Prolonged remission of SAPHO syndrome with low-dose leflunomide: A case report and literature review

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Abstract. This case report and literature review describes a 60-year-old woman from Southern Italy, diagnosed with synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome in 2015, who achieved sust ained remission through leflunomide therapy. Initially, the patient presented with severe sternoclavicular pain, osteitis and palmoplantar pustulosis. Following leflunomide initiation, the patient experienced significant clinical improvement, maintaining remission for ~5 years, even after a dose reduction to 20 mg on alternate days. No adverse events were reported during the entire treatment period. This case is contextualized within a concise review of the literature on leflunomide use in SAPHO, highlighting its potential as a long-term, low-dose therapeutic option with a favorable safety profile.

Introduction

Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome is a rare, heterogeneous autoinflammatory condition involving osteoarticular and dermatological manifestations. It is estimated to affect <1 in 10,000 individuals, with an onset typically in early adulthood (1). The pathogenesis involves a complex interplay between innate immune activation, cytokine dysregulation (notably TNF-α, IL-1β and IL-17), and genetic susceptibility, with occasional associations to *Propionibacterium acnes* as a triggering antigen (2). Therapeutic strategies include non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, conventional disease-modifying anti-rheumatic drugs (DMARDs) (methotrexate, sulfasalazine, cyclosporine) and biologics (TNF inhibitors, IL-1 and IL-17 blockers) (3,4). Leflunomide, a pyrimidine synthesis inhibitor, offers an oral, cost-effective alternative with immunomodulatory effects on T-cell proliferation, supported mainly by case reports and small series (5,6).

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Case report

A 60-year-old Caucasian female from Southern Italy, a homemaker and non-smoker, with no significant comorbidities or concurrent use of medications for major conditions, was diagnosed with SAPHO syndrome in early 2015 at the Madonna delle Grazie Hospital (Matera, Italy). The diagnosis was based on palmoplantar pustulosis (PPP) and severe, painful swelling of the manubriosternal joint. Thoracic pain was intense enough to require high-dose opioid analgesics (buprenorphine transdermal patch 20 μg/h) with modest benefit.

Baseline inflammatory markers were elevated [C-reactive protein (CRP) 18 mg/l (normal, <5 mg/l), erythrocyte sedimentation rate (ESR) 48 mm/h (normal, <20 mm/h)]. Imaging studies (Fig. 1A and B), including plain radiography and high-resolution computed tomography (CT), demonstrated structural joint pathology characterized by erosive changes and marked subchondral sclerosis at the manubriosternal articulation. Human leukocyte antigen (HLA) genotyping, performed according to the manufacturer's standard Luminex-based protocol (One Lambda; Thermo Fisher Scientific, Inc.), revealed no alleles of known clinical significance (specifically negative for HLA-B27, HLA-B51 and HLA-Cw6). Rheumatoid factor, comprehensive thyroid function tests, serum calcium, parathyroid hormone, alkaline phosphatase and other relevant biochemical parameters, together with an extended panel of immunological assays (including antinuclear antibodies and anti-cyclic citrullinated peptide antibodies), were all within normal limits or negative.

Initial treatment with NSAIDs, corticosteroids and methotrexate (150 mg/day diclofenac and 10 mg/day prednisone, together with 15 mg/week methotrexate) for 4 months yielded only partial improvement, as indicated by a reduction in pain and a mild decrease in inflammatory markers. After 5 months, leflunomide was initiated at 20 mg daily, resulting in gradual but complete resolution of both cutaneous and skeletal symptoms over 3 years. Within four months, CRP and ESR normalized and remained stable.

Table I. Published reports on leflunomide for Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis syndrome and present case.

First author, year	Patients, n	Dose and duration	Outcomes	Follow-up	Adverse events	(Refs.)
Scarpato, 2005	2	Leflunomide 20 mg/day; 6-12 months	Symptom resolution	~1 year	None reported	(5)
Li, 2023	1	Leflunomide 20 mg/day; 12 months	Nail and joint improvement	12 months	None reported	(6)
Present case	1	Leflunomide 20 mg/day → alternate days (maintenance)	Full remission	~5 years	None reported	-

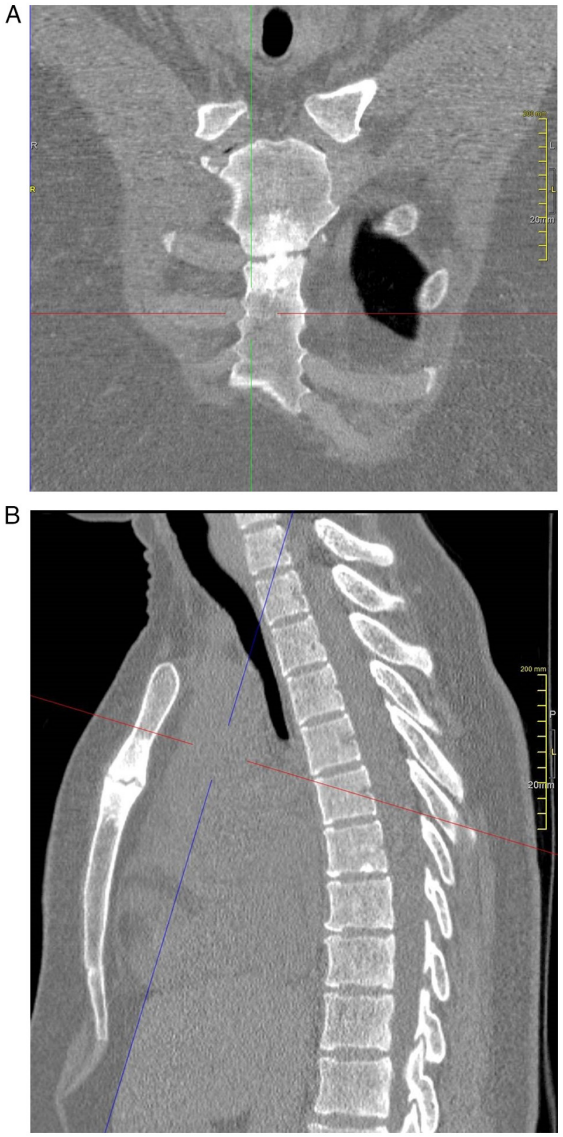

Figure 1. Computed tomography images in (A) coronal and (B) sagittal planes at diagnosis, showing sclerosis, irregularities and erosions of the manubriosternal joint (scale bar, 200 mm).

In the past 2 years, the leflunomide dose was tapered to 20 mg on alternate days, with sustained remission. The patient was clinically reviewed every 6 months, and CT scans performed during follow-up examinations every 2 years were reported as unchanged compared to baseline, with no new erosions or extension of sclerosis.

No adverse events occurred during the 10-year treatment period, with normal liver function tests and blood counts on regular monitoring every 2 months.

Discussion

The present case confirms leflunomide's potential for durable remission in SAPHO syndrome, even at reduced dosing. Its efficacy likely relates to sustained T-cell suppression via dihydroorotate dehydrogenase inhibition. The absence of adverse effects over prolonged therapy further supports its safety in selected patients.

Table I provides a comparison between the present case and previously published reports of leflunomide for treating SAPHO syndrome. The present case demonstrates several advantages compared to previously reported leflunomide use in SAPHO syndrome. Scarpato and Tirri (5) reported symptom resolution in two patients treated with leflunomide 20 mg/day for 6-12 months, with ~1 year of follow-up and no reported adverse events. Li *et al* (6) described nail and joint improvement in one patient receiving leflunomide 20 mg/day for 12 months, also without adverse events. By contrast, the present case represents the longest documented remission on leflunomide therapy (~5 years), with the additional benefit of successful dose reduction to alternate-day administration while maintaining clinical remission. Furthermore, the patient of the present study achieved complete normalization of inflammatory markers (CRP and ESR) within four months and demonstrated stable imaging findings throughout follow-up, indicating not only symptomatic improvement but also control of the underlying inflammatory process. The ability to maintain remission on reduced dosing (20 mg alternate days) represents a significant advantage in terms of long-term safety and cost-effectiveness, which was not reported in previous cases.

Regarding comparative efficacy and safety of treatment options, NSAIDs and short courses of systemic corticosteroids remain the first-line therapy for pain control and reduction of inflammation, with a generally favorable safety profile but limited disease-modifying potential, and carry gastrointestinal, cardiovascular and metabolic risks with prolonged use (7). Conventional DMARDs show a variable benefit: Methotrexate offers a benefit for peripheral arthritis but shows limited efficacy for axial bone lesions and may cause hepatotoxicity, cytopenia or gastrointestinal intolerance. Sulfasalazine can improve peripheral synovitis, though its impact on osteitis is modest; adverse effects include gastrointestinal upset, rash and, rarely, agranulocytosis. Cyclosporine

is occasionally used for refractory cases but is hampered by nephrotoxicity and hypertension risk. Bisphosphonates (e.g., pamidronate) have demonstrated consistent analgesic effects and radiologic improvement of osteitis in observational series, with acute-phase reactions and hypocalcaemia as the main adverse events (7). Among biologic agents, TNF inhibitors are highly effective in severe, refractory SAPHO, providing substantial improvement in both osteoarticular and cutaneous manifestations, yet are associated with variable cutaneous responses, but infection risk and secondary loss of response are concerns (8,9). IL-17 inhibitors (secukinumab/brodalumab) appear effective for osteitis and severe skin disease in emerging reports, with mucocutaneous candidiasis and neutropenia as recognized risks (10). IL-1 blockade (anakinra) is a reasonable option for refractory pustulosis/osteitis with a favourable safety profile dominated by injection-site reactions (11). Targeted synthetic agents (e.g., JAK inhibitors) have only anecdotal support and require caution due to infection, haematologic and cardiovascular signals (12). Overall, the choice should be individualized to the dominant phenotype (axial osteitis vs. peripheral synovitis vs. PPP) and comorbidities, balancing efficacy with toxicity and access.

The rarity of SAPHO, combined with heterogeneous presentation and course, complicates the establishment of standard treatment algorithms. The review of the literature performed in the present study [conducted in PubMed (https://pubmed.ncbi.nlm.nih.gov/) and Scopus (https://www.scopus.com/) and limited to English-language articles published in the past 10 years) highlights leflunomide as an underutilized but promising option, particularly when biologics are contraindicated or unavailable. Importantly, early initiation in the patient of the present study may have contributed to rapid normalization of inflammatory markers and prevention of structural progression, as evidenced by stable CT findings during follow-up.

In conclusion, low-dose leflunomide can maintain long-term remission in SAPHO syndrome with an excellent safety profile. While data remain limited, this case report and literature review supports its consideration as part of individualized treatment strategies, particularly for patients achieving remission on full-dose therapy and suitable for tapering. Larger studies are needed to confirm these findings.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

AN performed study conceptualization, data collection, clinical management, literature review, manuscript drafting and final approval. AN confirms the authenticity of all the raw data. AN has read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this case report.

Competing interests

The author declares that they have no competing interests.

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