Rapid and sustained remission of synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome with IL-23p19 antagonist (risankizumab)

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INTRODUCTION

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is an uncommon autoinflammatory syndrome, with an estimated prevalence of 1 in 10,000 in the Caucasian population.[1] SAPHO is defined by the diagnostic criteria proposed by Kahn et al,[2] which includes either a chronic multifocal sterile osteomyelitis, sterile osteitis, or arthritis.[1,3] The latter 2 require at least 1 accompanying dermatologic feature, which includes palmoplantar pustulosis, pustular psoriasis, or severe acne.[1-3]

The etiopathogenesis of SAPHO is incompletely defined due to the rarity of the condition and the limited amount of molecular and translational data about the disease. Currently, there is no universally agreed upon therapeutic approach with equal efficacy for the rheumatologic and dermatologic aspects of the disease.[3] Existing treatments are largely based on targeting the disparate manifestations of the syndrome. They include the use of non-steroid anti-inflammatory drugs; colchicine, methotrexate, sulfasalazine, and glucocorticoids for joint pain and osteitis; and oral antibiotics or retinoids for acne and hidradenitis suppurativa (HS).[1,3] Newer monoclonal antibody therapies trialed for SAPHO syndrome have been described in case reports and small case series and include interleukin 1 (IL-1) antagonist (anakinra), IL-17 (secukinumab), IL-12/23p40 (ustekinumab), and tumor necrosis factor (TNF)-α inhibitors (etanercept, adalimumab, and infliximab).[3] A systematic review of these biologic agents indicates that they often produce an incomplete or temporary clinical response.[3] Furthermore, these biologic agents have demonstrated a differential response in their ability to improve the bone and joint symptoms when compared with the skin symptoms.[3] Osteitis and synovitis appear to have a greater response to TNF-α blockade, whereas skin symptoms seem to improve with IL-17 blockade.[3]

Abbreviations used:

HS:	hidradenitis suppurativa
IL:	interleukin
SAPHO:	synovitis, acne, pustulosis, hyperostosis, and osteitis
Th:	helper T
TNF:	tumor necrosis factor

Given the role of IL-23 in the activation of the helper T (Th) 17 immune axis, the use of IL-23p19 antagonists has a theoretical potential in the treatment of SAPHO.[4-6] Here, we report, to our knowledge, the first known case of rapid and sustained remission of SAPHO syndrome with the use of an IL-23p19 antagonist risankizumab.

CASE REPORT

A 29-year-old woman of South Asian background presented with a 14-year history of severe

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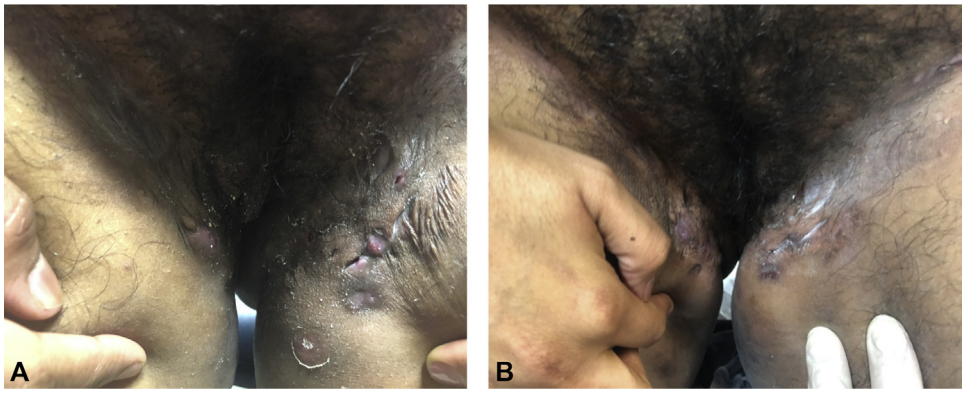

Fig 1. A, Clinical presentation at week 0 of risankizumab therapy demonstrating inflamed inguinal nodules, draining tunnels, and significant scarring. **B**, Clinical presentation at week 4, demonstrating significant reduction in erythema, swelling, and tunnel drainage, associated with dramatic reduction in pain.

nodulocystic facial acne, along with Hurley stage 2 hidradenitis suppurativa, manifesting as multiple nodules, abscesses, and chronically draining tunnels in the axillae and inguinal regions (Fig 1, *A* & *B*) as well as intermittent episodes of superficial pustulation of the forearms. She was a nonsmoker with no family history of autoinflammatory disease and a body mass index of 34.2. Two years ago, she developed bone involvement with a positron emission tomography scan demonstrating the involvement of the sternum and mandible. A subsequent magnetic resonance imaging demonstrated a bilateral mandibular condyle bone marrow edema and left temporomandibular joint synovitis (Fig 2). She had no history of pyoderma gangrenosum, immunodeficiency syndromes, or recurrent infections with a known pathogen. Her current joint symptoms were partially controlled with colchicine 500 μg daily and naproxen and prednisolone 15 mg daily, although she reported ongoing skin pain and purulent drainage.

Her previous therapies prior to this presentation included doxycycline 50 mg, minocycline 50 mg, rifampicin 300 mg, and clindamycin 300 mg twice a day, as well as isotretinoin up to 60 mg and dapsone 200 mg daily. She had also been on adalimumab (as monotherapy) 40 mg, weekly for 2 years, which had been partially effective; although, this was recently ceased due to the reduced efficacy and severe injection site reaction and urticaria. She reported that adalimumab partially improved her joint symptoms but only minimally improved HS-associated cutaneous pain and pustulation.

Risankizumab was commenced at the standard dose of 150 mg, subcutaneously at week 0, week 4, and every 12 weeks, thereafter. Within 4 weeks of the commencement, there was a dramatic reduction in the joint pain, skin pain, and drainage from the epithelialized tunnels of her HS (Fig 1, *B*). Twelve weeks post risankizumab therapy, the patient was weaned off oral prednisolone (previously 15 mg daily) and self-ceased colchicine and naproxen due to the complete resolution of symptoms as indicated by the Dermatology Life Quality Index and International Hidradenitis Suppurativa Severity Score System scores (Fig 3). Currently, the patient remains in remission with no pain, joint symptoms, and no need for adjuvant therapy at the time of the publication (9 months after the commencement of risankizumab).

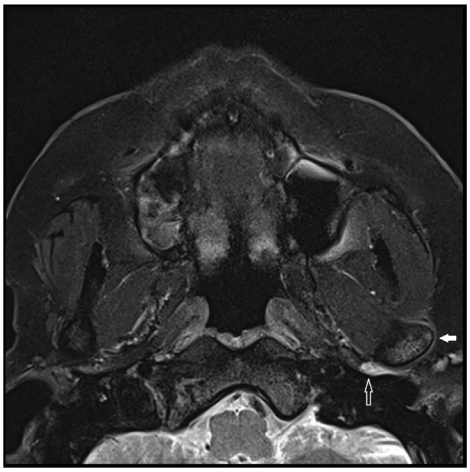

Fig 2. Magnetic resonance imaging of the left temporomandibular joint prior to risankizumab therapy, indicating areas of hyperintensity and inflammation (*black arrow*) with associated bone marrow edema (*solid white arrow*).

DISCUSSION

An observational study has identified an increase in the proinflammatory mediators, including IL-6,

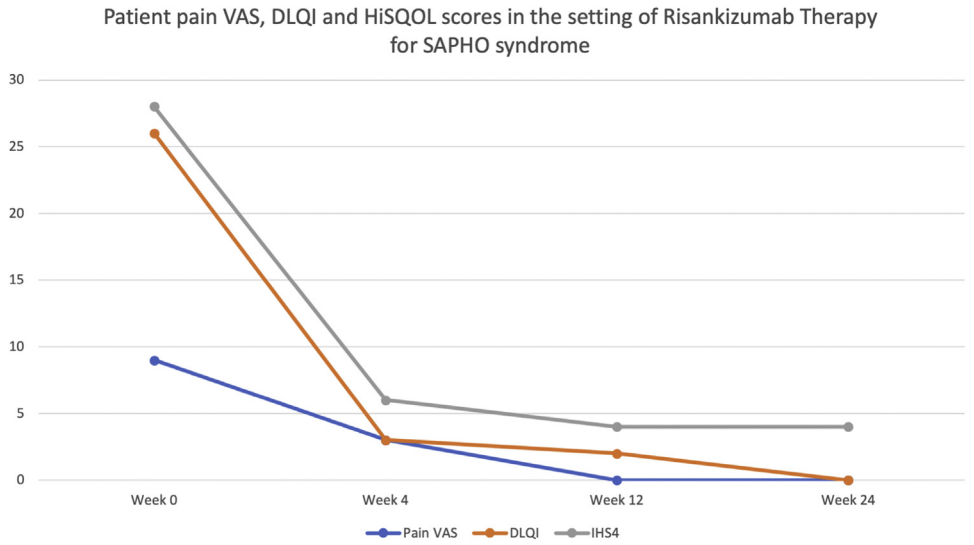

Fig 3. Graphical representation of pain scores (visual analog scale), Dermatology Life Quality Index, and Hidradenitis Suppurativa Quality of Life measures from week 0 to week 24 of risankizumab therapy. *DLQI*, Dermatology Life Quality Index; *IHS4*, International Hidradenitis Suppurativa Severity Score System; *VAS*, visual analog scale.

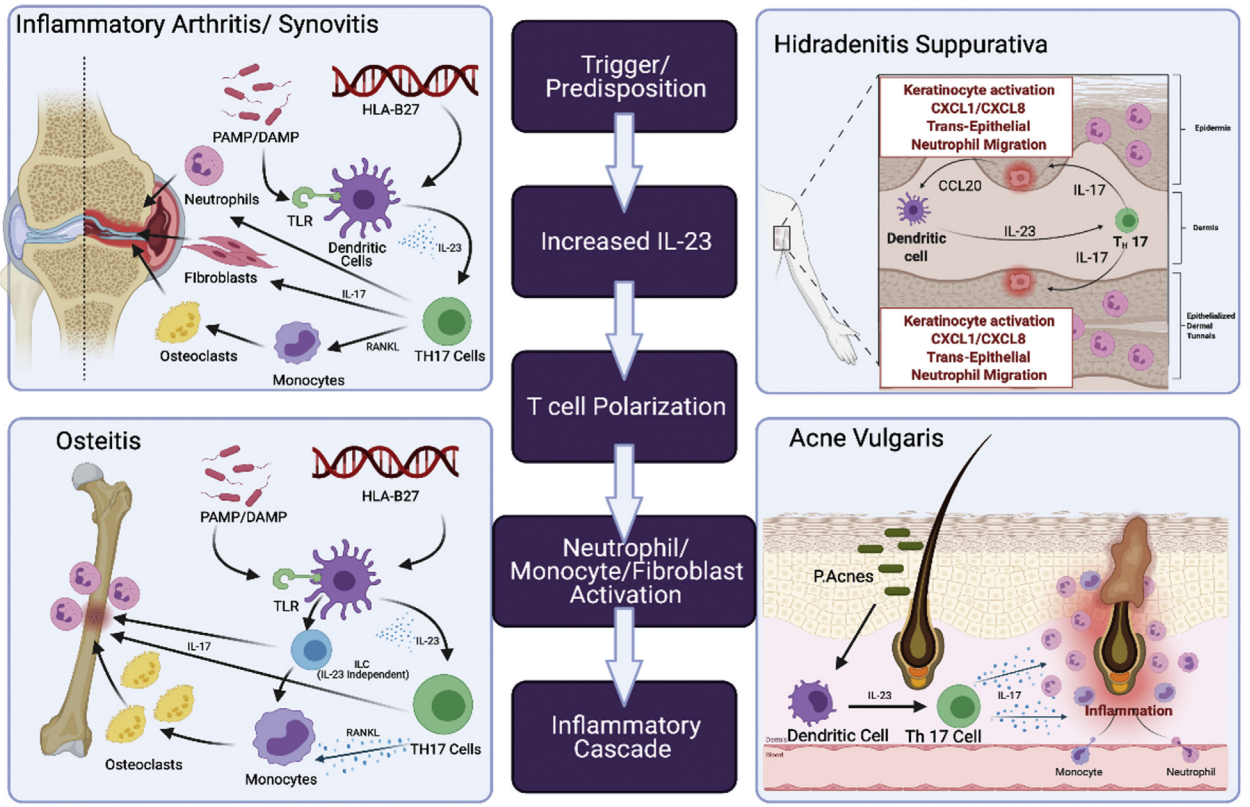

Fig 4. Schematic representation of pathogenic pathways in the various manifestations of SAPHO syndrome, including the central role of IL-23. *CXCL*, Chemokine (C-X-C motif) ligand; *DAMP*, damage-associated molecular pattern; *HLA*, human leukocyte antigen; *ILC*, innate lymphoid cell; *PAMP*, pathogen-associated molecular pattern; *RANKL*, receptor activator of nuclear factor kappa-B ligand; *SAPHO*, synovitis, acne, pustulosis, hyperostosis, and osteitis; *TLR*, toll-like receptor.

IL-8, IL-17A, and receptor activator of nuclear factor kappa B ligand, in the serum of patients with SAPHO syndrome compared to healthy controls.[5] Tissue immunohistochemistry performed on the clavicle of a patient with SAPHO syndrome has also detected the expressions of IL-17, IL-23, IL-6, IL-1β, and TNF-α[6] With regard to patients with HS and spondyloarthropathies, IL-17A, IL-17F, IL-23A, IL-6, IL-8, IL-1β, and TNF-α mRNA have all been upregulated along with their resultant proteins in the tissues.[7,8]

While the initiating trigger for the development of SAPHO is unknown, underlying predisposing factors such as human leukocyte antigen B27 genetic polymorphisms and gut and cutaneous microbiome alterations result in an increased production of IL-23 by monocyte/macrophage and dendritic cells. This may lead to a subsequent activation of the Th17 and Th22 inflammatory axes (Fig 3).[5,6,8] The subsequent downstream Th17-mediated synovial and keratinocyte mediated-chemokine (C-X-C motif) ligand 1 (CXCL1/CXCL8) production is consistent with the primarily neutrophilic nature of SAPHO and its associated conditions. Additionally, (Fig 4) IL-23 induces osteoclastogenesis via the receptor activator of nuclear factor kappa-B upregulation and is also known to activate synovial fibroblasts and subsequently, IL-6 production.[8]

Given that SAPHO is a heterogeneous disease, it is unclear whether the dramatic and sustained improvement seen in our patient with IL-23p19-targeted therapy would have a similar effect in all the individuals with SAPHO. The data from other biologic agents used in case reports and case series show benefits to either the skin or joints, with only adalimumab demonstrating a consistent response for both the disease manifestations.[3,9]

Recent clinical trials of IL-23 blockade (risankizumab) for ankylosing spondylitis have failed to meet the primary endpoints.[8] IL-17A blockade has demonstrated a significant response in ankylosing spondylitis, suggesting a role for the IL-23 independent activation of the Th17 axis (likely through innate lymphoid cells) in ankylosing spondylitis. (Fig 3).[7,8] However, given the lack of consistent response to both the skin and the joints with IL-17 blockade in SAPHO, this may suggest that the stratification of SAPHO patients by IL-23 dependent and IL-23 independent disease endotypes may lead to more targeted and effective therapeutic options.[3] In our case, we assume that the patient's skin and joint disease were IL-23 dependent, given the rapid and sustained clinical response.

In summary, IL-23p19 targeted therapy (with risankizumab) may represent a novel potential treatment option for SAPHO, particularly in the context of incomplete clinical response to TNF-α and IL-17A inhibition. The possibility of IL-23 dependent and IL-23 independent endotypes of the disease requires further investigation in larger cohorts. Skin and joint tissue inflammatory profiles in SAPHO require systematic examination to increase our understanding of the etiopathogenesis of the disease and enable the identification and/or development of more effective, targeted therapeutics.

Conflicts of interest

Dr Frew has conducted advisory work for Janssen, Boehringer-Ingelheim, Pfizer, Kyowa Kirin, LEO Pharma, Regeneron, Chemocentryx, Abbvie, and UCB; participated in trials for Pfizer, UCB, Boehringer-Ingelheim, Eli Lilly, and CSL; and received research support from Ortho Dermatologics and Sun Pharma. Drs Flora, Holland, and Smith have no conflicts of interest to declare.

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