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

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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

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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

Table I. Demographic data

	Rituximab, n = 24	Conventional, n = 25
Male	11 (46%)	6 (24%)
Female	13 (54%)	19 (76%)
Age (range) [SD], y	63.95 (35-84) [11.11]	66.76 (43-85) [10.22]
Ocular disease	18 (75%)*	15 (60%)†
Oral disease	19 (79%)‡	14 (56%)§
Nasal disease	3 (12.5%)	3 (12%)
Laryngeal disease	3 (12.5%)	2 (8%)
Anogenital disease	6 (25%)	2 (8%)
Cutaneous disease	6 (25%)	4 (16%)
Positive direct immunofluorescence	19 (79%)‖	14 (56%)¶
Positive indirect immunofluorescence or ELISA	8 (33%)	3 (12%)
Mean duration of disease before starting immunosuppression (range) [SD], mo	27.45 (2-160) [35.19]	70.91 (1-287) [81.23]

ELISA, Enzyme-linked immunosorbent assay.
*Four patients had only ocular disease.
†Eight patients had only ocular disease.
‡Two patients had only oral disease.
§Four patients had only oral disease.
‖Direct immunofluorescence was considered positive if linear deposits of IgG, IgA, IgM, ± C3 were seen along the basement membrane zone. Seven patients had positive direct and indirect immunofluorescence. One patient had positive indirect immunofluorescence but negative direct immunofluorescence. Twelve patients had positive direct, but negative indirect immunofluorescence. Four patients were negative for both direct and indirect immunofluorescence.
¶Indirect immunofluorescence titers were obtained using monkey esophagus as a substrate. All patients with positive indirect immunofluorescence on salt-split skin had reactivity against the epidermal side. One patient had positive direct and indirect immunofluorescence. Two patients had positive indirect but negative direct immunofluorescence. Thirteen patients had positive direct, but negative indirect immunofluorescence. Nine patients were negative for both direct and indirect immunofluorescence.

prednisone at last follow-up. Eight patients were on low-dose prednisone whereas 3 patients remained on high-dose prednisone. The difference in the number of patients off prednisone did not meet statistical significance (P = .15).

Relapse

Within the rituximab group, 10 patients (42%) experienced a relapse after achievement of disease control (Table III). Mean time from disease control to relapse was 9.6 months (range 3-19, SD 6.04). The mean time from last dose of rituximab to relapse was 15.22 months (range 8-32, SD 7.8). Six of 10 patients who experienced a relapse had recorded CD19 B-cell numbers at the time of relapse; 2 patients of the 6 (33%) had B-cell repopulation (defined by >5 cells/μL) at the time of relapse whereas the other 4 of 6 maintained persistent peripheral B-cell depletion.

Of the 10 patients who relapsed after rituximab, disease control was achieved with additional rituximab therapy in 5 patients. Mean time to disease control after relapse was 10 months (range 2-25, SD 9.3). One patient had a second relapse that was controlled with an additional course of rituximab.

Among the 10 patients treated with conventional immunosuppression who achieved disease control, 3 (30%) experienced a relapse after a mean time of 2.3 months (range 1-3, SD 1.15, P = .06). In all 3 patients who relapsed, disease control was achieved with increased immunosuppression in a mean time of 9 months (range 2-19).

There were no significant differences in outcomes when comparing patients with positive immunofluorescence or serum studies with those with negative studies.

Table II. Systemic immunosuppressive therapies and ophthalmologic interventions

	Rituximab, n = 24	Conventional, n = 25
Prednisone	22	23
Mycophenolate	16	12
Azathioprine	15	5
Dapsone	13	12
Intravenous immunoglobulin	9	1
Cyclophosphamide	4	0
Cyclosporine	4	0
Etanercept	1	0
Methotrexate	1	2
Adalimumab	0	1
Corneal procedure	5	3
Cataract procedure	7	7
Eyelid or eyelash procedure	13	8

Serious adverse events

Recorded severe adverse events are seen in Table IV. A serious systemic adverse event or a significant abnormal laboratory value was seen in 15 of 24 patients (63%) on immunosuppressive therapy before initiating rituximab. After rituximab 8 of the 24 patients (33%) experienced an adverse event. In the group of patients on conventional therapy, 12 of 25 (48%) experienced an adverse event (P = .2). Patients receiving rituximab infusions underwent monitoring of immunoglobulin and CD4 T-cell counts. Six patients had IgG levels below the lower limit of normal (694 mg/dL) and 10 patients had CD4

Table III. Treatment outcomes

	Rituximab, n = 24	Conventional, n = 25	*P* value
No. of patients achieving disease control	24	10	.01
Time to disease control (range) [SD], mo	10.17 (3-43) [8.74]	37.7 (2-162) [57.8]	.02
No. of patients off prednisone at last follow-up*	16	12	.15
No. of patients experiencing relapse after disease control	10	3	.52
Time to relapse after control (range) [SD], mo	9.6 (3-19) [6.04]	2.3 (1-3) [1.15]	.06

*Two patients in the rituximab group and 2 patients in the conventional group were not treated with prednisone.

Table IV. Adverse events

Adverse event	Therapy before rituximab (24)	Therapy after rituximab (24)	Conventional therapy (25)
Total no. of patients experiencing a serious adverse event	15	8	12
Anemia	5	1	6
Leukopenia	5	2	0
Nephrotoxicity	3	1	0
Thrombosis	3	0	1
Upper respiratory infection/pneumonia	3	5	4
Hypersensitivity reaction	5	0	0
Infusion reaction requiring cessation	0	1*	0
Death	0	1	1
Diabetes	3		1
Pancytopenia	0	1	0
GI bleed		1	1
Perforated diverticulum	0	0	1
Bone fracture	2	0	0

GI, Gastrointestinal.

*One patient experienced an infusion reaction that required premature discontinuation of the infusion. This patient was able to tolerate subsequent rituximab infusions. Five additional patients experienced a mild infusion reaction that did not require cessation. Minor infusion reactions included symptoms of palpitations, chills, myalgia, and anxiety.

counts less than 250/μL and were initiated on prophylaxis for *Pneumocystis jirovecii* pneumonia. All of the patients who had low serum levels of IgG received more than 2 courses of rituximab; 4 of 10 patients with low CD4 received only a single treatment of rituximab. Ten patients treated with conventional immunosuppression had measured CD4 counts; all were within the reference range.

DISCUSSION

Because of the heterogeneity and rarity of MMP, conventional treatments for refractive disease have been directed at nonselective immune suppressive therapies based on consensus guidelines, which tailor therapies based on site and severity.[1] There are several caveats to this approach in that the treatment responses in conventional therapy can be delayed, potentially resulting in further scarring and morbidities. In addition, the prolonged exposure to conventional immune-suppressing therapies can potentially increase the risks for medication-related severe adverse events.

Since demonstrating efficacy for pemphigus, rituximab therapy is being used in a greater number of patients with autoimmune blistering. With our cohort, now more than 60 patients with MMP treated with rituximab have been described.[3,4,7-15] In our study, rituximab was superior to conventional immunosuppression for achieving disease control: 100% of patients in our cohort who were treated with rituximab achieved control compared with only 40% of patients treated with conventional immunosuppression. Disease control was achieved within 10 months, which is a third of the time necessary for conventional therapy. Interestingly, previous studies have demonstrated a clinical response as early as 3 to 6 months after the first rituximab course.[8,9,11] Our cohort contained outliers with advanced disease that was very difficult to control, including 1 patient who took 43 months to achieve remission, extending our mean time to response. However, our time to disease control was consistent with published results by Kasperkiewicz et al[7] and Rübsam et al,[4] who had a mean time to remission of 9 and 10 months, respectively. In addition there was a

trend for rituximab to demonstrate improved steroid-sparing effect compared with conventional therapy that did not reach statistical significance. The group treated with conventional therapy had a significantly longer duration of disease before the initiation of immunosuppression, which may have been a potential confounder.

Relapses after rituximab therapy appear to be common in autoimmune blistering diseases with a recent large-scale meta-analysis in pemphigus reporting rates of 40% to 50%.[2,16] Given the rarity of MMP, published reports are limited to case series and individual case repots, and the length of follow-up influences the reported relapse rates. In our series, patients treated with rituximab and conventional therapies experienced relapses of 42% and 33%, respectively, which is more congruent with the study by Le Roux-Villet et al,[8] who reported a 45% relapse rate after achieving disease control with the use of rituximab. In the aforementioned study immunosuppressant regimens were discontinued at the initiation of rituximab and patients were continued on maintenance dapsone or sulfasalazine. Other case series have demonstrated relapse rates of 100% when rituximab was used predominantly as monotherapy.[4,15] Patients in our study were continued on systemic immunosuppression for disease control and maintenance of remission after therapy with rituximab. Use of continued immunosuppressive therapy may have increased the efficacy of therapy and delayed time to relapse. Optimal dosing and duration of adjuvant immunosuppressive treatments for MMP remains to be established.

After rituximab therapy, peripheral CD20 B cells become rapidly depleted from the circulation and begin to repopulate with transitional B cells at 6 to 9 months posttreatment. It has been suggested that in patients with pemphigus, B-cell repopulation tends to precede clinical relapse.[17] In MMP there has not been a clear trend of relapse after B-cell repopulation, although the number of patients with subsequent monitoring of B cells is limited. In our study B-cell repopulation was associated with relapse in a third of patients in whom this information was available. Previous studies have shown that 40% of patients with MMP who relapsed, this occurred in the absence of detectable peripheral B cells.[4,8] It is possible that in MMP, measurement of peripheral B-cell populations may not reflect clinical activity at the level of the mucosa. This is frequently reflected in the low positive serologies that are commonplace in patients with MMP, particularly in ocular disease. Improved biomarkers beyond measurement of just total peripheral B cells may be needed to effectively monitor response to rituximab therapy.

Adverse events, particularly the risk of severe infections, is a common concern in patients treated with rituximab therapy. Before the publication of our cohort there were 43 reported patients with MMP treated with rituximab therapy and only 3 patients developed an infection; these 3 patients were noted to have hypogammaglobulinemia.[8] In our study, there was no significant increase in infections in the rituximab group compared with conventional immune suppression. It is also difficult to ascertain whether these side effects were attributable only to rituximab for patients also on adjuvant immune suppression. Although deaths have been previously reported caused by infection after rituximab therapy,[8] the patient who died in our cohort after receiving rituximab was lost to follow-up after moving out of state, and subsequently developed disseminated herpes virus infection while on high-dose azathioprine and prednisone 4 months after her last dose of rituximab. In addition, the patient who died in the conventional group passed away at 92 years of age, which was unrelated to MMP.

As a retrospective review and not a head-to-head comparative trial, the design of this study limits its conclusions. Given the comparative efficacy it is reasonable to conclude that superior disease control was achieved with rituximab. The selection, dosing, duration of exposure, and adjustments of therapeutic agents were not standardized. Our results still confirm the potential efficacy of rituximab as demonstrated in currently published observations. Based on our study the addition of rituximab results in a superior clinical outcome than with conventional management. Future prospective randomized studies are necessary to determine the optimal patient selection, dosing regimen, necessary adjuvant therapies, and adverse effects of rituximab in MMP.

REFERENCES

1. Chan LS, Ahmed AR, Anhalt GJ, et al. The first international consensus on mucous membrane pemphigoid: definition, diagnostic criteria, pathogenic factors, medical treatment, and prognostic indicators. *Arch Dermatol*. 2002;138:370-379.
2. Wang HH, Liu CW, Li YC, Huang YC. Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. *Acta Derm Venereol*. 2015;95:928-932.
3. Shetty S, Ahmed AR. Critical analysis of the use of rituximab in mucous membrane pemphigoid: a review of the literature. *J Am Acad Dermatol*. 2013;68:499-506.
4. Rübsam A, Stefaniak R, Worm M, Pleyer U. Rituximab preserves vision in ocular mucous membrane pemphigoid. *Expert Opin Biol Ther*. 2015;15:927-933.
5. Thorne JE, Anhalt GJ, Jabs DA. Mucous membrane pemphigoid and pseudopemphigoid. *Ophthalmology*. 2004;111:45-52.

6. Murrell DF, Marinovic B, Caux F, et al. Definitions and outcome measures for mucous membrane pemphigoid: recommendations of an international panel of experts. *J Am Acad Dermatol*. 2015;72:168-174.
7. Kasperkiewicz M, Shimanovich I, Ludwig RJ, Rose C, Zillikens D, Schmidt E. Rituximab for treatment-refractory pemphigus and pemphigoid: a case series of 17 patients. *J Am Acad Dermatol*. 2010;65:552-558.
8. Le Roux-Villet C, Prost-Squarcioni C, Alexandre M, et al. Rituximab for patients with refractory mucous membrane pemphigoid. *Arch Dermatol*. 2011;147:843-849.
9. Schumann T, Schmidt E, Booken N, Goerdt S, Goebeler M. Successful treatment of mucous membrane pemphigoid with the anti-CD20 antibody rituximab. *Acta Derm Venereol*. 2009; 89:101-102.
10. Schmidt E, Seitz CS, Benoit S, Brocker EB, Goebeler M. Rituximab in autoimmune bullous diseases: mixed responses and adverse effects. *Br J Dermatol*. 2007;156: 352-356.
11. Lourari S, Herve C, Doffoel-Hantz V, et al. Bullous and mucous membrane pemphigoid show a mixed response to rituximab: experience in seven patients. *J Eur Acad Dermatol Venereol*. 2011;25:1238-1240.
12. Wollina U, Koch A, Hansel G. Rituximab therapy of recalcitrant bullous dermatoses. *J Dermatol Case Rep*. 2008;29:4-7.
13. Taverna JA, Lerner A, Bhawan J, Demierre MF. Successful adjuvant treatment of recalcitrant, mucous membrane pemphigoid with anti-CD20 antibody rituximab. *J Drugs Dermatol*. 2007;6:731-732.
14. Ross AH, Jaycock P, Cook SD, Dick AD, Tole DM. The use of rituximab in refractory mucous membrane pemphigoid with severe ocular involvement. *Br J Ophthalmol*. 2009;93:421-422, 548.
15. Heelan K, Walsh S, Shear NH. Treatment of mucous membrane pemphigoid with rituximab. *J Am Acad Dermatol*. 2013;69: 310-311.
16. Ahmed AR, Shetty S. A comprehensive analysis of treatment outcomes in patients with pemphigus vulgaris treated with rituximab. *Autoimmun Rev*. 2015;14:323-331.
17. Feldman RJ, Christen WG, Ahmed AR. Comparison of immunological parameters in patients with pemphigus vulgaris following rituximab and IVIG therapy. *Br J Dermatol*. 2012;166:511-517.