SAPHO syndrome treated with pamidronate: an open-label study of 10 patients

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Background. In recent years the SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis and osteitis) has been encountered more frequently. However, clinical evidence indicating superiority of a specific therapeutic modality is still absent. Pamidronate, a second-generation bisphosphonate, has a pronounced effect on bone metabolism by suppressing bone resorption. We report our clinical experience with intravenous pamidronate in SAPHO syndrome.

Methods. Between the years 1999 and 2003 we treated 10 patients with the SAPHO syndrome who did not respond to NSAIDs, oral corticosteroids, colchicine, methotrexate, sulphasalazine or infliximab. All patients were treated with 60 mg pamidronate, given intravenously within an hour. In cases of no response a subsequent dose was given within a month and if there was a partial response an additional infusion was given after 4 months. The primary endpoint was the disappearance of recurrent bouts of bone pain, osteitis or hyperostosis, or recurrent synovitis. Reduction of the frequency of attacks by 50% was regarded as a partial response.

Results. Seven of the patients were females and three were males. The age at diagnosis ranged from 26 to 68 yr. All patients had axial or peripheral arthritis and cutaneous involvement; three had severe acne, eight had pustulosis and two had concomitant psoriasis vulgaris. Hyperostosis of the anterior chest wall involving either sternocostal or sternoclavicular joints, as seen on technetium 99 bone scintigraphy, was detected in all patients. Complete remission was observed following therapy in six patients, three others partially responded and only one patient had no response. Two patients needed four cycles of pamidronate infusion, one patient needed three, six needed two infusions and one patient remitted following a single pamidronate infusion. In all but one patient pamidronate was effective in preventing recurrent bouts of pustulosis.

Conclusion. Pamidronate seems to be a very effective mode of therapy for patients with the SAPHO syndrome, by promoting remission in all components of the disorder, such as bone, joint and skin involvement, and ceases the bouts that characterize this disorder.

Key words: Pamidronate, SAPHO, Spondyloarthropathy, Bisphosphonates, Osteitis.

The syndrome of synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) was described more than 15 yr ago as a medical entity characterized by hyperostosis of one of the bones of the anterior chest wall and a chronic or a relapsing skin eruption [1]. Most patients have intermittent axial or peripheral synovitis accompanied by an acneform skin disorder, but palmoplantar pustulosis (PPP) and psoriasis vulgaris have also been associated with the disorder. Coexistence with inflammatory bowel diseases has been recorded [2, 3].

SAPHO patients have a high prevalence (up to 90%) of axial involvement, and 40% of the affected patients have clear evidence of sacroiliitis. These findings, together with the marginally increased prevalence of HLA-B27, have led many researchers to classify the SAPHO syndrome as a spondyloarthopathy [1, 4].

As no therapeutic modality has been shown to be effective, diverse therapeutic approaches have been tried in the management of SAPHO syndrome patients, with varying success. The disease is considered rare and most of the series are anecdotal, small or uncontrolled [1, 4].

The second-generation bisphosphonate pamidronate is one of the promising new therapeutic modalities in seronegative spondyloarthopathies [5]. In addition to their effect on bone remodelling, bisphosphonates also confer anti-inflammatory activity by abrogating the generation of proinflammatory cytokines, such as interleukin (IL)-1, tumour necrosis factor α and IL-6, and by inhibiting the antigen-presenting capacity of macrophages [6, 7]. A few reports have described the effects of pamidronate also in SAPHO patients [8, 9].

We report observations from an open-label study encompassing 10 patients with the SAPHO syndrome who were treated with pamidronate after the failure of other medications.

Materials and methods

Patients

All of the patients were recruited in the rheumatology unit between the years 1999 and 2003. All the patients complied with the inclusion criteria for SAPHO syndrome proposed by Benhamou et al. [10], in that they all had any one of the following: osteoarticular manifestations of severe acne, osteoarticular manifestations of PPP, hyperostosis with or without dermatosis, or chronic recurrent multifocal osteomyelitis involving axial or peripheral skeleton, with or without dermatosis. None of the patients had any of the defined exclusion criteria: septic osteomyelitis, infectious chest wall arthritis, infectious PPP, palmoplantar
keratodermia, diffuse idiopathic skeletal hyperostosis, or the osteoarticular manifestations of retinoid therapy.

From each patient the following clinical data were obtained: gender, age, type of dermatological involvement (acne, PPP or psoriasis vulgaris), type of arthritis (axial, peripheral), hyperostosis, involvement of the anterior chest wall, associated illnesses and previous medications. As in other reports, multifocal involvement of the anterior chest wall was regarded as an affliction of a single site. Axial involvement was defined as any involvement of true axial synovial articulations, sternoclavicular and sacroiliac joints, axial synchondroses such as the costomanubrial joints and symphyses such as the pubic symphysis. As in previous reports [1], temporal mandibular joint involvement was also regarded as axial involvement. The determination of osteitis and hyperostosis was based on radiographs, computed tomography, increased uptake on bone scintigraphy studies and bone biopsy when available.

As none of the patients had benefited from disease-modifying anti-rheumatic drugs, their use was not permitted during the study. However, non-steroidal anti-inflammatory drugs (NSAIDs) were taken as needed by the patients. The extent of their use was not recorded.

**Therapy**

All patients included in this study were given 60 mg pamidronate (Aredia, dry powder; Novartis) intravenously at an infusion rate of 1 mg/min.

The primary endpoint was defined as a decrease in either the intensity (semiquantitative basis) or the duration of pain by 50%, as defined by the patients, or by a decrease of 50% in the frequency of relapses.

Patients claiming no response received a second infusion of pamidronate a month later and in cases of partial response (defined as a response that did not reach the definition of the primary endpoint) an additional infusion was provided after 4 months.

During the follow-up period additional infusions were administered as needed at minimal intervals of 4 months.

All pamidronate treatments were provided following approval of the medication (if given for an unapproved indication) by the medication committee in each institute, authorized by the Ministry of Health, which is able to approve the use of such medications on an individual basis. Such approval was obtained individually for each subject included in the study. Each patient was informed about the potential benefits and risks of the medication.

### Results

#### Patients

Ten patients were included in this open-label study between the years 1999 and 2003. All patients met criteria for SAPHO, three of the patients had two inclusion criteria and seven had one criterion.

There were seven women and three men. All patients were Jewish: four were Sephardic (of Northern African descent) and six were Ashkenazi (of Eastern European descent). The mean duration of follow-up was 24 months (s.d. 15 months, maximum 38 months) and the average age at diagnosis was 46 yr (s.d. 13 yr). All patients had evidence of peripheral and axial arthritis and two of them had sacroiliitis. All patients had hyperostotic lesions involving the anterior chest joints; one patient had a lesion that involved 75% of his mandible and another had a hyperostotic lesion of the fifth cervical vertebra, which had revealed osteitis on biopsy. All patients had cutaneous involvement; nine had acne (severe, 1; moderate, 7; mild, 1) and eight patients had PPP (severe, 1; moderate, 4; mild, 3). Two patients had psoriasis vulgaris. Two patients had a concomitant inflammatory bowel disease (Crohn’s disease) and one had diabetes mellitus type 2.

**Table 1. Characteristics of patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Peripheral synovitis</th>
<th>Axial hyperostosis</th>
<th>ACWI</th>
<th>Acne</th>
<th>PPP</th>
<th>PV</th>
<th>Intestinal involvement</th>
<th>Previous medications/others</th>
<th>No. of cycles</th>
<th>Degree of improvement</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>30</td>
<td>+</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td></td>
<td></td>
<td>Sulphadiazine, calcitonin, NSAID</td>
<td>2</td>
<td>!!!</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>41</td>
<td>++++</td>
<td>++</td>
<td>++++</td>
<td>+</td>
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<td>Methotrexate, sulphadiazine, corticosteroids, NSAID</td>
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<tr>
<td>3</td>
<td>F</td>
<td>26</td>
<td>++</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td>Infliximab, sulphadiazine, NSAID</td>
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<tr>
<td>4</td>
<td>F</td>
<td>50</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td></td>
<td></td>
<td></td>
<td>Biopsy from hyperostotic lesion in 5th cervical vertebra, NSAID</td>
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<td>!!</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>54</td>
<td>++</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
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<tr>
<td>6</td>
<td>F</td>
<td>68</td>
<td>++</td>
<td>++++</td>
<td>++++</td>
<td>++</td>
<td>++</td>
<td></td>
<td></td>
<td>NSAID</td>
<td>72</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>F</td>
<td>41</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td></td>
<td></td>
<td>Sulphadiazine, NSAID</td>
<td>2</td>
<td>!!!</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>48</td>
<td>++</td>
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<td>++++</td>
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<td></td>
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<td>NSAID</td>
<td>3</td>
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<tr>
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<td>F</td>
<td>34</td>
<td>+</td>
<td>+</td>
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<tr>
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<td>F</td>
<td>73</td>
<td>+</td>
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<td>++</td>
<td></td>
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<td>NSAID</td>
<td>2</td>
<td>!!</td>
</tr>
</tbody>
</table>

**ACWI,** anterior chest wall involvement; **PV,** psoriasis vulgaris; **M,** male; **F,** female.

+, mild; ++, moderate; ++++, severe.

!!!, complete remission; !!, partial remission; 0, no response.
Five patients had received antecedent medical therapy before initiation of therapy with pamidronate (Table 1). One patient received a single infusion of infliximab, which did not lead to an improvement. Eight patients had tried NSAIDs for analgesia.

Therapy outcome

Nine of the 10 patients (90%) responded favourably to pamidronate: six experienced complete remission and three more obtained partial remission. A single patient did not respond (Table 1).

Nine patients needed more than a single infusion of pamidronate in order to attain a clinical remission. Three patients remitted fully after two infusions; one had a hyperostotic lesion involving two-thirds of his mandible. Although he recovered after pamidronate administration, the increased technetium uptake on bone scintigraphy remained unchanged. Two patients remitted completely after four infusions given every 4 months. The remission of two patients has been sustained for more than 2 yr since the last pamidronate dose.

Another patient who exhibited bouts of diffuse skeletal pain with PPP 2 weeks each month fully remitted. She was symptom-free for 8 months when the bouts recurred, albeit at a much lower frequency. Following an additional infusion of pamidronate, she regained complete remission.

Discussion

The prevalence of the SAPHO syndrome is unknown. Several reports indicate that, although previously considered to be rare, it is often overlooked [11]. A recent Japanese study reported that the SAPHO syndrome accounts for 4% of all patients with seronegative spondyloarthropathies [12]. Notwithstanding the growing experience with SAPHO, current treatment remains unsatisfactory. Hayem et al. [1] described the efficacy of various therapies in 120 patients treated (102 of them prospectively) for 5 yr. NSAIDs were prescribed for most patients but provided only minor benefit. Systemic or intra-articular corticosteroids, osmic acid and methotrexate were equally efficacious as NSAIDs. Interestingly, colchicine and sulpha-diazine were not advantageous [1].

Bisphosphonates are potent inhibitors of osteoclastic bone resorption and are an important therapeutic modality in the management of Paget’s disease, multiple myeloma, malignancy-associated hypercalcaemia, bone metastasis and osteoporosis [13–15]. Bisphosphonates such as pamidronate bind to bony surfaces and induce osteoclastic apoptosis [16]. Following phagocytosis by osteoclasts, bisphosphonates impair (probably because of their similarity to pyrophosphate) many biochemical reactions that lead eventually to osteoclastic apoptosis. Nitrogen-containing bisphosphonates also interfere with the mevalonate pathway, decreasing protein phenylation and resulting in aberration of the signalling functions of regulatory proteins and normal osteoclastic activity [H. Amital, Y. H. Applbaum, L. Vasiliev and A. Rubinow, submitted for publication]. Bisphosphonates modulate cytokine concentrations, exerting an anti-inflammatory response. Recent reports demonstrate that these agents are effective in several rheumatological conditions, such as ankylosing spondylitis, hypertrophic osteoarthropathy, reflex sympathetic dystrophy, diabetic neuropathic arthropathy and the SAPHO syndrome [4–9, 18–21].

In this communication we show the ability of pamidronate to ameliorate many of the clinical symptoms of SAPHO, skeletal and extraskeletal. In this open-label study we found pamidronate to be markedly beneficial in five of nine SAPHO patients (56%) and to elicit a partial response in three additional patients (33%). Our results are in concordance with other short series. Guignard et al. [9] described the effect of pamidronate on five patients who were refractory to standard treatments. They used pamidronate only during exacerbations of the disease, and four patients responded within a week. Sayag-Boukris et al. [21] treated six SAPHO patients with 60 mg of intravenous pamidronate for 3 days. All six patients achieved at least a 50% improvement in pain within 2 weeks of the infusions. All reports emphasize the significant pain relief provided by pamidronate. Pamidronate, given to a patient with SAPHO syndrome, decreased the urinary hydroxyproline:creatinine ratio, a measure of osteoclastic function and bone turnover [22].

In conclusion, pamidronate is a useful therapeutic agent for patients with refractory SAPHO syndrome. Unfortunately, the relatively rare occurrence of the syndrome precludes the conduct of a randomized controlled clinical trial at a single centre.

The authors have declared no conflicts of interest.

References


