Journal of Dermatological Case Reports

Fixed drug eruption followed by lichen aureus during abatacept add-on therapy of rheumatoid arthritis

Uwe Wollina[1], Leonore Unger[2]

1. Department of Dermatology and Allergology
2. Department of Internal Medicine I, Division Rheumatology/Osteology,
Hospital Dresden-Friedrichstadt, Academic Teaching Hospital of the Technical University of Dresden, Dresden, Germany

Corresponding author:

Prof. Dr. Uwe Wollina, MD

Department of Dermatology and Allergology

Hospital Dresden-Friedrichstadt

Academic Teaching Hospital of the Technical University of Dresden

Friedrichstrasse 41

01067 Dresden, Germany

e-mail: *wollina-uw@khdf.de*

Key words:

abatacept, rheumatoid arthritis, drug reaction, lichen aureus

Abstract

Background: Abatacept is a soluble fusion protein approved as add-on drug in rheumatoid arthritis.

Main Observations: Here we report the first case of fixed drug eruption followed by lichen aureus due to abatacept in a 67-year-old woman.

Conclusion: Fixed drug eruption is an unexpected drug reaction for abatacept, since T-cell activation is inhibited.

Introduction

Abatacept (CTLA4-Ig - Orencia®, Bristol Myers Squibb, New York, USA) is a soluble fusion protein consisting of the extra-cellular domain of human cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4, CD152) and a fragment of the Fc portion of human IgG1 (hinge and CH2 and 3 domains). It binds human B7 (CD80/86) more strongly than CD28.

CTLA-4 is expressed on in vitro activated T-cells and shares important sequence homology with CD28 and binds to the same ligands, CD80 (B7-1) and CD86 (B7-2). CTLA-4 probably functions as a negative regulator of T-lymphocyte activation.[1]

Abatacept is the only agent currently approved to treat rheumatoid arthritis (RA) that targets the co-stimulatory signal required for full T-cell activation.[2] It is approved for patients who failed TNF-alpha inhibition and methotrexate (MTX). The drug is used together with MTX in clinical practise. Across clinical trials, abatacept has been associated with clinically meaningful and statistically significant improvements in conventional measures of disease activity, health related quality of live, and physical function in studies for up to two years.[3,4]

Case report

A 67-year old woman with definite RA had been treated with various drugs including three TNF-alpha inhibitors but was either unresponsive or developed a pustular psoriasis. Therefore she was shifted to abatacept plus methotrexate, which was well tolerated. After her 3rd abatacept infusion, however, she noted a reddish, painful burning lesion on the left foot. She reported a worsening of the symptoms during and for more than 72h after each new infusion.

On examination we found a violaceous infiltrated plaque of about 1.5 x 0.6 cm on the plantar area of the left foot. It was sensible for heat and touch. The plaque showed spontaneous regression within 2 weeks after the infusion. In the neighbouring skin a lichen aureus with yellowish pigmentation developed (Figure 1).

The clinical pattern and the close relationship to abatacept infusions suggest a fixed drug eruption due to this compound. The drug was stopped.

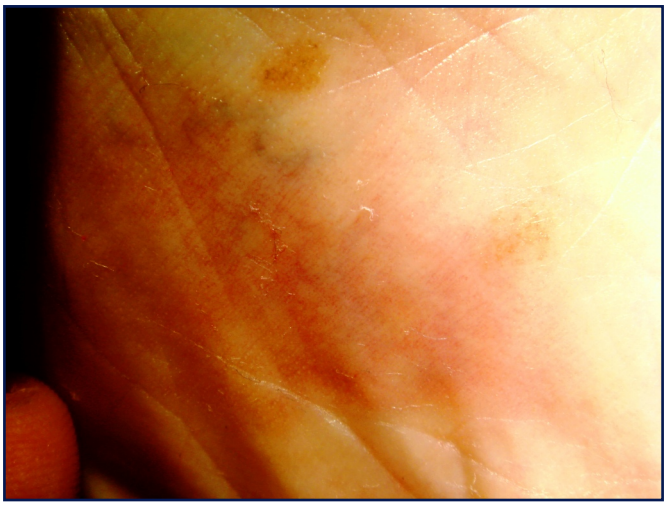

Figure 1

Remnants of the plantar fixed drug eruption can be seen two weeks after cessation of the drug leaving a yellowish pigmentation (lichen aureus) in the adjacent skin.

Discussion

Safety of abatacept has been assessed using data from double-blind placebo-controlled trials and a large-scale phase III trial in RA.[5] Experience with anti-TNF-alpha agents has shown that there is potential for unpredictable changes in the immune state when using targeted therapies. Regulatory T-cells (Treg) have been shown to have a role in preventing autoimmune disease and to have altered function in active RA. Since Treg development and function is dependent on CTLA4 signalling,[6] another area of concern was that CTLA4-Ig could interfere with their function and affect tolerance to other auto-antigens. Lastly, any protein-based biologic agent administered intravenously has the potential to cause infusion reaction. Although this is less likely for a fully humanized molecule, this adverse event has been monitored closely. In the clinical trials rates of discontinuation due to serious adverse events and adverse events (3.5% and 3.8%, respectively and 2.7% and 1.5%, respectively), serious adverse events (10.5% and 11.3%, respectively) and total adverse events (79.5% and 71.4%, respectively) were similar between the abatacept and placebo groups. There was no increase in serious infections or of opportunistic infections in the abatacept group.[4,7]

In the whole available literature there was not a single report about fixed drug eruption due to abatacept. The occurrence of fixed drug eruption (FDE) in this case seems to be a paradoxon. It has been suggested that in FDE CD8+ T-cells primed during viral infections could evolve into long-lived effector memory phenotype T-cells. Such cells would be subsequently trapped either specifically or non-specifically in the inflamed skin sites and eventually persist as a stable population. Once cross-reacted with exogenous stimuli, such as drug or self-antigens, however, they would become effectors of epidermal damage.[8]

Intraepidermal CD8+ T-cells, that are resident in the lesional epidermis as memory T cells, transiently acquire a natural killer-like phenotype and express cytotoxic granules upon activation. The epidermal influx of CD4+ T-cells including Foxp3+ regulatory T-cells (Tregs) during the evolution ameliorates epidermal damage induced by activation of the intraepidermal CD8+ T-cells. Interleukin-15 from the lesional epidermis could maintain survival of intraepidermal CD8+ T-cells over a prolonged period of time (> 4 years).[9]

Abatacept, however, is an inhibitor of T-cell activation. We are unable to explain the paradoxon that an inhibitor of T-cells is capable to induce T-cells including Tregs. Further investigations are needed. There is some analogy to the induction of psoriasis by tumour-necrosis-factor-alpha inhibitors.[10] Interestingly enough, this patient had developed pustular psoriasis due to TNF-alpha inhibitors twice before. It is not known weather such a reaction would be a risk for adverse drug reaction to abatacept. Nevertheless, physicians who treat patients with abatacept should be aware of the risk of a fixed drug eruption.

References

1. Wang Q, Zhang M, Ding G, Liu Y, Sun Y, Wang J, Zhang W, Fu Z, Cao X. Anti-ICAM-1 antibody and CTLA-4Ig synergistically enhance immature dendritic cells to induce donor-specific immune tolerance in vivo. *Immunol Lett*. 2003; 90: 33-42.

2. Buch MH, Boyle DL, Rosengren S, Saleem B, Reece RJ, Rhodes LA, Radjenovic A, English A, Tang H, Vratsanos G, O'Connor P, Firestein GS, Emery P. Mode of action of abatacept in rheumatoid arthritis patients having failed TNF blockade: a histological, gene expression and dynamic MRI pilot study. *Ann Rheum Dis*. 2008; Epub ahead of print.

3. Massarotti EM. Clinical and patient-reported outcomes in clinical trials of abatacept in the treatment of rheumatoid arthritis. *Clin Ther*. 2008; 30: 429-442.

4. Kremer JM, Genant HK, Moreland LW, Russell AS, Emery P, Abud-Mendoza C, Szechiński J, Li T, Teng J, Becker JC, Westhovens R. Results of a two-year followup study of patients with rheumatoid arthritis who received a combination of abatacept and methotrexate. *Arthritis Rheum*. 2008; 58: 953-963.

5. Todd DJ, Costenbader KH, Weinblatt ME. Abatacept in the treatment of rheumatoid arthritis. *Int J Clin Pract*. 2007; 61: 493-500.
6. Tang Q, Bluestone JA. Regulatory T-cell physiology and application to treat autoimmunity. *Immunol Rev*. 2006; 212: 217-237.
7. Vital EM, Emery P. Abatacept in the treatment of rheumatoid arthritis. *Ther Clin Risk Manage*. 2006: 2: 365-375.
8. Shiohara T, Mizukawa Y. The immunological basis of lichenoid tissue reaction. *Autoimmun Rev*. 2005; 4: 236-241.
9. Mizukawa Y, Yamazaki Y, Shiohara T. In vivo dynamics of intraepidermal CD8+ T cells and CD4+ T cells during the evolution of fixed drug eruption. *Br J Dermatol*. 2008; 158: 1230-1238.
10. Wollina U, Hansel G, Koch A, Schönlebe J, Köstler E, Haroske G. Tumor necrosis factor-α 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.