In SAPHO syndrome anti-TNF-\(\alpha\) therapy may induce persistent amelioration of osteoarticular complaints, but may exacerbate cutaneous manifestations

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Objectives. SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) is a rare disease combining skin, bone and joint manifestations. In recent years new therapeutic strategies have been tried, among them TNF-\(\alpha\)-blocking agents. We report our experience with infliximab in four cases of SAPHO syndrome refractory to conventional therapies.

Methods. Between 2002 and 2005, four cases of SAPHO syndrome (two females and two males; mean age 49.7 yr) responding poorly to conventional drugs were treated with infliximab. The dose was 5 mg/kg, according to the protocol used in spondyloarthropathies, with infusions at 0, 2 and 6 weeks followed by 6 weeks intervals. No active cutaneous manifestations were present at the time of starting therapy.

Results. Complete remission of osteoarticular involvement was achieved after the second or third infusion, and the positive response was maintained for up to 12 months. A patient relapsed after discontinuation of infliximab, because of infectious complication. Palmoplantaris pustulosis relapsed in two patients after three and six infusions, respectively; there was slight improvement after discontinuation of anti-TNF-\(\alpha\) drugs.

Conclusions. Infliximab seems to be a very effective therapy for osteoarticular complaints of SAPHO syndrome. Cutaneous involvement responded less favourably, palmoplantaris pustulosis relapse being a possible complication.

Key words: SAPHO syndrome, Anti-TNF-\(\alpha\) agents, Infliximab, Palmoplantaris pustulosis.

The term SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) encompasses a group of osteoarticular manifestations whose distinctive feature is an inflammatory, pseudo-infectious osteitis, frequently associated with skin lesions [1–3].

Treatment remains empirical with non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics being the first-line drugs; results are inconsistent and usually irrelevant. Among other drugs, sulphasalazine and methotrexate are the most frequently employed, but results are disappointing [4]. Recently, positive outcomes have been obtained with bisphosphonates, particularly pamidronate [5–7] and zolendronic acid [8], via their anti-osteoclastic effect and supposed anti-inflammatory action, related to a suppressive effect on tumour necrosis factor \(\alpha\) (TNF-\(\alpha\)).

Moreover, encouraging results have been reported with the new anti-TNF-\(\alpha\) biological drugs. To date, six cases of SAPHO syndrome treated with infliximab and etanercept have been described, five of them showing a sustained response with both osteoarticular and cutaneous involvement [9, 10].

We report here our experience on this topic with four additional patients treated with infliximab with an extended follow-up.

Case reports

Four cases with SAPHO syndrome diagnosed according to proposed criteria [11] were treated with the anti-TNF-\(\alpha\) agent infliximab between January 2002 and March 2005 (Table I). Before starting infliximab, informed consent was obtained and all the patients underwent screening for latent tuberculosis infection and other diseases following the standard recommendations.

Case 1

This patient, a 47-yr-old man, was first observed in 1995 with a 2-yr history of severe pain and swelling in his left clavicle and sternum. Radiography of the anterior chest wall revealed features of osteitis of the left clavicle with similar involvement of the manubrium sterni. Technetium 99m-methylene diphosphonate scanning showed increased uptake in the same regions. The rest of the physical examination was unremarkable. Laboratory evaluation was normal except for an increased concentration of C-reactive protein (CRP; 50 mg/l; normal value 0–5 mg/l). HLA-B27 was negative. The patient initially received methotrexate 10 mg/week, ibuprofen 150 mg/day and clodronate 100 mg/week. Pain and swelling gradually decreased, and methotrexate was stopped after 12 months because of total remission from symptoms. Six years later, palmoplantaris pustulosis appeared, without osteoarticular involvement, and resolved after a brief course of topical steroid.

In 2002 the patient experienced a severe flare of pain in the anterior chest wall. NSAIDs and methotrexate were reintroduced with poor clinical effect. Due to the persistence of anterior chest wall involvement despite increasing methotrexate to 20 mg/weekly,
Table 1. Demographic and clinical data of the SAPHO syndrome cases studied

<table>
<thead>
<tr>
<th>Patient</th>
<th>CRP valuea</th>
<th>Bone scan</th>
<th>Follow-up (months)</th>
<th>Osteoarticular manifestations</th>
<th>Cutaneous involvement</th>
<th>Osteoarticular response</th>
<th>Cutaneous response</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1, m, 47 yr</td>
<td>37 mg/l</td>
<td>Increased uptake in the manubrium sterni and 1st CSJ</td>
<td>20</td>
<td>Sternoclavicular hyperostosis</td>
<td>Palmoplantar pustulosis</td>
<td>+</td>
<td>Relapse of palmoplantar pustulosis</td>
<td>Infliximab</td>
<td>Complete remission</td>
</tr>
<tr>
<td>2, m, 43 yr</td>
<td>6 mg/l</td>
<td>No focal uptake in the ACW and SIJ</td>
<td>14</td>
<td>Sternoclavicular hyperostosis, Palmoplantar pustulosis</td>
<td>–</td>
<td>–</td>
<td>Relapse of palmoplantar pustulosis</td>
<td>Infliximab</td>
<td>Complete remission</td>
</tr>
<tr>
<td>3, f, 67 yr</td>
<td>3 mg/l</td>
<td>Increased uptake in the manubrium sterni, right clavicle and both SIJ</td>
<td>8</td>
<td>Sternoclavicular hyperostosis</td>
<td>Pustular lesions</td>
<td>–</td>
<td>–</td>
<td>Infliximab</td>
<td>Complete remission</td>
</tr>
<tr>
<td>4, f, 42 yr</td>
<td>1 mg/l</td>
<td>Reduced uptake in the right SIJ</td>
<td>8</td>
<td>Sternoclavicular joint, CSJ, chondrosternal joint, ACW, anterior chest wall, SIJ, sacroiliac joints</td>
<td>Palmoplantar pustulosis</td>
<td>+</td>
<td>–</td>
<td>Infliximab</td>
<td>Complete remission</td>
</tr>
</tbody>
</table>

Cases of SAPHO syndrome

**Case 2**

This patient is a 43-yr-old man whose complaints began in 1995 with palmoplantar pustulosis followed, 7 yr later, by persistent inflammatory low back and anterior chest wall pain. Technetium bone scanning revealed increased uptake at both sacroiliac joints and the anterior chest wall region. A computed tomography (CT) evaluation showed sternal osteitis. HLA-B27 was absent. The patient was initially treated with NSAIDs and salazopyrin (3 g/day), stopped after 6 months owing to loss of efficacy.

In November 2003, due to persistence of symptoms, the patient began infliximab at 5 mg/kg i.v. At the initial examination he had pain and stiffness in the lumber spine and pain in both sternoclavicular joints. Baseline evaluation showed a raised CRP value (37 mg/l); other routine laboratory tests and urinalysis were normal. After two infusions, chest pain and low back pain resolved and the patient was able to discontinue NSAIDs. CRP returned to normal after the first infusion (1 mg/l) and remained so. After 6 months of therapy, while osteoarticular complaints remained absent, there was a reappearance of palmoplantar pustulosis, which rapidly improved after a brief course of topical steroids. Pustular lesions appeared again 3 months later on the feet and are still present. A test for ANA was negative. After 14 months, the patient continues to receive infliximab with complete remission of osteoarticular symptoms. A repeat scintigraphic evaluation showed only slight uptake in the left sacroiliac joint.

**Case 3**

A 67-yr-old woman was admitted to our unit in 1997 because of a sudden onset of painful swelling of the right sternoclavicular joint associated with arthritis of the left ankle. Scintigraphy showed increased uptake in the manubrium sterni, right clavicle and sacroiliac joints. A radiographic evaluation showed enlargement and hyperostosis of the proximal part of the right clavicle. Inflammatory involvement of both sacroiliac joints was demonstrated by magnetic resonance imaging. No cutaneous involvement was noted. HLA-B27 was absent. Laboratory evaluation was normal. Bisphosphonates and NSAIDs were prescribed initially but had disappointing results, and the patient continued to experience recurrent episodes of pain and swelling of anterior chest wall.

Because of the persistence of symptoms, the patient began infliximab therapy in October 2002. Laboratory tests, including inflammatory parameters, were normal. After the first two infusions, joint pain and swelling subsided completely and the patient was able to suspend anti-inflammatory drugs. After
8 months of therapy, osteoarticular remission persists and no cutaneous manifestations have appeared.

Case 4

A 42-yr-old woman suffering from autoimmune thyroiditis was evaluated for the first time in 1995 following recurrent episodes of pain and swelling at the right sternoclavicular joint and the second and third right costochondral joints. CT evaluation showed both osteosclerotic and erosive lesions. Bone scintigraphy showed increased focal radionuclide uptake in the right sternoclavicular joint. HLA typing was negative for B27. She was initially treated with NSAIDs without effect and subsequently with corticosteroids (prednisolone from 25 to 5 mg/day). In 1997 the patient had reappearing episodes of palmoplantar pustulosis, partially resolved by local steroids. Because of the persistence of osteoarticular complaints, the patient was started on bisphosphonates i.v., NSAIDs and low-dose prednisolone (5 mg/day). In spite of such therapy, between 1998 and 2002 further episodes of arthritis of sternoclavicular joints occurred, with the addition of inflammatory low back pain. An X-ray showed osteitis on both upper and inner edges of the second lumbar vertebrae without evident sacroiliitis. A new CT showed an increase in erosive and sclerotic lesions of the sternum. Infliximab (5 mg/kg) was started and after three infusions there was a noteworthy improvement in chest wall pain, with complete resolution of sternoclavicular swelling and amelioration of low back pain. NSAIDs and steroids were gradually reduced and eventually stopped. After 8 months of therapy the patient continues to be well without cutaneous manifestations. A new scintigraphic evaluation showed only slightly increased uptake in the right sternoclavicular joint.

Discussion

The pathogenesis of SAPHO syndrome and its treatment remain a debated issue. Because of some clinical and radiological features, some authors include SAPHO syndrome in the group of seronegative spondyloarthropathies, while others consider it a reactive osteitis [2, 12]. Usually the disease has a protracted course, with relapses and improvements over several years.

Experience with biological TNF-α blocking agents in SAPHO syndrome are few and follow the use of these drugs on spondyloarthropathies. To the best of our knowledge, only six cases have been reported in literature. In two cases, Wagner et al. [9] observed a 9-month sustained response to continuous application of etanercept and infliximab at the dosage usually employed in spondyloarthropathies. In another two cases, Olivieri et al. used only four infusions of infliximab (5 mg/kg) and obtained remission of both skin and bone involvement maintained over a period of 18 months [10, 13]. The fifth case, reported in the study of Amital et al., received only one infusion of infliximab, then switched to pamidronate because of the lack of rapid efficacy [5]. The latest information concerns a case of severe acne fulminans related to SAPHO that was successfully treated with infliximab for up 10 months [14]. Osteoarticular complaints also remitted.

Data obtained from our four cases of SAPHO syndrome seem to confirm the value of anti-TNF-α therapy for osteoarticular manifestations, but raise some concerns related to the skin response. As in other reports, in all the four patients treated we obtained a rapid, sustained remission of rheumatological complaints, occurring after the first two or three infusions. The positive response persisted during a prolonged follow-up, ranging from 8 to 20 months, a result similar to that reported for anklyosing spondylitis, in which the maintenance of response was confirmed for up to 3 yr [15, 16]. A new bone scintigraphy evaluation, performed in three patients, revealed reduced radionuclide uptake in the skeletal sites involved. However, in the case where treatment was suspended, as in another reported case [9], a relapse occurred after a few months.

Moreover, despite a good result in osteoarticular complaints, two of the three patients who had skin manifestations (palmoplantar pustulosis) experienced mild recrudescence of these, confirming that, in this disease, osteoarticular and cutaneous involvement have a different course regarding their response to therapy.

The reasons for the skin relapses in our patients are unclear at present. In SAPHO syndrome, the skin lesions are usually characterized by a neutrophil infiltrate and may be poorly distinguishable from those of psutural psoriasis [1, 2]. TNF-α is a pivotal mediator of the activation of neutrophils, up-regulating adhesion molecules [17]. Otherwise, anti-TNF-α agents are effective in the treatment of psoriasis, specifically plaque-type psoriasis, the most common form of the disease [17–19]. There are also several reports of the efficacy of infliximab in the treatment of severe psutural psoriasis, an acute variant of the disease in which neutrophils seems to play a particularly important role [20–22].

Conversely, cases of psoriatic lesions induced by anti-TNF-α treatment have been reported in the recent literature. Dereure et al. [23] described two patients suffering from rheumatoid arthritis who developed psoriatic lesions after anti-TNF-α treatment. In one case the lesions were evident on the palms and soles and the histological features were reminiscent of psoriasis. A case of palmoplantar psoriasis in a patient receiving infliximab because of ulcerative colitis has also been described [24].

Furthermore, several other types of cutaneous manifestations can occur in patients taking anti-TNF-α therapy [25]. In a recent study by Flendrie et al. [26], dermatological events were reported in 25% of rheumatoid arthritis patients receiving TNF-α-blocking therapy. Infections and eczematous lesions represented the most frequent lesions encountered, but three cases of psoriasis-like eruptions were also reported: a vesiculopustular erythematous squamous rash on the hands and feet, a psoriasis guttata-like eruption on the lower legs and an eruption on the arms and legs with a histological picture compatible with psoriasis [26]. In another report, a pustular rash on both feet and hands developed in a rheumatoid arthritis patient taking infliximab [27]. Finally, in a case treated with adalimumab, an erythema multiform skin reaction involving both palms and soles followed by desquamation of the involved areas, strongly resembling the skin reaction observed in our patients, has been described [28].

The pathogenetic mechanism suggested to explain the occurrence of cutaneous lesions during anti-TNF-α therapy is the deposition of anti-TNF/TFN immune complexes triggering a type III hypersensitivity reaction or a switch from the predominant Th1 response to a Th2 response of T-lymphocytes [27, 29]. In SAPHO syndrome, another possibility is that anti-TNF-α treatment could impair the function of the host’s neutrophils, favouring the reactivation of slow-growing microorganisms, such as Propionibacterium acnes, which is implicated in the pathogenesis of the disease. In our patient, cultures from pustulotic lesions were not performed so we are unable to support this hypothesis. It is also possible that P. acnes acts only as an antigenic trigger leading to an immunological reaction inducing skin lesions [30]. The good response to topical steroid application in our patient supports this hypothesis.

In conclusion, our experience with four cases of SAPHO syndrome indicates that infliximab may be useful in the treatment of severe, refractory osteoarticular involvement and can lead to sustained remission from the disease. Maintenance of the response seems to persist over time, but relapses occur after withdrawal. Cutaneous involvement, especially severe palmoplantar pustulosis, seems to have a less predictable outcome, reactivation of cutaneous manifestations being a possible adverse event. Additional studies are needed to determine the impact of anti-TNF-α therapy on both aspects of the SAPHO syndrome.
The authors have declared no conflicts of interest.

References