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Original Article

Etanercept in the treatment of refractory SAPHO syndrome

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Abstract: Objective: To explore the application and efficacy of TNF-α inhibitors in the treatment of SAPHO syndrome. Methods: Two cases of refractory SAPHO syndrome were successfully treated with etanercept. And pain scores, laboratory parameters and functional index were used to judge the efficacies. Literature was also systemically reviewed. Results: Both patients achieved marked clinical remission. There was no obvious toxic or adverse response. Conclusion: Etanercept has rapid and definite efficacies in the treatment of patients with refractory SAPHO syndrome.

Keywords: SAPHO syndrome, tumor necrosis factor-alpha, etanercept, discitis

Introduction

With acronyms of synovitis, acne, pustulosis, hyperostosis and osteitis, SAPHO syndrome is defined as a chronic disease involving skin, bone and joints with various clinical and imaging signs. The bone and joint manifestations of SAPHO syndrome are mainly hypertrophy and hardening of first sternoclavicular joint. And the axial and peripheral joints may also be involved. The cutaneous lesions include pustulosis palmoplantaris, acne, psoriasis-like lesions and even rare suppurativeand proliferative impetigo, etc [1]. In 1961, Windom et al first uncovered the links between muscular skeleton diseases and acne conglobata [2]. In 1978, Bjorksten et al discovered the correlations between chronic recurrent multifocal osteomyelitis (CRMO) and pustulosis palmoplantaris [3]. Up until 1987, Chamot et al conducted an analysis of 85 relevant cases and first proposed the concept of SAPHO syndrome [4].

However, the therapeutics of SAPHO syndrome are only limited to such empirical medications as NSAIDs (Non-Steroidal Anti-Inflammatory Drugs), bisphosphonates, methotrexate and some antibiotics. As a result, it is rather difficult to evaluate the clinical efficacies. For few refractory patients, effective measurements of therapy are lacking. Up until the present day, only less than 20 adult cases of SAPHO syndrome using anti-TNF-alpha as treatment have been formally reported worldwide. And etanercept was used to treat 7 cases (refer to **Table 1**). Here, we present two patients of refractory SAPHO syndrome successfully treated with etanercept. And the relevant literature was also reviewed.

Profiles and methods

Diagnostic criteria

After excluding bacterial or fungal infection as well as tumors, the diagnosis of SAPHO syndrome should be considered if any of the following three items was fulfilled: (a) characteristic pustulosis or acne, aseptic synovitis, hyperostosis or osteitis; (b) aseptic synovitis, hyperostosis or osteitis involving axial/peripheral bones (esp. anterior chest wall, vertebra body & sacroiliac joint) with or without characteristic cutaneous lesions; (c) aseptic synovitis, hyperostosis or osteitis involving axial/peripheral bones (esp. metaphysis of multiple long bones in children) with or without cutaneous lesions. Furthermore, after receiving NSAIDs combined with any of the following drugs in long-term therapy, those cases having no improvement of clinical symp-

Table 1. Characteristics of 9 patients with SAPHO syndrome

	Gender/ age	Course (year)	Bone joint manifestations	Cutaneous manifestations	Previous medications	Outcomes
Wagner [9]	F/44	3	Mandibular hyperostosis	PPP	NSAID, CTX, ATB, MTX, BP	Improvement
	F/41	3	Sternal hyperostosis	None	CTX, MTX, BP CSA, INF	Improvement
Ben [10]	F/36	7	Sternal osteitis	PPP	NSAID, CTX, MTX	Improvement
	F/29	4	Sternal osteitis	PPP	NSAID, BP	Improvement
	F/53	13	Sternal osteitis	None	NSAID, MTX, BP	Improvement
Vilar-Alejo J [1]	M/47	2	Sacroiliac arthritis	PV	NSAID, BP, SSZ	Improvement
L.L. Zhang [11]	F/56	6	Sternal hyperostosis, discitis	PPP	NSAID, BP	Improvement
Case I	F/33	4	Sternoclavicular arthritis, sacroiliac arthritis	PPP	NSAID, BP	Improvement
Case II	F/29	3	Sternoclavicular arthritis, sacroiliac arthritis, discitis	PPP	NSAID, BP, LEF	Improvement

ATB: antibiotic; BP: bisphosphonates; CTX: cyclophosphamide; CSA: cyclosporin; ETN: etanercept; INF: infliximab; MTX: methotrexate; NSAID: non-steroid anti-inflammtory drug; SSZ: sulfasalazine; LEF: leflunomide; PPP: pustulosis palmoplantaris; PV: pyoderma vegetans. F (female) and M (male).

Table 2. The changes of VAS, BASFI and BASDAI before and after treatment

	Case I		Case II	
	Pre-therapy	Post-therapy	Pre-therapy	Post-therapy
VAS (mm)	88	30	90	8
BASFI	2.0	1.2	6.2	0.4
BASDAI	4.6	2.5	7.9	1.1

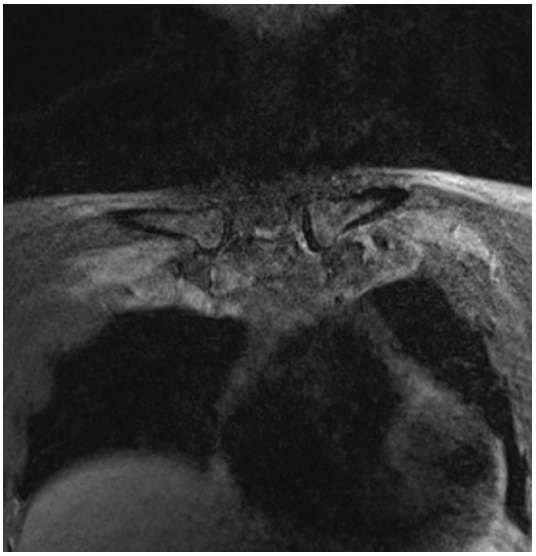

Figure 1. The hyperintense signal of Bilateral sternoclavicular joints surrounding soft tissue.

toms or laboratory parameters are defined as refractory SAPHO syndrome: (a) methotrexate; (b) leflunomide; (c) phosphates; (d) antibiotics.

Disease activity judgment

In accordance with reference [8], BASFI (Bath ankylosing spondylitis functional index), BASDAI (Bath ankylosing sponylitis disease activity index) and visual analogue pain score (VAS, 0-100 mm) were employed to judge the clinical efficacies (**Table 2**). Therapy was defined effective when reduction or withdrawal of painkillers by patient's decision and improvements of functional status occured.

Typical cases

Case I: A 33-year-old woman complained of repeated pain of bilateral shoulder joints for over 4 years. At another hospital, diclofenac 50-75 mg/day offered pain relief. Two years ago, there was an onset of anterior chest wall pain which could not be relieved by painkiller. Eight months ago, multiple pustules started to appear at both hands. Sternoclavicular MRI examination revealed inflammation of para-joint tissue (**Figure 1**). Upon the manifestations and results of laboratory tests showing ESR 38 mm/h and CRP 6.5 mg/L, SAPHO syndrome was diagnosed. After a 2-month therapy of alendronate monosodium 70 mg/week and diclofenac, the chest pain were relieved. However, there was an onset of severe loin pain and discomforts at left sacroiliac region. ESR and CRP were 45 mm/h and 7 mg/L respectively. A puncture biopsy of left sacroiliac joint revealed no evidence of infection or tumor. Scintigraphy revealed numerous concentrations of bilateral shoulder, sternoclavicular joint, the third lumbar vertebra (L3) and the left sacroiliac joint (**Figure 2**). An intradermal injection of recombinant human type II tumor necrosis factor receptor-antibody fusion protein was administered at 25 mg/dose twice weekly. After 3 weeks, the symptoms were markedly relieved, skin rashes of both hands improved, morning stiffness of loin disappeared with the decrease of BASDAI from 4.6 to 2.5 and BASFI from 2.0 to 1.2.

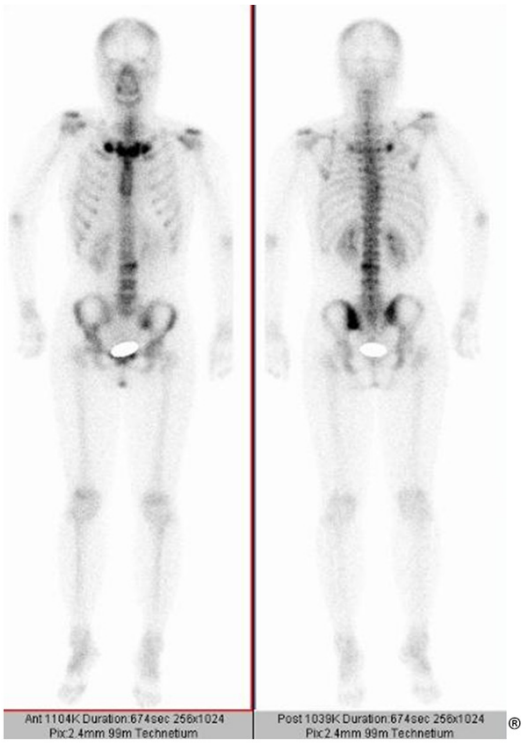

Figure 2. Technetium 99 bone scintigraphy shows: Concentration of radioactivity in the bilateral shoulder, sternoclavicular joint, the third lumbar vertebra (L3), the left sacroiliac joint.

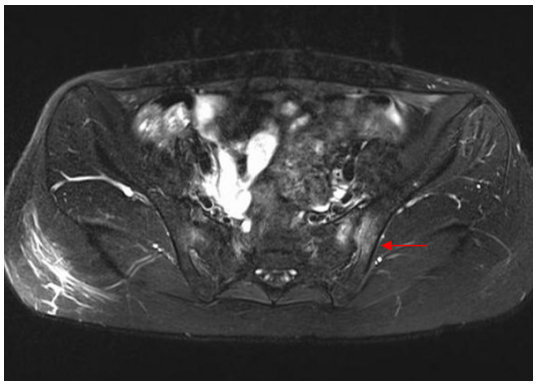

Figure 3. MRI T2WI: Hyperintense signal in the left sacro-iliac joint.

Case II: A female patient aged 29 suffered pain of right sternoclavicular region for 3 years. At another hospital, the analgesic medications of ibuprofen and diclofenac were offered. The symptoms persisted and she didn't receive any systemic therapy at that time. Fifteen months ago, she was hospitalized in the dermatology department due to multiple pustules of both hands. During hospitalization, there was an

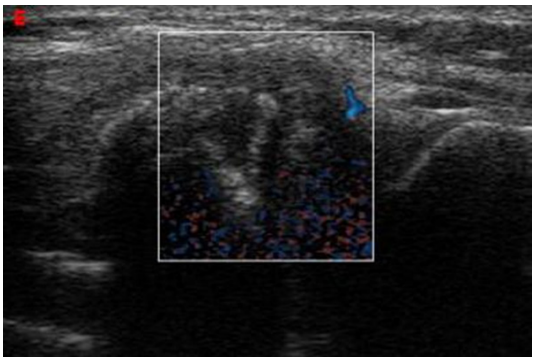

Figure 4. Sternoclavicular Ultrasound: the right sternoclavicular joint synovial thickening and its internal blood flow signal, the clavicle bone erosion.

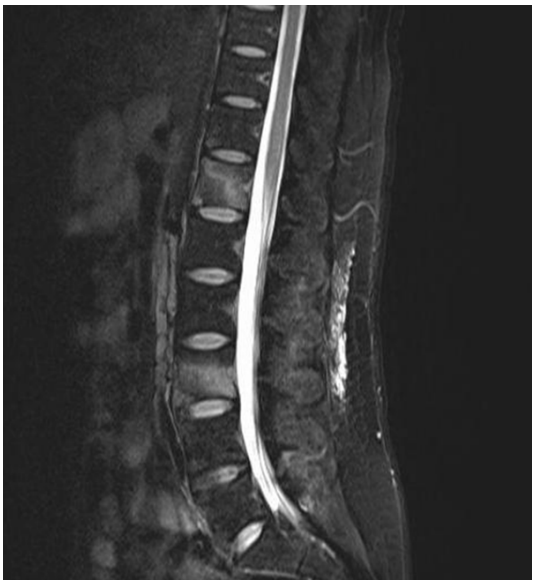

Figure 5. MRI T2WI fat suppression sequence: Hyperintense signals in the third lumbar vertebra (L3) and the 12th thoracic vertebrae (T12).

onset of bilateral buttock pain. The level of ESR and CRP were 27 mm/h and 7 mg/l respectively. The sacroiliac joint magnetic resonance imaging (MRI) examination revealed a rough joint surface with abnormal signals (**Figure 3**). After getting consultations from our rheumatology department, she was diagnosed as SAPHO syndrome. After excluding tumors, infections and tuberculosis, alendronate monosodium 70 mg/week, leflunomide 10 mg/day and lornoxicam 8 mg/day were initiated and lasted for over 3 months. During this process, hersymptoms went off and on repeatedly. Before long, she reported severe loin pain, swelling and pain of right sternoclavicular region and difficulty in

body-turning and daily activities. Laboratory test showed ESR 55 mm/h and CRP 38 mg/l. Ultrasonic examination revealed the manifestations of right sternoclavicular synovial hypertrophy and bone erosion (**Figure 4**). Further MR examination hinted at multiple discitis of thoracicolumbar vertebrae (**Figure 5**). After a comprehensive consideration of disease status, etanercept 25 mg/shot twice a week was injected subcutaneously. Two weeks later, analgesic medication was withdrawed upon a major relief of loin pain. At Week 4 after the initiation of etanercept, the sternoclavicular, loin and sacroiliac region pain basically disappeared. Skin rashes of both hands improved greatly. ESR decreased to 9 mm/h, CRP to 5 mg/l, BASFI from 6.2 to 0.4 and BASDAI from 7.9 to 1.1.

Discussion

SAPHO syndrome is a chronic disease involving skin, bone and joints. In recent years, ongoing studies of this disease have yielded some pathophysiological insights of its mechanisms. However, its exact etiology remains elusive. In the opinions of some scholars, SAPHO syndrome is probably a relatively independent disease [5]. However, in light of that this syndrome has spinal involvement, enthesitis, complicated IBD and response to the therapy of NSAIDs, most scholars proposed to classify this disease into the category of spondyloarthritis. And, due to insufficient evidence of controlled trials, the current therapy tends to follow the medication practices of spondyloarthritis. For example, NSAIDs could offer a marked relief of skeletal symptoms of SAPHO syndrome patients [6]. Some studies indicated that the pathogenesis of SAPHO syndrome was correlated with the infection of Propionibacterium acnes. Sustained mild infection of Propionibacterium acnes might trigger an abnormal activation of inherent non-specific T-cell immune response and cause specific inflammatory lesions. Thus, many drugs, including azithromycin and compound sulfamethoxazole, have been prescribed with indefinite clinical efficacies [7]. For those cases with more severe symptoms and a faster progression, phosphates have been utilized more frequently in recent years. It can not only participate in bone remodeling, but also inhibit the secretion of IL-1β, IL-6 and TNF-α [12]. Beneficial clinical outcomes were obtained in the phosphates treatment of SAPHO syndrome, especially in cases of chronic active osteitis with rapid pain relief after using this drug. However, it was disappointing that this therapy failed to achieve continuous clinical relief. Moreover, some patients didn't respond to this therapy at all. At this circumstance, the anti-TNF-α therapy became another viable option.

Presumably TNF-α played important roles in the occurrence and development of SAPHO syndrome. As demonstrated by a study of Wagner et al, there was a high expression of TNF-α in mandibular biopsy specimens of SAPHO syndrome patients. And more and more clinical reports have also proven the definite efficacies of TNF-α inhibitors. Various preparations of TNF-α inhibitors have been used to treat this disease over the years. However, the paradoxical manifestations of skin lesions are receiving more and more attention. For example, after the therapy of infliximab, skin rashes of patients often recurred and even worsened. Yet the application of etanercept could yield satisfactory efficacies without causing deterioration of skin lesions. And this finding was also confirmed in other rheumatic disease studies [13] on the therapies of other biological preparations. The reason was probably due to that biological preparations suppressed excessively the expression of TNF-α leading to the activation of Propionibacterium acnes [14].

Within the present study, etanercept was successful in treating two cases of refractory SAPHO syndrome patients. The immediate efficacy was marked without overt toxic or adverse effects, yet further follow-ups are needed to determine long-term outcomes of these patients.

Disclosure of conflict of interest

None.

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References

[1] Vilar-Alejo J, Dehesa L, de la Rosa-del Rey P, Novoa-Medina J, Valerón Almazán P, Santana Medina N, Bastida J. SAPHO syndrome with unusual cutaneous manifestations treated suc-

cessfully with etanercept. Acta Derm Venereol 2010; 90: 531-2.
[2] Windom RE, Sandford JP, Ziff M. Acne conglobata and arthritis. Arthritis Rheum 1961; 4: 632-635.
[3] Bjorksten B, Gustavson KH, Eriksson B, Lindholm A, Nordström S. Chronic recurrent multifocal osteomyelitis and pustulosis palmoplantaris. J Pediatr 1978; 932: 227-231.
[4] Chamot AM, Benhamou CL, Kahn MF, Beraneck L, Kaplan G, Prost A. Acne pustulosis hyperostosis osteitis syndrome. Result of a national survey. 85 cases. Rev Rhum Mal Osmoartic 1987; 54: 187-196.
[5] Rosner I. SAPHO: Disease, Syndrome or Gategory? J Clin Rheumatol 2002; 8: 3.
[6] Hayem G, Bouchaud-Chabot A, Benali K, Roux S, Palazzo E, Silbermann-Hoffman O, Kahn MF, Meyer O. SAPHO syndrome: a long-term follow-up study of 120 cases. Semin Arthritis Rheum 1999; 29: 159-71.
[7] Rozin AP. SAPHO syndrome: Is a range of pathogen-associated rheumatic diseases extended? Arthritis Res Ther 2009; 11: 131.
[8] Brockbank JE, Lapp V, Gladman DD. Infliximab therapy in 15 patients with psoriatic arthritis (PsA) [abstract]. J Rheumatol 2001; 28 Suppl 63: 62.
[9] Wagner AD, Andresen J, Jendro MC, Hülsemann JL, Zeidler H. Sustained response to tumor necrosis factor alpha-blocking agents in two patients with SAPHO syndrome. Arthritis Rheum 2002; 46: 1965-8.
[10] Ben Abdelghani K, Dran DG, Gottenberg JE, Morel J, Sibilia J, Combe B. Tumor necrosis factor-alpha blockers in SAPHO syndrome. J Rheumatol 2010; 37: 1699-704.
[11] Zhang LL, Zhao JX, Liu XY. Successful treatment of SAPHO syndrome with severe spinal disorder using entercept: a case study. Rheumatol Int 2012; 32: 1963-1965.
[12] Pennanen N, Lapinjoki S, Urtti A, Mönkkönen J. Effect of liposomal and free bisphosphonates on the IL-1 beta, IL-6 and TNF alpha secretion from RAW 264 cells in vitro. Pharm Res 1995; 12: 916-922.
[13] Wollina U, Hansel G, Koch A, Schönlebe J, Köstler E, Haroske G. Tumor necrosis factor-alpha inhibitor-induced psoriasis or psoriasiform exanthemata: first 120 cases from the literature including a series of six new patients. Am J Clin Dermatol 2008; 9: 1-14.
[14] Rozin AP. SAPHO syndrome: Is a range of pathogen-associated rheumatic diseases extended? Arthritis Res Ther 2009; 11: 131.