Tumor Necrosis Factor-α Blockers in SAPHO Syndrome

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ABSTRACT. ***Objective.*** To analyze the clinical efficacy of anti-tumor necrosis factor-α (TNF-α) therapy in treatment of synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome, we describe cases of refractory SAPHO syndrome and review cases treated with anti-TNF-α reported in the literature.

Methods. We describe 6 cases of patients with SAPHO syndrome treated with anti-TNF-α between 2004 and 2008. Therapeutic response was evaluated according to improvement in pain score, amelioration of disease activity, and improvement in function. The efficacy of treatment was considered to be reduced need for analgesics and/or antiinflammatory therapy.

Results. In our series, 4 patients received infliximab, 1 etanercept, and 1 adalimumab. These treatments brought clinical response in 4 patients (66.6%): response was sustained with infliximab in 1 case for 7 months; with adalimumab in another case for 22 months; and with etanercept in 2 cases for 1 and 42 months, respectively. In contrast, 2 other patients showed no response to infliximab. Improvement was initially temporary after infusions 1 and 2, then pain recurred at Week 14. Skin lesions were healed in 3 of 4 cases, but recurred or worsened in 2 cases, after infusion 2 of infliximab. Treatment was generally well tolerated. Paradoxical psoriasis was noted in 2 cases and urticaria in 1.

Conclusion. Given our results and those from the literature, TNF-α blockers should be considered in the therapeutic strategy of refractory cases of SAPHO syndrome, despite their effect seeming less impressive than in other spondyloarthropathies. (First Release May 15 2010; J Rheumatol 2010; 37:1699–704; doi:10.3899/jrheum.091086)

Key Indexing Terms:
SAPHO SYNDROME PALMOPLANTAR PUSTULOSIS INFLIXIMAB
ETANERCEPT ADALIMUMAB TUMOR NECROSIS FACTOR-α BLOCKERS

SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, osteitis) was defined as a clinicoradiological entity combining skin, bone, and joint manifestations. The denotation was first proposed in 1987[1] after investigation of 85 cases. The main target is the anterior chest wall, where common findings include osteosclerosis and enlargement of the internal portion of the clavicles and first ribs. The axial skeleton (spine and sacroiliac joints) and peripheral bones can be involved. Skin diseases associated with this type of osteitis include palmoplantar pustulosis (PPP), severe acne, and various patterns of psoriasis.

Converging arguments indicate that SAPHO syndrome can be classified with the inflammatory spondyloarthropathies, which typically affect the spine. The therapeutic strategy was largely inspired by that for spondyloarthropathies. Because of the low incidence and different patterns of disease expression, most reports describe treatment responses from anecdotal cases and small series of patients. Thus, the therapeutic strategy of SAPHO syndrome remains unclear. In general terms, treatment consists of nonsteroidal antiinflammatory drugs (NSAID) for osteoarticular symptoms and topical treatment for skin lesions. Efficacy is considered satisfactory in about two-thirds of cases[2].

A recent interventional study of patients with SAPHO syndrome showed positive bacteriological cultures for *Propionibacterium acnes* in 14 of 21 (67%) patients who had undergone a needle biopsy of osteitis lesions[3]. This is a significant addition to publications showing an association of SAPHO with *P. acnes*. Thus, different protocols of antibiotic therapy were tried: at least 6 uncontrolled studies showed efficacy of antibiotic therapy (azithromycin, doxycycline, sulfamethoxazole/trimethoprim), but decreased disease activity might be related to the natural remitting course of the disease and not to the efficacy of the antibiotic therapy[4]. Refractory forms have led to the use of disease-modifying antirheumatic drugs. Therapy with methotrexate (MTX) and sulfasalazine was attempted, but with unsatisfactory results[2]. Bisphosphonates were proposed, but their efficacy is difficult to assess in the absence of a randomized controlled study and requires more evidence. Nevertheless, in most reports, this treatment is considered effective for

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chronic active osteitis, usually with rapid and prolonged pain relief[5]. Refractory cases of SAPHO require intensive care. With analogy to spondyloarthropathy therapy, tumor necrosis factor-α (TNF-α) blockers have been proposed as third-line therapy.

We describe 6 cases of SAPHO syndrome treated with anti-TNF-α agents between 2004 and 2008 and review cases in the literature. Patients were selected according to 2 inclusion criteria: (1) diagnosis of SAPHO syndrome by clinical and radiologic criteria [on bone radiography, computerized axial tomography (CT), and scintigraphy]; and (2) a painful clinical progression despite therapy with several NSAID associated with at least one of the following treatments: MTX, pamidronate, antibiotics.

The therapeutic response was evaluated according to improvement in pain score on a visual analog scale (VAS, 0–100 mm), amelioration of disease activity [Bath Ankylosing Sponylitis Disease Activity Index (BASDAI)], and improvement in function [Bath Ankylosing Spondylitis Functional Index (BASFI)]. These latter 2 indexes, designed for measuring disease activity and function in primary ankylosing spondylitis, have been shown to have good internal consistency in peripheral and axial psoriatic arthritis[6]. For this reason, we adopted these scoring methods in our study.

The efficacy of treatment was considered to be reduced need for analgesics and/or antiinflammatory therapy. Treatment safety was evaluated.

Case report 1. A 58-year-old woman presented with a history of pain in the anterior chest wall with inflammatory dorsalgia for the previous 6 years. Erythrocyte sedimentation rate (ESR) was 4 mm/h and C-reactive protein 0.4 mg/l. Spinal magnetic resonance imaging (MRI) showed osteosclerosis of the T8 vertebra. Sacroiliitis was not observed on pelvic plain radiography. Biopsy of the T8 lesion demonstrated chronic inflammation but no tumor. Some months later, PPP developed. A diagnosis of SAPHO syndrome was made. She initially received NSAID, then several monthly infusions of pamidronate (60 mg over 2 yrs). However, right sternoclavicular pain persisted, as well as inflammatory talalgia. In light of the refractory SAPHO syndrome, treatment with infliximab (5 mg/kg at Weeks 0, 2, and 6 and then every 8 weeks) was started. The patient showed clinical response, with gradual amelioration of disease activity over 7 months. The BASDAI score decreased, from 6.2 before infusion 1, to 2.4 before infusion 5; the BASFI decreased from 5.5 to 2.2 and the VAS score from 65 to 50. Morning stiffness was alleviated, from 4 h before infusion 1 to 1.5 h before infusion 5. NSAID were stopped. Similarly, PPP was relieved. Tolerance to infliximab treatment was good.

Case report 2. A 36-year-old woman with a history of Hashimoto thyroiditis presented over a period of 7 years with recurrent episodes of swelling in the right knee. Knee arthroscopy in 2004 revealed active hyperplastic synovitis. Two years later, inflammatory, left sternoclavicular pain appeared, with PPP. ESR was 46 mm/h and CRP 7 mg/l. CT scan of the chest wall revealed marked erosion and narrowing in the left sternoclavicular and first left sternocostal joints, with irregularity in and sclerosis of the side rib and hypertrophy of the sternal side. MRI of the spine and sacroiliac joints gave normal results. She was given a diagnosis of SAPHO syndrome. NSAID and MTX were ineffective. The left sternoclavicular joint remained inflamed, with cervicodorsal rachialgia and oligoarthritis of the knees. Accordingly, treatment with infliximab (5 mg/kg at Week 0, 2, and 6 and then every 8 weeks) was started. Before infusion 2, clinical response was observed: the BASDAI decreased from 4.7 to 2.6 and the BASFI from 2.0 to 1.1. Morning stiffness decreased and ESR returned to the normal range. However, at Week 14, pain recurred in the anterior chest wall, and BASDAI increased to 3.4. The patient showed paradoxical psoriasis and substantial exacerbation of PPP confirmed on skin biopsy. A switch to etanercept was attempted. However, after 3 months of treatment, disease remained active, with BASDAI 4.6 and BASFI 3.2.

Case report 3. A 45-year-old woman presented with a rash of PPP and subsequent inflammatory pain of the left sternoclavicular joint present for 6 years. CT scan revealed osteosclerosis of the sternum, first left rib, and iliac side of the right sacroiliac joint. She was given a diagnosis of SAPHO syndrome. Symptoms were resistant to treatment (NSAID, antibiotics, and monthly infusion of pamidronate 60 mg). BASDAI was 5 and VAS score 85 mm. Treatment with infliximab 5 mg/kg was started. At Week 2 and before infusion 2, the BASDAI decreased to 1.0; the patient had no morning stiffness. NSAID were stopped; skin lesions had healed. By contrast, at Week 14 and before infliximab infusion 3, pain recurred in the anterior chest wall. The BASDAI increased to 6.4; NSAID were restarted. During infusion 5, due to an allergic urticaria reaction on the trunk and thighs, therapy was interrupted. A switch to adalimumab was attempted and led to partial improvement within 1 month; BASDAI was 4.6 and VAS score 60 mm.

Case report 4. A 61-year-old woman complained of inflammatory pain in the anterior chest wall; she had no skin lesions. A persistent biologic inflammatory syndrome (ESR 64 mm/h and CRP 26 mg/l) was noted. Bone scintigraphy revealed hyperfixation of the manubrium. CT scan revealed sclerosis of sternoclavicular joints without infiltration or involvement of soft tissue. Plain radiography of the pelvis revealed marked hyperostosis and osteosclerosis of the left sacroiliac joint. The patient was given a diagnosis of SAPHO syndrome, and treatment with several NSAID and pamidronate (2 infusions). However, disease remained active. Treatment with adalimumab 40 mg every 2 weeks was then introduced. Clinical remission occurred after injection 2 and during 2-year followup. BASDAI decreased from 7.9 before treatment to 1.1 after 22 months of therapy;

BASFI decreased from 6.2 to 0.4 and VAS score from 86 to 8 mm. ESR decreased from 55 to 9 mm/h after 2 years and CRP from 38 to 5 mg/l. Finally, NSAID were stopped after 14 months of treatment.

Case report 5. A 53-year-old woman presented with swelling of the right upper limb. Doppler venous ultrasonography revealed stenosis of the humeral, axillary, and right subclavian veins. She also complained of right clavicular and sternocostal pain. CT scan revealed hyperostosis and osteosclerosis of the right clavicle, first 3 ribs, and sternal manubrium. Bone scintigraphy revealed hyperfixation of these lesions. Biopsy of the clavicle showed a chronic aseptic inflammatory lesion without osteolytic reaction. She was given a diagnosis of SAPHO syndrome complicated by venous thrombosis. She showed no skin manifestations. Symptoms were resistant to different NSAID, i.e., several infusions of pamidronate 60 mg monthly during 18 months and MTX. She continued to have stiffness for 2 h in the morning and the VAS score was 90 mm; ESR was 51 mm/h and CRP 76 mg/l. Treatment with a TNF-α blocker (etanercept) was started. At Week 4, she reported no pain, with VAS score 0. She did not wake at night and had no morning stiffness; ESR was 19 mm/h and CRP 11 mg/l.

Case report 6. A 29-year-old woman had had rachialgia associated with inflammatory pain of the right sternoclavicular joint for 4 years. ESR was 20 mm/h and CRP 6 mg/l. Bone scintigraphy revealed hyperfixation of T5, T6 and T7, manubrium, and right sternoclavicular joint. CT scan revealed osteosclerosis of T6 and T7 suggesting inflammatory spondylitis, which was confirmed by spinal MRI. She was given a diagnosis of SAPHO syndrome and treatment was started with several NSAID and monthly infusions of pamidronate 60 mg, which initially relieved pain. Symptoms recurred, with PPP. She had morning stiffness for 2 h; ESR was 34 mm/h and CRP 10 mg/l. Infusions were started with infiximab 5 mg/kg at Weeks 0, 2, and 6 and then every 8 weeks. Clinical response occurred at Week 2, with no more morning stiffness. ESR (27 mm/h) and CRP (7 mg/l) were not significantly changed. Three weeks after infusion 1, a psoriatic rash appeared on the thighs, trunk, and face and was confirmed by skin biopsy. A switch to etanercept led to complete relief of pain and the inflammatory syndrome. No psoriasis or PPP was found. The current followup is 42 months.

DISCUSSION

In general terms, NSAID and analgesic treatments help control osteoarticular symptoms of SAPHO syndrome. In cases that do not respond, second-line therapies are tried. To date, SAPHO syndrome is commonly refractory to glucocorticoids and disease-modifying antirheumatic drugs including MTX and sulfasalazine. In some patients with refractory disease, anti-TNF-α therapy has been proposed as a third-line therapy. Its use in SAPHO syndrome is mostly based on the difficulties encountered when treating SAPHO syndrome. Indeed, as the pathogenesis of SAPHO syndrome is unknown and due to its low incidence and different patterns of disease expression, there is no well established therapy[7]. Most reports describe treatment responses based on anecdotal cases and small series of patients. Further, the use of anti-TNF-α therapy is also based on the efficacy of TNF blockers in spondyloarthopathies. Most investigators[8,9] have supported a link between SAPHO syndrome and spondyloarthopathies because of frequent axial involvement and association with psoriasis and inflammatory bowel diseases in 13% of cases[10], relatively high frequency of positive HLA-B27 in 15% of cases[11], and efficacy of NSAID. Some have also suggested that SAPHO syndrome could be an atypical form of psoriatic arthritis[12].

Proinflammatory cytokines such as TNF-α may be involved in generating or perpetuating the rheumatic manifestations of SAPHO syndrome. A group in Germany documented TNF-α overexpression in mandibular osteitis[13]. Further support for the involvement of TNF-α comes from the promising results obtained with TNF-α antagonists in patients with SAPHO syndrome.

In our cases of some refractory forms of SAPHO syndrome, TNF-α blockers were prescribed. Clinical response was achieved in 4 cases (Patients 1, 4, 5, and 6): response was sustained with infliximab in Case 1 for 7 months; with adalimumab in Case 4 for 22 months; and with etanercept in Case 5 for 1 month and in Case 6 for 42 months. Clinical response occurred after infusion 4 of infliximab and after injection 2 of etanercept and adalimumab. By contrast, 2 other patients (Cases 2 and 3) showed no significant response to infliximab.

Only 19 reports of adult cases of SAPHO syndrome treated with anti-TNF-α have been published; characteristics of these cases are given in Table 1[13-22]. These cases were in general refractory to alternative treatment such as bisphosphonates, MTX, sulfasalazine, and even cyclosporine. The only 2 anti-TNF-α agents used were infliximab and etanercept. Infliximab was prescribed in all cases except 2. Therefore, our Case 4 was the first reported case of SAPHO syndrome treated with adalimumab. In the 19 previous cases, the clinical response was rapid after infusion 1 in 13 patients (68.4%), after infusion 2 in 4 (21%), and after infusion 3 in 2 (10.5%). Clinical response was maintained in all patients. Osteoarticular pain did not recur; this result, often described as remission, was maintained with a followup of 8 to 18 months during treatment. The maximal followup was 42 months in our series. Sometimes the same result is maintained when anti-TNF-α therapy is stopped[14].

In parallel, we observed healed skin lesions after the first infusion in 3 of 4 of our cases (Cases 1, 2, and 3). These results support reports in the literature. Indeed, among the 15 cases of skin manifestations in the literature, healing was observed mainly for acne — in 12 (80%) of these cases. Of

Table 1. SAPHO syndrome treated with TNF-α blockers in the literature.

Study	Sex/age, yrs	Osteoarticular Findings	Skin Involvement	Duration, yrs	Prior Treatment	Anti-TNF Therapy	Outcome	Followup
Wagner[13]	F 44	Hyperostosis of mandible	PPP	3	NSAID, CTX, ATB, MTX, BP	ETN 25 mg × 2	Improvement after 1st dose and maintenance of response for 9 mo	9 mo
	F 41	Sternal hyperostosis	No		CTX, MTX, CSA BP	INF 5, then 3 mg, then ETN	Improvement after infusion 1 of INF (discontinued due to bronchospasm, 3rd bolus). Improvement and maintenance of response for 6 mo after starting ETN	9 mo
Olivieri[14]	M 35	Clavicular osteitis	Acne	17	NSAID, CSA, ATB	INF 5	Improvement of chest pain and skin lesions after infusion 1 (total bolus 4). Maintenance of remission	18 mo
	M 52	Sternal, clavicular, and rib osteitis	PPP	10	NSAID, SSZ, MTX, CSA	INF	Improvement after infusion 1 (total bolus 5). Maintenance of remission for 16 mo	18 mo
Iqbal[15]	M 23	Clavicular and vertebral osteitis	Acne	4	Isotretinoin, CTX, CSA, MTX	INF 5 mg/kg	Improvement of skin lesions 1 month after infusion 1. Remission of joint features after 10 mo	10 mo
Deutschmann[16]	M 16	Osteitis of the mandible, sacroiliac joint, and femoral metaphysis	No	10	NSAID, ATB, calcitonin, CTX	INF 5 mg/kg	Clinical remission maintained for more than 21 mo	21 mo
Massara[17]	M 47	Sternoclavicular osteitis	PPP	9	NSAID, MTX, BP	INF 5 mg/kg, 14 mo	Improvement of chest pain after infusion 2. PPP reappeared after 3rd bolus. Discontinuation of INF at 14 mo due to pneumonitis. Relapse of bone pain 6 mo after INF withdrawal	6 mo after INF withdrawal
	M 43	Sternoclavicular hyperostosis; bilateral sacroilitis	PPP	1	NSAID, SSZ	INF 5 mg/kg	Remission of chest pain after 2nd bolus that was maintained for 14 mo. Relapse of PPP at 6 mo of therapy	14 mo
	F 67	Sternoclavicular hyperostosis; peripheral arthritis	No	5	NSAID, BP	INF	Remission at 2nd bolus, and maintenance of remission for 8 mo	8 mo
	F 42	Sternoclavicular hyperostosis; vertebral osteitis	PPP	7	NSAID, BP, CTX	INF 5 mg/kg	Improvement of bone pain at infusion 3. No bone pain or skin lesions at 8 mo	8 mo
Widmer[18]	F 53	Chest wall osteitis	No		NSAID, MTX SSZ	INF	Clinical response at 2 weeks, and maintenance for 40 weeks	40 wks
	F 39	Chest wall osteitis; sacroilitis	PPP		NSAID, MTX, SSZ	INF	Clinical response at 2 weeks. Healing of skin lesions. Loss of efficacy after 6th bolus	
	F 37	Chest wall osteitis;	PPP		NSAID, MTX, SSZ	INF	Clinical response at 2 weeks. Healing of skin lesions. Maintenance of response for 40 weeks	40 wks
Asmussen[19]	F 25	Clavicular hyperostosis	PPP		MTX	INF	Improvement of pain at infusion 2, maintained after 5 infusions	22 wks
Kyriazis[20]	F 61	Chest wall osteitis	PPP		NSAID, MTX, CSA, colchicine, CTX	INF	Clinical response after infusion 1. Healing of skin lesion at 14 weeks. Duration of improvement 54 weeks	54 wks
	F 63	Chest wall osteitis	PPP		NSAID, MTX, CSA, colchicine, CTX	INF	Clinical response after infusion 1. Healing of skin lesion at 14 weeks. Duration of improvement 54 weeks	54 wks
Moll[21]	F 45	Ilium osteitis; clavicular hyperostosis	PPP	9	NSAID, CTX, MTX	INF 5	Resolution of osteoarticular symptoms after infusion 1 (total 8 boluses)	8 wks

Table 1. Continued.

Study	Sex/age, yrs	Osteoarticular Findings	Skin Involvement	Duration, yrs	Prior Treatment	Anti-TNF Therapy	Outcome	Followup
	F 28	Ilium osteitis; chest wall pain	PPP	10	NSAID, CTX, ATB, BP, SSZ	INF	Remission of bone pain after infusion 1. Increased chest pain after discontinuation of therapy. Resolution of symptoms after restarting INF. Persistence of mild skin lesions (total 28 boluses)	15 mo
Sabugo[22]	M 39	Chest wall osteitis	PPP		NSAID, CTX, SSZ	INF	Remission of bone pain and skin lesion after infusion 3	
Present case 1	F 58	Vertebral osteitis	PPP	6	NSAID, BP	INF	Remission of bone pain and skin lesion after infusion 1	7 mo
Present case 2	F 36	Chest wall osteitis	PPP	7	NSAID, CTX, MTX	INF then ETN	Improvement of chest pain after infusion 2 with healing skin lesion. Relapse of PPP after 2nd bolus with paradoxical psoriasis. No response with 3 mo ETN	7 mo
Present case 3	F 45	Chest wall osteitis	PPP	6	NSAID, ATB, BP	INF then ADA	Improvement of chest pain after 1st infusion with healing skin lesion. Relapse of PPP after the infusion. Discontinued due to allergic urticaria reaction. Partial response with ADA	9 mo
Present case 4	F 61	Chest wall osteitis	—	4	NSAID, BP	ADA	Resolution of osteoarticular symptoms after 2nd injection	2 yrs
Present case 5	F 53	Chest wall osteitis	—	13	NSAID, MTX, BP	ETN	Resolution of osteoarticular symptoms	1 mo
Present case 6	F 29	Chest wall osteitis	PPP	4	NSAID, BP	INF then ETN	Improvement of chest pain after 1st infusion with healing skin lesion. Discontinued due to paradoxical psoriasis. Remission of bone pain and skin lesion after 2nd injection	42 mo

ATB: antibiotics; BP: bisphosphonates; CTX: corticosteroids; CSA: cyclosporine; ETN: etanercept; INF: infliximab; ADA: adalimumab; MTX: methotrexate; NSAID: nonsteroidal antiinflammatory drug; PPP: palmoplantar pustulosis; SSZ: sulfasalazine; TNF: tumor necrosis factor.

note, the experience of the Italian investigators suggested lower efficacy of infliximab for PPP than for osteoarticular manifestations[17] detected in 4 cases of SAPHO syndrome. In our series, skin lesions recurred or worsened after infusion 2 of infliximab in 3 cases (Cases 2, 3, and 6). The effect of anti-TNF-α on skin lesions can be paradoxical. In a recent review of the literature concerning skin complications from anti-TNF-α therapy, among 120 patients (with rheumatoid arthritis, ankylosing spondylitis, SAPHO syndrome, psoriatic arthritis, and other diagnoses), 37 cases of recurring PPP were noted[23]. A possible reason for deterioration of skin pustulosis could be activation of *P. acnes* with anti-TNF-α. Thus, combined therapy including anti-TNF medication and an antibiotic may be a reasonable solution[4].

Treatment was generally well tolerated in our cases, with no severe side effects. Nevertheless, we observed drug-induced dermatitis of the lower limbs in 1 case and paradoxical psoriasis in 2 cases treated with infliximab (Cases 2 and 6). Various skin reactions have been reported with infliximab therapy, often several months after initiation of treatment; reactions include erythema multiforme, skin vasculitis, lichenoid eruption, and annular granuloma, as well as eczematous rashes.

Our series suggests the efficacy of anti-TNF-α therapy in accord with cases described in the literature. In all these cases, the effectiveness was quick, with longterm maintenance. Five of our patients had already received bisphosphonates, without pain relief. Four of these cases responded to anti-TNF-α therapy. Similarly, we observed ineffectiveness of bisphosphonates in 6 cases in the literature, which suggests anti-TNF-α therapy as having a positive response. Bisphosphonates have been given to patients with SAPHO syndrome because of the features of the bone lesions, with new bone formation a characteristic pathologic feature, and some positive but transient results obtained with these drugs in some patients with spondyloarthropathies but not in controlled studies[24]. Thus, anti-TNF-α therapy seems effective even for disease resistant to bisphosphonates. However, this efficacy seems to be less impressive than that usually reported for other spondyloarthropathies.

Because of difficulties of treatment of SAPHO syndrome, anti-TNF-α therapy was proposed for refractory forms as third-line therapy. In our series of 6 cases, treat-

ment seemed effective in 4 (66.7%). Reports of 19 cases of SAPHO syndrome treated with anti-TNF-α therapy in the literature show a positive response in most. These data suggest a real effectiveness of these biotherapies for SAPHO syndrome. We also report the first case of SAPHO syndrome treated effectively with adalimumab.

Given our results and reports in the literature, anti-TNF-α therapies are an efficient treatment for patients with refractory SAPHO syndrome, with an early response. Because randomized controlled trials are difficult to perform for this rare disease, confirmation of these findings in a study with a larger number of patients is required.

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