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Dr. Eloseily et al reply

To The Editor:

We thank Romano et al[1] for their thoughtful comments and for sharing their relevant clinical experience with systemic juvenile idiopathic arthritis (sJIA) complicated by macrophage activation syndrome (MAS) with hepatic involvement. Their report of recurrent hepatic flares requiring combined therapeutic strategies extends our observations and further supports the emerging concept of interferon (IFN)-γ–driven liver pathology in sJIA-MAS.

We agree that interleukin (IL)-18 and C-X-C motif chemokine ligand 9 (CXCL9) are valuable biomarkers for subclinical inflammation and disease monitoring. The persistent elevation of IL-18 described by Romano et al[1] mirrors our observation of markedly elevated baseline IL-18 levels in patients with liver-predominant MAS, supporting its role as a marker of ongoing immune activation despite apparent clinical remission.[2] In our cohort, elevations in CXCL9 and ferritin paralleled liver injury and improved following IFN-γ blockade, supporting their utility as dynamic markers of disease activity.[3] The findings of Romano et al[1] further emphasize that hepatic dysfunction may represent an isolated or predominant manifestation of MAS biology, even in the absence of overt systemic features, highlighting the limitations of current classification criteria, particularly in patients receiving biologic therapies.

We also agree with their point that hepatic involvement may occur in the absence of overt MAS. In our series, several patients had subclinical or organ-dominant MAS without fulfilling classification criteria, emphasizing that current criteria may underdiagnose disease in patients receiving biologic therapy.[4]

The differences in histopathologic findings between our cohorts likely reflect a spectrum of MAS-related liver injury. Whereas Romano et al[1] report mild inflammatory infiltrates, our patients demonstrated more severe features, including hepatocellular necrosis and parenchymal collapse. These differences could relate to timing of biopsy, disease severity, and concurrent immunosuppression, and support the concept that IFN-γ–mediated hepatic injury exists along a continuum.

We also note with interest their use of baricitinib following recurrence after emapalumab discontinuation. Although our patients showed rapid improvement with IFN-γ blockade, long-term durability of response remains uncertain. In our cohort, the 4 patients were followed for 45 months, 15 months, 96 months, and 24 months after the liver injury episode, respectively, without prior or recurrent liver dysfunction or MAS events during follow-up.[3] None required repeat treatment with emapalumab or later initiation of a Janus kinase inhibitor (JAKi) for recurrent or persistent liver disease. JAKi, by targeting downstream IFN-γ signaling, nevertheless represent a practical and accessible therapeutic option, particularly in settings where emapalumab is unavailable or where relapse occurs after discontinuation. Future studies should directly compare these strategies and define optimal sequencing or combination approaches.

In summary, both our report[3] and the report of Romano et al[1] highlight the importance of recognizing hepatic involvement as a key manifestation of sJIA-MAS and of tailoring therapy to underlying immune mechanisms. Collaborative studies with longitudinal follow-up will be essential to refine biomarker use, optimize treatment strategies, and define long-term outcomes in this heterogeneous disease phenotype.

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COMPETING INTERESTS

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