Infliximab as a Therapy for Idiopathic Hypereosinophilic Syndrome

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 77-year-old woman from Guyana presented with a 3-year history of a generalized, pruritic eruption associated with chronic chills, fatigue, generalized malaise, and a 14-kg weight loss over a 9-month period (Figure 1). Her medical history was significant for hypertension and diabetes, and her medications included glucophage, atenolol, and lisinopril. She had no personal or family history of atopy. Her physical examination findings were remarkable for exfoliative erythroderma and keratoderma associated with generalized lymphadenopathy (Figure 1). Complete blood cell counts were normal except for a persistently elevated absolute eosinophil count (1500-3000/µL) for more than 8 months. Positron emission tomographic scans detected enhanced fludeoxyglucose F 18 uptake bilaterally in the supraclavicular, axillary (largest node measuring 2.5 cm), and inguinal nodes (largest node measuring 2 cm). A left inguinal lymph node biopsy specimen revealed dermatopathic lymphadenitis and no evidence of a lymphoproliferative disorder. Histopathologic examination of a skin sample revealed parakeratosis, hypogranulosis, psoriasiform epidermal hyperplasia, mild spongiosis, a mild superficial perivascular lymphocytic infiltrate with occasional plasma cells and rare eosinophils, and numerous melanophages. Flow cytometry and skin and bone marrow biopsy specimens revealed no evidence of a clonal T- or B-cell population on immunophenotyping or molecular genetic analysis, and FIP1L1-PDGFRA gene fusion was not detected. Extensive studies were performed to rule out infectious, allergic, vasculitic, rheumatic, and malignant causes of eosinophilia. A transthoracic echocardiogram, which was obtained to rule out heart failure or mural thrombus in the setting of chronic hypereosinophilia, demonstrated no abnormalities.

THERAPEUTIC CHALLENGE

The pruritic eruption was initially thought to be caused by the use of a newly prescribed medication (lisinopril). Unfortunately, erythroderma and keratoderma persisted after therapy with the angiotensin-converting enzyme inhibitor was discontinued. In the following 3 years, the patient was treated unsuccessfully with a variety of therapeutic modalities, including systemic corticosteroids, psoralen–UV-A, isotretinoin, bexarotene, and extracorporeal photopheresis. Two years after her initial presentation, the patient required inpatient hospitalization for intense pruritus and failure to thrive, and
the decision was made to initiate treatment targeting T-cell activation. After 3 monthly cycles of denileukin difitox infusions (18 µg/kg/d) in combination with oral bexarotene, there was no improvement in erythroderma or pruritus. A 1-month course of oral imatinib mesylate therapy (400 mg/d) was not helpful. A trial of chemotherapy with 2 cycles of fludarabine–mitoxantrone–dexamethasone (fludarabine phosphate, 25 mg/m² days 1–3; mitoxantrone, 10 mg/m² day 1; and dexamethasone, 20 mg/d days 1–5), resulted in a transient decrease in the patient’s absolute eosinophil count but no clinical improvement. An effective treatment was needed to ameliorate her skin lesions and severe pruritus.

**SOLUTION**

Intravenous infusions of infliximab (5 mg/kg) were followed by a sharp decrease in the peripheral blood eosinophil count to 700/µL (Figure 2), with complete resolution of erythroderma, keratoderma, and pruritus after 3 monthly cycles of therapy (Figure 3). For maintenance, the patient received 5 additional monthly cycles of infliximab that were well tolerated, without reported adverse effects or evidence of recurrent disease. Infliximab therapy was subsequently discontinued, and the patient’s skin remained clear at the 1-month follow-up visit. Her debilitating skin condition, which was associated with hypereosinophilia, had responded quickly and dramatically to infliximab therapy alone, resulting in improved sleep and functional status.

**COMMENT**

Hypereosinophilic syndrome (HES) is a heterogeneous group of conditions that are characterized by blood hypereosinophilia and end-organ dysfunction due to eosinophilic infiltration and toxic mediator release.1-3 End-organ damage commonly affects the skin, heart, lungs, and nervous system. Idiopathic HES (IHES), which is a diagnosis of exclusion, is defined as blood eosinophilia exceeding an eosinophil count of 1500/µL for more than 6 consecutive months, of unknown etiology, with evidence of end-organ damage.1,3 The distinctions between myeloid and lymphoid lineages of IHES are based on differences in molecular pathogenesis, clinical presentation, complications, and prognosis and are necessary to guide patient treatment.4 Lymphocytic HES (l-IHES) is characterized by a nonmalignant expansion of a T-cell population that produces eosinophilopoietic cytokines (ie, interleukin 5). It carries a good prognosis, with prolonged survival, and may respond to glucocorticoid therapy or to treatment with human monoclonal anti–interleukin 5 antibody.4,5 Cutaneous lesions are common in l-IHES and vary from pruritic erythematous macules, papules, plaques, or nodules to urticaria and angioedema.4 Myeloproliferative HES (m-IHES) is characterized by clonally derived eosinophils, carries a poor prognosis, and may respond to imatinib mesylate (a tyrosine kinase inhibitor) therapy, particularly in the presence of *FIP1L1-PDGFRα* gene fusion.5,6 If left untreated, patients with m-IHES can undergo a rapidly fatal course owing to congestive heart failure or to the development of acute leukemic disease.4 Other therapies for m-IHES reported in the literature include hydroxyurea, interferon alfa,7 cyclosporine, and allogenic stem cell transplantation.8 Based on the results of clinical and molecular analysis, our patient had l-IHES: she presented with cutaneous end-organ damage in the absence of heart in-

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**Figure 2.** Eosinophil count in a patient with idiopathic hypereosinophilic syndrome. Infliximab therapy was initiated in late November 2005, with a sharp decrease in absolute eosinophil counts. Normalization of eosinophil count was achieved after 3 monthly doses of infliximab, and the effect was maintained after 7 monthly doses.

**Figure 3.** Full response to infliximab following 7 monthly infusions, with complete resolution of erythroderma (A) and keratoderma (B).
volvement, failed to improve with imatinib mesylate therapy, and did not harbor the FIP1L1-PDGFRα fusion gene. We report the first case (to our knowledge) of l-IHES that was responsive to infliximab therapy.

Infliximab is a chimeric, human-mouse antibody for tumor necrosis factor (TNF-α) that has been shown to be effective in the treatment of Crohn disease, rheumatoid arthritis, severe psoriasis (ie, calcitriol and erythrodermic psoriasis), and pityriasis rubra pilaris. Tumor necrosis factor α is a proinflammatory cytokine that contributes to lymphocyte and eosinophil recruitment by up-regulating vascular cell adhesion molecule 1 (VCAM-1), endothelial leukocyte adhesion molecule 1 (ELAM-1), and intercellular adhesion molecule 1 (ICAM-1) on activated endothelial cells. The precise mechanism by which infliximab therapy could induce remission in an erythodermic patient with HES is not fully understood but could be the result of inhibition of TNF-α-induced eosinophil-dependent recruitment, toxic effects, and leukocyte infiltration. It has been proposed that through a positive feedback loop of TNF interacting with TNF receptors on keratinocytes, “secondary” keratinocyte cytokines are released, including ICAM-1. Also, Costa et al have shown that blood eosinophils isolated from hypereosinophilic patients can also represent a potential source of TNF-α. By blocking TNF-α expression from primary sources in the skin, TNF-α inhibitors could break the cycle of cytokine feedback by down-regulating VCAM-1, ICAM-1, and ELAM-1 expressions on dermal endothelial cells, thereby preventing eosinophils from homing to skin and subsequent toxic mediator release.

Several adverse effects of infliximab therapy have been reported. In a recent meta-analysis, Bongartz et al showed an increased risk of serious infection and a dose-dependent increased risk of malignancy in patients with rheumatoid arthritis treated with anti–TNF antibody therapy. For this reason, the decision to initiate TNF-α therapy requires careful thought, and patients must be monitored closely during treatment. In our patient, the clinical response resulted in significantly improved functioning and symptom relief. The efficacy of a treatment suggested by a single report may serve to provide clues about the pathogenesis of the disease but will need to be subjected to further study before the treatment is widely used.

Accepted for Publication: September 28, 2006.

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Author Contributions: Dr Demierre had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study Concept and Design: Taverna, Lerner, and Demierre. Acquisition of Data: Taverna, Lerner, Werth, and Demierre. Analysis and Interpretation of Data: Taverna, Lerner, Goldberg, and Demierre. Drafting of the Manuscript: Taverna. Critical Revision of the Manuscript for Important Intellectual Content: Taverna, Lerner, Goldberg, Werth, and Demierre. Obtained funding: Demierre. Administrative, Technical, and Material Support: Taverna, Goldberg, and Demierre. Study Supervision: Taverna, Goldberg, Werth, and Demierre.

Financial Disclosure: Dr Demierre has acted as a speaker for Schering, Ligand, Therakos, Merck, and Gloucester; has received research support from Ligand, Therakos, Merck, Gloucester, Genmab, Curagen, and Novartis; has been a consultant for Ligand and Novartis; and has served on the advisory board of Gloucester.

Previous Presentation: This work was presented as a case series at the Annual Fall meeting of the Massachusetts Academy of Dermatology; September 17, 2006; Newport, Rhode Island.

Additional Contributions: We thank Robert E. Tigelaar, MD, for thoughtful discussions and Swarne Adikari for technical photographic assistance.

REFERENCES