Successful treatment of pemphigus with biweekly 1-g infusions of rituximab: A retrospective study of 47 patients

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Background: Rituximab is increasingly being appreciated as a remarkably effective treatment for pemphigus, mostly concomitantly with other immunosuppressive medications. The majority of studies have used a single cycle of rituximab with the same dosage as approved for the treatment of lymphomas, ie, 375 mg/m^2 weekly × 4 weeks. Rituximab is also approved for the treatment of rheumatoid arthritis, with a different dosing regimen: 1000 mg × 2, days 1 and 15.

Objective: We aimed to assess the clinical response of patients with pemphigus to a single cycle of rituximab at the dosage used in rheumatoid arthritis. We also evaluated the response to repeated cycles of rituximab.

Methods: A total of 47 patients with pemphigus who were treated with rituximab at a dosage of 1000 mg × 2, days 1 and 15, most with concurrent immunosuppressive medications, were retrospectively studied.

Results: Remission rates after the first treatment cycle reached 76%. Repeating the treatment further increased the remission rates to 91%. There was a 22% relapse rate at a median time of 8 months, but 75% of relapsing patients achieved remission again with additional cycles. The side-effect profile was similar to previous reports, except for an immediate postinfusion pemphigus exacerbation in 4 patients.

Limitations: This was a retrospective study with a limited follow-up period.

Conclusion: The rheumatoid arthritis dosage of rituximab was efficacious and well tolerated in patients with pemphigus. Patients who fail to achieve remission after 1 cycle or patients who relapse seem to benefit from repeated rituximab cycles. (J Am Acad Dermatol 2013;68:404-11.)

Key words: autoimmune bullous disease; pemphigus; rheumatoid arthritis; rituximab; treatment.

Pemphigus is a severe autoimmune blistering disease of the skin and mucous membranes. It is mediated by pathogenic autoantibodies directed against desmoglein 1 and 3, adhesion molecules of the epidermis.[1-3]

The traditional treatment for pemphigus uses systemic corticosteroids, often requiring high doses for prolonged periods, which expose the patients to well-documented severe side effects.[4] Immunosuppressive agents are often used to lower the cumulative exposure to systemic corticosteroids with varying efficacy.[5,6]

Abbreviations used:

CR: complete remission
PCP: pneumocystis pneumonia
PR: partial remission
RA: rheumatoid arthritis

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The most promising new treatment for pemphigus is the monoclonal antibody rituximab.[7-13] Rituximab is a chimeric IgG1 monoclonal antibody against CD20, a transmembrane glycoprotein, expressed exclusively on the surface of almost all B cells. Rituximab induces a transient depletion of $CD20^+$ B cells in peripheral blood within a few hours.[14]

The optimal dosage of rituximab in pemphigus has not been established. Rituximab was originally approved in 1997 for the treatment of $CD20^+$ B-cell non-Hodgkin lymphoma at a dosing schedule of 375 mg/m^2 once a week for 4 consecutive weeks.[15] Initial reports of rituximab treatment for pemphigus beginning in 2002 used this lymphoma dosage, the only approved protocol at the time, and it continues to be used in this manner with substantial success.[7,8,11]

CAPSULE SUMMARY

- Rituximab is increasingly being appreciated as an effective treatment for pemphigus, mostly administered at the same dosage as for treating lymphomas.
- A different dosing regimen, approved for treating rheumatoid arthritis, was effective and well tolerated in our relatively large cohort of patients with pemphigus.
- Patients who fail to achieve remission after rituximab therapy and patients who relapse may benefit from retreatment with rituximab.

In 2006 rituximab was approved in the United States for rheumatoid arthritis (RA) at a different dosing schedule, of two 1000-mg infusions with a 2-week interval in adults, irrespective of body weight.[16-18] Per treatment cycle, this RA dosage offers the advantage of requiring fewer infusions and usually less medication versus the lymphoma dosage. Pemphigus, like RA, is an autoimmune disease and does not require depletion of a malignant B-cell clone as in lymphoma. Nevertheless, the efficacy of RA dosage rituximab in pemphigus has not been established, with only 5 patients described in the literature to date.[10]

Questions remain, not only regarding the most appropriate dosage of a single cycle of rituximab in pemphigus, but also if and when patients should receive further cycles. Repeated monthly infusions of rituximab with intravenous immune globulin were reported to provide sustained clinical remissions in 9 of 11 patients with pemphigus.[12] In patients with RA, repeated cycles of rituximab have been necessary to maintain a reasonable level of comfort and a disease-free state.[19]

We aimed to assess the clinical response of patients with pemphigus to rituximab at the RA dosage. We also evaluated the success of repeated cycles of treatment.

METHODS

Patients

Data were collected retrospectively from the medical records of patients with pemphigus followed up in the immunodermatology clinics of Johns Hopkins University in Baltimore, Md, and Rabin Medical Center in Petah Tikva, Israel, between January 2007 and November 2011. All patients had an established diagnosis of pemphigus vulgaris or pemphigus foliaceus according to clinical, immunofluorescence, and histopathological criteria. The study was approved by both institutional review boards.

The study included patients who were treated with RA dosage rituximab. The indications for rituximab treatment were active disease after 1 to 1.5 mg/kg/d of prednisone equivalent for a minimum of 3 weeks with or without a concomitant conventional immunosuppressive drug; severe contraindications to conventional immunosuppressive therapy; severe adverse effects to corticosteroid therapy; or refusal to conventional immunosuppressive treatment including corticosteroids.

Assessment of response to treatment

Response to treatment was determined according to the definitions of an international consensus conference[20]: complete remission (CR) is the absence of new or established lesions; and partial remission (PR) is the presence of transient new lesions that heal within 1 week. Both can be either off or on minimal therapy ($\leq$ 10 mg/d of prednisone equivalent and/or minimal adjuvant therapy for at least 2 months). Relapse was defined as the appearance of 3 or more new lesions a month that do not heal spontaneously within 1 week.

Treatment protocol

Patients were treated with at least 1 cycle of 2 rituximab infusions at a dose of 1000 mg on days 1 and 15.

The majority of patients received concomitant immunosuppressive therapy during treatment with rituximab. In general, corticosteroids were tapered at a rate of 10-mg prednisone equivalent per month, to a maintenance dose of 2.5 mg/d (the common treatment approach in our institutions and others).[21] In patients receiving adjuvant immunosuppression who reached CR and maintenance corticosteroid dose, the adjuvants were discontinued after several months.

We aimed to administer additional rituximab cycles to patients who had not achieved CR at 6 months