

# Biologics for rare inflammatory diseases: TNF blockade in the SAPHO syndrome

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## ABSTRACT

**Introduction:** SAPHO is an invalidating syndrome characterised by Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis. The low prevalence and heterogeneous presentation often leads to a significant diagnostic delay. Here, we provide an up-to-date overview of current insights into the pathogenesis and different treatment options. In addition, we describe the effects of anti-TNF treatment in three refractory cases.

**Case reports:** Patient A is a 25-year-old female with hidradenitis suppurativa, inflammatory back pain and painful joints. After diagnosis, anti-TNF treatment was started resulting in clinical improvement. Patient B is a 44-year-old woman who presented with acne, palmoplantar pustulosis and anterior chest wall pain. Bone scintigraphy showed increased uptake at the anterior chest wall. Treatment with bisphosphonates resulted in temporary improvement and subsequent treatment with anti-TNF induced long-term clinical improvement. Patient C is a 37-year-old woman with palmoplantar psoriasis, relapsing hidradenitis and inflammatory back pain. MRI revealed osteitis of the pubic bone. Anti-TNF was started for SAPHO syndrome. However, despite a clinical response, our patient discontinued treatment, resulting in rapid deterioration. Anti-TNF treatment was re-introduced followed by clinical improvement.

**Conclusion:** These case reports illustrate, consistent with the current literature, that TNF blockers can be considered for treatment of refractory SAPHO syndrome.

## KEYWORDS

SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis, hidradenitis suppurativa, anti-TNF.

## INTRODUCTION

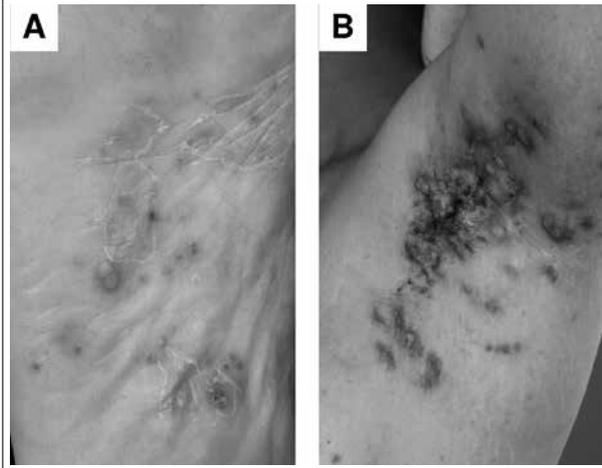
SAPHO syndrome is a relatively unknown disease that was first described in 1987 by A.M. Chamot.<sup>1</sup> The acronym SAPHO stands for: Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis. The diagnosis is often missed or delayed due to the low prevalence and heterogeneous presentation with symptoms of the skin, joints and bones. Recent insights into the pathogenesis of SAPHO and the evidence that TNF blockade can be effective for virtually all manifestations of the disease, allude to the fact that early recognition and treatment of this syndrome will improve the health and quality of life of SAPHO patients. In this report, we describe the cases of three patients with different clinical presentations who were all diagnosed with SAPHO syndrome and successfully treated with TNF blockers.

## CASE REPORTS

### Case 1

Patient A is a 25-year-old woman who was known with recurrent hidradenitis suppurativa of the armpits and groins for more than ten years. In 2008 pustular skin lesions on the palms of the hands and soles of the feet occurred (*figure 1A*). Simultaneously, she developed arthralgia and inflammatory back pain, accompanied by morning stiffness. The back pain improved with movement. On physical examination we observed extensive scarring in the armpits and groins together with moderately active hidradenitis (*figure 1B*). In addition, she had arthritis of the left sternoclavicular joint. Laboratory tests revealed an elevated erythrocyte sedimentation rate (ESR, 84 mm in the first hour) and normocytic anaemia (haemoglobin 6.9 mmol/l). Genetic testing indicated that the HLA-B27 gene was absent and X-rays of the sacroiliac

**Figure 1.** Typical skin lesions in SAPHO syndrome: palmoplantar pustulos footpad (A) and hidradenitis suppurativa in the axilla (B)



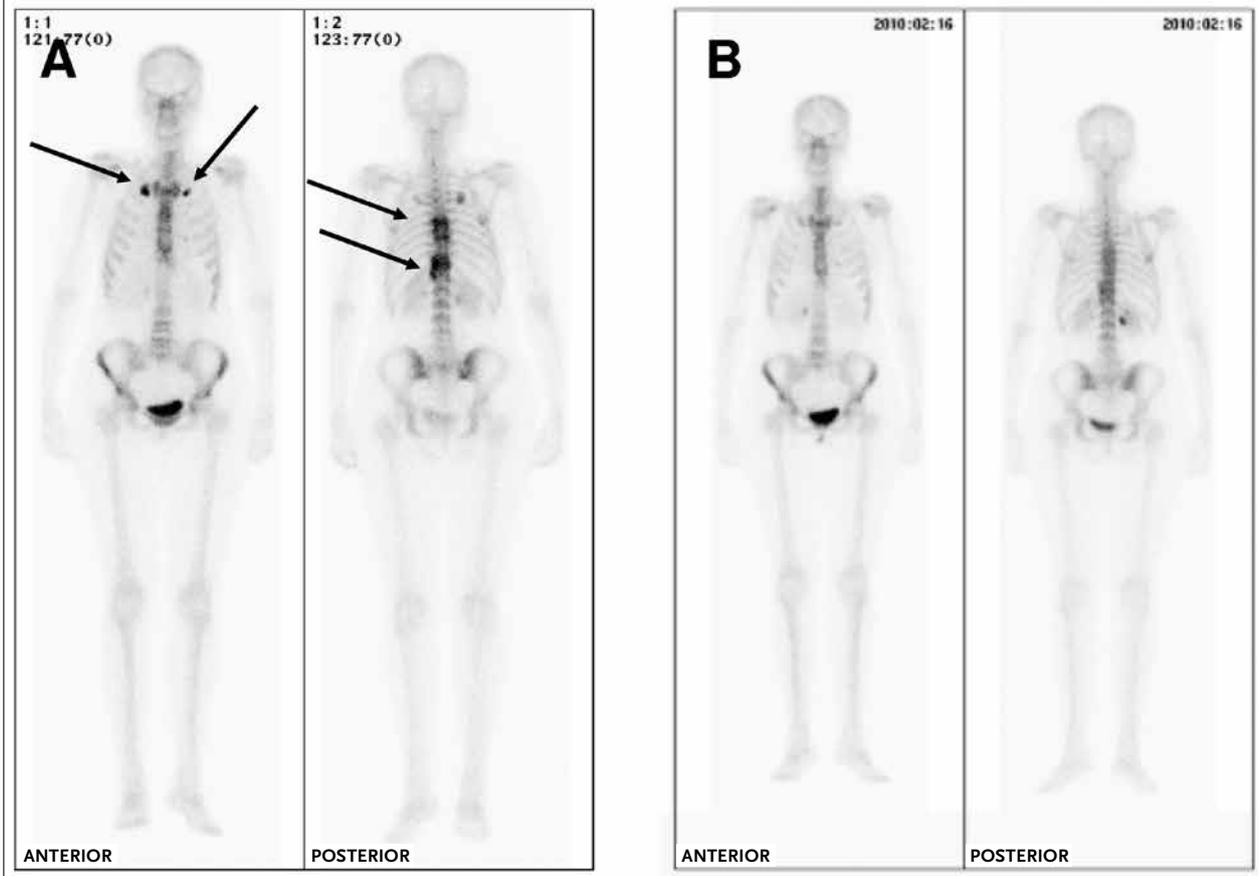
joints showed no sacro-iliitis. Given the combination of synovitis, hidradenitis and pustulosis, SAPHO syndrome was diagnosed. Local treatment of the pustular skin lesions including surgery and antibiotics (azithromycin)

did not persistently improve her symptoms. Subsequent systemic treatment with NSAIDs and prednisolone also proved ineffective. Therefore, she started on TNF blockade (infliximab 5 mg/kg every 8 weeks) in September 2009. This resulted in a rapid improvement of both the skin lesions and the arthritis. In six weeks time the ESR decreased to 25 mm in the first hour.

#### Case 2

Patient B is a 44-year-old woman who presented with pustular skin lesions and thoracic pain in 2004. She also experienced low back pain with morning stiffness lasting approximately one hour. In addition, she was regularly subfebrile, but did not have weight loss or night sweats. On physical examination a swelling of the right sternoclavicular joint was found. We also observed an extensive acneiform rash on her face, hands and feet. After dermatological consultation a skin biopsy was performed and the diagnosis of palmoplantar pustulosis was made. Laboratory tests showed a slightly elevated ESR (32 mm in the first hour). A chest X-ray revealed syndesmophytes of the thoracic spine and scintigraphy demonstrated increased uptake of technetium at the first costochondral

**Figure 2.** Scintigraphy before (A) and two years after (B) initiation of treatment with infliximab. The arrows point out the increased uptake (osteitis) of technetium at the first costochondral junction, the sternoclavicular joints and thoracic vertebrae



junction and the sternoclavicular joints on both sides (figure 2A). Besides this, there was enhanced uptake at the site of several thoracic vertebrae. The diagnosis of SAPHO was made and because NSAIDs in combination with topical glucocorticoids were not effective, alendronate was started at a dose of 70 mg once weekly for six months, as this has been described to be effective in some cases.<sup>2,3</sup> After a temporary improvement, the symptoms recurred and the patient was treated with a single-dose regimen of pamidronic acid 90 mg. This resulted in temporary improvement of her bone pain but had no effect on the skin lesions. Therefore, we decided to initiate treatment with TNF blockade (infliximab 5 mg/kg every 8 weeks). A few days after the first infusion the skin lesions disappeared and her back pain improved substantially. Also, her fatigue decreased and the patient was free of almost all her symptoms with this treatment. Interestingly, scintigraphy also showed a decrease in osteitis (figure 2B).

### Case 3

Patient C is a 37-year-old woman who had been diagnosed with palmoplantar psoriasis in 1999. In 2005 she developed hidradenitis suppurativa in the groin and genital region. In 2007 she visited the rheumatology outpatient clinic with inflammatory back pain. Physical examination revealed limited mobility of the lumbar spine (Schober test 10-12.5 cm). However, she did not have active skin lesions at that time. Laboratory tests showed an ESR of 21 mm in the first hour and HLA-B27 was negative. On a conventional X-ray of the pelvis no evidence for a sacro-iliitis was observed, but there was an irregular aspect of the os pubis (figure 3A). An MRI scan of the pelvis was compatible with osteitis pubis (figure 3B). Subsequently, the diagnosis of SAPHO syndrome was made and after insufficient improvement on NSAIDs she started on TNF

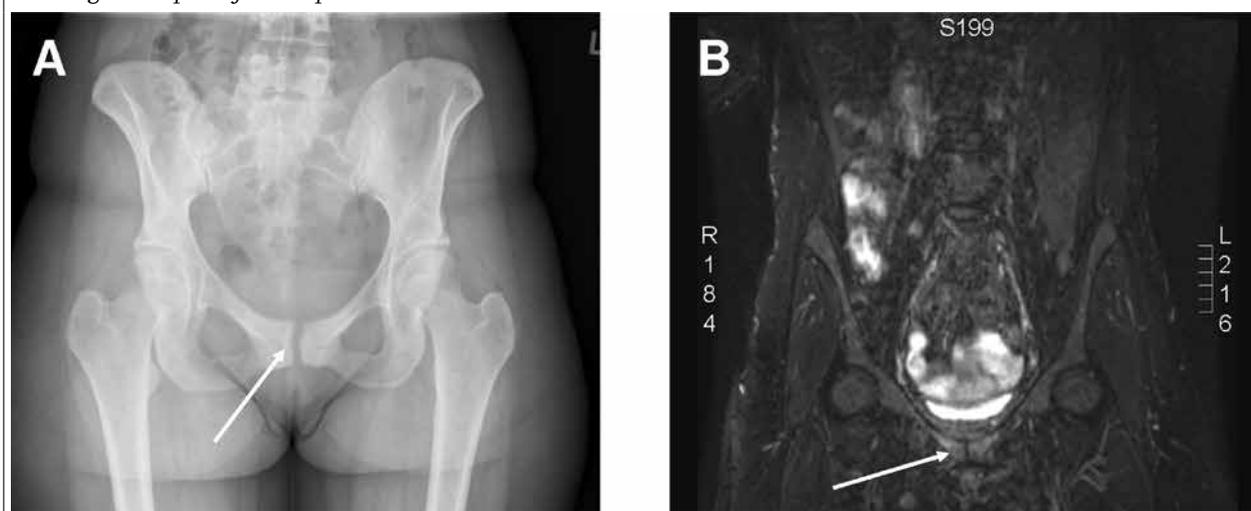
blockade (infliximab 5 mg/kg every 8 weeks) in early 2010. Despite a good clinical response the patient did not want to continue treatment. After discontinuation of infliximab, a rapid and strong increase in her back pain and pelvic pain occurred, as well as a significant increase in fatigue. Therefore, anti-TNF treatment was restarted and her complaints decreased again.

### BACKGROUND

As illustrated by the three cases, the interval between the symptoms and final diagnosis of SAPHO syndrome is usually very long, sometimes even years. This is mainly due to two factors. Firstly, the disease is rare (data on the exact incidence and prevalence are lacking) and therefore often unknown. Secondly, the clinical presentation is heterogeneous and patients may therefore present to different specialists. As illustrated by case 3, the various manifestations (pustulosis and osteitis) do not necessarily coincide. The variation in clinical presentation is also evident from the different names that were given to the disease spectrum before 1987. The best known names are: pustulotic arthro-osteitis, acne-associated arthropathy, sternocostoclavicular hyperostosis (SCCH) and chronic recurrent multifocal osteomyelitis (CRMO). CRMO is currently recognised as the paediatric manifestation of the disease.

Cohort studies indicate that SAPHO syndrome is more common in women than in men (2:1).<sup>4</sup> Approximately 70% of patients have anterior chest wall pain,<sup>4,5</sup> which is regarded as the most characteristic feature of the disease. Affected patients may present with pain, tenderness, and swelling of the sternum and its articulations. Upon imaging hyperostosis and osteitis are often observed.

**Figure 3.** Conventional radiologic (A) and MRI (B) image of osteitis pubis in SAPHO syndrome. The arrows indicate the irregular aspect of the os pubis



Next to sternoclavicular involvement, the entire axial skeleton can be affected, in particular the sacroiliac region (24-48%), spine (approximately 33%) and the symphysis pubis (7%).<sup>6</sup> Vertebral involvement is particularly characterised by the occurrence of discitis, asymmetric paravertebral calcifications and syndesmophytes. The bone damage is often associated with inflammation of adjacent joints such as the sternocostal and sternoclavicular joints. Peripheral arthritis occurs in 4-36% of patients and is also regarded as a local extension of a primary bone disorder. Often a non-specific sterile inflammation is observed when a bone biopsy is performed.<sup>7</sup>

Skin abnormalities are present in 55-80% of patients. These can occur simultaneously with the joint complaints, prior to the skeletal disorders, or may occur up to several years after the first articular symptoms. In 70% of the cases, the skin lesions occur prior to the development of skeletal abnormalities. Palmoplantar pustulosis is the most observed skin disorder (50-55%) and sometimes occurs in conjunction with psoriasis vulgaris, although psoriasis vulgaris can also occur alone. Approximately 25% of patients have severe acne which can present as acne conglobata or acne fulminans. In addition, other skin disorders such as hidradenitis suppurativa can occur. The association with neutrophilic dermatoses such as pyoderma gangrenosum and Sweet's syndrome is rare. The natural course of SAPHO syndrome is characterised by variable disease activity with exacerbations and remissions. Sometimes it leads to a serious, debilitating condition with persistent pain. Only a minority of patients have a self-limiting course of the disease.<sup>7</sup>

## DIAGNOSIS

SAPHO syndrome is primarily a clinical diagnosis based on the occurrence of a combination of typical skin disorders with bone pain and/or synovitis, often at the level of thoracic spine and pelvis (*table 1*). There is a limited role for laboratory testing: in about half of the cases the ESR and CRP values are elevated.<sup>5</sup> In contrast, imaging is extremely useful in the investigation of bone pain. Although conventional radiographs may show signs of osteosclerosis, erosions and hyperostosis, computed tomography (CT) is much more sensitive to detect these abnormalities. Scintigraphy can also be useful in establishing the diagnosis. In literature, a sensitivity of 93% is reported.<sup>6</sup> In active disease the typical 'bull's head sign' can be observed: increased technetium 99m uptake at the area of the manubrium sterni and the sternoclavicular joints resembles a bull's head. Magnetic resonance imaging (MRI) may, in addition to signs of osteitis, also provide evidence for enthesitis.

**Table 1. Criteria for SAPHO syndrome**

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| <ol style="list-style-type: none"> <li>1. Osteoarticular manifestations in combination with palmoplantar pustulosis and/or severe acne</li> <li>2. Hyperostosis with or without skin manifestations</li> <li>3. Chronic recurrent multifocal osteomyelitis of the axial and peripheral skeleton with or without skin manifestations</li> <li>4. Exclusion criteria: <ol style="list-style-type: none"> <li>a. Infectious osteomyelitis or septic arthritis</li> <li>b. Infectious palmoplantar pustulosis</li> <li>c. Palmoplantar keratoderma blennorrhagica</li> </ol> </li> </ol> |
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Differential diagnosis with related disorders is often difficult as SAPHO shows a broad overlap with related conditions. The skin manifestations of SAPHO often resemble palmoplantar pustulosis, psoriasis, or hidradenitis suppurativa. In that case the actual diagnosis is based on the simultaneous presence of bone or joint symptoms. From an articular perspective, SAPHO syndrome is clinically related to spondyloarthritis based on a) an association with psoriasis and inflammatory bowel disease, b) the occurrence of osteitis of the sternum, spine, and pelvis, and c) asymmetric peripheral arthritis.<sup>8</sup> However, dactylitis, arthritis of the proximal interphalangeal joints and uveitis do not belong to the inflammatory features found in SAPHO syndrome. Also, HLA-B27 positivity does not occur more frequently in patients with SAPHO syndrome than in the general population. Finally, SAPHO syndrome sometimes shows similarities with Behcet's disease, but uveitis, ulcers, and thromboembolic events usually do not occur (reviewed in Magrey and Khan<sup>7</sup>).

## PATHOPHYSIOLOGY

The underlying aetiological and pathophysiological mechanisms of SAPHO syndrome are not yet elucidated. SAPHO syndrome is considered to be a polygenic autoinflammatory disorder in which an abnormal, strong reaction of the innate immune system to pathogens gives rise to chronic sterile inflammation. In this respect SAPHO syndrome also shows similarities with spondyloarthritis, Behcet's disease and hidradenitis suppurativa.

A genetic contribution to the development and course of the disease is supported by the observation of familial clustering.<sup>9-11</sup> The genes that appear to play a role in SAPHO syndrome are located on chromosome 18 (cmo locus): LPIN2 and NOD2. LPIN2 encodes lipin 2 which may be involved in modulating apoptosis of polymorphonuclear cells.<sup>12</sup> Mutations in the NOD2 gene are also associated with inflammatory bowel disease and may lead to an abnormal immune response to bacterial

peptidoglycans via activation of the pro-inflammatory transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B).<sup>13,14</sup> In SAPHO syndrome it is hypothesised that an occult disseminated infection or an abnormal systemic immune response to low virulence bacteria such as *Propionibacterium acnes* is a trigger for a chronic inflammatory response with mainly production of IL-8, IL-18 and TNF.<sup>7</sup> This is substantiated by the presence of skin lesions in SAPHO syndrome and also by the fact that this commensal skin bacterium has been demonstrated in cultures of the affected bone lesions.<sup>15</sup> The hypothesis is further supported by the fact that some patients improve under chronic antibiotic therapy.<sup>16</sup> In agreement with the concept that SAPHO is an autoinflammatory rather than autoimmune condition, autoantibodies do not appear to play a role in the pathogenesis of the disease.<sup>17</sup>

## TREATMENT

The natural history of SAPHO syndrome is not well defined. Although a minority of patients have a self-limited course, the majority have either a relapsing-remitting pattern or chronic indolent pattern. A number of therapies have been reported to be useful in patients with SAPHO syndrome.<sup>18</sup> Several case reports and descriptions of small case series indicate that NSAIDs improve osteoarticular pain. There are also reported beneficial effects of colchicine, glucocorticoids and disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate and sulphasalazine. However, there are no double-blind, randomised controlled trials to substantiate the effectiveness of these drugs. Interestingly, in 2009 an intervention study demonstrated that patients with positive cultures for *Propionibacterium acnes* can improve using azithromycin or clarithromycin. After discontinuation of the antibiotics this effect is nullified.<sup>16</sup>

In recent years, many case reports have appeared on the use of bisphosphonates in the treatment of SAPHO syndrome, in which both partial and complete remission have been described.<sup>2,3</sup> The beneficial effect of bisphosphonates may result from possible anti-inflammatory activity and inhibition of bone turn-over.<sup>19</sup> However, this treatment has little or no effect on the skin lesions.<sup>3</sup>

The clinical and pathophysiological relationship of SAPHO syndrome with spondyloarthritis, psoriasis and Behcet's disease has led to the use of TNF blockade in this syndrome. In line with our descriptions, case reports and case series often demonstrate a marked improvement in the clinical picture and the inflammatory response.<sup>20</sup> However, also in TNF blockade no double-blind randomised placebo-controlled trials have been performed to confirm these observations. The largest case series of 45

SAPHO syndrome patients treated with TNF inhibitors<sup>21</sup> indicates that skin, joint and bone symptoms respond to TNF inhibition, although it is not clear whether this treatment is permanently effective. Another problem is the reimbursement of this treatment, as SAPHO syndrome is not a registered indication for TNF blockers. In the current financial regulations of the Dutch healthcare system, the reimbursement of TNF blockade for unregistered indications is difficult, if not impossible. Nevertheless, given the impossibility to carry out randomised clinical trials in this rare and heterogeneous disease, and the reported clinical improvement after treatment with TNF antagonists, the use of TNF blockade should be considered in severe and treatment-resistant patients.<sup>22</sup>

Recently, an autoinflammatory disease based on deficiency of the interleukin-1-receptor antagonist was described under the name DIRA.<sup>23</sup> This disease is associated with sterile multifocal osteomyelitis, periostitis and pustulosis, which looks similar to SAPHO. Interestingly, DIRA patients exhibit a good response to anakinra, an interleukin 1 (IL-1) receptor antagonist. The positive effects of this drug in a disease with overlapping clinical features prompted investigators to evaluate the effects of anakinra in SAPHO syndrome. Anakinra proved to be beneficial in five out of six SAPHO patients, two of which previously failed to respond to TNF blockers.<sup>24</sup>

## CONCLUDING REMARKS

SAPHO syndrome is a rare disease which should be considered in patients presenting with acne or pustular skin disease in combination with chest and/or bone pain. The diagnosis relies on the clinical picture in combination with imaging (bone scintigraphy, CT or MRI) to detect osteitis. Treatment consists of NSAIDs and sometimes bisphosphonates, although the latter have no effect on skin disease. In refractory cases TNF blockade or IL-1 receptor antagonist treatment may be considered.

## GRANT SUPPORT

S.W.T is supported by a Clinical Fellowship of the Netherlands Organisation for Scientific Research (NWO).

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