

Long-term Clinical Outcomes in Synovitis, Acne, Pustulosis, Hyperostosis, and Osteitis Syndrome

Francis H.X. Yap, MBBS; Deborah Olsson-White, MBBS, FRACP;
Janet Roddy, MD, FRACP; Nicola J. Cook, BM, MRCP, FRACP;
D. Robert Langlands, MBBS, FRACP; Prue J. Manners, MD, FRACP;
and Graeme J. Carroll, MD, FRACP

Abstract

Objective: To assess the outcome of empirical therapeutic interventions for synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome.

Methods: The clinical features and treatment outcomes of a cohort of 21 patients diagnosed with SAPHO in Western Australia were reviewed retrospectively.

Results: All 21 patients met published diagnostic criteria; 20 (95%) were Caucasian, and the median age was 47 years. The median follow-up was 6 years (range, 2 to 32 years). Three patients (14%) received no treatment; 18 (86%) required conventional synthetic disease-modifying antirheumatic drug (DMARDs). Thirteen (62%) had an initial good response to methotrexate; 8 relapsed and progressed to biologic DMARDs (bDMARDs) during a period of 14 years. Of the 13 recipients on a tumor necrosis factor inhibitor, 11 (85%) continued treatment for a median of 4 years (range, 1 to 14 years), whereas none of 3 recipients of interleukin 17/23 continued treatment (median, 4 months). Higher Physician Global Assessment scores (better outcomes) were observed in bDMARD recipients (mean, 7.06 ± 2.24 [SD]) compared with non-bDMARD recipients (mean, 5.63 ± 2.50 ; $P = .1672$) after a median of 3 years of therapy.

Conclusion: This study describes the broad range of clinical manifestations in SAPHO, variable courses over time, and inconsistent outcomes with diverse empirical therapies. Moderately good long-term treatment outcomes were observed in most recipients of tumor necrosis factor inhibitor. Poorer outcomes were observed with bisphosphonates and interleukin 17/23 axis inhibitors; however, low numbers preclude robust comparison. Suboptimal treatment may be associated with poorer clinical outcomes and greater skeletal damage.

Trial Registration: Australian and New Zealand Clinical Trials Registry: ACTRN12619000445178

© 2021 Mayo Foundation for Medical Education and Research. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) ■ Mayo Clin Proc Inn Qual Out 2021;5(3):574-582

From the PathWest (F.H.X.Y.) and Department of Rheumatology (D.R.L.), QEII Medical Centre, Nedlands, Western Australia; Redcliffe Hospital, Redcliffe, Queensland, Australia (D.O.-W.); Department of Rheumatology, Fiona Stanley Hospital, Murdoch, Western Australia (J.R., G.J.C.); Western Rheumatology, Wyllie Arthritis Foundation, Shenton Park,

Affiliations continued at the end of this article.

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a rare immunoinflammatory disorder characterized by cutaneous and osteoarticular manifestations. The acronym SAPHO was coined by Chamot et al¹ in 1987. Diagnostic criteria were subsequently proposed and revised by Khan and Khan² in 1994. The SAPHO syndrome has been estimated to affect fewer than 1 in 10,000 adults. It has been defined by Kahn and Khan as multifocal

osteitis with or without skin symptoms, sterile acute or chronic joint inflammation with either palmoplantar pustulosis (PPP) or psoriasis, or acne or hidradenitis; sterile osteitis with any one of these sets of criteria is deemed sufficient for diagnosis. As the symptoms and signs of SAPHO syndrome are nonspecific and the osteoarticular and cutaneous manifestations are broad and not always present initially or simultaneously, SAPHO is mainly a clinical diagnosis of exclusion. Many

physicians recognize inclusion and exclusion features of SAPHO as described by Kahn and Khan.² These were proposed more than 30 years ago and last revised in 1994. Given significant medical advances in clinical and microbial science and particularly with respect to bone and joint imaging, a review of these criteria is long overdue.

The precise etiopathologic process of SAPHO is unknown. An autoinflammatory basis to the disorder is favored by some, but no specific genes have yet been implicated. The possibility remains that it may be incited by an infectious agent. Given overlap with the full spectrum of manifestations of cutaneous psoriasis and psoriatic and other spondyloarthropathies, including infection-triggered reactive arthritis, a postinfectious basis for SAPHO remains plausible. The clinical manifestations vary in frequency. Most common are osteitis and other bone lesions; chest wall pain, likely to be of mixed origin; and synovitis, mostly monoarticular or oligoarticular, that also has a predilection for the axial skeleton and joints, notably the medial clavicles, manubrium-sternum, mandible, vertebrae, and sacroiliac joints. Also common are diverse pustular skin lesions, including severe acne, solitary pustules, hidradenitis suppurativa, and PPP.³ Responses, although partial and poorly sustained in many cases, to moderate- or high-dose prednisone/prednisolone as well as to other conventional and biologic immunosuppressive therapies further support an osteoarticular condition in which there may be discrete subsets, such as noncutaneous or minimal cutaneous disease. A spondyloarthropathy subset may also exist, more easily distinguishable on the basis of computed tomography and magnetic resonance imaging. Importantly, it is unusual with immunosuppressive treatment for any unequivocal exacerbation of the musculoskeletal features of SAPHO to be observed, as might be expected were it due to persistent infection alone.

Notwithstanding the low frequency of HLA-B27 in all cohorts studied, the finding of sacroiliitis and vertebral inflammatory lesions in an appreciable subset adds further weight to the notion that SAPHO is a member of the spondyloarthropathy family of rheumatic diseases. Taken together, these observations in conjunction with the usual absence of

a typical quotidian fever argue against an auto-inflammatory syndrome.

There has been considerable interest in an infective cause, in part because the pustules and osteitis lesions sometimes contain potentially relevant organisms, such as *Cutibacterium acnes* (formerly *Propionibacterium acnes*), and in part because there are similarities between the osteitis lesions and those found in osteomyelitis. A mostly juvenile equivalent of the disorder is referred to as chronic recurrent multifocal osteomyelitis.⁴ By definition, the osteomyelitis in chronic recurrent multifocal osteomyelitis must be sterile, and likewise in adults with acne or hidradenitis suppurativa or PPP, sterility in the osteitis lesions is obligatory. However, tissue biopsy and culture in relevant lesions may overlook infection as there may be hitherto unrecognized infective agents or there may be failure to isolate indolent organisms. Microorganisms are not often isolated, despite thorough investigation for sepsis. In a meta-analysis, it was found that *C. acnes* was isolated from 42% of bone lesions.⁵ In 1987, Trimble et al⁶ observed that intra-articular injection of inactivated “*P. acnes*” in laboratory animals resulted in joint and bone erosions. Thus, an inciting and possibly perpetuating role for this or perhaps other microbes cannot be entirely excluded. The possibility also exists that persistent low-grade infection may perpetuate the reaction as opposed to triggering it and then playing no further part in sustaining it. Germane to this idea are the observations in respect to empirical antibiotic therapy, which has been found to be partially and temporarily effective in 6 independent studies, mostly small in scale.⁵ Impressively, azithromycin was reported to improve symptoms and radiologic findings in a short-term study, and this was followed by relapse after treatment.⁷

The relative rarity of SAPHO has hindered the implementation of therapeutic trials and in turn restricted the development of clear guidelines for treatment. Many therapies have been described in the literature, including antibiotics, methotrexate (MTX), bisphosphonates, and biologic disease-modifying antirheumatic drugs (bDMARDs). To date, most treatment options have been tailored to the individual case. With the advent of tumor necrosis factor (TNF) inhibitors, a potentially useful

additional therapeutic option has become available for the management of SAPHO, and it seems likely that other biologic therapies, including interleukin (IL) 17/23 inhibitors and also Janus kinase inhibitors, will be tested empirically as they too become increasingly accessible. Two large studies have catalogued responses to bDMARDs.^{8,9} Should the concept of an autoinflammatory syndrome gain further traction, there may be impetus to further explore IL-1 antagonists, including longer half-life agents, such as rilonacept and canakinumab.

A small to intermediate rise in inflammatory markers is often seen in SAPHO. The C-reactive protein (CRP) concentration is usually elevated, but not often does it increase to above 40 mg/L (to convert CRP values to nmol/L, multiply by 9.524). Likewise, the erythrocyte sedimentation rate is usually raised, but it is mostly less than 60 mm/h. Accordingly, much higher values should heighten concern in respect to infection.

Chronic recurrent multifocal osteomyelitis and nonbacterial osteomyelitis, which probably represent the same condition, are mostly encountered in children or adolescents. They are remarkably similar clinically. Chronic recurrent multifocal osteomyelitis and SAPHO may constitute different phenotypic expressions of the same fundamental pathologic process.

The aim of this retrospective study was to describe the clinical and treatment outcomes as well as the natural history of SAPHO in a small cohort of patients observed intensively for up to 32 years. We also reviewed published reports concerning SAPHO and related conditions. This report is a description of SAPHO outcomes during a relatively long time. Furthermore, it provides long-term follow-up and outcome data for both treated and untreated or minimally treated patients with SAPHO.

METHODS

Participants were collected from an audit of case records and by consultant recall at Fiona Stanley Hospital and Fremantle Hospital and Health Services Group, Royal Perth Hospital, and Sir Charles Gairdner Hospital during the period 1986 to 2018. All 4 hospital precincts service metropolitan Perth and the state of Western

Australia. Accordingly, the study is a retrospective, single-geographic regional cohort study. Information was collected concerning sex, age, ethnicity, time at diagnosis, and relevant clinical characteristics, including pertinent negatives, such as the absence of psoriasis, inflammatory bowel disease, rheumatoid nodules, tophi, and signs of classic spondyloarthropathies. Laboratory data were also collected, including rheumatoid factor and cyclic citrullinated peptide antibody concentrations. Special note was made of microbiologic findings, positive or negative. The erythrocyte sedimentation rate and CRP concentration at baseline, wherever possible and over time, were collected, but only the CRP concentration is shown for brevity. Details of exposure to the following therapeutic agents were collected: nonsteroidal anti-inflammatory drugs, conventional synthetic DMARDs, corticosteroids, antibiotics, bisphosphonates, and bDMARDs. None of our patients received targeted synthetic DMARDs. Available imaging data were reviewed. The diagnosis of SAPHO was based on the criteria proposed by Kahn and Khan.² Those who met these diagnostic criteria are listed in [Table 1](#).

Ethics

This project was registered and approved as a quality assurance project (QA26150) by Fiona Stanley Hospital on March 19, 2018, and as such did not require formal Human Research Ethics Committee review.

Statistical Analyses

The statistical estimates are mostly descriptive (numerical tallies and medians). Raw data were entered in GraphPad QuickCalcs online statistical calculator. Physician Global Assessment (PGA) scores were compared by unpaired *t*-test.

RESULTS

There were 21 patients with a median follow-up of 6 years (range, 2 to 32 years) identified. All 21 patients met the diagnostic criteria described by Kahn and Khan² (applied retrospectively). Age at diagnosis is shown in [Figure 1](#). The median age at the time of diagnosis was 48 years (range, 25 to 84 years). All were Caucasian except 1 patient, who was Asian.

TABLE 1. Range of Therapeutics Employed, Outcome, and Duration of Follow-up in 21 Patients With SAPHO

Case No.	Previous treatment	Current treatment	Outcome	Follow-up (y)
1	Nil	Nil	Disease progressed	26
2	SAS	SAS	Good response	17
3	MTX, LEF, PRED	ETA 11 y	Good response	14
4	MTX	ETA 14 y	Good response	15
5	MTX	ETA 5 y	Good response	5
6	Nil	Nil	Good response	3
7	MTX	MTX	Good, disease progressed	22
8	MTX	MTX	Good response	5
9	MTX, PRED	MTX, PRED, ETA 2 y	Disease progressed before ETA	3
10	PRED, ZA	ETA 5 y	Good response to ETA, flare at year 4	6
11	NSAIDs, P	ADA 5 y	Good response to P, flare at year 4	6
12	PRED, LEF, MTX	No biologic	Good response	14
13	PIROX, PLQ, SAS	MTX	Good response	18
14	IA steroid, MTX	ADA 3 y	Good response	20
15	NSAIDs, SAS	SEC 4 mo; ineffective	Good response to DMARD, not to biologic	32
16	NSAIDs, MTX, AP	ETA 2 y	Good response	6
17	NSAIDs only	SEC 4 mo	Poor response	2
18	NSAID, MTX, SAS, P	ADA 3 y, MTX	Good response	7
19	MTX and LEF	ETA 2 y	Good response	3
20	No prior treatment, wished to conceive	Clindamycin 3 mo	Good response at 3 mo, relapse at 4 mo	3
21	MTX, LEF	ETA (4 mo) and CERT (10 mo), then IXEK (4 mo)	Poor response to IXEK with exacerbation of pustulosis	3

ADA, adalimumab; AP, apremilast; CERT, certolizumab; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; IA steroid, intra-articular steroid; IXEK, ixekizumab; LEF, leflunomide; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; P, pamidronate; PIROX, piroxicam; PLQ, hydroxychloroquine (Plaquenil); PRED, prednisolone; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis; SAS, sulfasalazine; SEC, secukinumab; ZA, zoledronic acid.

Osteoarticular Features at Diagnosis

Of the 21 patients, 14 (67%) had synovitis and 10 (47%) had hyperostosis; 13 (62%) had osteitis, 2 of whom were severely disabled by osteitis in the spine (Figure 2). Interestingly, sternoclavicular joint tenderness or swelling was found in 16 of 19 (84%) at first presentation and in 1 patient much later, manifesting 18 years after onset (85% after long-term follow-up).

Cutaneous Features at Diagnosis

Of the 21 patients, 13 (62%) had pustulosis, 4 (19%) of whom had PPP. Only 2 of 21 (9%) had acne (Figure 2). Diverse treatments reflecting real-world experience and the historical availability of therapies for these

patients were employed. Clinical responses were judged by treating physicians, taking clinical, laboratory, and imaging data into account. The PGA scores on a scale of 0 to 10 were used to assess long-term disease outcome in those receiving bDMARDs but also in those who did not. Of the 21 patients, 3 (14%) received bisphosphonates with unsustained benefits; 13 of 21 (62%) had an initial good response to MTX, but 8 of these 13 then relapsed and progressed to bDMARDs. In total, 15 different bDMARDs were used in 12 patients. Of the 21 patients, 13 (62%) were treated with either a TNF inhibitor (etanercept, 8; adalimumab, 3; certolizumab, 1) or an IL-17/23 inhibitor (secukinumab, 2; ixekizumab, 1; Table 1). Of the 13 who required bDMARDs, 9 received the same agent

throughout follow-up; thus, failure/switching was uncommon. Of the 13 recipients of TNF inhibitors, 11 (85%) have continued treatment for a median of 4 years (range, 1 to 14 years), whereas none of 3 recipients of IL-17/23 have continued treatment (median, 4 months). Of the 11 TNF inhibitor recipients, 8 (73%) have had relapse-free courses to date, representing a moderately good overall outcome for this treatment category.

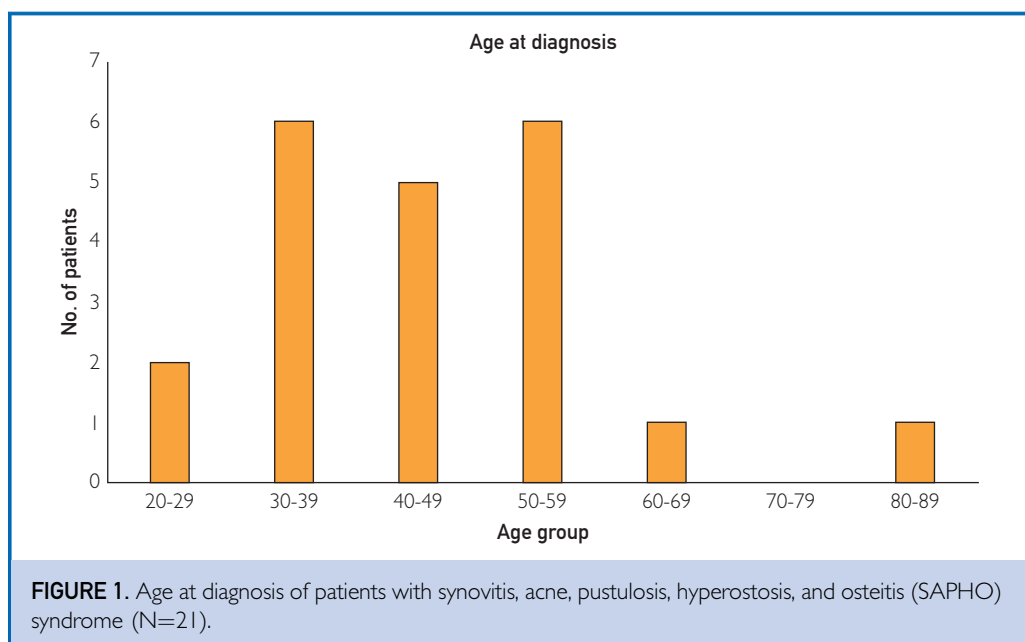
The CRP concentration was determined before and after initiation of therapy in 15 participants. Patients were included in this analysis only if there were baseline and follow-up CRP measurements. The pretreatment and post-treatment CRP values represent single assay results for standard CRP concentration, not high-sensitivity CRP. The CRP concentration was determined by enzyme-linked immunosorbent assay in diverse laboratories as participants underwent pathologic testing in community laboratories, mostly in the private health care sector. The upper limit of normal in these laboratories ranged between less than 5 mg/L and less than 10 mg/L.

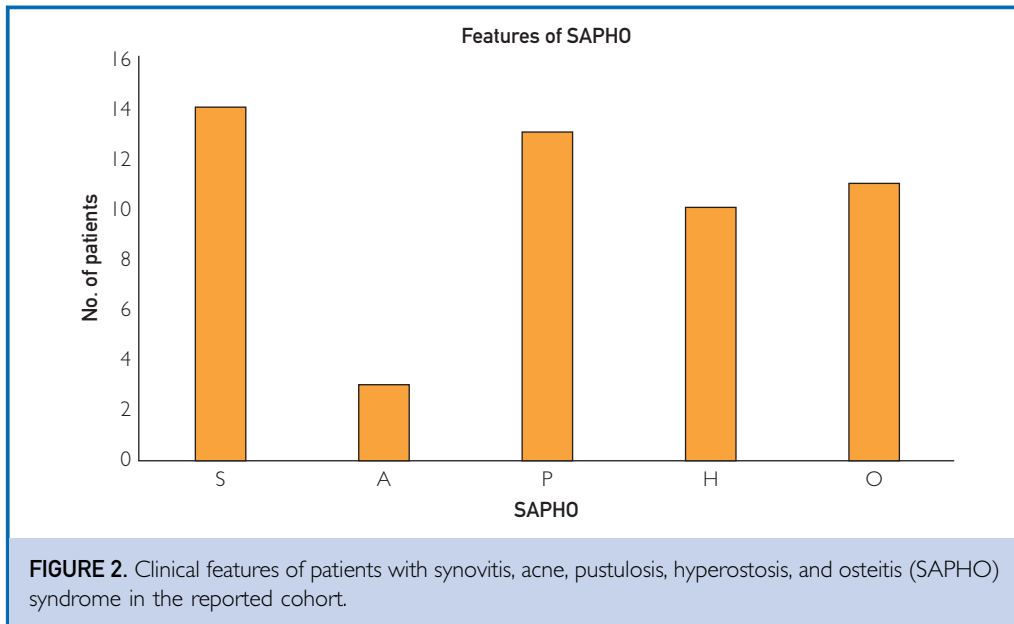
The CRP data are depicted in the plots shown for biologic and nonbiologic therapy in Figure 3. In almost all patients studied, there was a sustained fall in the CRP concentration, which accords with the clinical

observation that most patients responded to therapy and achieved stable disease improvement or remission over time. Similar declines were noted irrespective of treatment. This is not surprising because all patients were treated incrementally and often “to target” in an effort to achieve minimal disease activity.

No clinically apparent progression in joint or spinal damage was observed in those treated with bDMARDs, despite more than a decade of follow-up in some patients. In contrast, substantial progression was clearly apparent in 1 untreated patient and in 2 other patients not receiving bisphosphonate or a TNF inhibitor. Thus, there is a suggestion that no or minimal treatment may result in worse structural outcomes. Importantly, however, because the study was retrospective and imaging was not performed systematically, it is not possible to report the exact frequency of skeletal damage over time, either in those receiving no or minimal treatment or in any of the treatment subsets, including those receiving bDMARDs.

The PGA scores were used at the most advanced time of follow-up possible to appraise outcomes. Better outcomes were observed in bDMARD recipients (mean, 7.06 ± 2.24 [SD]) compared with non-bDMARD recipients (mean, 5.63 ± 2.50 ; $P = .1672$) after a median of 3 years





of therapy. A trend toward better outcomes in recipients of bDMARDs, especially TNF inhibitors, was observed; however, this was not statistically significant, possibly because of the relatively small number of patients studied.

DISCUSSION

This retrospective case series illustrates the diversity of clinical manifestations in SAPHO and the inherent difficulties that beset diagnosis and management. Only 1 or just a few features may be manifested at the time of initial presentation, and it can be several or even many years sometimes before other well-recognized features of the syndrome emerge. Furthermore, it is rare for any patient to develop all the recognized features, even with long-term follow-up. The SAPHO syndrome is a multisystem immunoinflammatory disorder, and not all the manifestations are familiar to internal medicine physicians, immunologists, dermatologists, or orthopedists, for example, all of whom are likely to encounter cases from time to time. It evolves during years and sometimes many years, thereby confounding and delaying diagnosis.

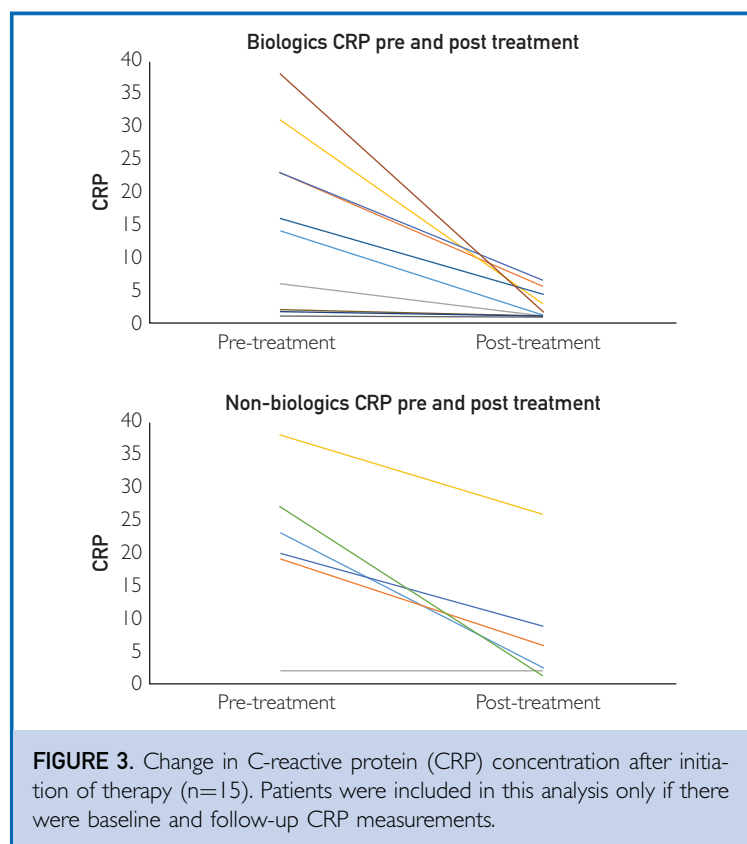
This report illustrates the broad spectrum of disease presentations and the range of severity in SAPHO. It also illustrates evolution over time and catalogues responses to a variety of treatments. The patients were observed for a

relatively long time (median duration of follow-up was 6 years; range, 2 to 32 years). Extended observations of outcomes were possible, including the extent to which sustained responses to treatments were observed.

Disease progression with unequivocal skeletal damage was observed in 3 patients, 1 of whom was receiving no treatment during a period of 26 years and 2 of whom received MTX alone (no bDMARD) during periods of 3 years and 22 years. Thus, disease progression with more skeletal damage may have been more frequent in those who did not receive a bisphosphonate or a TNF inhibitor; however, the small numbers and absence of systematically collected imaging data preclude rigorous analysis and any definitive conclusions. In our experience, moderate to severe SAPHO at the outset rarely went into spontaneous sustained remission.

Patients with mild disease were responsive to minimal intervention. Rarely did these patients progress to warrant more aggressive therapy, whereas others were less responsive initially or relapsed. Notably, 13 patients had an initial good response to MTX; however, 8 of these 13 then relapsed and progressed to bDMARDs over time.

Historically, bisphosphonates have been used as first-line agents after conventional synthetic DMARDs have failed. Favorable outcomes



have mostly been reported. Amital et al¹⁰ and Zwaenepoel and Vlam¹¹ have reported positive results in this regard. In our limited experience, lasting benefits from bisphosphonates were unusual. Li et al³ similarly reported low response rates among 164 Chinese patients who received oral bisphosphonates. Only 16 of 54 (30%) of those with severe bone pain responded.³ In this study, 3 patients were treated with intravenous administration of bisphosphonates for up to a maximum of 3 years. All 3 patients progressed to a biologic agent because of inadequate disease control.

At the time that bDMARDs were first used in any of the patients in this series, there were only anecdotal reports of biologic bDMARD use in SAPHO. Other reports have appeared since.^{12,13} More than a decade later, there remain no randomized controlled trials. In our cohort, patients who were either intolerant of or unresponsive to conventional synthetic DMARDs or who had an inadequate response to bisphosphonates were treated with bDMARDs. The duration of biologic therapy ranged from 2 to 14 years. The small numbers

preclude assessment of individual TNF inhibitors. The patients in this cohort received etanercept, adalimumab, and certolizumab. A trend toward better disease responses to treatment was observed for TNF inhibitors. Responses to TNF inhibitors have been reported previously in multiple studies. These outcomes are summarized together with ours in Table 2. Taken together, these studies and our study describe moderately good responses to TNF inhibitors in 55 of 74 recipients (74%).

On the basis of the collective open treatment data reported from multiple centers and encompassing several races, it can reasonably be considered that both bisphosphonates and TNF inhibitors are probably safe and efficacious for SAPHO. Therapy with TNF inhibitors appears to be superior on the basis of treatment survival considerations, but of course, without randomized head-to-head studies, these agents cannot be properly compared. Furthermore, it must be acknowledged that without well-designed and adequately powered studies in large cohorts, neither TNF inhibitors nor bisphosphonates can be considered unequivocally proven, nor can their relative efficacies be determined. Spontaneous fluctuations in disease activity, imprecise measures of disease activity, and regression to the mean likely confound empirical assessment. There remains a need to consider further trials of antibiotic therapy. More powerful diagnostic tools to discover microbial infections, including polymerase chain reaction, for example, and perhaps shotgun metagenomics, may need to be applied to persons presenting with SAPHO, and where appropriate, alternative antibiotic treatment strategies, including possibly combinations of agents and cycling/repetitive antibiotic treatment regimens, may need to be examined.

One of the important strengths of this study is the length of follow-up and the capacity to demonstrate relative disease stability and mostly good long-term disease or treatment outcomes over time, perhaps greatest in those receiving TNF inhibitor therapy. Furthermore, there is a suggestion that patients either untreated or minimally treated may be subject to more clinical and skeletal damage in the long term. It is important that this prognostic uncertainty be resolved because with more

TABLE 2. Summary of Published Reports Providing Data Concerning the Number and Proportion of SAPHO Patients Responsive to bDMARD Therapy^a

Reference, year	No. of participants treated with biologic agent	Biologic responders, No. (%)	No. responsive to TNF inhibitor, cumulative subtotal (% of total) ^b
Ben, ¹⁴ 2010	6	4 (67)	4
Aljuhani, ¹⁵ 2015	2	1 (50)	5
Li, ⁹ 2016	41	28 (68)	33
Colina, ⁸ 2009	9	9 (100)	42
Zwaenep, ¹¹ 2016	3	3 (100)	45
Yap, 2020 (this report)	13	10 (77)	55/74 (74)

^abDMARD, biologic disease-modifying antirheumatic drug; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis; TNF, tumor necrosis factor.
^bThis column contains cumulative data, so the percentage is shown only in the final line for the total group.

evidence, this consideration has the potential to inform decision-making in management.

The study has several limitations. The number of participants is small in keeping with the relative rarity of the condition and single-center/region experience. There is no “gold standard” for diagnosis, so we must admit some potential diagnostic heterogeneity, despite that accepted criteria have been satisfied. Follow-up, however, in comparison to most reports is long, which reduces the likelihood of diagnostic error. In only 1 patient was revision of the diagnosis to possible psoriatic spondyloarthritis under consideration after more than 20 years, and here there was still uncertainty with respect to disease classification. Attempts to exclude infection were thorough. Although microbial isolates were uncommon in our series, there still exists a possibility that a common organism or more than 1 organism may act to trigger or to sustain SAPHO, or provoke flares, at least in a subset of cases. Treatments were heterogeneous and empirical. All but 1 of the participants in this study was Caucasian. Accordingly, our findings may not be generalizable to other racial groups. Nevertheless, the results are consistent with those reported in China and Europe. Furthermore, there was no long-term structured evaluation of skeletal or joint tissues, so we are unable to determine the full extent of bone and joint damage over time or to correlate poor structural outcomes in joints and bone with disease characteristics at outset and thereby to predict prognosis. Use of tobacco and alcohol, infection history, exposure to ionizing radiation in probands as well as in family members, family history

(including a history of psoriasis, acne, or other pustular skin disease), and comorbidities were not consistently elicited. Challenges that will confront treating physicians in the future include refinement of diagnostic criteria, selection and justification of treatments in the absence of clear guidelines, and development of strategies to identify those most at risk of preventable bone and joint damage, especially in the seemingly stable or well-controlled patient.

Tofacitinib has been reported to be effective in a patient with SAPHO who had recalcitrant aggressive unilateral wrist synovitis, refractory to conventional synthetic DMARDs and etanercept.¹⁶ This and other Janus kinase inhibitors represent yet another potentially valuable therapeutic option. Other agents with reasonable prospects but not yet critically evaluated for SAPHO include leflunomide, apremilast, IL-1 antagonists,¹⁷ and the extended family of IL-17/23 inhibitors, although among our patients, the 3 treated with IL-17/23 inhibitors (secukinumab, n=2; ixekizumab, n=1) proved to be refractory. The PGA scores were used to further evaluate outcomes. A trend toward more favorable responses was observed in recipients of biologic therapies, particularly TNF inhibitors. There is a need for incorporation of patient-reported outcomes in future studies.

CONCLUSION

The SAPHO syndrome remains an exacting condition to diagnose and to manage. There is a need to revisit diagnostic criteria because 30 years have elapsed since the concept of SAPHO first emerged and, importantly, because there have been major advances in

microbial science, diagnostic imaging, and therapeutics during that interval. Treatment remains empirical and intuitive rather than protocol or guideline directed; but with the advances that have occurred in antirheumatic therapeutics during the past 2 decades especially, the number of options and scope for achieving superior disease control and better long-term disease outcomes have improved considerably. More robust and patient-focused measures of disease and treatment outcome are still much needed. Because SAPHO is relatively rare, aggregated case series and expert consensus rather than controlled trials may be required for some time yet to guide contemporary and future therapy.

ACKNOWLEDGMENTS

We are indebted to our colleagues who provided patients' details so we could assemble this case series and to our patients for their cooperation and assistance with the preparation of the report. We also thank the Western Australian teaching hospital staff for their critical assessment of applications for the provision of bDMARD therapy in selected cases. The authors are also grateful to A/Prof Helen Keen for incisive criticism and helpful guidance in respect to manuscript preparation.

Abbreviations and Acronyms: bDMARD = biologic disease-modifying antirheumatic drug; CRP = C-reactive protein; DMARD = disease-modifying antirheumatic drug; IL = interleukin; MTX = methotrexate; PGA = Physician Global Assessment; PPP = palmoplantar pustulosis; SAPHO = synovitis, acne, pustulosis, hyperostosis, and osteitis; TNF = tumor necrosis factor

Affiliations (Continued from the first page of this article.): Western Australia (N.J.C.); and Faculty of Health and Medical Sciences, University of Western Australia, Nedlands, Western Australia (P.J.M.).

Potential Competing Interests: The authors report no competing interests.

Data Previously Presented: These data were presented as a poster at the 51st Annual Scientific Meeting of the Australasian College of Dermatologists, May 19-22, 2018.

Correspondence: Address to Graeme J. Carroll, MD, FRACP, Department of Rheumatology, Fiona Stanley Hospital, 11 Robin Warren Dr, Murdoch, Western Australia 6150, Australia (gjcarrollmd@gmail.com).

ORCID

Graeme J. Carroll:  <https://orcid.org/0000-0002-2324-2227>

REFERENCES

1. Chamot AM, Benhamou CL, Kahn MF, Beranek L, Kaplan G, Prost A. Acne-pustulosis-hyperostosis-osteitis syndrome. Results of a national survey. 85 cases [in French]. *Rev Rhum Mal Osteoartic.* 1987;54(3):187-196.
2. Kahn MF, Khan MA. The SAPHO syndrome. *Baillieres Clin Rheumatol.* 1994;8(2):333-362.
3. Li C, Cao Y, Zhang W. Clinical heterogeneity of SAPHO syndrome: challenge of diagnosis. *Mod Rheumatol.* 2018;28(3):432-434.
4. Roderick MR, Shah R, Rogers V, Finn A, Ramanan AV. Chronic recurrent multifocal osteomyelitis (CRMO)—advancing the diagnosis. *Pediatr Rheumatol Online J.* 2016;14(1):47.
5. Rozin A. SAPHO syndrome: is a range of pathogen-associated rheumatic diseases extended? *Arthritis Res Ther.* 2009;11(6):131.
6. Trimble BS, Evers CJ, Ballaron SA, Young JM. Intraarticular injection of *Propionibacterium acnes* causes an erosive arthritis in rats. *Agents Actions.* 1987;21(3-4):281-283.
7. Assmann G, Kueck O, Kirchoff T, et al. Efficacy of antibiotic therapy for SAPHO syndrome is lost after its discontinuation: an interventional study. *Arthritis Res Ther.* 2009;11(5):R140.
8. Colina M, Govoni M, Orzincolo C, Trotta F. Clinical and radiologic evolution of synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome: a single center study of a cohort of 71 subjects. *Arthritis Rheum.* 2009;61(6):813-821.
9. Li C, Zuo Y, Wu N, et al. Synovitis, acne, pustulosis, hyperostosis and osteitis syndrome: a single centre study of a cohort of 164 patients. *Rheumatology (Oxford).* 2016;55(6):1023-1030.
10. Amital H, Applbaum YH, Aamar S, Daniel N, Rubinow A. SAPHO syndrome treated with pamidronate: an open-label study of 10 patients. *Rheumatology (Oxford).* 2004;43(5):658-661.
11. Zwaenepoel T, Vlam K. SAPHO: treatment options including bisphosphonates. *Semin Arthritis Rheum.* 2016;46(2):168-173.
12. Garcovich S, Amelia R, Magarelli N, Valenza V, Amerio P. Long-term treatment of severe SAPHO syndrome with adalimumab: case report and a review of the literature. *Am J Clin Dermatol.* 2012;13(1):55-59.
13. Zhang LL, Zhao JX, Liu XY. Successful treatment of SAPHO syndrome with severe spinal disorder using entercept: a case study. *Rheumatol Int.* 2012;32(7):1963-1965.
14. Ben AK, Dran DG, Gottenberg JE, Morel J, Sibilia J, Combe B. Tumor necrosis factor- α blockers in SAPHO syndrome. *J Rheumatol.* 2010;37(8):1699-1704.
15. Aljuhani F, Toumadre A, Tatar-Z, et al. The SAPHO syndrome: a single-center study of 41 adult patients. *J Rheumatol.* 2015; 42(2):329-334.
16. Yang Q, Zhao Y, Li C, Luo Y, Hao W, Zhang W. Case report: successful treatment of refractory SAPHO syndrome with the JAK inhibitor tofacitinib. *Medicine (Baltimore).* 2018;97(25):e11149.
17. Wendling D, Prati C, Aubin F. Anakinra treatment of SAPHO syndrome: short-term results of an open study. *Ann Rheum Dis.* 2017;71(6):1098-1100.