

## Response to: 'Effectiveness and safety of ruxolitinib for the treatment of refractory systemic idiopathic juvenile arthritis like associated with interstitial lung disease: case report' by Bader-Meunier *et al*

We were very interested to read the correspondence from Dr Bader-Meunier and colleagues, who report a case of systemic juvenile idiopathic arthritis (sJIA) with associated lung disease.<sup>1</sup> This case indeed matches the description of and provides further evidence for the striking and unusual clinical characteristics we recently detailed in an international case series of such patients.<sup>2</sup> We thank the authors for this communication.

One aspect of particular importance in the reported case is the development of drug reaction with eosinophilia and systemic symptoms (DRESS), a delayed hypersensitivity reaction, to canakinumab (monoclonal antibody to interleukin (IL)-1 $\beta$ ). As we noted, DRESS is a possibly under-recognised event preceding the clinical recognition or development of this lung disorder in at least a subset of patients.<sup>2</sup> The authors' correspondence, along with Drs Bader-Meunier and Povlika's prior publication of two cases of probable DRESS in association with IL-1 inhibitors,<sup>3</sup> highlights the need to consider this type of drug hypersensitivity.

Further studies will be required to evaluate the potential benefit of ruxolitinib for sJIA and lung disease and will be of considerable interest to clinicians caring for children with this condition. In addition, and importantly, removal of the IL-1 inhibitor in this case may also have contributed to the improved lung status. Early cessation of the suspect drug is a key to controlling DRESS progression, and DRESS can continue for a period of time subsequent to withdrawal of the causative medication.<sup>4</sup> High-dose steroids, well-known to be efficacious in active sJIA, also may have provided broader clinical benefit,<sup>4</sup> including for lung disease. Indeed, the apparent increased incidence of parenchymal lung disease in children with sJIA occurred concurrent with changes in sJIA management that typically involve reduced steroid use.<sup>2</sup>

The patient in this report showed increased expression of interferon (IFN)-stimulated genes during anti-IL-1 treatment, consistent with evidence that a subset of patients on cytokine inhibition for sJIA developed an IFN signature/heightened response.<sup>5,6</sup> Together with the observation of elevated circulating Th1 cells, the findings raise the possibility that IFN- $\gamma$  signalling is a target of ruxolitinib in this patient. There may be other targets, as the authors acknowledge. A role for IFN- $\gamma$  in lung disease in sJIA has been proposed<sup>7</sup> and requires more investigation. IFN- $\gamma$  is strongly implicated in macrophage activation syndrome (MAS).<sup>8,9</sup> In sJIA cases with the constellation of lung disease and unusual clinical features, we looked at the occurrence of MAS in relation to lung disease. We found that, whereas 33% had MAS before lung disease detection (most at disease onset and responsive to treatment), 78% had MAS at or during lung disease, 52% being overt MAS and 26% being subclinical (table 1). More research is needed to determine whether MAS in sJIA with lung disease is triggered by DRESS<sup>10</sup> or by lung disease, or reflects the immune dysfunction that causes lung disease.

Based on these observations, it is very difficult to assign the sources of improvement in this case with certainty. Nonetheless, as the authors suggest, further testing of the safety and effectiveness of ruxolitinib or other Janus kinase inhibitors in sJIA with lung disease appears warranted.

**Table 1** MAS in relation to lung disease

MAS before lung disease*†	MAS at or during lung disease‡	P value
Total MAS 15 (33%)§	Total MAS 36 (78%)	<0.0001
Overt 15	Overt 24	0.059
Subclinical only 0	Subclinical only 12	0.016
At sJIA onset 12 (26%)	First MAS episode 20 (43%)	
>1 episode 6 (13%)		

\*MAS definitions were per Ravelli *et al*.<sup>11</sup>

†Before lung disease: up to 6 months before diagnosis of lung disease, because true onset of lung disease is not known.

‡At or during lung disease: from 6 months before diagnosis of lung disease and thereafter.

§n=46 patients with sJIA, parenchymal lung disease and exposure to IL-1/IL-6 inhibition.

IL, interleukin; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

Vivian E Saper,<sup>1</sup> Guangbo Chen,<sup>2</sup> Purvesh Khatri,<sup>2</sup> Elizabeth D Mellins <sup>3</sup>

<sup>1</sup>Department of Pediatrics, Stanford University, Stanford, California, USA

<sup>2</sup>Institute for Immunity, Transplantation and Infection, Center for Biomedical Informatics, Medicine, Stanford University, Stanford, California, USA

<sup>3</sup>Department of Pediatrics, Program in Immunology, Stanford University, Stanford, California, USA

**Correspondence to** Dr Elizabeth D Mellins, Department of Pediatrics, Program in Immunology, Stanford University, Stanford, CA 94305, USA; mellins@stanford.edu

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### ORCID iD

Elizabeth D Mellins <http://orcid.org/0000-0003-2577-139X>

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