Rituximab: A monoclonal antibody to CD20 used in the treatment of pemphigus vulgaris

Abdul Kader El Tal, MD,[a] Marshall R. Posner, MD,[b] Zachary Spigelman, MD,[c] and A. Razzaque Ahmed, MD[a,d]
Boston, Massachusetts

Background: Rituximab is an anti-CD20 chimeric antibody that selectively targets B lymphocytes. Recently, it has been reported to be beneficial in treating pemphigus vulgaris.

Objective: Our aim was to review the English-language literature on the treatment of pemphigus vulgaris (PV) with rituximab and to determine its efficacy and influence on clinical outcome(s).

Material and methods: A retrospective review of the literature on the use of rituximab in the treatment of PV was conducted. Seventeen patients in 10 reports were described and their data were reviewed.

Results: The majority of patients received one course of rituximab along with conventional immunosuppressive therapy as concomitant therapy; 88% of the patients demonstrated improvement. More than half of the patients were followed up for more than 6 months after rituximab treatment; they appeared to be clinically disease free, but were still receiving conventional immunosuppressive therapy. Side effects in most patients were transient and infusion related. Serious infections occurred in 4 patients. One patient died.

Limitations: The sample size of this study is small; there is no uniformity of data collection or measurement of key and critical indices, and follow-up was limited.

Conclusion: Rituximab may be a promising agent in treatment of PV. (J Am Acad Dermatol 2006;55:449-59.)

Pemphigus vulgaris (PV) is a potentially fatal autoimmune, mucocutaneous blistering disease.[1,2] Long-term high-dose systemic corticosteroids, with or without the addition of immunosuppressive or anti-inflammatory adjuvant agents, constitute the mainstay of therapy for PV.[3,4] However, prolonged immunosuppression produces severe side effects, including increased susceptibility for malignancies, opportunistic infections, and infertility.[5-7] The first biologic agent reported to be effective in treating PV is intravenous immunoglobulin (IVIg).[8] IVIg has been used to successfully treat several antibody-mediated autoimmune diseases.[9] Some patients with PV do not have an optimal response to IVIg.

Abbreviations used:

IVIg: intravenous immunoglobulin
PV: pemphigus vulgaris
RTX: rituximab

Because the pathogenic and clinical manifestations of PV appear to be antibody related, it can be hypothesized that eliminating the production of pathogenic antibody might be more effective than general nonspecific immunosuppression. This implies that, although the pathogenesis of PV may include dysregulation of both B- and non-B-cell immunity, the effector arm of the disease is the pathogenic antibody-producing B cells. Rituximab (RTX) is an anti-CD20 chimeric antibody that selectively targets B lymphocytes; it has been approved by the Food and Drug Administration for the treatment

From the Department of Medicine, New England Baptist Hospital and Department of Oral Medicine, Infection & Immunity, Harvard School of Dental Medicine[a]; Dana Farber Cancer Institute and Harvard Medical School[b]; Parker Hill Oncology and Harvard Medical School[c]; and Center for Blistering Diseases, New England Baptist Hospital (Director).[d]

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Reprint requests: A. Razzaque Ahmed, MD, Center for Blistering Diseases, New England Baptist Hospital, 70 Parker Hill Ave, Suite 208, Boston, MA 02120. E-mail: arahmedmd@msn.com.

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of B-cell lymphomas.[10] CD20, the antigen, is not present on plasma cells, but is expressed on mature antibody-producing B cells.[11] Success with RTX treatment has been observed in several autoimmune diseases in which autoantibodies are either the cause or are a major contributing factor, such as immune thrombocytopenic purpura and systemic lupus erythematosus.[11]

At the time this manuscript was written, there were 17 patients with PV described in 10 studies who have received RTX therapy.[12-21] The purpose of this study is to review this literature and to determine the efficacy of RTX and its influence on clinical outcome.

MATERIAL AND METHODS

Eleven reports, published between 2002 and 2005 that described use of rituximab in 17 patients, were reviewed.[12-21] One patient was described initially in a case report[22] and subsequently in a follow-up report.[20]

The following information was recorded in each case:

1. Documentation of the diagnosis of PV
2. Patient's sex; age at onset (in years)
3. Extent or severity of the disease based on the description in the text
4. Treatment used before RTX therapy
5. Duration of PV (in months) before RTX
6. Dose, duration, and side effects of RTX
7. Concomitant therapy (ies) used with RTX
8. Clinical outcome of disease after RTX use, duration of follow-up after RTX was discontinued, total duration of follow-up (ie, duration since the diagnosis was first made to date of writing of the manuscript, as reported by authors)
9. Effects of RTX on PV antibody titers and B-cell count in peripheral blood

RESULTS

Demographics and previous therapy

The data obtained from the literature on each patient are presented in Table I. Eleven of the 17 patients (65%) were female and 6 (35%) were male. The mean age was 38 years (range, 11.5-60 years). Details of the severity and extent of disease were unavailable. However, on the basis of the therapy used, duration, and course of disease, it would appear all the patients had severe and widespread disease that had not responded to corticosteroids and immunosuppressive agents. Three patients (18%) had only mucosal involvement, two patients (12%) had only cutaneous involvement, and 12 patients had mucocutaneous involvement. The mean duration of disease before the use of rituximab was 79 months (range, 9.5-168 months).

Previous therapies were usually documented. Sixteen patients (94%) received oral corticosteroids at high doses and some received additional intravenous pulse doses.

Azathioprine was used in 14 patients (82%), mycophenolate in 13 patients (76%), and IVIg in 11 patients (65%). In 6 patients, the dosage of IVIg was not mentioned. In the remaining patients, the mean dose was 1.5 g/kg per cycle (range, 0.8-4 g/kg/cycle). The mean number of cycles used was 9 (range, 1-22 cycles). Cyclophosphamide was used as pulse and/or daily oral therapy in 9 patients. The dose varied from 1.5-2 mg/kg per day. Several other adjuvant therapies were used: methotrexate in 7 patients (43.75%); dapsone in 5 patients (31.25%); cyclosporine in 2 patients (12.5%), and gold compounds in 2 patients (12.5%). Additional therapies included plasmapheresis in 6 patients (35%) and extracorporeal photopheresis, minocycline, etanercept, and staphylococcal protein A absorbent column in one patient (6%) each.

Despite the use of these intensive therapies in clinically effective doses for adequate periods, significant clinical remission was not observed in these patients. The exact incidence of side effects of these therapies could not be determined in 7 patients. In 9 patients for whom side effects were reported, the majority could be attributed to systemic corticosteroids. Hence, "conventional therapy," consisting of high doses of systemic corticosteroids and/or immunosuppressants had clearly failed to control the disease in this group of patients.

RTX treatment

The dosage of RTX in all patients in this study was 375 mg/m^2 weekly (Table II). Most of the patients received one course, consisting of 4 doses, given weekly for 4 consecutive weeks. One patient was given an additional two doses at 6 and 8 weeks, each, because of a delay in response. Another patient received additional doses at 4-week intervals up to 12 weeks. Three of 17 patients (18%) received a second course because of relapses. Of the 3 patients who received two courses, two had improvement in their conditions that lasted 6 and 9 months. The third patient received a second course at the time of relapse, but continued to have severe disease. The mean follow-up duration for all patients after the initiation of RTX therapy was 13 months (range, 3-36 months). Two patients were followed up for less than 6 months.

All 17 patients (100%) were given concomitant immunosuppressive therapy with RTX. Systemic corticosteroids were used in 16 patients (94%). Next in frequency was cyclophosphamide, used in 5