

Abatacept in psoriatic arthritis: Case report and short review

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ABSTRACT

Psoriatic arthritis (PsA) is a chronic inflammatory disease affecting about 6-10% of patients with cutaneous psoriasis. According to current knowledge, activated T-cells seem to play a pivotal role in the pathogenesis of both psoriasis and PsA. Abatacept is a novel biologic agent selectively designed to interfere with T-cells co-stimulation. Structurally, it is a soluble, fully human fusion protein consisting of the extracellular domain of CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4) linked to a modified Fc portion of human IgG1. Abatacept is now approved as a first-line treatment for rheumatoid arthritis (RA), but preliminary data disclose a potential role of abatacept in the treatment of other autoimmune diseases. In this article, we report a case of successful treatment with abatacept of a psoriatic arthritis patients who developed adverse drug reactions (ADRs) to medication commonly used in PsA, including three different anti-TNF- α agents. In addition, we review the scientific evidences supporting a possible role of abatacept in treatment of patients with psoriasis and PsA and the paradox of abatacept-induced psoriasis.

Key words: Abatacept, psoriasis, psoriatic arthritis

INTRODUCTION

Psoriasis is a chronic immune-mediated skin disease with a prevalence varying among ethnic groups from 0.91% to 8.5%.^[1] Psoriatic arthritis (PsA) is a chronic inflammatory disease affecting about 6-10% of patients with cutaneous psoriasis. However, the prevalence of PsA is significantly higher (20-40%) in patients with extensive skin involvement.^[2]

Abatacept is a novel biologic agent now approved as a first-line treatment for rheumatoid arthritis (RA),^[3] selectively designed to interfere with T-cells co-stimulation. Structurally, it is a soluble, fully human fusion protein consisting of the extracellular domain of CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4) linked to a modified Fc portion of human IgG1.^[4]

T-cells activation requires two distinct receptor interactions between antigen-presenting cells (APC) and T-cells in order to be initiated. The first is the "classic" interaction between the major histocompatibility complex (MHC) present on the surface of APCs and the T-cell receptor (TCR) found on the membrane of T cells. The second, the so-called co-stimulatory signal, is mainly, but not only, mediated by the interaction between the CD80 (B7-1)/CD86 (B7-2) receptors on the membrane of APCs with the CD28 receptor expressed by T-cells.^[5] Other molecules, such as CD2, deliver similar costimulatory signals.^[6] CD28 is expressed constitutively

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on T-cells, and its engagement leads to full activation.^[7] In contrast, CTLA-4 is transiently expressed following T-cell activation and delivers a signal that down-regulates cellular function and inhibits excessive expansion of activated T-cells.^[8]

In this context, abatacept prevents activation of T-cells by binding to the ligands CD80/CD86 on the surface of APCs, thus competing for them with CD28 expressed by T-cells. As an important indirect effect within the inflammatory cascade, the production of cytokines and autoantibodies is inhibited.^[9]

The role of T-cells in psoriasis pathophysiology is now well recognized,^[10] furthermore, T-cells have been shown to play a central role in the pathogenesis of PsA.^[11] Activated T-cells are abundant in the inflamed joints of both PsA and RA, showing a similar profile of pro-inflammatory cytokine expression.^[12] Alefacept, a fusion protein that inhibits T-cell co-stimulation by blocking the interaction of lymphocyte function-associated antigen 3 (LFA-3) with CD2, has been shown to improve the psoriatic skin lesions and the signs and symptoms of arthritis in patients with active PsA.^[13]

Abatacept for psoriatic arthritis: Case report

Our patient was a 56-years-old Caucasian female diagnosed with vulgar psoriasis since 2004. After five years, she developed knee and ankle joint arthritis, and after appropriate clinical and laboratory evaluation, she was diagnosed with psoriatic arthritis. In the past medical history, of interest, the patient developed drug hypersensitivity during treatment with antibiotics and clonidine.

For this reason, she was treated with methotrexate 15 mg/weekly with a moderate response after three months. However, after about six months, the drug was discontinued for persistently elevated liver enzymes.

Disease activity worsened; therefore, infliximab was started at the dosage recommended of 5 mg/kg. At the second administration, the patient presented with a systemic allergic response (dyspnea, urticaria, glottic edema) despite premedication with metilprednisolone and chlorphenamine.

Infliximab was discontinued, and adalimumab was started after appropriate wash-out period. At the third administration, the patient developed whole body urticaria that needed hospitalization and high dose corticosteroids to recover. After few months, etanercept was finally tested, but generalized urticaria developed also in this case after few administration.

Therefore, after appropriate informed consent, abatacept was started in November 2012 at the dosage recommended for weight range. Premedication with metilprednisolone and chlorphenamine was carried out before each infusion. At the initiation of the treatment, disease activity was high

(DAS28: 5.16). A strict monitoring of possible allergic reaction was carried out. Any adverse event was recorded. After three months, disease activity was significantly reduced (DAS28: 3.84) and the response was maintained also at subsequent six-month's follow-up visit.

Abatacept: Evidences for efficacy in psoriasis and psoriatic arthritis

In a phase I, multicenter, open-label, dose-escalation trial, abatacept produced a dose-dependent improvement in skin lesions of psoriatic patients, refractory to at least one anti-psoriatic therapy.^[14] Nineteen (46%) of the 41 patients achieved a 50% or greater improvement in their Physician's Global Assessment of disease activity, compared with baseline evaluation. In particular, 9 of 11 patients in the top dosing groups achieved a 50% or greater improvement in psoriasis clinical scores. The duration of clinical response was sustained during the 147-d median observation period after the final drug administration.

Subsequently, the same group revealed the mechanisms underlying this effect of abatacept.^[15] Clinical improvement of psoriasis correlated with reduced intralesional T-cells and neutrophils in serial biopsies during the treatment period. As a consequence, also keratinocyte proliferation and epidermal thickness were reduced. In addition, also dendritic cells, the mayor partners of T-cells activation, were reduced in number and morphology.

In 2011, Mease *et al.* published data from a double-blind, placebo-controlled trial of abatacept in psoriatic arthritis.^[16] A total of 170 patients refractory to DMARDs (Disease-modifying anti-rheumatic drugs) including anti-tumor necrosis factor alpha (TNF- α) were randomized to three different abatacept dosing regimens or placebo. The percentage of patients achieving ACR20 response on day 169 was higher compared to placebo for all dosing regimens, although the difference was not statistically significant in patients receiving the lower dose (3 mg/kg).

Additional evidences of successful response to abatacept in patients with psoriatic arthritis refractory to DMARDs have been reported sporadically in the last years.^[17-19]

Safety profile

In the study by Mease *et al.*,^[16] abatacept demonstrated a good safety profile. Adverse events were reported in about 70% patients, both treated with abatacept or placebo. Seven patients experienced serious adverse events, four of whom were in the 30/10 mg/kg arm, two in the 10 mg/kg arm, and one in the placebo arm. This profile was similar to that reported for patients with rheumatoid arthritis treated with abatacept as reported by an integrated safety analysis of five randomized, placebo-controlled, double-blind clinical trials^[20] [Table 1].

Table 1: Adverse drug reactions (ADRs) occurring in ≥1% of patients treated with ORENCIA during placebo-controlled, double-blind, rheumatoid arthritis studies (adapted from Bristol-Myers Squibb, Orencia (Abatacept) Product Monograph, Bristol-Myers Squibb Canada, Montreal, Canada)

	Orencia n=1955 %	Placebo n=989 %
Gastrointestinal disorders		
Nausea	6.0	5.1
Diarrhea	3.5	3.0
Dyspepsia	1.3	0.9
Abdominal pain	1.2	0.9
Vomiting	1.2	1.4
General disorders and administration site conditions		
Fatigue	3.5	3.2
Asthenia	1.5	1.3
Pyrexia	1.4	1.5
Infections and infestations		
Upper respiratory tract infection	4.8	3.9
Nasopharyngitis	3.2	1.9
Sinusitis	2.8	2.7
Bronchitis	2.2	1.6
Urinary tract infection	2.1	1.3
Influenza	1.6	1.7
Pharyngitis	1.3	1.1
Herpes Simplex	1.2	0.5
Herpes Zoster	1.0	1.1
Rhinitis	1.0	0.4
Investigations		
Blood pressure increased	1.5	0.5
Musculoskeletal, connective tissues, and bone disorders		
Myalgia	1.0	1.0
Nervous system disorders		
Headache	10.0	6.3
Dizziness	4.6	3.5
Somnolence	1.9	2.0
Respiratory, thoracic, and mediastinal disorders		
Cough	2.4	1.0
Pharyngolaryngeal Pain	1.0	1.1
Skin and subcutaneous tissue disorders		
Rash	2.1	1.6
Vascular disorders		
Flushing	1.0	0.5
Hypertension	2.1	1.1

Development of psoriasis during treatment with abatacept: The other side of the coin

Although some evidences suggest that abatacept could be an effective alternative for psoriasis and psoriatic arthritis in selected patients, literature reports suggest that, in a small number of patients, abatacept could induce paradoxical development or recrudescence of cutaneous psoriasis.

Data from five randomized, placebo-controlled, double-blind clinical trials revealed that nine patients out of 1,955 treated with abatacept presented with psoriasis, compared to zero cases in the patients receiving placebo.^[20] Subsequently, other reports sporadically reported the development or recrudescence of skin psoriasis during treatment with abatacept.^[21-27] Psoriatic skin lesions are well-known cutaneous adverse events of anti-TNF- α antagonists.^[28] The pathogenesis of this phenomenon appears to involve a disruption in cytokine balance following TNF- α inhibition, resulting in the up-regulation of plasmacytoid dendritic cells and the subsequent production of unopposed interferon- α , following a triggering event in predisposed individuals.^[29]

CONCLUSION

In this article, we reviewed the scientific evidences, although limited, supporting a moderate efficacy of abatacept in cutaneous psoriasis and psoriatic arthritis. According to these data, the degree of improvement observed with abatacept and the number of patients achieving a significant response is substantially lower when compared to anti-TNF- α agents.^[30,31]

This could at least in part explained by the intrinsically resistant phenotype of the patients recruited in these trials, including patients who failed previous anti-TNF- α therapy. However, taking into account the good safety profile of abatacept, this molecule could be considered in patients with psoriatic arthritis and multiple anti-TNF- α failures. In addition, to the current knowledge, patients eligible for off-label abatacept must have no axial involvement, given the discouraging data obtained in two small clinical trials in patients with axial spondyloarthritis^[32] and ankylosing spondylitis.^[33]

More studies are needed to explore further the efficacy of abatacept in anti-TNF- α -naïve patients and to evaluate the maintenance over time of response.

REFERENCES

1. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM; Identification and Management of Psoriasis and Associated Comorbidity (IMPACT) project team. Global epidemiology of psoriasis: A systematic review of incidence and prevalence. *J Invest Dermatol* 2013;133:377-85.
2. Gelfand JM, Gladman DD, Mease PJ, Smith N, Margolis DJ, Nijsten T, *et al.* Epidemiology of psoriatic arthritis in the population of the United States. *J Am Acad Dermatol* 2005;53:573.
3. Ruderman EM, Pope RM. The evolving clinical profile of abatacept (CTLA4-Ig): A novel co-stimulatory modulator for the treatment of rheumatoid arthritis. *Arthritis Res Ther* 2005;7 Suppl 2:S21-5.
4. Moreland L, Bate G, Kirkpatrick P. Abatacept. *Nat Rev Drug Discov* 2006;5:185-6.
5. Yamada A, Salama AD, Sayegh MH. The role of novel T cell costimulatory pathways in autoimmunity and transplantation. *J Am Soc Nephrol* 2002;13:559-75.
6. Green JM, Karpitskiy V, Kimzey SL, Shaw AS. Coordinate regulation of T cell activation by CD2 and CD28. *J Immunol* 2000;164:3591-5.

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7. Lenschow DJ, Walunas TL, Bluestone JA. CD28/B7 system of T cell costimulation. *Annu Rev Immunol* 1996;14:233-58.
8. Chambers CA, Allison JP. CTLA-4 — the costimulatory molecule that doesn't: Regulation of T-cell responses by inhibition. *Cold Spring Harb Symp Quant Biol* 1999;64:303-12.
9. Weisman MH, Durez P, Hallegua D, Aranda R, Becker JC, Nuamah I, *et al.* Reduction of inflammatory biomarker response by abatacept in treatment of rheumatoid arthritis. *J Rheumatol* 2006;33:2162-6.
10. Cai Y, Fleming C, Yan J. New insights of T cells in the pathogenesis of psoriasis. *Cell Mol Immunol* 2012;9:302-9.
11. Choy E. T cells in psoriatic arthritis. *Curr Rheumatol Rep* 2007;9:437-41.
12. van Kuijk AW, Reinders-Blankert P, Smeets TJ, Dijkmans BA, Tak PP. Detailed analysis of the cell infiltrate and the expression of mediators of synovial inflammation and joint destruction in the synovium of patients with psoriatic arthritis: Implications for treatment. *Ann Rheum Dis* 2006;65:1551-7.
13. Mease PJ, Gladman DD, Keystone EC. Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: Results of a randomized, double-blind, placebo-controlled study. *Arthritis Rheum* 2006;54:1638-45.
14. Abrams JR, Lebowitz MG, Guzzo CA, Jegasothy BV, Goldfarb MT, Goffe BS, *et al.* CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. *J Clin Invest* 1999;103:1243-52.
15. Abrams JR, Kelley SL, Hayes E, Kikuchi T, Brown MJ, Kang S, *et al.* Blockade of T lymphocyte costimulation with cytotoxic T lymphocyte-associated antigen 4-immunoglobulin (CTLA4Ig) reverses the cellular pathology of psoriatic plaques, including the activation of keratinocytes, dendritic cells, and endothelial cells. *J Exp Med* 2000;192:681-94.
16. Mease P, Genovese MC, Gladstein G, Kivitz AJ, Ritchlin C, Tak PP, *et al.* Abatacept in the treatment of patients with psoriatic arthritis: Results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Arthritis Rheum* 2011;63:939-48.
17. Canete JD, Celis R, Hernandez V, Pablos JL, Sanmarti R. Synovial immunopathological changes associated with successful abatacept therapy in a case of severe refractory psoriatic arthritis. *Ann Rheum Dis* 2010;69:935-6.
18. Rodrigues CE, Vieira FJ, Callado MR, Gomes KW, de Andrade JE, Vieira WP. Use of the abatacept in a patient with psoriatic arthritis. *Rev Bras Reumatol* 2010;50:340-5.
19. Altmeyer MD, Kerisit KG, Boh EE. Therapeutic hotline. Abatacept: Our experience of use in two patients with refractory psoriasis and psoriatic arthritis. *Dermatol Ther* 2011;24:287-90.
20. Sibilia J, Westhovens R. Safety of T-cell co-stimulation modulation with abatacept in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2007;25(5 Suppl 46):S46-56.
21. Jost C, Hermann J, Caelen Lel-S, Graninger W. New onset psoriasis in a patient receiving abatacept for rheumatoid arthritis. *BMJ Case Rep* 2009; doi:10.1136/bcr.09.2008.0845.
22. Brunasso AM, Laimer M, Massone C. Paradoxical reactions to targeted biological treatments: A way to treat and trigger? *Acta Derm Venereol* 2010;90:183-5.
23. Florent A, Albert C, Giaccherio D, Roux C, Euler-Ziegler L. Reactivation of cutaneous psoriasis during abatacept therapy for spondyloarthritis. *Joint Bone Spine* 2010;77:626-7.
24. Kato K, Satoh T, Nishizawa A, Yokozeki H. Psoriasiform drug eruption due to abatacept. *Acta Derm Venereol* 2011;91:362-3.
25. Brigant F, Clavel G, Chatelain D, Lok C, Chaby G. Letter: A case of generalized guttate psoriasis induced by etanercept with relapse after abatacept. *Dermatol Online J* 2011;17:11.
26. Silverman D, Oliver A. Abatacept-induced psoriasis. *Cutis* 2011;88:117-8.
27. Konsta M, Rallis E, Karameris A, Stratigos A, Sfikakis PP, Iliopoulos A. Psoriasiform lesions appearing in three patients with rheumatoid arthritis during therapeutic administration of abatacept, a selective inhibitor of T-cell costimulation. *J Eur Acad Dermatol Venereol* 2012;26:257-8.
28. Flendrie M, Vissers WH, Creemers MC, de Jong EM, van de Kerkhof PC, van Riel PL. Dermatological conditions during TNF-alpha-blocking therapy in patients with rheumatoid arthritis: A prospective study. *Arthritis Res Ther* 2005;7:R666-76.
29. Collamer AN, Guerrero KT, Henning JS, Battafarano DE. Psoriatic skin lesions induced by tumor necrosis factor antagonist therapy: A literature review and potential mechanisms of action. *Arthritis Rheum* 2008;59:996-1001.
30. Mease PJ, Gladman DD, Ritchlin CT, Ruderman EM, Steinfeld SD, Choy EH, *et al.* Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: Results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005;52:3279-89.
31. Antoni CE, Kavanaugh A, Kirkham B, Tutuncu Z, Burmester GR, Schneider U, *et al.* Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: Results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum* 2005;52:1227-36.
32. Lekpa FK, Farrenq V, Canoui-Poitrine F, Paul M, Chevalier X, Bruckert R, *et al.* Lack of efficacy of abatacept in axial spondylarthropathies refractory to tumor-necrosis-factor inhibition. *Joint Bone Spine* 2012;79:47-50.
33. Song IH, Heldmann F, Rudwaleit M, Haibel H, Weiss A, Braun J, *et al.* Treatment of active ankylosing spondylitis with abatacept: An open-label, 24-week pilot study. *Ann Rheum Dis* 2011;70:1108-10.

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