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Sustained remission of SAPHO syndrome with pamidronate: a follow-up of fourteen cases and a review of the literature

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ABSTRACT

Objective. *To evaluate the efficacy of intravenous (i.v.) pamidronate in patients with SAPHO syndrome refractory to first line treatments and to review the available literature on pamidronate for this indication.*

Methods. *We report 14 cases of SAPHO syndrome refractory to non-steroideal anti-inflammatory drugs (NSAIDs), glucocorticoids and disease modifying anti-rheumatic drugs (DMARDs) treated with i.v. pamidronate. All patients received i.v. 60 mg pamidronate/day for 3 consecutive days. The primary evaluation criterion was the disappearance of bone pain, considered as the reduction in the visual analogic scale for pain (VAS) greater than 50%.*

Results. *Ten patients were females and 4 were males. The mean age at onset was 40.4 years old. Ten patients presented a relapsing-remitting course, while in 4 cases the disease followed a prolonged course. In all cases anterior chest wall involvement occurred early in the disease. In 2 cases there was also a peripheral monoarthritis. Eleven patients experienced several flares of palmo-plantar pustulosis, while severe acne was present in 2. In one case there was no cutaneous involvement. Twelve of the 14 patients had a good response after 3 infusions and in 8 of these patients a sustained remission was observed. The recurrence of skin manifestations does not seem to be influenced by pamidronate.*

Conclusions. *Pamidronate appears to be an effective treatment in the osteoarticular manifestations of SAPHO syndrome. As far as cutaneous lesions are concerned, evidence of efficacy is not so impressive.*

Introduction

The syndrome of synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) combines cutaneous and osteo-articular manifestations. Palmo-plantar pustulosis (PPP) and severe acne (SA) with all its variants are the most frequent skin lesions, while the basic feature of the disease is the presence of osteitic/hyperostotic aspects, in particular at the anterior chest wall (ACW) (1). The nosological framing of SAPHO syndrome is still a matter of debate, some Authors including it in the group of spondyloarthropathies, in particular as a subset of psoriatic arthritis, and others considering it an osteitis probably related to polygenic autoinflammatory disorders (2, 3).

To date, the therapeutic approach to the disease remains empirical and has to be tailored to each single case. Different treatment including NSAIDs, glucocorticoids and several DMARDs have been tried in small and uncontrolled reports. Antibiotics, especially macrolides, tetracycline and co-trimoxazole have been used with conflicting results due to the occasional isolation of *Propionibacterium acnes (P. acnes)* and other micro-organisms from bone lesions and synovial tissue. Neverthless, they have not represented a turning point in the therapy of the disease.

Due to the presence of osteitis and periostitis, suggesting a high rate of bone remodelling process, bisphosphonates have been proposed in the treatment of this syndrome, in particular the amino-bisphosphonate pamidronate. The drug has been proved to be effective in relieving bone pain in Paget's disease, in malignancy-associated hypercalcaemia, in bone metastases, in multiple myeloma and in osteoporosis. Besides, it has been demonstrated of some interest in seronegative spondyloarthropathies. Some published data are already available on the efficacy of pamidronate in the treatment of SAPHO syndrome and recurrent multifocal osteomyelitis, considered the juvenile variant of SAPHO (4-9). We report our experience on this topic describing a large series of adult SAPHO patients treated with intravenous (i.v.) pamidronate and followed for a long period of time.

Patients and methods

Sixty-six patients with SAPHO syndrome (48 females, 18 males; mean age 44±14 years) were identified in our tertiary referral center until October 2007 complying with currently proposed classification criteria (1). In 14 cases (10 females, 4 males) in which NSAIDs, glucocorticoids and other DMARDs were not effective, pamidronate i.v. was used to better control the disease.

For each patient the following clinical

data were collected: gender, age, type of skin involvement, type of peripheral arthritis, pattern of osteitis, previous medications and laboratory analysis. Osteitis and hyperostosis were detected by conventional radiography, increased uptake on ^{99}technetium bone scintigraphy, computed tomography and/or MRI.

Treatment with DMARDs for at least 6 months and/or glucocorticoids had been tried in all these patients (prednisone ≥25 mg/day), but it was ineffective in all of them.

Pamidronate (Aredia®, Dry powder, Novartis) 60 mg per day was given intravenously at an infusion rate of 1 mg/min for three consecutive days, as recommended in Paget's disease of bone. The courses were repeated as needed during relapses. Before treatment, blood samples were taken for inflammatory markers, kidney and liver function and standard bone chemistry. The primary end-point was the disappearance of bouts of bone pain, considered as a reduction in the visual analogic scale score for pain (VAS) greater than 50%. A reduction between 30 and 50% was considered moderate and lower than 30% poor. NSAIDs need was computed and considered an index of efficacy of the therapy. The patients were informed of the potential benefits and risks of this medication and gave informed consent.

All patients have been subsequentely examined twice a year in our outpatient's clinic. Follow-up consisted of clinical examination, complete laboratory evaluation including full blood count, erythrocyte sedimentation rate (ESR), CRP, kidney and liver function, standard bone chemistry and, if necessary, further radiologic evaluation. A statistical analysis was not conducted due to the small number of patients.

Table I. Characteristics of patients.

Patients	Gender	Age at diagnosis	Disease duration (ys)	Axial involvem.	ACW involvem.	Peripheral synovitis	Skin involvem.	Previous medications	Pamidronate n. of cycles
1	F	40	4	+	+++	–	PPP	Prednisone, NSAIDs	1
2	F	38	4.5	++	++	–	PPP	Sulfasalazine, prednisone, NSAIDs	1
3	M	46	5	+	+	+	SA	MTX, prednisone, NSAIDs	1
4	F	31	10	+++	+++	–	PPP	Sulfasalazine, prednisone, NSAIDs	2
5	F	22	6	+	++	–	PPP	Sulfasalazine, prednisone, NSAIDs	1
6	F	56	4.2	+	++	–	PPP	Sulfasalazine, prednisone, NSAIDs	1
7	M	41	8.5	–	++	–	PPP	Prednisone, NSAIDs	1
8	F	50	5.2	–	+++	–	PPP	Prednisone, NSAIDs	1
9	F	48	6	++	+++	–	none	Prednisone, NSAIDs	1
10	M	20	4	+	++	+	PPP	MTX, prednisone, NSAIDs	1
11	M	47	10.4	+	+++	–	SA	Sulfasalazine, prednisone, NSAIDs	1
12	F	50	9.5	–	++	–	PPP	Sulfasalazine, prednisone, NSAIDs	2
13	F	46	5.2	+++	+++	–	PPP	Sulfasalazine, prednisone, NSAIDs	1
14	F	30	4.8	–	++	–	PPP	Prednisone, NSAIDs	1

ACW: anterior chest wall; PPP: palmo.plantar pustulosis; SA: severe acne; M: male; F: female; +: mild; ++: moderate; +++: severe

Table II. Biochemical markers before and after therapy.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14
before	VAS	65.3	56.6	80.1	93.3	37.7	46.3	53.1	71	80.2	71.3	44.5	88.9	78.4	60.6
	CRP	0.7	0.9	2.1	1.9	1.6	1.5	1.8	0.9	0.9	1.4	1.4	1.3	0.7	0.8
	AP	55	82	90	60	58	195	150	80	88	102	65	89	78	95
after	VAS	19.6	22.6	0.4	74.6	0.6	9.3	5.3	7.1	32.1	7.2	22.3	62.2	7.8	12.3
	CRP	0.3	0.5	0.6	0.6	0.4	0.4	0.5	0.3	0.1	0.3	0.5	0.5	0.3	0.2
	AP	68	91	104	120	68	93	65	77	75	116	158	65	90	89
T 6	VAS	20.2	19.8	3.4	73.1	10.1	6.4	16.2	8.3	34.5	7.5	23.4	53.4	5.6	10.8
	CRP	0.5	0.6	0.3	0.7	0.5	0.6	0.3	0.2	0.2	0.4	0.6	0.9	0.6	0.5
	AP	93	69	101	89	116	52	71	80	79	65	102	96	65	80
T 12	VAS	15.6	17.4	5.7	43.9	9.4	6.8	20.1		30.3	5.6	20.2	55.8	3.4	0.9
	CRP	0.4	0.7	0.4	0.5	0.6	0.6	0.6		0.2	0.5	0.4	0.7	0.6	0.6
	AP	85	86	94	92	65	85	60		65	101	69	81	87	104
T 18	VAS	13.8	20.4	6.2	39.5	8.6	7.1	18.7		31.1	5.9	19.7	33.9	4.3	3.6
	CRP	0.4	0.3	0.5	0.5	0.6	0.7	0.4		0.5	0.2	0.6	0.4	0.6	0.6
	AP	65	93	92	88	75	64	100		95	69	64	66	102	88
T 24	VAS	16.9	21.3	5.8	42.1	6.8	9.4	20.1		30.6	6.4	20.1	34.3	6.7	5.2
	CRP	0.6	0.4	0.4	0.7	0.5	0.7	0.4		0.4	0.4	0.5	0.6	0.4	0.5
	AP	85	102	69	101	90	85	65		89	81	64	56	69	85

VAS: visual analogic score; CRP: C-reactive protein (normal value: < 0.6 mg/dl); AP: alkaline phosphatase (normal value: 50-190 UI/l); T: time from first pamidronate course (months); grey zone: values after the cycle of therapy. Case 4 and 12 have repeated the cycle.

Table III. Literature review: patients with SAPHO syndrome treated with pamidronate.

Author/Year	Number of cases	Gender	Disease duration (ys)	Skin involvement (no. of patients)	Osteoarticular improvement	Degree of cutaneous improvement	Time to sustained response
Bouvier *et al.*[11] 1993	2	NA	NA	NA	2 / 2	NA	NA
Collange *et al.*[12] / 1996	2	NA	NA	NA	2 / 2	NA	NA
Van Doornum *et al.*[13] /2000	2	NA	4,5	2	2 / 2	NA	prompt
Guignard *et al.*[4] /2002	5	4F /1M	10,4	5	4 / 5	NA	NA
Courtney *et al.*[5] / 2002	1	M	NA	1	1 / 1	NA	6 months
Marshall *et al.*[3] /2002	1	F	NA	1	1 / 1	0	5 months
Crisp[14] / 2003	1	NA	NA	NA	1 / 1	NA	NA
Susanto *et al.*[15] / 2003	1	F	1	1	1 / 1	++	prompt
Amital *et al.*[6] / 2004	10	7F / 3M	NA	10	9 / 10	+++	NA
Kerrison *et al.* [8] / 2004	7	7F	2,7	5	7 / 7	NA	prompt
Valls-Roc *et al.* [16] /2005	6	4F / 2M	5,5	NA	3 / 6	NA	NA
Solau-Gervais *et al.*.[7] / 2005	13	12F / 1M	3	6	7 / 13	NA	3 months
Tehrani [17] / 2005	1	M	4	1	1 / 1	+++	NA
Kuhn *et al.*[18] / 2007	1	F	NA	1	1 / 1	0	NA
Our study	14	10F / 4M	6,2	13	12 / 14	0	prompt

M: male; F: female; NA: not available; +: mild; ++: moderate; +++: severe.

Results

Table I summarizes the characteristics of our patients. Mean age at the onset of osteo-articular complaints was 40.4 years, while mean time elapsed between the onset of the disease and diagnosis was 4.4 years. Mean disease duration at pamidronate initiation was 6.2 years (range 4 to 10.4 years). In 10 cases the disease course was relapsing-remitting, while in the other four it was persistent. Each patient experienced prolonged flares of pain and swelling of ACW structures occurring with a peripheral monoarthritis involving a wrist and a knee in 2 cases. In these 2 patients, the peripheral arthritis was transient and not erosive. No patient was positive for HLA-B27 antigen. Cutaneous manifestations included PPP in 11 patients, SA in 2 cases, while in one case no skin involvement was detected.

All 14 patients were taking NSAIDs as required; all patients tried a low-moderate dose of steroid, while 3 of them were on 25 mg per day of prednisone equivalent, with no benefit. Seven patients were on sulfasalazine (2 to 3 g/day) therapy and the other 2 cases tried methotrexate (15 mg/week). These medications were given for a period longer than 6 months, with no benefit at all. None of these patients were treated with biologic agents.

Before starting pamidronate therapy, all patients presented a slight increase in C-reactive protein (CRP) value (mean value: 1.1 mg/dl, range 0.7-2.1). Bone alkaline phosphatase (bAP) resulted within the normal range in all the cases.

After 1 cycle of infusions twelve patients had a persistent improvement >50% for more than 2 years. In the other two cases the response was unsatisfactory because of a recrudescence of pain and a pamidronate course was repeated after 6 and 14 months respectively. Treatment was well tolerated in all cases and no side effect occurred during or after the infusions.

Mean follow-up period was 5.4 years (range 7 months to 10.5 years).

In 8 patients (5 with relapsing-remitting and 3 with prolonged course) we observed a sustained remission of the disease for a period longer than 5 years. In those patients in which pamidronate was not able to remit the disease, the introduction of this therapy was however associated with a decrease in the frequency of exacerbations and in a reduction of glucocorticoid requirements (tapered to 5 mg per day of prednisone equivalent). In the 2 cases with an incomplete response, the second course was also unsatisfactory in both cases.

After pamidronate infusions, a meaningful reduction of the values of PCR has been observed (mean value 0.3 mg/dl, range 0.1-0.6), while no difference in bAP before and after treatment was observed (Table II). The perypheric arthritic involvement was responsive to the pamidronate course as well; after i.v. infusion patients number 3 and 10 experienced no more perypheric arthritis. As far as cutaneous lesions are concerned, pamidronate courses demonstrated no benefit at all.

Discussion

SAPHO syndrome is currently considered a rare disease and its aetiopathogenesis is not yet fully understood. Because of the rarity of the disease, there is no randomized controlled trial indicating the superiority of one therapy over another and treatment frequently remains unsatisfactory.

In a certain subset of patients, an aetiopathogenetic role of *P. acnes* (a slowly growing microorganism) in the development of the disease has been suggested. As a consequence, antibiotics have been used in SAPHO syndrome, but they have not demonstrated efficacy, except for some cases of early disease (10). Anti-TNFα agents are now considered the mainstay in the treatment of spondyloarthropathies and there is growing evidence about their utility in cases of recalcitrant SAPHO syndrome (11).

Bisphosphonates are pyrophosphate analogues characterized by a P-C-P structure. They have high affinity for bone mineralized matrix and they exert

a potent and long-lasting anti-osteoclastic effect. This leads to inactivation and increased apoptosis of mature osteoclasts. These effects decrease bone resorption and bone remodelling, justifying their utility in diseases characterized by an increase in osteoclastic resorption. Bisphosphonates have also shown chondroprotective effect reducing juxta-articular bony erosions in animal models of experimental arthritis. These data prompted a trial of pamidronate in rheumatoid arthritis, with amelioration of clinical activity of the disease. Besides anti-osteoclastic activity, bisphosphonates have anti-inflammatory effects too. *In vitro* evidence also indicates that bisphosphonates, in particular pamidronate, reduce the secretion of pro-inflammatory cytokines, such as interleukin 1β (IL-1β), TNF-α and IL-6, resulting in the inhibition of chronic inflammation.

The immunomodulating effects of bisphosphonates are complex, depending primarily on cellular type, bisphosphonate class, its concentration and the mode of administration of the drug. For instance, amino-bisphosphonates were shown to favour the production of pro-inflammatory cytokines in whole blood cultures, while the opposite occurs in macrophage culture systems. Besides, it has been demonstrated that in a model of macrophage cell-like culture, a low concentration of pamidronate is able to stimulate the production of IL-6, while a high concentration of this compound inhibits this cytokine production, an effect attributed to the cytotoxicity of the drug. Furthermore, amino-bisphosphonates inhibit mevalonate pathway, impairing the signal transduction from cytokine receptors on the cell surface to the nucleus favouring macrophages' apoptosis. Another important effect of bisphosphonates relies on their anti-angiogenic activity.

Few data have been published on pamidronate in the therapy of SAPHO syndrome (Table III). The first report dates back to 1993, when Bouvier *et al*. (12) treated 2 patients with consistent pain reduction. In 1996 Collange *et al*. (13) described 2 more cases. Kahan *et al*. have followed some patients for a period longer than 5 years, with encouraging results (5). Hayem *et al*. reported a series of 120 cases of whom 4 out of 6 received a benefit with pamidronate (13). Amital *et al*. have then described 10 SAPHO patients not responding to traditional therapies treated with pamidronate, with complete remission in 6 cases and partial in 3 (7).

Our series confirms pamidronate capacity to a rapid and long-lasting amelioration of osteo-articular symptoms of SAPHO syndrome, while it seems less satisfactory for the cutaneous lesions. In contrast with other reports, in our case series pamidronate did not show any benefit on palmo-plantar pustulosis and severe acne, which tend to recur independently of treatment. A similar trend has been observed regarding anti-TNFα agents (11). A possible explanation could rely on a different pathogenesis of osteo-articular and cutaneous manifestations, the latter being sustained from another inflammatory/infectious process. As a consequence, it would be important to better identify different subsets of the disease (with respect to both the age of the disease and the prominent clinical features) in order to identify different therapeutic options.

It is also interesting to notice that in our patients pamidronate had a better efficacy the earlier it was administered during the course of the disease, suggesting a potential role of this drug as an "inductor of remission" in SAPHO syndrome. Unfortunately, the relative rarity of the disease has not yet permitted the institution of a randomized controlled trial with a larger number of patients.

In conclusion, pamidronate may be considered a good choice in the treatment of SAPHO syndrome in late and refractory phases, but especially in the early stages of the disease.

References

1. BENHAMOU CL, CHAMOT AM, KAHN MF: Synovitis-acne-pustulosis-hyperostosis. osteomyelitis (SAPHO). A new syndrome among the spondyloarthropathies? *Clin Exp Rheumatol* 1988; 6: 109-12.
2. ROHEKAR G, INMAN RD: Conundrums in nosology: synovitis, acne, pustulosis, hyperostosis and osteitis syndrome and spondylarthritis. *Arthritis Care Res* 2006; 55: 665-9.
3. QUEIRO R, MORENO P, SARASQUETA C, ALPERI M, RIESTRA JL, BALLINA J: Synovitis-acne-pustulosis-hyperostosis-osteitis syndrome and psoriatic arthritis exhibit a different immunogenetic profile. *Clin Exp Rheumatol* 2008; 26: 125-8.
4. MARSHALL H, BROMILOW J, THOMASAL, ARDEN NK: Pamidronate: a novel treatment for the SAPHO syndrome? *Rheumatology* 2002; 69: 392-6.
5. GUIGNARD S, JOB-DESLANDRE C, SAYAG-BOUKRIS V, KAHAN A: Pamidronate treatment in SAPHO syndrome. *Joint Bone Spine* 2002; 69: 392-6.
6. COURTNEY PA, HOSKING DJ, FAIRBAIRN KJ, DEIGHTON CM: Treatment of SAPHO syndrome with pamidronate. *Rheumatology* 2002; 41: 1196-8.
7. AMITAL H, APPLBAUM YH, AAMAR S, DANIEL N, RUBINOW A: SAPHO syndrome treated with pamidronate: an open-label study of 10 patients. *Rheumatology* 2004; 43: 658-61.
8. SOLAU-GERVAIS E, SOUBRIER M, GEROT I *et al*.: The usefulness of bone remodelling mrkers in predicting the efficacy of pamidronate treatment in SAPHO syndrome. *Rheumatology* 2006; 45: 339-42.
9. KERRISON C, DAVIDSON JE, CLEARY AG, BERESFORD MW: Pamidronate in the treatment of childhood SAPHO syndrome. *Rheumatology* 2004; 43: 1246-51.
10. COLINA M, LO MONACO A, KHODEIR M, TROTTA F: *Propionibacterium acnes* and SAPHO syndrome: a case report and literature review. *Clin Exp Rheumatol* 2007; 25: 457-60.
11. MASSARA A, CAVAZZINI PL; TROTTA F: In SAPHO syndrome anti-TNFα therapy may induce persistent amelioration of osteoarticular complaints, but may exacerbate cutaneous manifestations. *Rheumatology* 2006; 45: 730-3.
12. BOUVIER M, LIENS D, TEBIB JG, NOEL E: Les osteites amicrobiennes. *Ann Radiol* 1993; 36: 293-302.
13. COLLANGE C, BRANTUS JF, SIDOT C, MEUNIER PJ: SAPHO syndrome with femoral hyperostosis. Two case-reports. *Rev Rhum* [Engl] 1996; 63: 367-70.
14. VAN DOORNUM S, BARRACLOUGH D, MCCOLL G, WICKS I: SAPHO: rare or just not recognized ? *Semin Arthritis Rheum* 2000; 30: 70-7.
15. CRISP AJ: Pamidronate for SAPHO syndrome. *Rheumatology* 2003; 42: 491.
16. SUSANTO CR, NANAYAKKARA PW: The skin is the clue. *Eur J Intern Med* 2003; 14: 493-4.
17. VALLS-ROC M, SANMARTI M, SALLES M, HOLGADO S, OLIVE A: SAPHO syndrome and pamidroate revisited. *Rheumatology* 2005; 44: 137-8.
18. TEHRANI R: SAPHO syndrome treated with pamidronate. *Indian J Dermatol Venereol Leprol* 2005; 71: 273-5.
19. KUHN F, FEHR S, STOLL T: Back pain and acne conglobata: SAPHO syndrome. Schweiz *Rundsch Med Prax* 2007; 96: 591-5.