with a median time to remission of 25 days. In all patients, emapalumab led to a rapid regression of all MAS parameters and to a significant steroid-sparing effect. No deaths or serious adverse events related to emapalumab were reported. Viral infection/seropositivity was the most frequent side effect (mainly CMV; of note, all patients received acyclovir prophylaxis). Interestingly, the combination of emapalumab with anakinra (up to 4 mg/kg/day) seemed to reduce the occurrence of sJIA flare without

increasing serious events and infection rate. In the trial 1 patient received emapalumab together with high-dose anakinra (7.5 mg/kg/day), with good tolerability and without the mention of specific adverse events.

Other biologics

The use of other biologics in the treatment of MAS was reported in 22 studies: canakinumab and tocilizumab were the most commonly reported biologic agents for sJIA-MAS, while infliximab was mainly used in patients with KD-MAS (7 patients treated with a dose range 3-10 mg/kg/day and a positive outcome).

Thirty-five patients[33-37] received tocilizumab, and in 26 of them outcome data were available: 22 patients (85%) had MAS remission, in 1 tocilizumab was discontinued for lack of response (4%), and in 3 (12%) for an allergic reaction. Of note, in the two main cohorts of sJIA-MAS patients successfully treated with TCZ[33,36], none of them previously received an IL-1 inhibitor.

Canakinumab was used in 16 patients[37-40], with a positive response in 14 of them (88%). In particular, Kostik et al.[37] described 8 sJIA-MAS patients all treated with canakinumab: 7 achieved MAS remission, and 1 required the addition of tofacitinib to control MAS recurrency. In 3 patients, canakinumab was successfully used as 1st line biologic treatment. Interestingly, 3 patients developed severe MAS despite canakinumab standard treatment, and responded to an increase of canakinumab dose, up to 12 mg/kg.

In a cohort of MAS associated to thrombotic microangiopathy (TMA)[41], 9 patients received complement inhibition (eculizumab) in addition to MAS-target treatment: 7 patients achieved regression of both MAS and TMA, and 2 died.

JAK-inhibitors

In our SLR only one study reporting JAK-i was specifically focused on MAS[38]. In this paper, authors described 10 refractory sJIA, 3 of whom with severe MAS resistant to high-dose GCs and tocilizumab (1 also to etoposide). All of them were treated with ruxolitinib (2.5-5 mg x 2/day) with a rapid regression of MAS without adverse events. Notably, none received IL-1 inhibitors or CsA before Jak-i introduction, and all required the further addition of canakinumab to control underlying sJIA.

Three other studies[14-16] reported the use of ruxolitinib in mixed cohorts of sHLH patients. In a retrospective case series of 9 patients (5 EBV-HLH, 2 fHLH, 1 MAS, 1 unspecified) refractory to the HLH94 protocol, 3 patients (1 MAS) achieved MAS remission, while others required the association with DEX-P[14]. In a case-control study[15], 11 patients (including 2 sJIA-MAS and 1 KD-MAS) were successfully treated with ruxolitinib (7 refractory to HLH04 protocol, 4 naïve). In a pilot, open-label, single arm trial[16] 12 sHLH patients (8 EBV-HLH, 2 MAS, 2 unspecified) received ruxolitinib as 1st line treatment with a positive response in 10 of them.

The only other JAK-i mentioned as a treatment for sJIA-MAS was tofacitinib in 2 patients: in one case tofacitinib was ineffective and was switched to ruxolitinib[38], while in the other it contributed to control MAS recurrency together with canakinumab[37].

HSCT

Six studies reported data about HSCT in patients with refractory MAS[,23,34,35,42-44]. In a case series Silva et al.[35] described 5 patients with refractory sJIA-MAS treated with allogeneic HSCT: 1 patient died from pulmonary haemorrhage 85 days after HSCT, 3 developed graft versus host disease, and 5/5 had severe infections following HSCT. All but one patient developed 100% chimerism, and all patients who survived achieved disease remission after HSCT. Chellapandian et al.[44] described a 4-year-old child with sJIA, recurrent MAS and LD, refractory to GCs, anakinra,

methotrexate, tocilizumab and canakinumab, who was successfully treated with emapalumab as bridge therapy to a matched sibling donor allogenic HSCT. HSCT was further mentioned in 4 MAS and 4 sHLH [23,34,42,43]: outcome data were available for 2 MAS, who survived without disease reactivation, and for sHLH patients, of whom one died.

Other treatments

Use of IVIG was reported in 280 sJIA, 46 SLE, 37 KD and 48 other rheumatic diseases, from 41 studies. However, specific data on IVIG efficacy are extremely hard to be extracted, as IVIG was almost always used as part of a combined regimen and no studies focused on IVIG efficacy were found. In 15 studies, plasma-exchange (PE) was mentioned as additional treatment for MAS. Overall, 48 patients with sJIA, 9 with SLE, and 6 with other rheumatic diseases received PE for MAS. In particular, PE was used as part of a combination therapy in 17 patients to control MAS-associated TMA[41].

Treatment of MAS in other rheumatologic diseases other than sJIA

Fourteen papers presented detailed data about SLE-MAS, for a total of 105 patients, with an overall mortality of 7% (**Table 2**). Bennett et al.[42] compared the differences in MAS treatment between SLE and sJIA in a cohort of 102 sJIA and 19 SLE. SLE patients were more frequently given DEX (32% vs 14%, $p = 0.05$), cyclophosphamide (21% vs 3%, $p = 0.01$), and MMF (32% vs 2%, $p < 0.001$); only children with underlying sJIA received IL-1 antagonists. Similarly, in the cohort by Aytac et al.[45], all patients with sJIA seen after 2011 received anakinra, while patients with SLE were treated more frequently with IVIG (68% vs 33%) and etoposide (50% vs 32%), and received IL-1 blockade in 30% of cases. In the large cohort of SLE-MAS described by Borgia et al.[46], only 2 patients were treated with anakinra: both patients were refractory to several treatments, including PE and in one case alemtuzumab and intrathecal methotrexate, and eventually died.

Eleven studies reported detailed information about KD-related MAS in 58 patients **(Table 3**). Treatment of MAS included GCs (85%), IVIG (73%), CsA (19%), and infliximab (12%). Fifteen patients (26%) received etoposide (11 within HLH protocol). Two KD-MAS patients were successfully treated with IVIG alone[47,48] . In our SLR, only one patient received anakinra, with rapid remission[49]. Three patients died (5%, all treated with HLH protocol), and only 1 had persistent coronary artery ectasia.

Differences between paediatric sub-specialties and geographic areas.

Treatments of the cohort of 362 sJIA-MAS described by Minoia et al.[10,20] were stratified, both according to the geographic area of the referral centre and to the subspecialty of the treating physician. Patients followed in North America (NA) more frequently received IVIG and biologics than patients treated in Europe or in other continents (IVIG: NA 54%, Europe 26%, other continents 43%; biologics: NA 34%, Europe 16%, other continents 7%). No significant differences were observed in the percentage of patinets treated with GCs, CsA and etoposide. Paediatric haemato-oncologists more frequently used biologic agents (24% vs 3%, $p = 0.02$) and etoposide (18% vs 10%, $p = 0.04$), whereas paediatric rheumatologists more frequently prescribed CsA (67% vs 40%, $p < 0.0001$).

DISCUSSION

MAS represents a life-threatening condition that requires prompt effective treatment to avoid potentially fatal outcome; however, the therapeutic approach to MAS is still a challenge for clinicians worldwide. Recently, international collaborative efforts have strived for a common standardized approach[11]. In this context, the METAPHOR project is aimed to capture the real-life therapeutic strategies in MAS in different clinical settings, and, in particular, the current

SLR had the main purpose of uncovering areas in which evidence regarding MAS treatment is still lacking, leading to major discrepancies among practitioners.

Despite the sizable amount of data regarding MAS patients reported in literature, the global level of evidence on treatment outcome is still poor, with a scarcity of comparative data across papers, mainly due to the heterogeneous nature of most studies, the lack of standardized outcome measures, and the high risk of bias in attributing effectiveness or safety to a specific medication or condition. Indeed, outcome data on the concomitant use of different therapies are really difficult to extract, as the timing of start of drugs is rarely specified. Furthermore, although MAS is a unique syndrome, the heterogeneity of the underlying rheumatologic backgrounds may differently affect its course and influence the treatment used.

Although not based on any formal clinical trial, high-dose GCs are confirmed as the mainstay of treatment of MAS in all rheumatologic backgrounds across the literature, and GC were used in almost all patients. Together, MPN and prednisolone accounted for 90% of MAS patients, while DEX was mainly used in the context of HLH protocol and in patients with a potential higher risk of CNS involvement[42]. GCs were mostly used as co-medications, and only 14% of MAS were treated with GCs as monotherapy. Interstingly, this data is in line with what we observed in the cohort of 362 sJIA-MAS, where only 19% of patients survived with GCs alone[20] (unpublished data, courtesy dr. F. Minoia and dr. A. Ravelli). Despite difficulties in assessing their specific efficacy, due to the heterogeneity of conditions reported and co-medications used, the role of GCs in MAS is life-saving especially in low-income countries; of note, a tapering scheme of MPN pulses was proposed for severe MAS in resource limited settings[17]. Furthermore, despite limited numbers, DEX-P was successfully used in MAS refractory to MPN pulses and CsA in Japan[19].

Data on CsA in MAS come only from retrospective cohort studies in which it was mainly used together with several other agents, with variable dosages and routes of administration,

making a reliable evaluation of its efficacy highly biased. However, CsA was confirmed as the most frequently used medication besides GCs, with a global positive efficacy and safety profile. CsA is widely accessible at affordable costs and might play a key role in the treatment of MAS refractory to high-dose GCs, especially in low-income countries or in those centres in which biologic medications are not accessible in a timely manner.

Anakinra is by far the most used biologic treatment for MAS, especially for sJIA-MAS. Despite the fact that no (randomised) controlled clinical trial tested the efficacy of anakinra in MAS, more than 80% of patients with sJIA-MAS treated with anakinra reported a complete regression of MAS, with a high safety profile. An unbiased evaluation of its efficacy and best therapeutic scheme is impossible to make, given the heterogeneity of the studies included. However, data collected strongly support the use of anakinra in patients with sJIA-associated MAS. Evidence of anakinra role in other subtypes of MAS is less robust; however, its safety profile and short half-life make it a valuable option for all sHLH, especially in critical care settings[50]. Data regarding other biologics in MAS are limited. Although no specific biologic used at the indicated regular dose seems to provide full protection against MAS[24,51,52] , small case-series showed positive results of canakinumab and tocilizumab in sJIA-MAS, raising the possibility of a therapeutic alternative in countries where anakinra is not available; however, further data are needed to confirm this preliminary observation.

Emapalumab is the only medication tested in a clinical trial in MAS and showed extremely positive results in high-dose GCs refractory sJIA-MAS with more than 90% of remission[31]. Given its specific target effect on IFNγ, emapalumab has a highly promising role for all subtypes of MAS, although these preliminary results need to be confirmed in larger cohorts and in patients with other rheumatologic backgrounds. Notably, emapalumab is still not accessible in most countries worldwide. Given their effect on the IFNγ pathway, JAK-i could potentially play an important role

in MAS treatment; however, so far, evidence on MAS is limited to case reports and to mixed sHLH cohorts. For sJIA-MAS, it should be noted that neither IL-1 nor IL-18 receptors signal through JAKs. IL-18 blockade might also represent a promising approach[53], and an ongoing international trial with a biclonal anti-IL-1β/IL-18 antibody is exploring its effect in monogenic diseases associated with inflammatory MAS (NCT04641442)

Since etoposide is a key medication in HLH protocols, its use in severe MAS was extensively reported, albeit associated with a significant toxicity and mortality. In the 362-cohort of sJIA-MAS described by Minoia et al.[20], etoposide was used in almost 12% of cases and was most frequently prescribed by haemato-oncologists[10]. Interestingly, a low-dose etoposide protocol was successfully used in a small-cohort of highly refractory MAS patients, with a positive outcome[26], and its role, especially in countries without access to targeted medications, needs to be better explored.

Data reflecting different therapeutic approaches according to geographic areas or sub-specialty of the treating physician were assessable only from one cohort of sJIA-MAS.[10,20]. In a recent survey[54], not included in the SLR due to publication type, GCs were confirmed as the 1st-line medication for MAS across all the subspecialties; notably, haemato-oncologists preferred DEX over MPN. IL-1 inhibitors were chosen as 1st-line therapy in MAS more frequently by rheumatologists compared to haemato-oncologists, while etoposide was more frequently the 2nd-line choice of haemato-oncologists.

In conclusion, data regarding MAS treatment are progressively increasing, especially for sJIA-associated MAS, with highly promising results for IL-1 and IFNγ inhibitors. However, global level of evidence on MAS treatment, especially in other rheumatologic conditions, is still poor with high biases and scarce reliability in attributing efficacy to a specific medication, due to the retrospective nature and heterogeneity of most studies and the lack of agreed outcome measures.

As a consequence, therapeutic approaches to MAS are still extremely variable, with potential significant discrepancies across different centres and countries. An international effort is needed to optimize therapeutic strategies, reduce gaps in access to medications and harmonize MAS treatment worldwide.

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Data availability statement. All data relevant to the study are included in the article. Data are available upon request from Dr. Francesca Minoia (francesca.minoia@policlinico.mi.it)

Contributorship. We confirm that all authors have contributed in the study by participating in design and conduct, validity evaluation, data analysis, manuscript preparation

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TABLES AND FIGURES

Figure 1. Flowchart for the systematic literature review, including detailed exclusion criteria, and results of the selection process. *Seven case reports were exceptionally included after a discussion within the core team for the relevancy of the medication or the condition reported.

Table 1. Data available on patients with MAS treated with anakinra

First author, year (ref)	Type of publication	Population	Pts treated with ANK	ANK dose/route of administration#	Previous treatments for MAS	Other treatments	Outcome	Validity score, EULAR CoE
Miettunen PM, 2011 (49)	Retrospective case series	12 MAS (8 sJIA, 2 AAV, 1 KD, 1 ARF)	12/12	2 mg/kg/day s.c. (max 100 mg/day) once daily	MPN (100%), IVIG (75%), CsA (83%), etoposide (16%), antiTNF (8%)	etoposide, anti TNF stopped; all other treatments continued	12/12 CR (median time to remission: 13 days)	Moderate, 3
Bennett TD, 2012 (42)	Retrospective case series	102 JIA (90 sJIA) 19 SLE	15 JIA-MAS	NA	NA	GCs (93%), CsA (33%), etoposide (7%)	NA	Moderate, 3
Minoia F, 2014 (20)	Retrospective case series	362 sJIA-MAS	33 sJIA-MAS	NA	NA	GCs (98%), CsA (61%), IVIG (36%), etoposide (12%) *	NA	High, 3
Ozturk K, 2015 (55)	Case report	1 sJIA-MAS	1 sJIA-MAS	2 mg/kg/day	MPN, DEX, etoposide, CsA, tacrolimus	ATG	1/1 CR	Low, 4
Barut K, 2015 (40)	Retrospective case series	10 sJIA-MAS	5 sJIA-MAS	NA	NA	GCs (100%), CsA (80%), CNK (40%) *	NA	Low, 3
Aytac S, 2016 (45)	Retrospective case series	31 sJIA-MAS 6 SLE-MAS	13 sJIA-MAS 2 SLE-MAS	NA	NA	GCs (100%), IVIG (68% sJIA, 33% SLE), CsA (74% sJIA 68% SLE). etoposide (32% sJIA, 50% SLE)	11/13 sJIA-MAS CR	Moderate, 3
Silva JMF, 2018 (35)	Retrospective case series	16 refractory JIA (4 sJIA-MAS)	4 sJIA-MAS	NA	NA	3 pts HSCT for refractory MAS, 1 pt developed MAS after HSCT GCs (100%), CsA (100%), etoposide (25%), ATG (25%)	3/4 CR 1/4 died	Moderate, 3
Borgia RE, 2018 (46)	Retrospective cohort	38 SLE-MAS	2 SLE-MAS	NA	NA	GCs (100%), IVIG (58%), CsA (29%) etoposide (13%) * 2/2 pts treated with ANK received PE, 1/2 intrathecal MTX, 1 alemtuzumab	2/2 death	High, 3
Sonmez HE, 2018 (30)	Retrospective case series	15 sJIA, 2 AID (19 MAS episodes)	19/19	2-6 mg/kg/day	All pts received ANK as 1st line	GCs (100%), CsA (63%), etoposide (16%), IVIG (% not reported)	13/15 sJIA CR 2/15 sJIA recurrent MAS	Moderate, 3
Eloseily EM, 2020 (28)	Retrospective case series	28 MAS (13 sJIA, 5 SLE, 3 MCTD, 7 others)	44/44	sJIA: 2.9 - 11.9 mg/kg/day	NA	sJIA: GCs (54%), CsA (23%) SLE/MTCD: GCs (87%), CYC (13%)	13/13 sJIA-MAS CR 2/5 SLE death	Moderate, 3

		16 sHLH (3 malignancies)		SLE/MCTD: 2-48mg/kg/day (latter as continuous IV infusion).				
Charlesworth JEG, 2021 (29)	Case report	2 sHLH	2/2	Pt1: 12 mg/kg/day → 48 mg/kg/day Pt2: 11 mg/kg/day 2/2 received continuous iv infusion	2/2: MPN, IVIG	Pt1: etoposide (1 dose), CsA	2/2 CR	High, 4
Phadke O, 2021 (56)	Retrospective case series	14 MAS (10 sJIA, 3 SLE, 1 vasculitis) 5 sHLH	19/19	Initial dose: 1.7 - 10 mg/kg/day iv Max. dose: 4.2–15.4 mg/kg/day iv (max 400 mg/day)	NA	NA	No SAE reported 1/10 sJIA-MAS died (MPN, DXA, VP16, JAK-i) for sepsis 1/1 vasculitis-MAS died (CYC, RTX, ECZ) with stroke and MOF	Moderate, 3
Horne AC, 2021 (26)	Retrospective case series	7 MAS (5 sJIA, 2 SLE)	3 sJIA-MAS	2.7-15 mg/kg/day	NA	3/3: GCs, CsA, low-dose etoposide 1/3: IVIG	3/3 no response, requiring low dose etoposide (2/3 discontinued ANK)	Moderate, 3
Minoia F, 2021 (41)	Retrospective case series	23 MAS-TMA (17 sJIA, 2 SLE, 1 JDM, 1 MCTD, 2 UCTD)	10 MAS (7 sJIA)	NA	NA	GCs (100%), CsA (61%, 12 sJIA), IVIG (74%, 13 sJIA). etoposide (17%, 4/4 sJIA) PE (74%, 11 sJIA), ECZ (39%, 4 sJIA), RTX (26%, 3 sJIA) *	NA	High, 3
Aydin F, 2021 (39)	Retrospective case series	7 sJIA-MAS	4 sJIA-MAS	NA	NA	GCs (100%), CNK (75%), CsA (50%), IVIG (25%)	3/4 CR 1/4 death (GCs, CNK)	Low, 3
Baglan E, 2022 (57)	Retrospective cohort	10 sJIA-MAS	5 sJIA-MAS	NA	NA	GCs (100%), IVIG + PE (80%), CsA (10%), TCZ (10%)*	NA	Moderate, 3
De Benedetti F, 2023 (31)	Controlled clinical trial	14 sJIA-MAS	7 sJIA-MAS	1.6-15 mg/kg/day	NA	GCs (100%), CsA (57%), IVIG (21%)* All patients treated with emapalumab	Incomplete response, requiring emapalumab (2/7 discontinued ANK)	High, 2A
Chellapandian N, 2023 (44)	Case report	1 refractory sJIA-LD, recurrent MAS	1/1	2-4 mg/kg/day	NA	MPN, CsA, CNK, TCZ Emapalumab added on top of ANK, HSCT	Incomplete response, requiring emapalumab and HSCT	High, 4

Rossano M, 2023 (32)	Retrospective case series	14 MAS (6 sJIA, 3 SLE, 2 JDM, 3 unknown)	3 sJIA-MAS	5 mg/kg/day	NA	3/3: MPN, CsA	3/3 CR	Moderate, 3

* data referred to the overall population included in the study and not specific for patient treated with anakinra

AAV: ANCA (anti neutrophil cytoplasmic antibodies) associated vasculitis; AID: autoinflammatory disease; ANK: anakinra; ARF: acute rheumatic fever; ATG: anti-thymocyte globulin; CNK: canakinumab; CoE: category of evidence; CsA: ciclosporin A; CR: complete remission; CYC: cyclophosphamide; DEX: dexamethasone; ECZ: eculizumab; GCs: glucocorticoids; i.v. intravenous; HSCT: hematopoietic stem cell transplant; IVIG: intravenous immunoglobulin; JAK-i: Janus Kinasis inhibitor; JDM: juvenile dermatomyositis; KD: Kawasaki disease; LD: lung disease; MAS: macrophage activation syndrome; MPN: methylprednisolone; MCTD: mixed connective tissue disease; MOF: multiorgan failure; MTX: methotrexate; NA: not available; PDN: prednisone; PE: plasma exchange; RTX: rituximab; SAE: severe adverse event; s.c. subcutaneous; sHLH: secondary hemophagocytic lymphohistiocytosis; sJIA: systemic juvenile idiopathic arthritis; SLE: systemic lupus erythematosus; TCZ: tocilizumab; TMA: thrombotic microangiopathy; TNF: tumor necrosis factor; UCTD: undifferentiated connective tissue disease

Table 2. Treatment data available on patients with SLE-associated MAS.

First author, year (ref)	Type of publication	Country	Pts with SLE-MAS	MAS prevalence	Treatment	Outcome	Validity score, EULAR CoE
Cortis E, 2006 (58)	Retrospective case series	Italy	1	NA	MPN pulses + CsA	Remission	Low, 3
Lambotte O, 2006 (59)	Retrospective case series	France	12 (15 episodes)	1.0%	14/15 GCs (9 MPN + PDN, 3 PDN); 2/15 oral PDN in monotherapy; 6/15 IVIG (5/6 as 1st line, 3/6 1st line monotherapy); 2/15 CYC (1 after failure of etoposide + CsA and RTX) 1 pt without specific treatment	Patient without specific treatment relapsed → MPN; 3/3 IVIG monotherapy did not respond → GCs; 5/15 ICU	Moderate, 3
Islam MI, 2007 (60)	Retrospective case series	Bangladesh	2	NA	MPN, followed by oral PDN	NA	Low, 3
Bennett TD, 2012 (42)	Retrospective case series	US	19	NA	19/19 GCs (6/19 DEX); 8/19 CsA alone, 1/19 etoposide + 1 VP16 and CsA; 7/19 IVIG; 2/19 PE; 6/19 MMF; 2/19 RTX	12/19 (63%) ICU; 2/19 (11%) mortality	Moderate, 3
Gokce M, 2012 (61)	Retrospective case series	Turkey	6	NA	6/6 CS (3 MPN, 3 DEX); 3/6 HLH-2004 protocol; 3/6 CsA + IVIG; 2/6 PE (TMA)	1/6 (16% mortality) treated with HLH-2004 protocol	Low, 3
Lin CI, 2012 (62)	Retrospective case series	Taiwan	2	NA	Pt1: IVIG + PDN; pt2: 3 MPN pulses + IVIG	1/2 (50%) mortality	Moderate, 3
Aytac S, 2016 (45)	Retrospective case series	Turkey	6	7%	6/6 GCs (MPN → PDN); 4/6 CsA; 3/6 etoposide; 2/6 IVIG, 2/6 ANK, 2/6 PE (median of 3 sessions)	1/6 (16%) mortality	Moderate, 3
Borgia RE, 2018 (46)	Retrospective cohort	Canada	38	9%	38/38 GCs (26/38 MPN pulses → PDN, 7/38 PDN, 6/38 DEX). 22/38 IVIG; 11/38 CsA, 5/38 etoposide, 2/38 ANK, 2/38 tacrolimus, 1/38 intrathecal MTX, 1/38 alemtuzumab	2/38 (5%) mortality (both refractory cases: both treated with ANK+PE, 1 also received alemtuzumab + intrathecal MTX for severe CNS involvement	High, 3
Buda P, 2018 (63)	Retrospective case series	Poland	1	NA	MPN pulses + CsA	Remission	Low, 3
Sato S, 2019 (64)	Retrospective case series	Japan	11	NA	11/11 GCs (6 MPN pulses); 2/11 IVIG, 2/11 CYC; 4/11 MMF, 1/11 AZA for underlying disease	11/11 remission. 5/6 CNS involvement (1 persistent anxiety disorder)	Moderate, 3

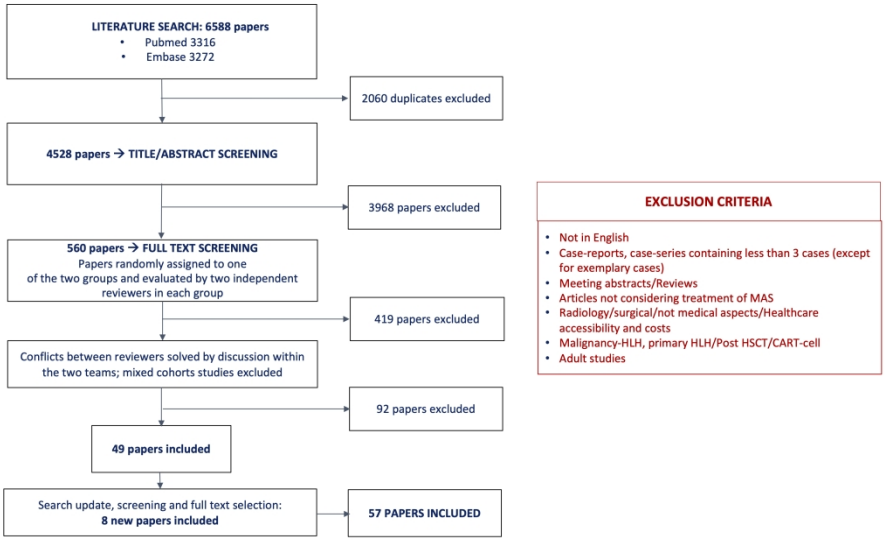
Eloseily EM, 2020 (28)	Retrospective case series	US	5	NA	5/5 ANK. Concomitant treatment reported for a mixed cohort of 8 SLE/MCTD: GCs (87%), CYC (13%)	2/5 died	Moderate, 3
Horne AC, 2021 (26)	Retrospective case series	Sweden	2	NA	2/2 PDN + low dose etoposide	2/2 MAS remission (1 CNS long-term sequelae)	Moderate, 3
Minoia F, 2021 (41)	Retrospective case series	Multinational	2	NA	2/2 MPN pulses, 2/2 CsA, 2/2 CYC, 1/2 IVIG 2/2 PE (1 for TMA, 1 for SLE-MAS severity), 1/2 ECZ (for TMA)	2/2 associated TMA, 2/2 ICU, 2/2 remission (1 severe osteonecrosis, 1 CKD)	High, 3
Rossano M, 2023 (32)	Retrospective case series	Italy	3	NA	3/3 MPN pulses + CsA; 1/3 IVIG.	3/3 remission	Moderate, 3

ANK: anakinra; AZA: azathioprine; CKD: chronic kidney disease; CNS: central nervous system; CoE: category of evidence; CsA: ciclosporin A; CYC: cyclophosphamide; DEX: dexamethasone; ECZ: eculizumab; GCs: glucocorticoids; HLH: hemophagocytic lymphohistiocytosis; ICU: intensive care unit; i.v. intravenous; IVIG: intravenous immunoglobulin; MAS: macrophage activation syndrome; MPN: methylprednisolone; MCTD: mixed connective tissue disease; MMF: mycophenolate mofetil; MTX: methotrexate; NA: not available; PDN: prednisone; PE: plasma exchange; RTX: rituximab; s.c. subcutaneous; SLE: systemic lupus erythematosus; TMA: thrombotic microangiopathy

Table 3. Treatment data available on patients with KD-associated MAS.

First author, year (ref)	Type of pubblication	Country	Pts with KD-MAS	MAS prevalence	Treatment	Outcome	Validity score, EULAR CoE
Al-Eid W, 2000 (65)	Case report	Saudi Arabia	1	NA	MPN + etoposide	Remission	Low, 4
Latino GA, 2010 (47)	Retrospective case series	Canada	12	1.9%	12/12 IVIG + high dose ASA; 8/12 2nd and 2/13 3rd IVIG doses. 11/12 GCs (1 DEX); 3/12 CsA; 1/12 IVIG alone (2 doses)	12/12 remission; 4/12 mild CAA (resolved)	High, 3
Miettunen PM, 2011 (49)	Retrospective case series	Canada	1	NA	MPN, CsA, etoposide → ANK (etoposide discontinued)	Remission	Moderate, 3
Kang HR, 2013 (66)	Retrospective case series	Korea	12	NA	2/12 2nd IVIG. 10/12 HLH protocol (2 HLH94, 8 HLH2004); 2/12 GC	2/12 died (15% - both received HLH protocol) – 1 lost at follow-up) 9/12 remission	Moderate, 3
Wang W, 2015 (48)	Retrospective case series	China	8	1.1%	8/8 IVIG + high-dose ASA; 7/8 GCs (6 MPN, 1 DEX); 1 DEX + etoposide and CsA	1/8 died (13% - received etoposide+CsA); 2/8 CAA (1 persistent); 6/8 discontinued ASA for thrombocytopenia	Moderate, 3
Islam MI, 2017 (60)	Retrospective case series	Bangladesh	1	NA	MPN + oral GCs	NA	Low, 3
Buda P, 2018 (63)	Retrospective case series	Poland	1	NA	MPN + IVIG	Remission	Low, 3
Mousavi MS, 2019 (67)	Retrospective case series	Iran	4	1.8%	4/4 MPN pulses, 1 2nd IVIG, 2 CsA, 1 IFX, 1 CYC	4/4 remission, no CAA	Low, 4
Pilania RK, 2021 (68)	Retrospective case series	India	12	1.3%	12/12 IVIG + MPN pulses; 1 3rd IVIG; 4/12 IFX, 1/12 oral CsA	12/12 remission	Moderate, 3
Rivera-Rodriguez L, 2021 (69)	Case report	Mexico	2	NA	2/2 IVIG + MPN; 1 DEX, 1 CsA 2/2 IFX	2/2 remission after IFX	Low, 4
Rhee S, 2022 (70)	Retrospective case series	Korea	4	0.8%	4/4 2nd IVIG dose; 4/4 additional GCs (1 MPN, 3 DEX); 1 3rd IVIG, 1HLH-2004, 1 CsA	2/4 ICU. 4/4 remission, no CAAs.	Moderate, 3

ANK: anakinra; ASA: acetylsalicylic acid; CAA: coronary artery aneurism; CoE: category of evidence; CsA: ciclosporin A; CYC: cyclophosphamide; DEX: dexamethasone; GCs: glucocorticoids; HLH: hemophagocytic lymphohistiocytosis; ICU: intensive care unit; IFX: infliximab; IVIG: intravenous immunoglobulin; KD: Kawasaki disease; MAS: macrophage activation syndrome; MPN: methylprednisolone; NA: not available; PDN: prednisone



Flowchart of the systematic literature review, including detailed exclusion criteria, and results of the selection process. *Seven case reports were exceptionally included after a discussion within the core team for the relevancy of the medication or the condition reported.

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Lukjanovič̌a K, 2023 (36)	Medicina	Single-centre retrospective case series	10 sJIA-MAS	Latvia	10/10 MPN + CsA → 8/10 were added TCZ with positive response	10/10 complete recovery 8/8 treated with TCZ had positive response within 48 hours Adverse events: 1 CsA-induced PRES No serious complications were associated with the use of TCZ (1 mild persistent thrombocytopenia)	Moderate, 3
De Benedetti F, 2023 (31)	Ann Rheum Dis	Single-arm, open label, multicentre clinical trial	14 sJIA-MAS	Multinational	14/14 refractory to high-dose GCs (8/14 also to CsA and 7/14 also to ANK up to 15 mg/kg/day) 14/14 treated with emapalumab Emapalumab protocol: 6 mg/kg on D0, followed by 3 mg/kg every 3 days until D15, then twice weekly until D28 (all patients received at least 3 administration); frequency or dose could be increased or treatment prolonged if required Median treatment duration: 27 days (range, 7–39) Concomitant treatments: GC, CsA (discontinued in 2 patients within D10, and in further 4 during follow up), ANK (continued in 4 patients at ≤4 mg/kg and in one patient at 7.5 mg/kg). 14/14: acyclovir prophylaxis	At 8 weeks, 13/14 met MAS remission criteria (93% response) 1/14 never met remission criteria only due to LDH levels 1.5-fold above the ULN (emapalumab stopped after 3 administrations due to clinical remission). Median time to MAS remission: 25 days (the earliest 9 days) Median daily dose of PDN-equivalent at w8: 0.56 mg/kg/day No deaths. 1 SAE (CMV infection, treated with standard care). Most frequently reported adverse events were viral infections (2) and positive tests for viral infectious agents (4) in the absence of clinical symptoms (mainly CMV). Rate of adverse events and infections not increased during concomitant treatment with ANK compared with EMP alone 6/14 had a flare of sJIA (6/9 patients not treated with ANK together with EMP). No sJIA flares in the 5 patients	High, 2A

						who continued ANK together with emapalumab	
Shimizu M, 2023 (19)	Int J Rheum Dis.	Multicentre retrospective case series	28 sJIA-MAS	Japan	9/28 treatment naïve, 8/28 on GC, 11/28 on TCZ 1st line: 28/28 GCs (15 DEX-P, 7 PSL, 6 MPN) + 14/28 CsA 2nd line: 1MPN, 5 DEX-P, 5 CsA, 2 PE 3rd line: 2 PE DEX-P was given iv at 3.2–8.6 mg/m^2/day (max 10 mg/d) CsA was given iv by continuous infusion (0.83–3.3 mg/kg/day) in 11 patients and orally (2.7–5.7 mg/kg/day) in 5 patients	28/28 complete recovery. No SAE related to DEX-P	Moderate, 3
Chellapandian D, 2023 (44)	Front in Pediatr	Case report	1 sJIA-MAS	US	4-year-old girl with sJIA complicated by recurrent MAS (1stepisode at 21 m, treated with MPN pulses, ANK; 2nd at 30 m, treated with MPN pulses, ANK escalation to 3 mg/kg/day, 3rd at 36 m, treated with MPN pulses, ANK 4 mg/kg/day) and progressive LD. Due to refractory MAS, emapalumab was started (1st dose 6 mg/kg, then 3 mg/kg twice weekly for 4 weeks) + oral PDN 0.5-1 mg/kg/day → MAS remission The patient received a matched sibling donor allo-HSCT after a reduced-intensity conditioning regimen with fludarabine/melphalan/thiotepa and alemtuzumab, along with TAC and MMF for GVHD prophylaxis.	At 20 months follow-up: full donor engraftment with complete donor-derived immune reconstitution + complete resolution of sJIA and marked improvement in LD (normalization of serum interleukin-18 and CXCL9 levels)	High, 4

Rhee S, 2023 (70)	Children	Single-centre retrospective case series	4 KD-MAS	Korea	4/4 2nd IVIG dose; 4/4 additional GC (1 MPN, 3 DEX); 1 3rd IVIG, 1 HLH-2004, 1 CsA	2/4 ICU admission. 4/4 complete recovery, no cardiac sequelae	Moderate, 3
Kostik MM, 2022 (37)	Front in Pediatr	Single-centre retrospective case series	8 sJIA-MAS	Russian Federation	8/8 MAS refractory to high-dose MPN, 5/8 IVIG, 3/8 CsA. 5/8 already on CNK and 3/8 on TCZ 8/8 treated with CNK for MAS CNK range 2-12 mg/kg/dose In 3 patients CNK was used as 1st line biologic treatment (4 mg/kg/day). 3 patients developed MAS under CNK standard treatment and responded to an escalation of CNK up to 12 mg/kg/day	7/8 complete recovery 1 patient required the addition of tofacitinib to control recurrent MAS 2 patients with sJIA-LD: 1 switched to TCZ for persistent arthritis after 3 years from MAS; 1 maintained on CNK together with MMF with stable lung disease control	Moderate, 3
Rossano M, 2023 (32)	Children	Single-centre retrospective case series	12 MAS (6 sJIA, 3 SLE, 2 JDM, 3 undefined)	Italy	12/12 MPN pulses (10–30 mg/kg/day for 3-5 days) + CsA; 4/12 IVIG, 3/12 ANK (5 mg/kg/day sc)	11/12 complete response 1/12 developed CNS sequalae (sJIA, with a triggering sepsis by Staphylococcus and brain hemorrhage before MAS diagnosis)	Moderate, 3

AAV: ANCA (anti neutrophil cytoplasmic antibodies) associated vasculitis; AID: autoinflammatory disease; ANK: anakinra; APS: antiphospholipid syndrome; ARF: acute rheumatic fever; ASA: acetylsalicylic acid; ATG: anti-thymocyte globulin; AZA: azathioprine; AVN: avascular necrosis; CAA: coronary artery aneurism; CINCA: cryopyrin associated periodic syndrome; CNK: canakinumab; CoE: category of evidence; CMV: Cytomegalovirus; CNS: central nervous system; CsA: ciclosporin A; CYC: cyclophosphamide; DEX: dexamethasone; DEX-P: dexamethasone palmitate; EBV: *Ebstein-Barr* virus ECZ: eculizumab; ETA: etanercept; ERA: enthesitis related arthritis; GCs: glucocorticoids; G-CSF: granulocyte colony stimulating factor; GVHD: graft versus host disease; i.v. intravenous; HLH: hemophagocytic lymphohistiocytosis; HSCT: hematopoietic stem cell transplant; ICU: intensive care unit; IFX: infliximab; IVIG: intravenous immunoglobulin; JAK-i: Janus Kinasis inhibitor; JDM: juvenile dermatomyositis; KD: Kawasaki disease; LD: lung disease; MAS: macrophage activation syndrome; MMF: mycophenolate mofetil; MPN: methylprednisolone; MCTD: mixed connective tissue disease; MOF: multiorgan failure; MTX: methotrexate; MKD: mevalonato kinase deficiency; NA: not available; PAN: panarteritis nodosa; PCP: *Pneumocystis* pneumonia; PDN: prednisone; PE: plasma exchange; PRES: posterior reversible encephalopathy syndrome; PSL: prednisolone; RTX: rituximab; SAE: severe adverse event; s.c. subcutaneous; sJIA: systemic juvenile idiopathic

arthritis; SLE: systemic lupus erythematosus; TAC: tacrolimus; TCZ: tocilizumab; TMA: thrombotic microangiopathy; TNF: tumor necrosis factor; UCTD: undifferentiated connective tissue disease; VCR: vincristine; VP16: etoposide; VZV: *Varicella-zoster* virus

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Are you using a treatment that addresses all 6 key manifestations of PsA?

The key clinical manifestations of PsA are joints, axial, skin, enthesitis, dactylitis and nails.[1]

Joint relief in PsA:

68% of patients achieved **ACR50** with Cosentyx® (secukinumab) at **Year 1** (observed data)[2]

Results from ULTIMATE (N=166). The primary endpoint of GLOESS mean change from baseline vs placebo at Week 12 was met (−9 vs −6, p=0.004)[2,3]

Click here to visit our HCP portal and learn more

Skin clearance in PsO:

55% of patients achieved **PASI100** at **Week 52** with Cosentyx 300 mg AI (secondary endpoint, observed data, N=41)[4]

Results from MATURE. The co-primary endpoints PASI 75 and IGA mod 2011 0/1 at Week 12 were met for Cosentyx 300 mg (N=41) vs placebo (N=40), (95% vs 10% and 76% vs 8% respectively, p<0.0001)[4]

Axial joint relief in PsA:

69% of patients achieved **ASAS40** at **Week 52** with Cosentyx 300 mg (secondary endpoint, observed data, N=139)[1]

Results from MAXIMISE. The primary endpoint of ASAS20 with Cosentyx 300 mg (N=164) vs placebo (N=164) at Week 12 was met (63% vs 31% respectively, p<0.0001)[1]

Cosentyx is the first and only, fully human biologic that directly blocks IL-17A regardless of its source[5–10]

8 years

A **consistent safety profile** with **over 8 years** of real-world experience[5,6,11]

The most frequently reported adverse reactions are upper respiratory tract infections (17.1%) (most frequently nasopharyngitis, rhinitis).[5,6]

Cosentyx licensed indications in rheumatology: Cosentyx is indicated for the treatment of active psoriatic arthritis in adult patients (alone or in combination with methotrexate) when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein and/or magnetic resonance imaging evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; moderate to severe plaque psoriasis in children and adolescents from the age of 6 years, and adults who are candidates for systemic therapy; active enthesitis-related arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate conventional therapy; active juvenile psoriatic arthritis in patients 6 years or older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy.[5,6]

ULTIMATE (N=166), a multicentre, randomised, double-blind, placebo-controlled, 52-week Phase III trial in patients with PsA. Patients were randomly assigned to receive either weekly subcutaneous Cosentyx (300 mg or 150 mg according to the severity of psoriasis) or placebo followed by 4-weekly dosing thereafter. The primary outcome of mean change in the ultrasound GLOESS from baseline to Week 12 was met (−9 vs −6; p=0.004).[2,3]
MATURE (N=122), a 52-week, multicentre, double-blind, randomised, placebo-controlled, Phase III trial in patients with PsO. Eligible patients were randomised to Cosentyx 300 mg or placebo. The co-primary endpoints were PASI75 and IGA mod 2011 0/1 responses at Week 12. The study met the co-primary endpoints: PASI75 and IGA mod 2011 0/1 response at Week 12 were met for Cosentyx 300 mg vs placebo (95% vs 10% and 76% vs 8% respectively, p<0.0001).[4]
MAXIMISE (N=498) a double blind, placebo-controlled, multicentre, Phase IIIb study in patients with PsA. Patients were randomised in a 1:1:1 ratio to receive Cosentyx 300 mg, 150 mg or placebo. The primary endpoint of the proportion of patients achieving and ASAS20 response with Cosentyx 300 mg at Week 12 vs placebo was met (63% vs 31% respectively, p<0.0001).[1]

ACR, American College of Rheumatology; AI, auto-injector; ASAS, Assessment of SpondyloArthritis International Society; BASDAI, Bath; ankylosing spondylitis disease activity index; EULAR, European Alliance of Associations for Rheumatology; GLOESS, Global EULAR and OMERACT synovitis score; IGA mod 2011 0/1, investigator global assessment modified 2011 0/1; OMERACT, outcome measures in rheumatology; PASI, psoriasis area and severity index; PsA, psoriatic arthritis; PsO, plaque psoriasis.

References: 1. Baraliakos X, et al. *RMD open* 2019;5:e001005; **2.** Conaghan PG, et al. Poster 253. *Rheumatology* 2022;61(Suppl1). DOI:10.1093/rheumatology/keac133.252; **3.** D'Agostino MA, et al. *Rheumatology* 2022;61:1867–1876; **4.** Sigurgeirsson B, et al. *Dermatol Ther* 2022;35(3):e15285; **5.** Cosentyx® (secukinumab) GB Summary of Product Characteristics; **6.** Cosentyx® (secukinumab) NI Summary of Product Characteristics; **7.** Lynde CW, et al. *J Am Acad Dermatol* 2014;71(1):141–150; **8.** Fala L. *Am Health Drug Benefits* 2016;9(Special Feature):60–63; **9.** Schön M & Erpenbeck L. *Front Immunol* 2018;9:1323; **10.** Gorelick J, et al. *Practical Dermatol* 2016;12:35–50; **11.** European Medicines Agency. European public assessment report. Medicine overview. Cosentyx (secukinumab). Available at: https://www.ema.europa.eu/en/documents/overview/cosentyx-epar-medicine-overview_en.pdf [Accessed May 2024].

NOVARTIS

Prescribing information, adverse event reporting and full indication can be found on the next page.

UK | May 2024 | 425034

Cosentyx® (secukinumab) Great Britain Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 75 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled syringe; Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. Consider discontinuation if no response after 16 weeks of treatment. Each 75 mg dose is given as one injection of 75 mg. Each 150 mg dose is given as one injection of 150 mg. Each 300 mg dose is given as two injections of 150 mg or one injection of 300 mg. If possible avoid areas of the skin showing psoriasis. *Plaque Psoriasis:* Adult recommended dose is 300 mg. Based on clinical response, a maintenance dose of 300 mg every 2 weeks may provide additional benefit for patients with a body weight of 90 kg or higher. Adolescents and children from the age of 6 years: if weight ≥ 50 kg, recommended dose is 150 mg (may be increased to 300 mg as some patients may derive additional benefit from the higher dose). If weight < 50 kg, recommended dose is 75 mg. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 75mg and 150 mg pre-filled syringe and 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common (≥1/10):* Upper respiratory tract infection. *Common (≥1/100 to <1/10):* Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions:* Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity:* Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** PLGB 00101/1205 – 75 mg pre-filled syringe x 1 - £304.70; PLGB 00101/1029 - 150 mg pre-filled pen x2 £1,218.78; PLGB 00101/1030 - 150 mg pre-filled syringe x2 £1,218.78; PLGB 00101/1198 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** June 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

UK | 290802 | June 2023

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report.

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com

Cosentyx® (secukinumab) Northern Ireland Prescribing Information.

Please refer to the Summary of Product Characteristics (SmPC) before prescribing.

Indications: Treatment of: moderate to severe plaque psoriasis in adults, children and adolescents from the age of 6 years who are candidates for systemic therapy; active psoriatic arthritis in adults (alone or in combination with methotrexate) who have responded inadequately to disease-modifying anti-rheumatic drug therapy; active ankylosing spondylitis in adults who have responded inadequately to conventional therapy; active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence in adults who have responded inadequately to non-steroidal anti-inflammatory drugs; active enthesitis-related arthritis and juvenile psoriatic arthritis in patients 6 years and older (alone or in combination with methotrexate) whose disease has responded inadequately to, or who cannot tolerate, conventional therapy; active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy. **Presentations:** Cosentyx 150 mg solution for injection in pre-filled pen; Cosentyx 300 mg solution for injection in pre-filled pen. **Dosage & Administration:** Administered by subcutaneous injection at weeks 0, 1, 2, 3 and 4, followed by monthly maintenance dosing. 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However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Psoriatic Arthritis:* For patients with concomitant moderate to severe plaque psoriasis see adult plaque psoriasis recommendation. For patients who are anti-TNFα inadequate responders, the recommended dose is 300 mg, 150 mg in other patients. Can be increased to 300 mg based on clinical response. *Ankylosing Spondylitis:* Recommended dose 150 mg. Can be increased to 300 mg based on clinical response. *nr-axSpA:* Recommended dose 150 mg. *Enthesitis-related arthritis and juvenile psoriatic arthritis:* From the age of 6 years, if weight ≥ 50 kg, recommended dose is 150 mg. If weight < 50 kg, recommended dose is 75 mg. However, 150mg solution for injection in pre-filled pen is not indicated for administration of this dose and no suitable alternative formulation is available. *Hidradenitis suppurativa:* Recommended dose is 300 mg monthly. Based on clinical response, the maintenance dose can be increased to 300 mg every 2 weeks. **Contraindications:** Hypersensitivity to the active substance or excipients. Clinically important, active infection. **Warnings & Precautions:** *Infections:* Potential to increase risk of infections; serious infections have been observed. Caution in patients with chronic infection or history of recurrent infection. Advise patients to seek medical advice if signs/symptoms of infection occur. Monitor patients with serious infection closely and do not administer Cosentyx until the infection resolves. Non-serious mucocutaneous candida infections were more frequently reported for secukinumab than placebo in the psoriasis clinical studies. Should not be given to patients with active tuberculosis (TB). Consider anti-tuberculosis therapy before starting Cosentyx in patients with latent TB. *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* New cases or exacerbations of inflammatory bowel disease have been reported with secukinumab. Secukinumab, is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, secukinumab should be discontinued and appropriate medical management should be initiated. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been observed. If an anaphylactic or serious allergic reactions occur, discontinue immediately and initiate appropriate therapy. *Vaccinations:* Do not give live vaccines concurrently with Cosentyx; inactivated or non-live vaccinations may be given. Paediatric patients should receive all age appropriate immunisations before treatment with Cosentyx. *Latex-Sensitive Individuals:* The removable needle cap of the 150mg pre-filled pen contains a derivative of natural rubber latex. *Concomitant immunosuppressive therapy:* Combination with immunosuppressants, including biologics, or phototherapy has not been evaluated in psoriasis studies. Cosentyx was given concomitantly with methotrexate, sulfasalazine and/or corticosteroids in arthritis studies. Caution when considering concomitant use of other immunosuppressants. **Interactions:** Live vaccines should not be given concurrently with secukinumab. No interaction between Cosentyx and midazolam (CYP3A4 substrate) seen in adult psoriasis study. No interaction between Cosentyx and methotrexate and/or corticosteroids seen in arthritis studies. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during and for at least 20 weeks after treatment. *Pregnancy:* Preferably avoid use of Cosentyx in pregnancy. *Breast feeding:* It is not known if secukinumab is excreted in human breast milk. A clinical decision should be made on continuation of breast feeding during Cosentyx treatment (and up to 20 weeks after discontinuation) based on benefit of breast feeding to the child and benefit of Cosentyx therapy to the woman. *Fertility:* Effect on human fertility not evaluated. **Adverse Reactions**: *Very Common* (≥1/10): Upper respiratory tract infection. *Common* (≥1/100 to <1/10): Oral herpes, headache, rhinorrhoea, diarrhoea, nausea, fatigue. *Uncommon (≥1/1,000 to <1/100):* Oral candidiasis, lower respiratory tract infections, neutropenia, inflammatory bowel disease. *Rare (≥1/10,000 to <1/1,000)*: anaphylactic reactions, exfoliative dermatitis (psoriasis patients), hypersensitivity vasculitis. *Not known:* Mucosal and cutaneous candidiasis (including oesophageal candidiasis). *Infections:* Most infections were non-serious and mild to moderate upper respiratory tract infections, e.g. nasopharyngitis, and did not necessitate treatment discontinuation. There was an increase in mucosal and cutaneous (including oesophageal) candidiasis, but cases were mild or moderate in severity, non-serious, responsive to standard treatment and did not necessitate treatment discontinuation. Serious infections occurred in a small proportion of patients (0.015 serious infections reported per patient year of follow up). *Neutropenia:* Neutropenia was more frequent with secukinumab than placebo, but most cases were mild, transient and reversible. Rare cases of neutropenia CTCAE Grade 4 were reported. *Hypersensitivity reactions:* Urticaria and rare cases of anaphylactic reactions were seen. *Immunogenicity*: Less than 1% of patients treated with Cosentyx developed antibodies to secukinumab up to 52 weeks of treatment. *Other Adverse Effects:* The list of adverse events is not exhaustive, please consult the SmPC for a detailed listing of all adverse events before prescribing. **Legal Category:** POM. **MA Number & List Price:** EU/1/14/980/005 - 150 mg pre-filled pen x2 £1,218.78; EU/1/14/980/010 – 300 mg pre-filled pen x 1 £1218.78. **PI Last Revised:** May 2023. Full prescribing information, (SmPC) is available from: Novartis Pharmaceuticals UK Limited, 2nd Floor, The WestWorks Building, White City Place, 195 Wood Lane, London, W12 7FQ. Telephone: (01276) 692255.

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Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis via uk.patientsafety@novartis.com or online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report

If you have a question about the product, please contact Medical Information on 01276 698370 or by email at medinfo.uk@novartis.com