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Basic science

Long-term efficacy of MAS825, a bispecific anti-IL1β and IL-18 monoclonal antibody, in two patients with systemic JIA and recurrent episodes of macrophage activation syndrome

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Abstract

Introduction: Systemic JIA (sJIA), a multifaceted autoinflammatory disorder, can be complicated by life-threatening conditions such as macrophage activation syndrome (MAS) and interstitial lung disease. The management of these conditions presents a therapeutic challenge, underscoring the need for innovative treatment approaches.

Objectives: To report the possible role of MAS825, a bispecific anti-IL1β and IL-18 monoclonal antibody, in the treatment of multi-drug-resistant sJIA.

Methods: We report two patients affected by sJIA with severe and refractory MAS and high serum IL-18 levels, responding to dual blockade of IL-1β and IL-18.

Results: The first patient is a 20-year-old man, presenting a severe MAS complicated by thrombotic microangiopathy, following SARS-CoV-2 infection. He was treated with MAS825, with quick improvement. Eighteen months later, the patient is still undergoing biweekly treatment with MAS825, associated with MTX, ciclosporin and low-dose glucocorticoids, maintaining good control over the systemic features of the disease. The second patient, a 10-year-old girl, presented a severe MAS case, complicated by posterior reversible encephalopathy syndrome, following an otomastoiditis. The MAS was not fully controlled despite treatment with i.v. high-dose glucocorticoids, anakinra and ciclosporin. She began biweekly MAS825, which led to a prompt amelioration of MAS parameters. After 10 months, the patient continues to receive MAS825 and is in complete remission.

Conclusion: In light of the pivotal role of IL-1β and IL-18 in sJIA, MAS and interstitial lung disease, MAS825 might represent a possible valid and safe option in the treatment of drug-resistant sJIA, especially in the presence of high serum IL-18 levels.

Keywords: systemic JIA, macrophage activation syndrome, interstitial lung disease, multi-drug-resistance, IL-1β, IL-18, MAS825

Rheumatology key messages

- MAS825, a bispecific anti-IL1β and IL-18 monoclonal antibody, can be effective in patients with sJIA complicated by MAS and ILD
- Interleukin-18 can be considered a treatment target in patients with sJIA
- Cytokine assays can support the choice of targeted treatment in patients with MAS

Introduction

Macrophage activation syndrome (MAS) is a serious and potentially fatal disease characterized by an uncontrolled hyperinflammatory reaction. MAS belongs to the family of haemophagocytic lymphohistiocytosis (HLH); specifically, the term MAS refers to a secondary HLH complicating a rheumatologic disease [1, 2]. MAS can complicate several autoimmune and autoinflammatory diseases, but it is more frequent in patients with systemic JIA (sJIA) and adult-onset Still's disease (AOSD), complicating 10–30% of cases [3].

To date, there are no standardized guidelines for the treatment of MAS, and no currently used therapy has been subjected to prospective studies. Recently, the EULAR/ACR HLH/MAS task force emphasized that the selection of treatment for these conditions should consider various factors, including severity and rate of progression, specific organ

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involvement, potential contributors, comorbid conditions and concurrent medications [4]. Ideally, targeted immunomodulation should be initiated as early as possible [4]. In recent years, various chemokines and cytokines have been correlated to the development of sJIA, AOSD and MAS, such as IL-1 beta (IL-1β), IL-6, IL-18, interferon-γ (IFN-γ), S-100 proteins, CXCL9 and CXCL10 [2]. Some of these molecules have been suggested as potential therapeutic targets [5, 6].

Methods

In this study, we retrospectively reviewed the clinical records of two patients with severe and refractory MAS with high serum IL-18 levels (>1000 pg/ml), who responded to dual blockade of IL-1β and IL-18. Plasma cytokines were analysed through the ELISA kit (IL-18, CXCL9, CXCL10, IFNγ Human ELISA Kit, Invitrogen, Thermo Fisher Scientific, Waltham, Massachusetts, USA) and Ella (cartridge for IL-18/IL-1RA/IL-6/TNFRI, Bio-Techne, Minneapolis, Minnesota, USA) according to the manufacturer's instructions. Genetic analysis for primary immunodeficiencies, autoinflammatory diseases and familial HLH were performed by a large NGS panel in patient 1, as reported previously [7], while in patient 2, whole exome sequencing was performed.

Results

The first patient is a 20-year-old Italian man with sJIA, diagnosed at the age of 2. His clinical condition, characterized by persistent systemic and joint involvement, demonstrated steroid-dependence and partial response to both synthetic and biologic DMARDs since disease onset. The NGS panel performed did not reveal any causative mutation in the 312 tested genes (Supplementary Table S1, available at *Rheumatology* online) [7] and the functional tests for HLH (perforin and CD107a expression of NK cells) were normal. Over his disease course, he received various combinations of conventional (MTX, thalidomide, ciclosporin), and biologic (anakinra, etanercept, adalimumab, tocilizumab, abatacept, canakinumab) immunomodulatory drugs, alongside with glucocorticoid courses (Supplementary Table S2, available at *Rheumatology* online). From July 2020, the patient was treated with oral baricitinib (4 mg/day) and subcutaneous methotrexate (15 mg weekly), achieving good control of both systemic and articular manifestations and requiring only minimal oral glucocorticoids (prednisone 5 mg/day, 0,08 mg/kg/day).

In February 2022, after a systemic and joint exacerbation, requiring i.v. methylprednisolone (MPN) and intra-articular steroid injections, baricitinib was increased to 6 mg/day.

In March 2022, the patient developed rhinitis and pharyngitis, and tested positive for SARS-CoV-2. Antiviral therapy with Nirmatrelvir-ritonavir and prophylactic enoxaparin were then started; the infection progressed with mild symptoms (low-grade fever, rhinitis and cough with mild interstitial thickening at the chest X-ray and no need for oxygen supplementation). In the following days, a new increase of both inflammatory and MAS indices was noticed, even in the absence of fever or other symptoms. Anti-inflammatory therapy was optimized with high-dose glucocorticoids (MPN 1 g/day for three consecutive days, followed by 30 mg three times a day), i.v. anakinra (200 mg/day) and oral ciclosporin (75 mg twice a day), along with the ongoing treatment with baricitinib (Fig. 1). Persistent high ferritin led to a switch from oral to i.v. ciclosporin; moreover, in light of previous favourable experiences in patients with MAS, anakinra was switched to s.c. canakinumab (300 mg) in combination with steroids and ciclosporin [8], without improvement. Anakinra was then re-started at the dosage of 400 mg/day. In the following days, signs of thrombotic microangiopathy (TMA) (decreased platelet count, complement and haptoglobin consumption) emerged. Treatment with eculizumab and plasmapheresis was started, resulting in rapid improvement. ADAMTS13 assay and genetic complement factors study were normal. Eculizumab was therefore withdrawn after two infusions. However, despite the ongoing treatment with i.v. high-dose glucocorticoids, high-dose i.v. anakinra and ciclosporin, ferritin levels and other MAS-related parameters were persistently high. Cytokine assays performed over the period of admission showed persistently elevated serum IL-18 levels (Fig. 1); CXCL9, CXCL10 and IFNγ levels, when measured, were accordingly elevated (data not shown).

Of note, during the admission, the patient experienced severe side effects secondary to the aggressive immunosuppressive treatments. These included osteoporosis leading to vertebral crashes that necessitated bisphosphonates infusions; generalized Varicella Zoster Virus and CMV reactivation, requiring prolonged treatment with valganciclovir; Pneumocystis carinii pneumonia treated with cotrimoxazole; Pseudomonas aeruginosa sepsis, for which meropenem was administered, subsequently switched to ceftazidime; and an oral-oesophageal candidosis, which was successfully treated with anidulafungin.

Seeking better control of MAS parameters and reduced immunosuppression, we sought compassionate use approval for MAS825, a bispecific monoclonal antibody targeting IL-1β and IL-18, from the Ethical Review Board of Regione Liguria. Biweekly i.v. treatment with MAS825 (700 mg) was then started in June 2022, leading to rapid clinical and laboratory MAS parameter improvement, enabling significant glucocorticoid tapering, baricitinib withdrawal and discharge (Fig. 1). After 18 months, the patient is still on biweekly MAS825 treatment, combined with MTX, ciclosporin and low-dose glucocorticoids (prednisone 15 mg/day), with complete control of systemic features. The patient displayed a persistence of articular involvement, requiring periodic intra-articular glucocorticoid injections. No adverse events from MAS825 have been observed so far.

The second patient is a 10-year-old girl from Brasil with sJIA, diagnosed at the age of 1. Her disease course was characterized by numerous systemic and articular flares, along with recurring episodes of MAS. These episodes exhibited incomplete response to both synthetic (MTX, ciclosporin) and biologic (anakinra, tocilizumab, canakinumab, baricitinib) DMARDs (Supplementary Table S3, available at *Rheumatology* online), requiring high doses of glucocorticoids, which led to a clear cushingoid appearance and other signs of glucocorticoid-related toxicity.

In addition, the patient had a history of recurrent infections since early childhood, including pyelonephritis requiring a right nephrectomy at the age of 2 and several episodes of sepsis. Notably, diffuse verrucosis affecting the fingers, face and perineum became evident from the age of 6. An extensive immunological work-up, including a large NGS panel, ruled out a primary immune defect; perforin expression and NK degranulation assay were normal. Whole exome sequencing with in silico analysis for genes associated with autoinflammatory diseases, primary immunodeficiency and HLH (Supplementary Table S1,

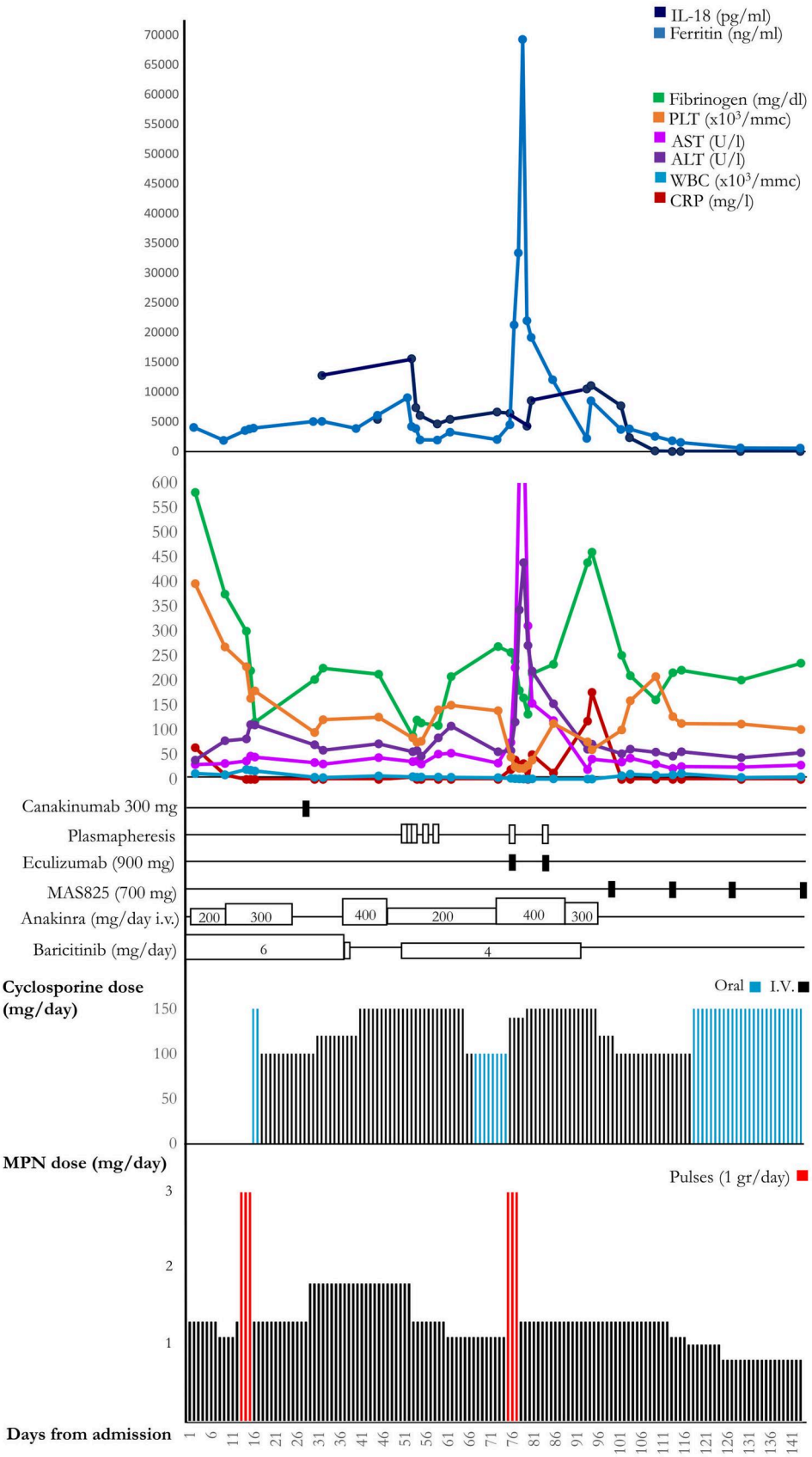

Figure 1. Ferritin, IL-18 levels and other MAS parameters in patient 1, alongside the ongoing treatment with immunosuppressants and MPN. MAS: macrophage activation syndrome; MPN: methylprednisolone

available at *Rheumatology* online) did not show any relevant pathogenic variant. At the age of 8, digital clubbing (class 3) was noticed, and a chest computed tomography scan revealed mild interstitial fibrosis and bronchiectasis.

Due to glucocorticoid dependence, she also developed osteoporosis with vertebral crashes, requiring bisphosphonate infusions from the age of 9. While on treatment with canakinumab (4 mg/kg/4 weeks), baricitinib (4 mg/day), ciclosporin (4 mg/kg/day) and low-dose prednisone (0.3 mg/kg/day), the girl presented with acute purulent otitis media complicated by otomastoiditis, requiring i.v. antibiotic therapy and trans-tympanic drainage. Due to the severe infection, administration of canakinumab was postponed. A few days post-discharge, the girl developed high-grade fever and hypovolemic shock. In the suspicion of sepsis, i.v. antibiotics were started without clinical amelioration. Blood tests were consistent with MAS, therefore the girl was treated with glucocorticoid pulses (MPN 30 mg/kg/day for 3 days) followed by i.v. glucocorticoid treatment (MPN 3 mg/kg/day), i.v. anakinra (4 mg/kg/day) and oral ciclosporin (4 mg/kg/day), resulting in progressive clinical improvement (Fig. 2A).

Later, arterial hypertension resistant to treatment with amlodipine and bisoprolol was observed, followed by seizures, indicative of posterior reversible encephalopathy syndrome (PRES), as documented by brain MRI. Neuro-protective treatment with levetiracetam was started, and ciclosporin withdrawn. In the following days, the patient presented again fever and a worsening of MAS parameters, along with reduced blood oxygen saturation, necessitating oxygen supplementation (Fig. 2A). Due to the clinical picture, the patient was again treated with glucocorticoid pulses (MPN 30 mg/kg/day for 3 days). Furthermore, given the observation of elevated serum IL-18 levels at various time points (Fig. 2B), we sought and obtained permission for the compassionate use of MAS825 from the Ethical Review Board of Regione Liguria. i.v. MAS825 treatment (10 mg/kg biweekly) resulted in rapid improvement of clinical and laboratory parameters, allowing progressive glucocorticoid tapering (Fig. 2A) and oxygen supplementation withdrawal.

After 10 months, the patient is still on treatment with biweekly MAS825 10 mg/kg. After 1.5 years of continuous treatment and the occurrence of many side effects (hypertrichosis and gingival hypertrophy), ciclosporin was withdrawn. Currently, the patient is on treatment with MAS825 and low-dose prednisone (2.5 mg/day – 0.05 mg/kg/day), with improved systemic arterial hypertension, allowing reduction in anti-hypertensive treatment. Brain MRI normalized and anti-epileptic drugs were withdrawn.

After 10 months of treatment with MAS825, respiratory functional tests and the degree of clubbing were stable. Furthermore, the dramatic reduction in immunosuppressive treatment and the administration of anti-papillomavirus vaccinations prompted the complete resolution of diffuse verrucosis [9]. No adverse events related to MAS825 were observed.

Discussion

The present cases highlight the complexities in managing multi-drug resistant sJIA, especially when associated with severe, recurrent MAS episodes, that are poorly responsive to standard treatments, and/or interstitial lung disease (ILD). In light of the pivotal role of IL-18 in the development and maintenance of MAS and ILD, IL-18 has been proposed as a possible and specific therapeutic target in IL-18-mediated inflammatory conditions [10, 11].

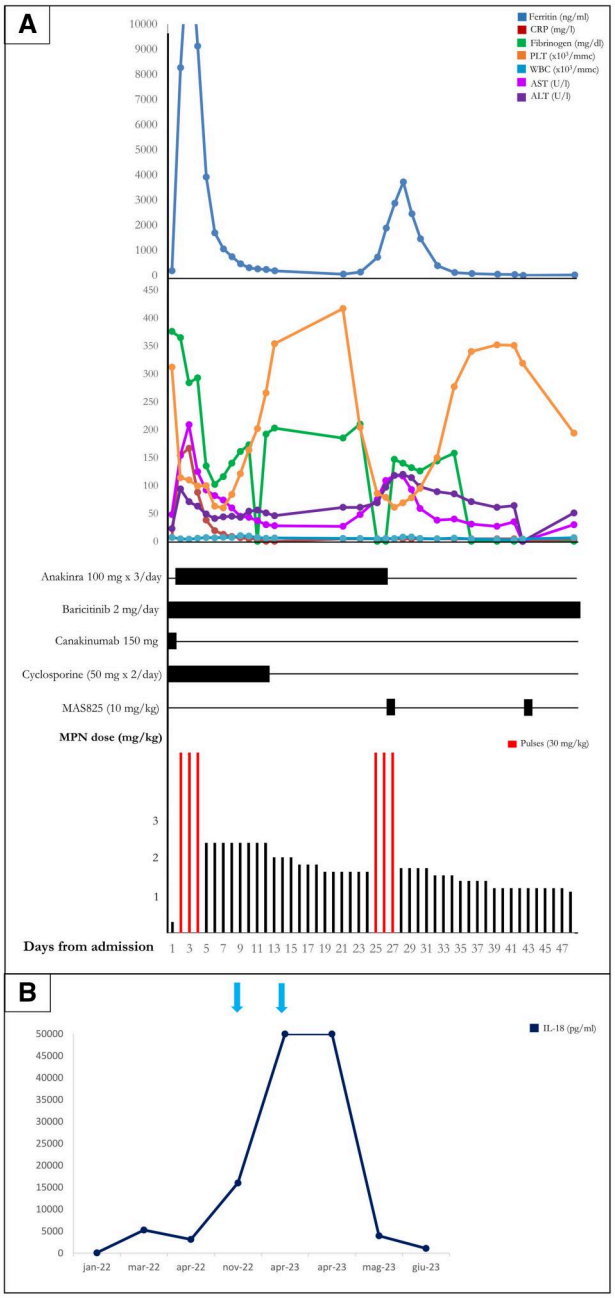

Figure 2. (A) ferritin levels and other MAS parameters during the last MAS episodes in patient 2, along with treatment with immunosuppressants and methylprednisolone (MPN). (B) IL-18 levels (pg/ml) overtime in patient 2 (arrow = MAS episode). MAS: macrophage activation syndrome

Tadekinig alfa, a recombinant IL-18 binding protein, was successfully used to treat severe cases of NLRC4-associated diseases, characterized by very high circulating IL-18 levels and recurrent MAS episodes [12]. However, in a phase 2 clinical trial, Tadeking alfa showed only modest efficacy in AOSD patients without MAS or ILD [13], though improvement in both systemic disease manifestations and inflammatory parameters was observed [13]. Of note, this drug was adopted, under compassionate use, in a 6-year-old girl with refractory sJIA and recurrent MAS episodes, leading to an

improvement of the clinical picture and glucocorticoid dosage reduction [11].

MAS825, a bispecific anti-IL-1β/IL-18 monoclonal antibody, has recently been developed. Its safety and efficacy have been tested in patients with severe COVID-19 pneumonia [14]; moreover, a clinical trial assessing its efficacy, safety and tolerability in patients with monogenic IL-18-driven autoinflammatory diseases, including NLRC4-GOF, XIAP Deficiency and CDC42 mutations, is currently ongoing (ClinicalTrials.gov).

In light of the crucial role of IL-1β and IL-18 in sJIA, MAS and ILD [10, 11], MAS825 might represent a possible valid option in the treatment of sJIA patients with repeated and/or drug-resistant MAS and/or ILD.

Rood *et al.* reported the efficacy of MAS825 in a sJIA patient with ILD, observing a reduction in both total and free IL-18 levels in both serum and bronchoalveolar lavage. After 10 months of treatment, the patient presented an improvement in oxygen saturation, exercise tolerance and quality of life, allowing glucocorticoid withdrawal [15]. More recently, MAS825 was used in a 16-year-old girl with relapsing MAS episodes, allowing better disease control and glucocorticoid reduction [16].

In our experience, MAS825 was able to allow complete control of a recalcitrant and long MAS episode requiring a high level of immunosuppression in patient 1, presenting as further complication the occurrence of TMA, a complication rarely reported in a particular severe subset of MAS patients [17]. Similarly, in patient 2, the drug prompted a quick and complete control of disease activity, allowing a significant reduction of the dependence on immunosuppressive treatment and amelioration of lung manifestations. In both patients, MAS825 substantially reduced the iatrogenic side effects due to the previous aggressive immunosuppressive treatments, including severe infections.

In recent years, parenchymal lung involvement has been observed in patients with sJIA who have a severe clinical course, particularly in the presence of recurrent episodes of MAS [10, 18]. It's still under debate whether biological drugs, in particular anti-cytokines, may increase the risk of developing such condition [18]. On the other and, a prominent role of pro-inflammatory cytokines, in particular IL-18, in patients with recurrent episodes of MAS and/or lung involvement [10, 11], suggests the therapeutic role of IL-18 blockade in such cases, as recently reported [15, 19].

Notably, the absence of any adverse events in the 18- and 10-month follow-up of our patients, along with similar findings in other reported cases [15, 16], suggests a good safety profile of MAS825.

The unique availability of a parenteral formulation, alongside the bimonthly administration schedule, represents a limitation for the use of this drug in daily clinical practice, particularly when the drug is used long term. A subcutaneous formulation, which is currently unavailable, would improve the daily care of such patients.

According to the preliminary experience presented in the current article, MAS825 could be used as a safe and effective drug not only in acute MAS, but also as continuous treatment in sJIA patients with repeated MAS and/or ILD. In light of the here presented experience and other literature evidence, we strongly advocate for a therapeutic trial to provide more robust evidence on the possible role of the bispecific anti-IL-1β and IL-18 inhibition strategy, especially in a subgroup of sJIA and Still's disease patients with high serum IL-18 levels.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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