

spite the limited power in one trial to detect a dose effect.

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Rituximab and Omalizumab in Severe, Refractory Insulin Allergy

TO THE EDITOR: We describe the sequential use of two targeted biologic agents to treat a patient with severe systemic insulin allergy accompanied by marked metabolic dysregulation and corticosteroid toxicity.

In 1996, a 50-year-old woman received the diagnosis of type 1 diabetes. Shortly after insulin therapy was initiated, a generalized urticarial rash (resulting in excoriation, bleeding, and disrupted sleep) developed. Insulin allergy was diagnosed on the basis of positive skin-prick tests and a level of insulin-specific IgE of 5.75 kU per liter (normal value, <0.70 kU per liter). Until 2000, she was treated with a standard stepwise approach of trying various insulin preparations, antihistamines, and prednisolone and attempting insulin desensitization.^{1,2} Prednisolone alone provided symptomatic relief, and from 2000 through 2003 her allergic symptoms were under control. However, by 2004, her prednisolone requirement increased from 5 mg to 15 mg daily because of worsening symptoms. Corticosteroid-related complications included a glycated hemoglobin level ranging from 9.6 to 11.3%, weight gain, memory impairment, and osteoporosis.

In 2004, therapy with continuous subcutaneous insulin infusion was attempted, and glycemic control initially improved, with the glycated hemoglobin level falling to 8.4%; however, the treatment did not reduce her dependence on corticosteroids. By 2005, the glycated hemoglobin level had begun to rise again. More aggressive immunologic monitoring and treatment were instituted (Fig. 1).

Azathioprine and methotrexate were introduced

but were soon discontinued because of severe side effects. Omalizumab was considered at this stage but was contraindicated because of the highly elevated IgE level (3710 IU per milliliter). Consequently, we adopted a two-step therapeutic approach. First, we administered rituximab, a B-cell-depleting monoclonal antibody, to reduce the total IgE level so that omalizumab could be given. (The manufacturer of omalizumab had recommended against its use owing to concern about excess immune-complex formation.) After 4 weekly doses of rituximab (at a dose of 375 mg per square meter of body-surface area) had been administered, circulating B cells were fully depleted, and mycophenolate mofetil was started. The total IgE level fell to 657 IU per milliliter, allowing for the initiation of treatment with omalizumab. Within 2 weeks, the patient's symptoms had improved markedly, and 9 months later, the patient remained asymptomatic while receiving 2 mg of prednisolone daily, with falling glycated hemoglobin levels. The serum IgE levels increased as expected after the initiation of treatment with omalizumab, which binds IgE, forming drug-IgE complexes that diminish the level of bioavailable IgE.

We believe that omalizumab represented an appropriate second-stage agent, given its highly targeted nature and the low associated risk of infection, a potential major concern with further immunosuppression. Mycophenolate may have also played a role in the patient's response, but even a slight reduction in the dose of corticosteroids while she was receiving mycophenolate was accompanied by increased (and eventually unbearable)

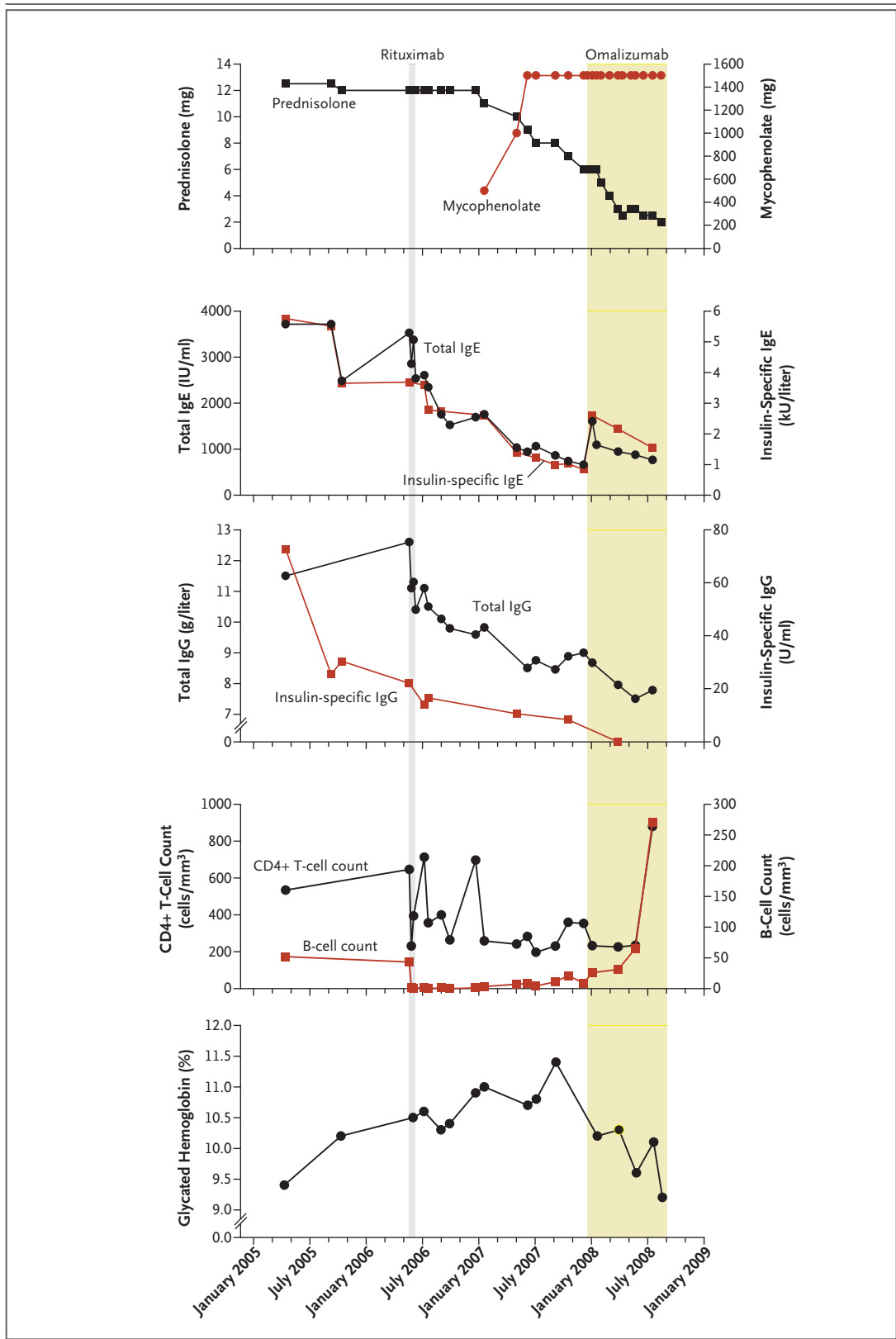


Figure 1 (facing page). Treatments and Outcomes for the Patient (2005–2009).

Serial data from January 2005 to January 2009 are shown for the principal immunologic interventions (prednisolone, mycophenolate, rituximab, and omalizumab) and laboratory measures (levels of IgE, IgG, and glycated hemoglobin and the CD4+ T-cell and B-cell counts).

able) symptoms that ceased only with omalizumab therapy. Although combined therapy is relatively expensive, we thought it was more economical and safer than pancreatic transplantation for insulin allergy³ and safer than further corticosteroid therapy. Most cases of insulin allergy can be managed with the use of protocols described previously,^{2,4} but we thought that the intractable allergy in this patient warranted the two-step approach.

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