Which JAKi is better for SAPHO syndrome?

Sirs,

SAPHO syndrome is a rare group of autoinflammatory disorders characterised by synovitis, acne, pustulosis, hyperostosis, and osteitis. Currently, TNF inhibitors (TNFis) and Janus kinase inhibitors (JAKis) are widely used for the management of SAPHO syndrome (1-5), TNFis have been shown to relieve bone pain rapidly; however, their efficacy in treating skin rashes remains unsatisfactory, and TNFis may even induce paradoxical dermatitis (6-7). JAKis exhibit superior efficacy in treating skin rashes (1-2), although the comparative effectiveness of different JAKis remains unclear. We report the case of a patient who achieved complete resolution of bone pain and skin rashes following sequential treatment with a TNFi, baricitinib, and subsequently upadacitinib.

A 60-year-old woman presented with pustular rashes on both hands, accompanied by anterior chest wall pain (Fig. A1). Laboratory testing revealed elevated C-reactive protein (94.49 mg/L) and an elevated erythrocyte sedimentation rate (53 mm/h). HLA-B27 was negative. 99mTc-MDP20 bone scintigraphy revealed increased tracer uptake in the left clavicular sternal end (Fig. B). Therefore, based on imaging examinations and symptoms, she was diagnosed with SAPHO syndrome. The patient was initially treated with 40 mg of adalimumab q2w, which significantly relieved her pain but slightly exacerbated her rash, as indicated by the emergence of new lesions on her middle finger (Fig. A2). Consequently, treatment was switched to 2 mg of baricitinib qd for 3 months, which resulted in partial alleviation of the rash but not complete resolution (Fig. A3). Then, after 2 months of treatment with 15 mg qd upadacitinib, the rash completely disappeared (Fig. A4). In a follow-up period of 6 months during which upadacitinib therapy was continued, the rash did not recur.

SAPHO syndrome is a rare group of autoinflammatory disorders in which some patients may develop paradoxical rashes after treatment with biologics, which is commonly associated with the IFN-α (JAK1/TYK2) pathway. IFN-α can activate plasmacytoid dendritic cells to produce TGF-β, IL-6, IL-1, and IL-23, promoting the development of IL-17-producing Th17 cells, and thus leading to the occurrence of paradoxical rashes such as palmoplantar pustulosis (PPP) and psoriasis (6). JAKis inhibit the expression of proinflammatory cytokines and the differentiation of Th17 cells through the inhibition of JAK-STAT signalling (1, 8). Research conducted by McInnes *et al*. demonstrated that baricitinib suppresses IFN-α (JAK1/TYK2) more effectively than tofacitinib (3, 9). However, after treatment with baricitinib, the patients' PPP failed to resolve completely, which was related to the insufficient dose administered and the low selectivity of the JAKi. Considering that adverse reactions are more likely with first-generation JAKis (3-4, 10) and that the highly selectivity of upadacitinib would render it safer and more precise for therapeutic interventions, Taylor *et al*. performed a cell assay comparing the selectivity of baricitinib, tofacitinib, and upadacitinib, and the results demonstrated that upadacitinib is the most potent inhibitor of IFN-α signalling (3). Therefore, we ultimately used upadacitinib. After switching to upadacitinib, the patient's pustules on the palms completely disappeared. The therapeutic outcomes of baricitinib and upadacitinib demonstrated that the efficacy of upadacitinib in treating the rash caused by SAPHO was superior to that of baricitinib. This report presents a novel approach for the treatment of refractory SAPHO syndrome, but further clinical investigations are necessary to substantiate these findings.

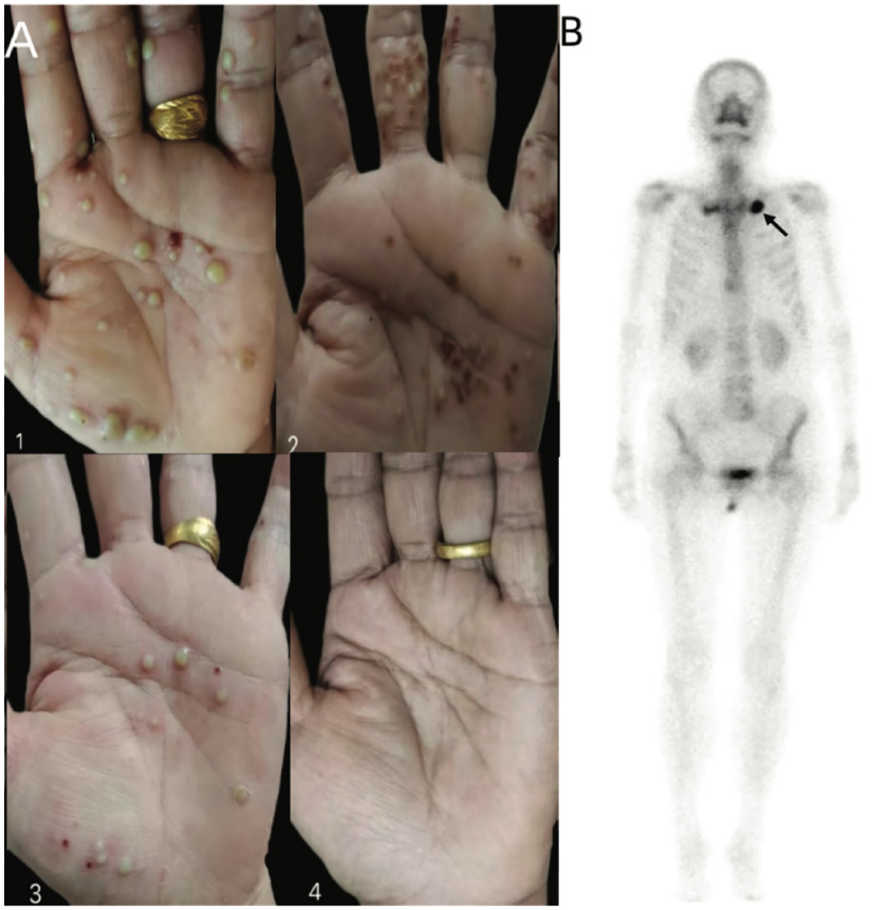

Fig. 1. A: 1. Prior to receiving treatment, the patient had pustules on her left hand. 2. After adalimumab treatment, the patient experienced a slight worsening of the pustules, as evidenced by new pustules appearing on part of the middle finger. 3. After baricitinib treatment, the patient's symptoms were partially relieved. 4. After treatment with upadacitinib, the patient's symptoms completely resolved.
B: Radiological image of a patient with SAPHO syndrome: 99mTc bone image showing increased radioconcentration in the left clavicular sternal end. (arrows).

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