

Clinical Communications

Use of abatacept in eosinophilic asthma

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Clinical Implications

- This case report describes the use of an inhibitor of T-cell costimulation (abatacept) in a patient with rheumatoid arthritis with coexistent eosinophilic asthma.
- Frequent use of abatacept failed to resolve her sputum eosinophilia, which questions the role of T-cell stimulation in the generation and persistence of pulmonary eosinophilia in at least some asthma phenotypes.

TO THE EDITOR:

Asthma is a disease that is associated with considerable morbidity, and, whereas severe asthma is relatively uncommon, it is associated with the highest health care costs.¹ Glucocorticoid drugs are established in the management of severe asthma but are associated with adverse effects. Novel therapeutics have been developed as the underlying immunologic basis of the disease has been elucidated. One successful development has been the use of a monoclonal antibody against IL-5, and these drugs are now entering phase III studies. The role of T cells, and, specifically, the T_H2 response, in the asthmatic airway has been well described in the literature.^{2,3} One of the consequences of this T_H2 stimulation is the recruitment of eosinophils to the lungs, and these can be measured in sputum samples and used to guide treatment.⁴ Novel anti-T-cell directed therapeutic strategies for asthma are currently being investigated. For T cells to be fully activated, 2 processes must occur. First, the T-cell receptor must bind to the antigen-major histocompatibility complex expressed on an antigen-presenting cell. Second, a second costimulatory receptor interaction is needed, the most important of which is a CD28 interaction with either CD80 or CD86. CD28 has been shown to be essential to the development of allergic airway inflammation in a preclinical model.⁵

There is a soluble inhibitor of CD28, CTLA4Ig, available that has been shown to reduce inflammation *ex vivo* in a human allergen challenge model and *in vivo* in a murine model.^{6,7} There is a humanized form of CTLA4Ig available as abatacept. This drug is already in use to treat another T-cell-mediated disease, rheumatoid arthritis. There has been a randomized control trial of abatacept in an allergen challenge model of subjects with mild atopic asthma. This treatment failed to alter the inflammatory response to segmental bronchial allergen challenge.⁸ The short duration of treatment during that study may explain the negative result, and the investigators discuss that it is possible that longer-term treatment or the treatment of more severe asthma may show a treatment effect of this drug. We present a case report of a patient with severe eosinophilic asthma who received abatacept for control of her rheumatoid arthritis.

We present the case of a 63-year-old woman who presented for management of her difficult to control asthma. She had a medical history significant for asthma as well as seropositive erosive rheumatoid arthritis (rheumatoid factor, 110) with bilateral hip, unilateral knee, and elbow replacements. She has never smoked. Her asthma was diagnosed at the age of 7 years but was well controlled until she was 30 years old. Since that time, she has had difficult-to-control asthma, with multiple hospital admissions, including an admission to the intensive care unit, as well as significant use of oral prednisone, with 6 courses in the past year. She also had symptoms consistent with chronic rhinosinusitis. There was no history of aspirin sensitivity. Repeated tests for the presence of anti-neutrophil cytoplasmic antibody (ANCA) have been negative. Her rheumatoid arthritis has been difficult to control since 1990. She has been on multiple agents, including methotrexate, hydroxychloroquine, leflunomide, infliximab, adalimumab, and, most recently, abatacept for 2 years before being seen in the respiratory clinic. Infliximab therapy met with some response as measured clinically with swollen joint count and c-reactive protein (CRP) as an inflammatory marker. Over time, efficacy waned and, as such, was a secondary failure. Adalimumab failed due to toxicity (rash after 4 doses). These agents were used during the course of this patient's active asthma.

Despite being on fluticasone/salmeterol Diskus (Glaxo-SmithKline, Mississauga, Canada) 250/25 mcg 1-2 puffs daily, she had diffuse expiratory wheezing bilaterally. She underwent sputum induction by using hypertonic saline solution and was found to have an extremely high eosinophil count, at 93%, which would account for her ongoing respiratory symptoms and frequent exacerbations. Her FEV₁ at that time was 1.22 L (54% of predicted) with a FEV₁-forced vital capacity ratio of 0.54. Methacholine challenge was not performed due to her low initial FEV₁. However, inhalation of hypertonic saline solution caused bronchoconstriction. Before inhalation of saline solution during sputum induction, the patient was given 200 µg salbutamol. Despite this, after inhalation of 4% saline solution, the FEV₁ fell by 350 mL (16.9%), which indicated moderate-severe airway hyperresponsiveness and considered diagnostic of asthma. In response to the sputum cell count, her inhaled corticosteroids were increased to fluticasone/salmeterol Diskus 500/25 mcg 1 puff twice a day and fluticasone Diskus 500 mcg 1 puff twice a day. She was referred for a computed tomography of her sinuses. Her skin prick tests to common aeroallergens were negative.

She was seen in follow-up 1 month later, when she was found to have a significant improvement in her symptoms on the increased inhaled corticosteroid. Her FEV₁ also had increased by 300 mL to 1.52 L. Her computed tomography of her sinuses showed significant nasal polyposis and sinus disease. She was reassessed in follow-up 3 months later; she was found to have become significantly worse in the past 10 days, with an audible wheeze, increasing productive cough, and dyspnea. She was prescribed a short course of oral prednisone. When seen 3 months later, she continued to be significantly symptomatic, despite completion of her course of prednisone. Her FEV₁ was 1.62 L. Repeated sputum induction showed a significant eosinophilia of 74% in her sputum. She was prescribed another course

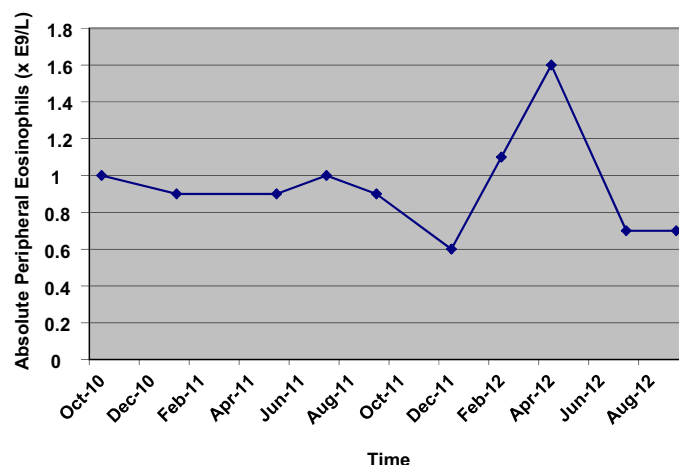


FIGURE 1. Peripheral eosinophil count.

of oral prednisone and will continue to be followed up. Her complete blood count had been monitored; while receiving her rheumatoid arthritis therapies, we extracted her peripheral eosinophil count from these results (Figure 1). Although our patient has been on abatacept monthly for 33 months (from April 2010 to January 2013), her asthma symptoms continue to be poorly controlled, with persistent eosinophilic inflammation in both her sputum and peripheral blood.

The observations in our patient suggest that even prolonged treatment with abatacept may not be effective in controlling the T_H2 -mediated eosinophilic inflammatory response seen in patients with asthma. A possible explanation is that the T-cell responsiveness may be predominantly a memory response and hence less dependent on costimulation via CD28 and suggests that this needs further study and clarification to determine new therapeutic treatments for severe eosinophilic asthma. In addition, the development of eosinophilic inflammation in some types of asthma may not be dependent on T cells. Asthma has long been recognized clinically as a very heterogeneous disease, and, with increased knowledge from the study of the pathobiology of asthma, there are clearly distinguishable phenotypes of asthma.⁹ A phenotype of patients has been described with nonatopic eosinophilic asthma. Increased levels of type 2 innate lymphoid cells have been found in these patients, and, upon stimulation with thymic stromal lymphopoietin (TSLP) and IL-33, these cells produce high amounts of IL-5, which could produce the eosinophilic inflammation in the absence of T_H2 cell activation.¹⁰ This may, in part, explain the lack of response to a therapy targeted at reducing T-cell-driven inflammation.

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