Successful Adjuvant Treatment of Recalcitrant Epidermolysis Bullosa Acquisita With Anti-CD20 Antibody Rituximab

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 46-year-old man of Turkish origin presented with a 4-month-history of blisters on both erythematous and apparently normal skin as well as erosions on oral mucous membranes. At a body weight of 75 kg, he had been treated with dapsone (150 mg/d) and prednisolone (initially 250 mg/d, then 100 mg/d), while new lesions continued to arise. After 1 month, dapsone was changed to azathioprine (100 mg/d). On physical examination, multiple blisters and extensive erosions on erythematous skin were seen on the entire integument, especially on the chest, abdomen, upper back area, and dorsal aspect of both hands (Figure 1A). Scars and milia were found on the upper back area, and postinflammatory hyperpigmentation had developed at the sites of healed lesions. Also, erosions were present on the hard palate, the left buccal mucosa, and the gingiva of the upper and lower jaws. The nasal, genital, and perianal mucous membranes as well as the pharynx and larynx were unaffected. Upper gastrointestinal tract endoscopy and colonoscopy revealed no abnormalities.

Histopathologic examination of a blister showed a subepidermal split and a dense inflammatory infiltrate in the upper dermis, dominated by lymphocytes and neutrophils. Direct immunofluorescence microscopy of a perilesional skin biopsy specimen revealed linear deposits of IgG, IgM, and C3 at the dermoepidermal junction (Figure 2A). Circulating IgG autoantibodies labeled the dermal side (bottom) of the artificial split on indirect immunofluorescence microscopy of 1M sodium chloride–split human skin at a titer of 1:80 (Figure 2B) and reacted with the recombinant noncollagenous domain 1 of type VII collagen on Western blotting (Figure 2C and D). No reactivity with the p200 protein (as seen in anti-
p200 pemphigoid) or laminin 5 (as found in mucous membrane pemphigoid) was detected on immunoblotting of dermal extracts and keratinocyte-derived extracellular matrix (data not shown). Based on these findings, the diagnosis of epidermolysis bullosa acquisita (EBA) was made.

Treatment with prednisolone (100 mg/d) was continued and, because thiopurine methyltransferase activity was found to be normal, the azathioprine dose was increased to 175 mg/d. Also, 4 immunoadsorptions using tryptophan-linked polyvinylalcohol gel adsorbers (Immusorba TR-350; Asahi Medical, Tokyo, Japan) were performed within 10 days. Although circulating autoantibodies became undetectable on indirect immunofluorescence microscopy of split-skin, type VII collagen–specific antibodies were still present, as detected by immunoblotting. Clinically, blister formation did not cease. Therefore, colchicine (2.5 mg/d) was added to the patient’s regimen, and topical 0.1% betamethasone valerate was applied on lesional skin twice daily. With this regimen, blister formation slightly improved over the next 5 weeks; however, 2 to 5 new lesions continued to arise every day.

**THERAPEUTIC CHALLENGE**

Epidermolysis bullosa acquisita is known as a difficult-to-treat disease.1,2 Usually, high doses of systemic corticosteroids are used, either alone or in combination with immunosuppressants such as azathioprine, methotrexate, cyclophosphamide, and cyclosporine.1,2 Good clinical responses to colchicine therapy and adjuvant treatment with dapsone have been reported.1,2 Because the use of high-dose systemic immunosuppressants, including prednisolone and azathioprine in combination with anti-inflammatory drugs such as dapsone and colchicine, as well as several immunoadsorptions failed to control dis-
ease activity in our patient, a new treatment modality was required.

**SOLUTION**

We decided to initiate therapy with rituximab (Mab-Thera; Roche, Basel, Switzerland), a humanized anti-CD20 monoclonal antibody that has recently been used successfully for the treatment of refractory pemphigus. After informed written consent was obtained from our patient, 4 courses of rituximab were administered intravenously at an individual dose of 700 mg (ie, 375 mg/m² of body surface) in weekly intervals. The infusions were preceded by the administration of oral allopurinol (300 mg), oral acetylsalicyclic acid, and intravenous clemastine. No complications were observed during rituximab infusions. Oral azathioprine (175 mg/d) and colchicine (250 mg/d) therapy and tapering doses of oral prednisolone (reduction schedule is shown in Figure 2D) were continued. Between the first and second infusions of rituximab, a deep venous thrombosis developed in the lower part of the patient’s left leg and was treated with compression stockings and oral warfarin therapy (international normalized ratio, 2-3).

Eleven weeks after the first rituximab infusion, the lesions had healed completely, leaving postinflammatory hyperpigmentation on the trunk and superficial hypopigmented scars on the upper back area (Figure 1B). Also, more than 1 year after the application of rituximab, 14 weeks after discontinuation of colchicine therapy, and 14 weeks after discontinuation of treatment with oral glucocorticosteroids, the patient was still free of skin lesions. The dosage of azathioprine has been reduced to 100 mg/d and is currently being tapered off. Although immunoadsorptions may have contributed to the reduction of circulating autoantibodies, it is reasonable to assume that disease control and long-term clinical remission were achieved with rituximab therapy.

**COMMENT**

Epidermolysis bullosa acquisita is a rare subepidermal blistering skin disease, with an estimated incidence of 0.22 cases per 1 000 000 persons per year. It is characterized by autoantibodies to type VII collagen, the major component of anchoring fibrils. In addition to the mechanobullous form of EBA (also referred to as classic EBA), inflammatory variants mimicking mucous membrane pemphigoid, bullous pemphigoid, and linear IgA disease have been reported. There have been no randomized controlled therapeutic trials for this disease.

Treatment with high-dose intravenous immunoglobulins and plasmapheresis has been reported to lead to marked clinical improvement in severe cases of EBA. High-dose intravenous immunoglobulins were not used in our patient because we frequently observed relapses when tapering them off in patients with other autoimmune bullous diseases such as pemphigus. As we have experienced good clinical responses with immunoadsorption therapy for pemphigus, our patient initially received similar treatment. Immunoadsorption offers several advantages compared with plasmapheresis: (1) it allows selective removal of immunoglobulin from the circulation; (2) it does not require substitution of plasma components such as human albumin and fresh-frozen plasma; (3) it allows the processing of 2 to 3 times more plasma volume per treatment session; and (4) it is associated with fewer adverse effects. In our patient, immunoadsorption resulted in a decrease of circulating autoantibodies, as detected by indirect immunofluorescence and immunoblotting; however, autoantibodies were still present and blisters continued to arise.

Rituximab targets CD20-positive B lymphocytes, including pre-B cells and mature B cells but not stem cells or plasma cells. Initially developed for the treatment of B-cell malignancies, rituximab is increasingly being used for the therapy of autoimmune diseases such as autoimmune hemolytic anemia, Wegener granulomatosis, rheumatoid arthritis, and pemphigus. In malignant B cells, rituximab is effective by complement- and antibody-mediated cytotoxic effects and by inhibition of cell proliferation with direct induction of apoptosis, which results in depletion of CD20-positive B cells from the circulation. Such a mode of action appears to be particularly attractive in managing autoimmune diseases such as autoimmune bullous disorders in which pathogenically relevant autoantibodies are present. Indeed, samples of anti-type VII collagen antibodies from patients with EBA that had been affinity purified were recently observed to induce a subepidermal split when incubated with cryosections of human skin.

In our patient, circulating B lymphocytes expressing CD19, which is usually coexpressed with CD20 on peripheral B cells, became undetectable within 7 days after the first rituximab infusion. Interestingly, while the levels of herpes simplex virus–specific IgG remained within normal limits, IgG immunoblot reactivity to type VII collagen was undetectable 12 weeks after the initiation of rituximab therapy (Figure 2D). The reason for the apparently higher susceptibility of autoantigen-specific CD20-positive B lymphocytes to rituximab compared with normal CD20-positive B cells remains elusive. It may be speculated that long-lived plasma cells (that are CD20 negative) account for normal immunoglobulin levels but may not be responsible for the generation of pathogenic autoantibodies.

Adverse effects of rituximab therapy include fever, chills, urticaria, bronchospasm, pruritus, transient hypotension and hypertension, cough, and headache during infusion. These effects tend to be less frequent with subsequent infusions and may be avoided, as in our patient, by the addition of allopurinol, paracetamol (acetaminophen), and antihistamines to the regimen. Serious adverse effects such as cardiac arrhythmias, systemic infections, and aggravation of concomitant ischemic or vascular heart diseases were not seen. The deep venous thrombosis that was observed between the first and second rituximab infusions might have been caused by the high dose of prednisolone that was administered at that time. In larger series, rituximab administration has not been associated with venous thrombosis. A direct association with the use of rituximab, however, cannot
be excluded, and a careful investigation of risk factors for thrombosis should therefore be performed.

In conclusion, our report shows that rituximab may be an effective and safe therapeutic option for otherwise treatment-resistant EBA.

Acknowledgment: We thank Christa Knaus and Silvian Noll for excellent technical assistance. We are grateful to Anja Gesierich, MD, Susanne Herzog, MD, and Ellen Rose, MD, who were involved in the clinical care of our patient.

Financial Disclosure: None.

Accepted for Publication: February 2, 2005.

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