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Letters to the Editor

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Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: case series with 12 patients

SIR, Macrophage activation syndrome (MAS) belongs to the haemophagocytic lymphohistiocytic (HLH) disorders, and is one of the most feared complications of paediatric inflammatory diseases with mortality rates up to 53% [1]. Its early recognition and treatment are critical in improving outcome [2]. However, current therapeutics, including corticosteroids, ciclosporin and intravenous immunoglobulin (IVIG), do not work for all children, and the next-line treatments, such as etoposide, are associated with sepsis, a risk of secondary malignancy and up to 44% mortality rate [3]. A less immunosuppressive but effective targeted therapy is in demand. Anakinra, an IL-1 receptor antagonist, has been highly effective in treating systemic juvenile idiopathic arthritis (sJIA) [4], and MAS may occur in up to half of sJIA patients [5]. Recently, three case reports have demonstrated anakinra to effectively treat MAS as part of panniculitis, sJIA and adult onset Still's disease [6–8]. Herein, we report the benefit of anakinra in 12 children with paediatric rheumatic disease-related MAS (prMAS). All patients at the Alberta Children's Hospital and the Children's Hospital of Philadelphia, who received anakinra between 2006 and 2009 for prMAS were studied retrospectively. The diagnosis of MAS was based on the combination of: (i) Ravelli's preliminary criteria for sJIA-associated MAS [9] and (ii) HLH-2004 criteria for inherited HLH [10]. Resolution of MAS was defined by the HLH-2004 criteria [10], and included no fever, splenomegaly, cytopenia (haemoglobin $\geqslant 90$ g/l, platelets $\geqslant 100 \times 10^9$/l, absolute neutrophil count $\geqslant 500$ cells/μl) or hypertriglyceridaemia (>500 mg/l) and normalization of soluble CD25 (sCD25) if the test was performed.

When prMAS occurred, all patients initially received corticosteroids ($n = 12$) and other immunosuppressants [IVIG ($n = 9$), ciclosporin ($n = 10$), etoposide ($n = 2$, one dose each) and etanercept ($n = 1$)] with limited benefit. Anakinra was given for better prMAS control. Etanercept and etoposide were discontinued when anakinra was initiated. In all other patients, anakinra was added to pre-existing MAS therapy at 2 mg/kg/day s.c. (maximum dose 100 mg/day) once daily. Laboratory measurements as per Ravelli's and HLH-2004 criteria were measured before and after anakinra administration. CRP was additionally measured in selected patients. During hospitalization for prMAS, five patients were diagnosed with new-onset sJIA by the ILAR criteria, three patients with vasculitis using ACR criteria and one patient with acute rheumatic fever. Institutional Review Board approval was obtained from both institutions before the study for publication of the results of the case series.

In total, 12 patients with prMAS were treated with anakinra between 2006 and 2009. Baseline characteristics are shown in Table 1. Before anakinra, five patients required intensive care, and potential infectious triggers were present in seven patients. All patients met diagnostic criteria for Ravelli's sJIA-associated MAS [9]. Seven of 12 met the HLH-2004 criteria [10], including elevated ferritin ($n = 12/12$), haemophagocytosis in the bone marrow ($n = 5/7$), abnormal NK cell activity ($n = 1/2$) and elevated sCD25 ($n = 4/6$). The median hospitalization stay before anakinra was 11 (range 1–27) days. All patients achieved MAS remission after addition of anakinra within a median of 13 (range 2–19) days. Corticosteroids were discontinued by 6 weeks in seven patients. Of all laboratory parameters, CRP and ferritin correlated the best with MAS activity (Table 1). Median (interquartile range) CRP ($n = 9/12$) 2 days before the use of anakinra was 125 (95.5–183.5) mg/l compared with median 6.8 (1.9–8.9) mg/l 5 days after the use of anakinra ($P = 0.0039$). Patients were followed for a median of 22 (range 2–40) months, and all were in remission of MAS at the final follow-up with excellent control of the underlying rheumatic disease. There were no noted side effects from anakinra administration.

We report resolution of severe prMAS following addition of anakinra to conventional immunosuppressive therapy. In these severely ill patients, anakinra was chosen over HLH-2004 treatment with etoposide and high-dose dexamethasone because of concern for sepsis, potential future malignancy and the high mortality rate associated with this protocol [3]. The clinical response was dramatic and rapid, occurring within days. All patients fully recovered, including five who had required intensive care support.

In sJIA-related MAS, the mortality rate was reported in 2001 as 28% [2], yet all our patients with sJIA did well. Our three patients with vasculitis and one with rheumatic fever-associated MAS also remitted. Ravelli's 2005 preliminary MAS criteria [9] allowed for early confirmation of MAS, although we also utilized ferritin, sCD25 and NK cell activity from the HLH-2004 criteria to confirm the diagnosis [10]. We attribute the excellent outcome in our patients to early diagnosis and immediate therapeutic intervention, including early use of anakinra. As all patients were treated with anakinra and traditional therapies, it is possible that the combination of medications contributed to the resolution of MAS. We therefore recommend anakinra in combination with high-dose corticosteroids, ciclosporin and IVIG, rather than as a sole agent. Further studies with larger patient numbers are required to better define

Table 1 Baseline patient characteristics, selected laboratory results pre- and post-anakinra and eventual outcome

Patient	Age, years	Sex	Eventual rheumatic diagnosis	ICU	Prior medications for MAS	Ferritin[a] −2 days	Ferritin +14 days	CRP[a] −2 days	CRP +5 days	MAS resolution, days	CS stopped after anakinra, days	Follow-up, months	Outcome, resolution of MAS
1	13.5	M	ARF	+	Mpred, IVIG, Csp	8900	438	ND	8.9	15	48	13	+
2	17	M	sJIA	−	Mpred, IVIG, Csp	4787	201	121	8.7	15	51	11	+
3	9	F	sJIA[b,c]	−	Mpred, IVIG, Csp	2279	393	125	11.8	12	5	23	+
4	12	M	sJIA[b,d]	−	Mpred, IVIG, Csp, etanercept	3141	125	263	9.1	8	30	40	+
5	0.5	M	ANCA + vasculitis	+	Mpred, IVIG	500	276	78	0.1	19	35	19	+
6	8	F	sJIA	−	Mpred, IVIG, Csp	423	11	89	5.8	7	48	24	+
7	1.5	F	sJIA[b,e]	−	Mpred, IVIG, Csp	438	19	102	0.3	17	105	15	+
8	6	F	Churg–Strauss vasculitis	+	Mpred, IVIG	758	260	131	6.8	14	463	38	+
9	15.5	M	sJIA[c]	−	Mpred, IVIG, Csp	1055	389	198	3.5	15	Not yet	2	+
10	13	M	sJIA	−	Mpred, IVIG, Csp	1285	31	169	7.2	2	43	33	+
11	5	M	KD[b]	+	Mpred, Csp, Eto	>10 000	ND	ND	ND	10	NA[f]	24	+
12	8	F	sJIA[b]	+	Mpred, Csp, Eto	>10 000	430	ND	ND	10	NA[f]	5	+

[a]Ferritin (normal range 10–110) is expressed as μg/l and CRP (normal range 0–8) is expressed as mg/l. Time '0' refers to initiation of anakinra. Known rheumatic diagnoses before development of MAS: sJIA in Patients 3, 4, and 9. Potential infectious triggers: positive anti-streptolysin A-titre in Patients 1, 3, 6, 7 and 9. Patient 1 met the criteria for ARF and also had positive PCR for EBV. Patient 10 had positive monospot. Patient 5 developed *Escherichia coli* septicaemia at the time of MAS after having been hospitalized with pulmonary haemorrhage and acute renal failure requiring dialysis. [b]Patients who met <5 out of 8 HLH-2004 criteria. Three patients (Patients 3, 4 and 7) did not have a bone marrow biopsy, and NK function assessment was not available for these same patients. sCD25 was not measured in three patients (Patients 3, 11 and 12). [c]Both these patients with known sJIA were on etanercept when they developed MAS. Etanercept was discontinued as soon as MAS was diagnosed. [d]This patient was initially suspected of Kawasaki disease, and was treated with IVIG and aspirin before diagnosis of MAS and sJIA. [e]This patient had received etanercept for MAS after incomplete response to IVIG, Csp and CS, with no improvement. [f]Detailed data for corticosteroid taper were not available for these two patients. ICU: intensive care unit; ARF: acute rheumatic fever; KD: Kawasaki disease; ND: not done; NA: not available; Mpred: methylprednisolone; Csp: ciclosporin; Eto: etoposide; CS: corticosteroids.

the promising role of anakinra in the management of prMAS.

Rheumatology key message

- Early use of anakinra, in conjunction with standard immunosuppression, is effective in severe MAS.

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An unusual phenotype in Muckle–Wells syndrome associated with *NLRP3* E311K

Sir, Muckle–Wells syndrome (MWS) is part of the spectrum of auto-inflammatory disease now known as the cryopryin-associated periodic syndromes (CAPSs), along with familial cold urticaria/familial cold auto-inflammatory syndrome and chronic infantile neurological cutaneous and articular syndrome. These dominantly inherited disorders share a common genetic basis [1], in which *NLRP3* gene mutations result in up-regulated activity of the NLRP3 inflammasome and overproduction of IL-1 [2]. MWS was originally described as the combination of urticaria, sensorineural deafness and propensity to amyloid A amyloidosis [3], although this triad is typically accompanied by conjunctivitis, fever and arthralgia. Diagnosis of this rare disorder is especially important given its extraordinary response to IL-1 inhibitors. We report here a family with MWS that presented atypically with prominent joint involvement and virtually no rash, hence broadening the phenotype, but which nevertheless responded dramatically to anakinra therapy.

A 47-year-old gentleman was diagnosed to have MWS following a 40-year history of intermittent large-joint arthralgia and swelling, conjunctivitis and fevers. He had had a few episodes of cellulitic rashes in his teens but no urticaria, and had developed sensorineural hearing loss in his twenties. During the 6 months preceding diagnosis, his articular symptoms had intensified; he had also been hospitalized with steroid-responsive pericarditis during which time a renal cell carcinoma (RCC) was indentified and resected. Three of the patient's eight children, including identical twins, had a similar syndrome of recurrent articular and ocular symptoms three to four times per year along with sensori-neural hearing impairment to differing extents. None had ever had more than the most fleeting urticaria. All four affected family members were heterozygous for *NLRP3* E311K, which has been reported in one other MWS patient. Following the introduction of anakinra, the ocular and articular symptoms resolved completely over a 1- to 2-month period in each of the four patients and each of the three children demonstrated