

Atopic Dermatitis Flare during Abatacept Therapy*To the Editor:*

Abatacept is a recent biologic disease-modifying antirheumatic drug (DMARD) approved in the United States, Europe, and Japan in the treatment of moderate to severe acute rheumatoid arthritis (RA) and juvenile idiopathic arthritis. It is a recombinant fully human fusion protein consisting of the extracellular domain of cytotoxic T-lymphocyte antigen 4 (CTLA-4) linked to the modified fragment of the Fc portion of human immunoglobulin G₁.¹ Abatacept (CTLA-4-Ig) binds with high affinity to both CD80 and CD86 receptors on the surface of antigen-presenting cells, preventing their binding to CD28 on T cells and resulting in a negative signal for T cell activation.² Several studies suggest the benefits of abatacept even in other immunologic diseases, such as type 1 diabetes, systemic lupus erythematosus, psoriasis, and psoriatic arthritis, as well as asthma, multiple sclerosis (MS), and morphea profunda.¹⁻⁴

We present the case of a 39-year-old woman with RA who developed flares of atopic dermatitis (AD) after having received intravenous administration of abatacept. The patient has suffered from RA since she was 22 years old. She was initially treated with sulfasalazine and then azathioprine and cyclosporine; all were suspended owing to inefficacy. Methotrexate was suspended for intolerance (nausea). Leflunomide was administered with good compliance but low efficacy. From 2008 to 2010, the patient was treated with subcutaneous adalimumab 40 mg every 2 weeks, which was suspended for loss of efficacy and because one of the patient's aunts was diagnosed with MS. Since 2010, the patient has been treated with intravenous abatacept 750 mg every 4 weeks, with good disease control.

In September 2013, she came to our attention for the presence of eczematous lesions with erythematous papulae, serous exudates, excoriations, and crusted erosions located on the antecubital fossae, interscapular area, neck, face, upper chest, and wrists. She notably reported that such lesions had developed with flares and partial remissions; afterwards, she started therapy for her RA with abatacept. She also reported to have suffered from mild AD, which was successfully treated with steroidal creams, when she

was an infant; she did not remember any similar lesions occurring in adulthood and could not recall the last flare. The patient had been working as a secretary for the last 5 years, and she denied exposure to new irritants or contact allergens and had not changed her lifestyle recently. The patient denied having celiac disease, and IgA antibodies versus transglutaminase and endomysium were negative. Standard patch tests were negative as well.

The diagnosis of AD was established according to Hanifin and Rajka's criteria.⁵ A biopsy specimen confirmed the presence of acanthosis, spongiosis, small subcorneal vesicles in the epidermis, and a perivascular lymphocytic infiltration with occasional eosinophils in the dermis. The patient did not agree to discontinue abatacept. She was successfully treated with mometasone cream applied once daily for 2 weeks and an emollient cream, but a recurrence was seen after 4 weeks owing to the discontinuation of mometasone. It is not possible to determine with certainty the relationship between an AD flare and abatacept intake. However, the coincidence of the AD flare occurring with the administration of the biologic drug cannot remain unnoticed.

Both intravenous and subcutaneous abatacept were well tolerated in a randomized, double-blind, placebo-controlled, multicenter trial performed in adults with active RA resistant to at least one biologic or nonbiologic DMARD.⁶ In a pooled analysis of placebo-controlled trials, the most frequent adverse effects reported were headache, nasopharyngitis, dizziness, cough, back pain, and hypertension.³⁻⁷ The literature contains descriptions of some rare adverse effects reported in the postmarketing phase, such as psoriasis⁸ and asthma.⁴

To our knowledge, this case represents the first report of AD worsened by the biologic antirheumatic drug abatacept. The mechanism underlying this side effect is unclear, and we cannot be sure that the blockage of CD28-CD80/CD86 by CTLA-4 is paramount for AD to develop. In our patient, the worsening of AD during treatment with abatacept might be explained by the concept of balance between the T-helper type 1 (Th1) and the T-helper type 2 (Th2) response. As a matter of fact, RA is known to be a typical Th1 disease, whereas the lesions of acute AD are caused by Th2 cytokine production. In our case, surely the overactivation of Th1 lymphocytes led to the development of RA. In this context, abatacept might have provoked an

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undermodulation of such an immune response, interfering with the proportion between Th1 and Th2, which might have caused an overexpression of the Th2 response in terms of AD lesions, which had remained latent before.

A study conducted in 33 patients with RA treated with abatacept showed a significant downregulation of Th1, Th2, and T-helper type 17 (Th17) subsets, especially in anti-trullinated protein antibody-positive patients.⁹ It seems that CTLA-4-Ig, thanks to its mechanism of action, has a wide effect in multiple cell types, depending on their state of activation.¹ In our patient, there was a hyperactivation of Th1 lymphocytes, and the action of abatacept inhibiting T cell activation resulted in good clinical control of her RA.

We cannot state for certain that the development of AD lesions in this woman was only due to abatacept treatment, since the biologic drug was not suspended because of its good clinical and radiologic disease control in a patient suffering from a multiresistant form of RA. We wanted to present this case because it could be the first report of an unusual side effect of abatacept. Further investigation is needed, even in terms of postmarketing surveillance. This report may signal an additional warning when prescribing CTLA-4-Ig in a patient with atopic diathesis.

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