

Use of the abatacept in a patient with psoriatic arthritis

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ABSTRACT

Psoriatic arthritis (PA) is an inflammatory seronegative arthritis of unknown origin. Classically, PA has five clinical forms, and asymmetric oligoarthritis is the most common type. We describe the case of a patient with PA refractory to disease-modifying drugs, who developed drug-induced hepatitis after chemoprophylaxis with isoniazid, administered prior to the treatment with an anti-TNF α agent. Due to the risk of activating latent tuberculosis with the administration of anti-TNF α and hepatotoxicity onset caused by the TB treatment and based on the fact that the treatment of PA is similar to the treatment of rheumatoid arthritis, a decision was made to use the empirical treatment with abatacept. Approximately twenty days after the second infusion of the drug, the patient showed clinical improvement, resolution of the arthritis, almost complete disappearance of the skin lesions and improvement of anemia and inflammatory tests.

Keywords: psoriatic arthritis, drug-induced hepatitis, tuberculosis, abatacept.

INTRODUCTION

Psoriatic arthritis (PA) is an inflammatory arthritis, seronegative for rheumatoid factor, associated with cutaneous psoriasis (CP).¹ Cutaneous psoriasis is a disease that affects 2% to 3% of the general population.² Approximately 10% of those patients develop arthritis.³ Its etiology is unknown, but it is suspected that an infectious agent would be the trigger factor.⁴ Typically, arthritis appears after or concomitantly with the onset of psoriasis. However, in 10% to 15% of the cases, arthritis precedes the onset of psoriasis by more than two years.³ Classically, PA has five clinical types: asymmetrical oligoarthritis (70%), symmetrical polyarthritis (15%), distal and ungueal lesions (5%), mutilating arthritis (< 5%), and spondylitis (5%).¹ Changes in humoral and cellular immunity have been observed in the physiopathogeny of PA. The skin, joints, and entheses share similar mechanisms. An infiltrate consisting of activated T cells is located in the dermal

papilla, in the subsynovial layer and entheses. Dendritic cells, macrophages, and B cells are other cell types involved. They all release pro-inflammatory cytokines that lead to the activation of other cells, promoting angiogenesis and bone resorption.⁵ One of the co-stimulatory signs of T cells is mediated by the CD28-CD80(B7-1)/86(B7-2), interaction, present in antigen-presenting cells,^{6,7} regulating the production of IL-2 and the expression of anti-apoptotic molecules, such as Bcl-x.⁷ Antigen 4 associated with cytotoxic T lymphocyte (CTLA-4) is a regulator of this co-stimulation, inhibiting the activation of T cells.⁷

The treatment of PA consists in non-steroidal anti-inflammatory drugs (NSAIDs), low dose corticosteroids, especially in cases of peripheral arthritis, disease-modifying drugs (DMARDs), such as methotrexate (MTX), sulfasalazine, and leflunomide, in addition to anti-TNF α drugs.⁸ Pilot studies with other biological agents, such as T lymphocyte activation

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blockers (CD2, alefacept; CD11a, efalizumab; CD80/CD86, abatacept) and monoclonal antibodies against the interleukin-6 receptor (tocilizumab), are in progress.⁹

Abatacept is a recombinant human fusion protein containing the extracellular domain of CTLA-4, which binds to the CD80/86 receptor of an antigen-presenting cell. This interaction blocks the activation of the CD28 receptor on T cells.⁴ This mechanism justifies a possible action in PA.

The present study describes the case of a patient with long-term psoriatic arthritis, refractory to DMARDs, who presented drug-induced hepatitis after the use of isoniazid for tuberculosis (TB) prophylaxis before the anti-TNF α therapy was instituted. Due to the severity of the articular involvement, the risk of developing Tb and hepatotoxicity due to the treatment of this infection and the absence of another internationally-approved therapeutic option, it was decided to use abatacept empirically.

CASE REPORT

This is a report of a 57-year-old single female, that developed pain and edema in the right heel eight years ago, hindering ambulation. Two months later, she developed pain in the left heel. Treatment with anti-inflammatory drugs was instituted without a satisfactory response. In 2004, she developed arthritis in the left knee and developed erythematous and desquamative plaques on the sacral region and intergluteal fold, when treatment with 5 mg/day of prednisone and 15 mg/week of methotrexate was instituted. Laboratory tests showed: CBC within normal limits, elevated inflammatory markers, ANF 1:80 (homogenous nuclear pattern), negative rheumatoid factor, positive HLA-B27, negative serology for hepatitis B and C as well as HIV and non-reactive for VDRL. Due to the persistence of the articular involvement with sustained synovitis in the left knee, the MTX dose was increased to 20 mg/week and sulfasalazine, 2 g/day, was added to the therapeutic regimen. The patient remained on this treatment for approximately one year. In 2006, due to the persistence of arthritis in the left knee and arthritis in the wrists and ankles, treatment with leflunomide, 20 mg/day, was instituted and MTX was maintained. The patient underwent arthroscopy with biopsy of the left knee, which showed non-specific chronic synovitis. X-Rays of the pelvis showed sclerosis and irregularities in the margins of the sacroiliac joints with symmetrical articular spaces, without clinical symptoms.

One year ago, the patient presented right knee involvement, at which time it was decided to institute anti-TNF α therapy. Screening for TB showed a 14-mm PPD with normal chest X-rays; chemoprophylaxis with 300 mg/day of isoniazid was instituted. After 15 days, the patient developed asthenia

and choloria with high levels of transaminases and she was hospitalized for seven days for drug-induced hepatitis. Due to the severe hepatitis, persistence of predominantly peripheral articular involvement, and contraindication to isoniazid, treatment with abatacept was instituted when aminotransferase levels reached normal range (AST = 16 IU/l and ALT = 35 IU/l).

Two infusions of the biological agent, with a 20-day interval between them, were performed and the patient showed significant clinical improvement with resolution of the arthritis, pain reduction at the visual analogue scale (VAS), and improvement of anemia and inflammatory markers (Table 1). The skin lesions showed regression to residual maculae, but wrist arthralgia persisted.

Table 1

Hemoglobin (Hb), inflammatory markers (ESR and CRP), and VAS pain levels

Dates	Hb (g/dL)	ESR (mm)	CRP (g/dL)	Pain (VAS)
05.10.2008 (before 1 st infusion)	11.9	86	17.47	100
10.23.2008 (after 2 nd infusion)	12.9	38	4.14	20

DISCUSSION

The diagnosis of PA is difficult when the skin manifestations are subtle or arthritis develops before the onset of the skin lesions. The wide variety of the clinical manifestations, the lack of well-defined diagnostic criteria, and the possibility of coexistence of other rheumatic diseases add up to the complexity of the diagnosis.³

In the present case report, articular manifestations preceded the onset of skin lesions by four years. The severity of the articular involvement and refractoriness to treatment with NSAIDs and DEMARDs justified the indication of treatment with an anti-TNF α agent. However, the drug-induced hepatitis due to the use of isoniazid for TB prophylaxis contraindicated the use of those biological agents due to the risk of infection development and posterior difficulties to establish an adequate treatment.

In view of what has been exposed and due to the lack of therapeutic options, the patient was treated with abatacept. Some studies^{10,11} have shown that this medication has a lower risk of adverse events and it has been used in the treatment of RA unresponsive to MTX and anti-TNF α agents. This biological agent has shown favorable results in the treatment of psoriasis, although the studies are still in the experimental phase.⁹

Schiff *et al.*¹⁰ observed that the safety and tolerability profiles of abatacept are more acceptable than those of infliximab, with fewer serious adverse events, including severe infections and acute infusion events. In another study with 1,286 patients with rheumatoid arthritis, followed for over a one-year period, Schiff *et al.*¹¹ observed that only one patient had a serious infection, but no cases of opportunistic infections, including tuberculosis, occurred. In conclusion, this study demonstrated acceptable safety and tolerability of abatacept in patients with inadequate response to anti-TNF therapy.

Abatacept, a biological agent not yet available at the Brazilian Public Health System (SUS), is currently at the IIB, multiple dose, randomized, double blind, placebo-controlled study phase to determine a dosage regimen for the treatment of patients with active psoriatic arthritis and inadequate response to treatment with DEMARDS, including methotrexate and anti-TNF agents.¹²

The current knowledge of the pathogenesis of PA involves a complex cascade of B and T cells activation and the consequent release of inflammatory cytokines. Abatacept attenuates the co-stimulation of CD80/CD86-CD28 of T lymphocytes and it has proven to be effective in the treatment of psoriasis and rheumatoid arthritis.^{13,14} The real efficacy of abatacept in PA depends on the results of clinical assays.

In the present case report, a good initial response to abatacept was observed, but we cannot establish at the present that this patient will have a sustained response to the treatment over time. It is necessary to wait for the results of additional clinical studies to establish the role of abatacept in the treatment of PA.

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