Rituximab combined with conventional therapy versus conventional therapy alone for the treatment of mucous membrane pemphigoid (MMP)

Alexander Maley, MD,[a] Maxine Warren, BS,[a] Ilyse Haberman, MD,[b] Robert Swerlick, MD,[a] Bhairavi Kharod-Dholakia, MD,[b] and Ron Feldman, MD, PhD[a]
Atlanta, Georgia

Background: The use of rituximab for refractory autoimmune blistering diseases is increasing. Data related to rituximab for the treatment of mucous membrane pemphigoid (MMP) are limited.

Objective: We sought to compare the efficacy of adding rituximab with traditional immunosuppressive therapies in the treatment of MMP. The primary outcome was achievement and time to disease control.

Methods: Patients with a diagnosis of MMP from August 2001 to June 2015 who had greater than 6 months of follow-up after the initiation of therapy were reviewed.

Results: In all, 24 patients were treated with rituximab and 25 were treated with conventional immunosuppression. Of patients, 100% in the rituximab group achieved disease control compared with 40% in the conventional group ($P < .01$), with a mean time to disease control of 10.17 months and 37.7 months ($P = .02$). Adverse events were seen in 33% of patients after rituximab, compared with 48% of patients in the conventional group ($P = .2$).

Limitations: Rituximab dosing was not uniform and the 2 groups were not matched in terms of disease severity, nor were they randomized.

Conclusions: Our study indicates that the addition of rituximab to conventional therapy in patients with MMP results in more rapid and sustained disease control with potentially fewer adverse events. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.01.020.)

Key words: autoimmune blistering disease; cicatricial pemphigoid; immunosuppression; mucous membrane pemphigoid; ocular pemphigoid; rituximab.

Mucous membrane pemphigoid (MMP) is a heterogeneous group of chronic, progressive autoimmune blistering diseases with the potential for significant morbidity caused by tissue destruction and scarring.[1] Immunopathologically, MMP exhibits deposition of immune reactants at various mucosal surfaces with subsequent clinical sequelae including severe erosions, bullae, and—if allowed to progress—fibrosis and formation of scar tissue. Conjunctival disease can progress to blindness and laryngeal involvement can result in airway loss.

Treatment for MMP has relied on conventional immunosuppressive therapies in an attempt to halt disease progression and prevent further scarring and morbidity.[1] More recently anti-CD20 therapy with rituximab has been used in the treatment of autoimmune blistering diseases, including pemphigus, where a recent meta-analysis of close to 600 patients demonstrated a complete remission in 76% of

From the Departments of Dermatology[a] and Ophthalmology,[b] Emory University School of Medicine.
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Reprint requests: Ron Feldman, MD, PhD, Department of Dermatology, Emory University School of Medicine, 1525 Clifton Rd NE First Floor, Atlanta, GA 30322. E-mail: ron.j.feldman@emory.edu.
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patients with severe adverse events in 3.3%.[2] Mechanistically, autoantibodies decrease after B-cell depletion resulting in healing of mucosal and cutaneous disease. Currently there is a paucity of data for the use of rituximab in patients with MMP. In a 2013 review of all published cases of patients with MMP treated with rituximab, 20 of 28 experienced complete response with a low rate of adverse events (2 of 28).[3] A more recent case series of patients with severe ocular disease demonstrated a response in all 6 patients.[4] As to the duration of response and relation to immunologic responses after rituximab therapy, limited data are currently available.

We sought to determine the efficacy of rituximab therapy for MMP and compare the outcomes of patients treated with rituximab with those who were treated with conventional systemic immunosuppression at a single institution.

CAPSULE SUMMARY

- Conventional therapy in mucous membrane pemphigoid may not result in effective disease control and can be limited by side effects.
- Rituximab in combination with conventional immunosuppression resulted in greater clinical efficacy, trend toward improved steroid sparing, and fewer adverse events.
- Rituximab is an effective adjuvant for mucous membrane pemphigoid.

METHODS

After institutional review board approval, a total of 49 patients with moderate to severe MMP treated at a single academic center were retrospectively reviewed. The diagnosis of MMP was made on the basis of clinical presentation and laboratory evaluations, including histologic and serologic investigation consistent with established diagnostic criteria.[1] Patients with ocular disease who did not demonstrate deposition of immunoreactants on repeated biopsy specimens and serologies, and lacked another cause for cicatrization, were considered to have immunonegative ocular cicatricial pemphigoid.[5] Charts were reviewed from August 2001 to June 2015. To be included, patients must have had follow-up for 6 months or greater after the initiation of therapy. All patients treated with rituximab had been treated and failed therapy with a systemic immunosuppressive agent. Patients treated on rituximab were continued on concomitant immunosuppressive therapy, and dosing was adjusted based on clinical response. Disease control and relapse were defined in accordance with the 2015 consensus conference on MMP.[6] All patients underwent ophthalmologic examination; those who were found to have ocular disease were followed up regularly by ophthalmology. Severe adverse events monitored by laboratory testing were defined as follows: anemia = a hemoglobin less than 10 g/dL; leukopenia = a white blood cell count less than $4.0 \times 10^3/\mu L$; pancytopenia = presence of anemia, leukopenia, and platelet count less than $100{,}000/\mu L$; and nephrotoxicity = an elevation of creatinine greater than 2 × baseline.

RESULTS

Demographic data are presented in Table I. The mean duration of disease before starting immunosuppression was significantly different between the rituximab and conventional immunosuppressive group (27.45 vs 70.91 months, $P = .05$).

Systemic immunosuppression therapy is displayed in Table II. The mean length of immunosuppression before starting rituximab was 19.875 months (range 3-52, SD 14.48). Ten patients were initially treated with the lymphoma protocol for rituximab (4 weekly infusions of 375 mg/m^2) and 14 patients were initially treated with the rheumatoid arthritis protocol (2 infusions of 1000 mg given 15 days apart). Eleven patients were treated with a single course of rituximab, whereas 13 required additional therapy. The mean total infusions of rituximab were 5.25 (range 2-16, SD 3.98). There was a mean duration of follow-up after receiving rituximab of 28.5 months (range 6-71, SD 20.85) and for conventional therapy, the mean duration of follow-up after the initiation of immunosuppression was 44.46 months (range 6-138, SD 39.89).

Primary outcomes

In all, 24 patients (100%) achieved disease control in the rituximab group, versus 10 (40%) in the conventional group ($P < .01$) (Table III). The mean time from first dose of rituximab to disease control was 10.17 months (range 3-43, SD 8.74). In the conventional group the mean length of time from the initiation of immunosuppressive therapy to disease control was 37.7 months (range 2-162, SD 57.8, $P = .02$).

Within the rituximab group, 16 of 22 patients (73%) treated with prednisone were off prednisone at last follow-up. Five patients were on low-dose (<5 mg) prednisone; 1 patient remained on high-dose (>10 mg) prednisone. In the conventional therapy group 12 of 23 patients (52%) were off