Autoimmunity Reviews 21 (2022) 103119

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Use of rituximab in the treatment of mucous membrane pemphigoid: An analytic review

M. Mughees Farooq [a], Eli M. Miloslavsky [c,d], Nellie Konikov [e], A. Razzaque Ahmed [a,b,*]

[a] Center for Blistering Diseases, Boston, MA 02135, USA
[b] Department of Dermatology, Tufts University School of Medicine, Boston, MA 02111, USA
[c] Massachusetts General Hospital, Department of Medicine, Division of Rheumatology, Boston, MA 02114, USA
[d] Harvard Medical School, Boston, MA 02215, USA
[e] Boston VA health Care System, Jamaica Plain, Boston, MA 02130, USA

ARTICLE INFO

Keywords:
MMP
Rituximab
Clinical outcomes
Treatment protocols
Conventional therapy
Rituximab failure

ABSTRACT

Mucous Membrane Pemphigoid (MMP) is a potentially fatal mucocutaneous autoimmune blistering disease. Autoantibodies are produced against various components of the dermo-epidermal or mucosal-submucosal junction are referred to as basement membrane zone (BMZ). The hallmark is deposition of of Ig and C3 on the perilesional tissues and in some patients detection of anti-BMZ autoantibodies. A unique characteristic of MMP is that as the blisters or erosions heal, they leave irreversible scarring. This scarring results in serious and catastrophic sequelae that affect the quality of life. Conventional therapy consists of anti-inflammatory and immunosuppressive agents (ISA). In patients who fail conventional therapy or develop significant side effects to them, rituximab (RTX) has been used off label. In this review, the clinical outcomes of patients with MMP treated with RTX were studied. 124 patients were identified, 47.58% being male. 72 patients were treated by the Lymphoma Protocol and 51 by Rheumatoid Arthritis (RA) protocol. Follow up for the entire cohort was 36 months (range 0.5–72). On follow-up 64 patients (51.61%) achieved complete clinical remission (CR) off therapy, 25 patients (20.16%) were in CR on therapy, 5 patients (4.03%) were non-responders, and 9 patients (7.25%) were failures. 52 patients (41.93%) experienced a relapse, after 36 months follow-up. Duration between last RTX infusion and relapse was 10.5 months (range 1–30). Most patients with relapses were treated with additional RTX. A statistically significant better outcome was observed in patients treated with RTX as monotherapy compared to those who received RTX with ISA. Clinical outcomes in patients treated with Lymphoma protocol were better than RA protocol at a statistically significant level. Data on CD20+ B cell depletion and repopulation was limited. Interestingly relapses were seen in patients with CD20+ B cell depletion and after repopulation. In the final analysis, 89 patients (71.77%) were in complete remission. Data in this review indicated that RTX was a useful agent to treat MMP. While a randomized control trial may not be practically possible, better and disease specific protocols need to be developed. When publishing, authors should attempt to provide complete and detailed information. In doing so, they will benefit their colleagues and the patients with MMP they treat with RTX.

1. Introduction

Mucous membrane pemphigoid (MMP) is an autoimmune blistering disease affecting mucous membranes of the eye, nose, oral cavity, throat, larynx, trachea, bronchi, esophagus, genitalia and anal canal [1]. The skin is involved in 20% of the patients. The oral mucosa is most frequently involved and can manifest as desquamative gingivitis [2]. A unique feature of MMP is that in untreated or partially treated patients, as the erosion and blister heal, they produce irreversible scarring, except in the oral cavity [3]. This was the reason why it was previously known as cicatricial pemphigoid (CP) [4]. The blisters are subepithelial or submucosa on histology and the dermis or submucosa contains a mixed cell inflammatory infiltrate [5]. Deposition of IgG and C3 occurs at the basement membrane zone (BMZ) which is similar to the dermo-

* Corresponding author at: Dermatology, Tufts University School of Medicine, Center for Blistering Diseases, 697 Cambridge Street, Suite 302, Boston, MA 02135, USA.
E-mail address: a.razzaque.ahmed@tufts.edu (A.R. Ahmed).

https://doi.org/10.1016/j.autrev.2022.103119
Received 19 April 2022; Accepted 15 May 2022
Available online 8 June 2022

epidermal junction [6]. Anti BMZ autoantibodies can be detected in the sera of some, but not all patients [7].

In severe cases of MMP, the consequences of scarring can be fatal [8]. MMP can result in scarring alopecia, blindness, [4,9] restricted airway access due to nasal scarring [10], involvement of the larynx can cause laryngeal stenosis and acute asphyxiation [11]. Esophageal scarring causes dysphagia and potential need for gastric feeding [12]. Rupture of esophagus can cause fatal mediastinitis [12]. Vaginal stenosis not only eliminates sexual activity but due to scarring, even pap smears cannot be done. Anal scarring results in constant fecal leakage and need for life long adult diapers [13]. Recent studies have demonstrated that when there is tracheal and bronchial involvement, scarring of the larynx and bronchi can result in respiratory distress, respiratory failure and eventually death [11,14].

The incidence of MMP ranges from 1 to 2 patients per year per million population [15]. The incidence depends on specialty of the author and on the reporting and record keeping system of the country at large.

Several studies have reported women to be more frequently affected [16]. The mean age of onset is in mid to late sixties (60s). In the US, in one study, conducted between 1992 and 2002 the mortality associated with MMP was about 0.029 per 100,000 [17]. Mortality was higher when the disease involves trachea, bronchi and the esophagus [11,12,14].

For early diagnosis as well as appropriate treatment and monitoring, a team of physicians from multiple specialties are needed.

Several drugs alone or in combination with others, used for treating other autoimmune diseases, have been used for treating MMP. Review of the literature has shown that initial treatment of MMP was with anti-inflammatory drugs (glucocorticoids and dapsone), later with immunosuppressive agents (ISA) and frequently the combination of both [18]. Rituximab (RTX) is an anti-CD 20 chimeric monoclonal antibody and has been used off-label to treat MMP [19]. One of its main actions is depleting B cells [20–23]. Even though RTX has yielded promising results for Pemphigus Vulgaris (PV), there is scarcity of concrete data on its true efficacy in MMP patients [24]. The objective of this review was to conduct a comprehensive and critical analysis of the published data on the treatment of MMP with RTX.

2. Materials and methods

Publications with the keywords of "Mucous Membrane Pemphigoid, Cicatricial pemphigoid and Rituximab" were searched on PubMed, Medline and Embase.

Studies published between 1992 and 2021 were included in this analysis.

Inclusion criteria included (1) Publications limited to the English language. (2) Diagnosis based on clinical profile and histology and confirmed by immunopathology (direct immunofluorescence (DIF), indirect immunofluorescence (IIF), and salt-split skin alone or in combination. Many of these patients had IgA deposition on the BMZ on DIF. (3) Availability of follow-up after the treatment. (4) Patients treated with RTX with or without adjuvant therapy.

Exclusion criteria were (1) Patients with MMP not treated with RTX. (2) Studies that included only ocular cicatricial pemphigoid (OCP) or ocular MMP. (3) Patients that did not have confirmatory immunopathological studies. (4) Patients that lacked follow up data.

The following information was obtained from each study, which produced the data base: demographics, age at onset, extent and severity of disease, serological data, treatment with conventional therapy, indications for use of RTX, serological studies whenever available (before during and after the RTX therapy), protocols for use of RTX, clinical outcomes, relapse, treatment of relapse, flow cytometry for $CD20^{+}$ B cells and adverse events.

Clinical outcome was recorded as complete remission off therapy (CR-OF), defined as no disease and the patient is not receiving any treatment. Clinical remission on therapy (CR-OT) was no sign of disease on treatment, partial remission (PR) was defined as incomplete recovery from disease (not getting new lesions), non-responders (NR) were patients who showed some response but there was still active disease and failures (F) showed no clinical response even after the treatment lasted longer than 6 months [25].

3. Results

Based on the inclusion and exclusion criteria there were a total of 124 patients with MMP treated with rituximab (RTX). These were described in 23 studies, 16 of which were case reports [11,26–40], six were case series and one was a case control study. (Table 1).

3.1. Demographics

The data base consisted of 59 (47.58%) males and 65 (52.41%) females. The mean age at onset of disease was 57 years (range 17–89). The mean duration of disease before initiating Rituximab was 38 months (range 3–180) in the case series and 15 months (range 2–30) in the case reports. Most of the patients in case reports had mucosal involvement of the ocular, oral cavity, pharynx, nasopharynx, larynx, trachea, bronchi, esophagus, conjunctiva,genitalia and skin [11,26–40]. Follow up for the entire cohort was 36 months (range 0.5–72). Mean duration of follow up was 33 months (range 22–72) for case series and case controlled studies. In case reports, the mean follow up was 19.5 months (range 0.5–48).

3.2. Treatment with conventional therapy before RTX

Treatment with conventional therapy before initiation of rituximab is presented in Table 2.

Most of these drugs were used as a combination of an anti-inflammatory drug with an immunosuppressive agent. In most patients when one drug was not effective, it was replaced by another drug.

3.3. RTX therapy: indications and protocols

Indication for rituximab in all studies included one or more of the following: (1) rapid progression of disease (12.09%) (2) disease non-responsive to conventional therapy (81.45%) and (3) serious adverse effects of conventional therapy (37.90%), warranting their discontinuation.

Out of 124 patients, 46 patients were treated by the Rheumatoid Arthritis (RA) protocol (1000 mg RTX on day 1 and day 14) [44,18,26,29,34,35,37,40,42,43], 51 were treated by the Lymphoma Protocol (LP) (375 mg/m2 for 4 weeks) [44,21,27,30–32,36,38,39,42]. 25 patients were treated by a modified LP protocol. 24 patients received 500 mg of RTX for four weeks and one patient received two doses of RTX consisting of 862.5 mg at two-week interval [3,37]. One patient received a modified lymphoma protocol (two doses of 375 mg at two-week interval) [28] and in one patient the RTX protocol was not mentioned [33].

3.4. Clinical outcome

In 24 (19.35%) patients RTX was used as monotherapy [21,26,27,29,39,40]. In 100 (80.64%) patients RTX was used in combination with either an immunosuppressive agent (ISA) or systemic corticosteroids (CS) [3,13,44,22,26,28,30–38,43,42]. In two of the patients, concomitant therapy was not mentioned. [13]. In one study of 25 patients, ISA were discontinued at the initiation of RTX but previous ongoing treatment with dapsone (1 mg/kg/day) or sulfasalazine (1-3 g/day) were continued in patients with tracheal and bronchial involvement until the lesions healed [21].

In this cohort of 124 patients, 64 patients (51.61%) achieved complete clinical remission off therapy, 25 patients (20.16%) achieved

Table 1
Data on protocol used and follow up in different categories of studies.

Studies	Protocol used (n = no of patients)	Follow up (months)	Relapse (n = no of patients)	Treatment of relapse/ no response
Case Reports	LP (***n* = 9**)	Mean 13 months	No relapse during reported follow up	-
N = 16	[27,28*,30–32,36, 38–39]	(range 0.5–36)		bortezomib[a]
	RA (***n* = 10**)	Mean 22 months	No relapse reported during follow up[a]	
	[45,29,34,35,37**,40]	(range 2–48)	One patient did not respond to RTX [41]	
	Not mentioned	Ref 11=5 months		
	(**n = 2**) [11,33]	Ref 33=36 months		
Case Series	LP (*n* = **53**)	Mean 38 months	20 patients (37.73%)	RTX
N = 6	[21,31,42]	(range 18–72)		[1]treatment of relpase not presented
	RA (*n* = **27**)	Mean 27 months	22 patients (81.48%)	RTX
	[22,26,43]	(range 22–30)		
Case Control	LP in 10 patients	Mean 28 months	10 patients (41.66%)	RTX
N = 1	RA in 14 patients	(range 6–71)		
	[44]			

* Modified LP (375 mg/m^2 at 2 week interval x 2.
** Modified RA (862.5 mg × 2),
[a] RTX failure, responded to bortezomib.

Table 2
Treatment with conventional therapy before RTX.

Treatment used	No of patients
Systemic corticosteroids	87 (70.16%)
Dapsone	68 (54.83%)
Cyclophosphamide	52 (41.93%)
Mycophenolate Mofetil	48 (38.70%)
Azathioprine	34 (27.41%)
Sulfasalazine	24 (19.35%)
IVIG	21 (16.93%)
Methotrexate	13 (10.48%)
Cyclosporine	8 (6.41%)
IV dexamethasone	6 (4.82%)
IV methylprednisolone	5 (4.03%)
Doxycycline	4 (3.22%)
Etanercept	3 (2.41%)
Infliximab	2 (1.61%)
Nicotinamide	1 (1.24%)
Chloramphenicol	1 (1.24%)

clinical remission on therapy, 21 patients (16.93%) were in partial remission, five patients (4.03%) were non-responders and nine (7.25%) were failures, based on clinical assessment and follow up provided by each individual author. Time to achieve complete remission was 5.71 months (range 1–18), partial remission 4.83 months (range 1–12), five showed no response and nine were failures even after a treatment duration of 11 months (range 6–24). In the analysis if MMP patients in this cohort, complete clinical remission was achieved in 75% of patients treated with the Lymphoma protocol and in 55% of patients treated with the Rheumatoid Arthritis protocol. This difference was statistically significant (*P* value = 0.02). thus lymphoma protocol had better outcome. Data on protocol used and treatment of relapse is presented in Fig. 1. There is a statistically significant difference in time to remission between both therapies (rituximab monotherapy vs combination therapy) ($p = 0.0415$). (Table 3).

4. Relapse

Out of 124 patients, 52(41.93%) patients experienced relapses during 36 months (range 0.5–72) of follow up. Duration between last infusion and relapse was 10.5 months (range 1–30).

One study showed relapses occurred in 10 of 24(41.66%) patients. These 10 patients had achieved disease control in 9.6 months. Nonetheless in 15.2 months after disease control a relapse occurred. Time for disease control after relapse was 10 months (range 2–25). 14 of these 24 patients were treated with rheumatoid arthritis protocol and 10 with lymphoma protocol [44].

In one study of six patients, treated with RA protocol, five patients (83.33%) relapsed. Time to relapse was 10 months after initiation of RTX. All five of them had ocular involvement and in addition two patients had oral cavity involvement [26].

In another study of 14 patients, treated with RA protocol, nine patients (64.28%) relapsed. Seven of these 14 patients had ocular involvement, 11 had oral involvement, four with laryngeal involvement and two had genital involvement as well. Time to relapse was 18 months from initiation of RTX [43]. Data on relapse is presented in fig. I. 72 patients were treated by the lymphoma protocol. After the first cycle 55 (76.38%) were in complete remission, seven (9.72%) were in partial remission, five (6.94%) were non responders and five (6.94%) were failures.

Relapse occurred in 27 (37.5%) patients who then received second cycle according to the LP protocol. 16 (59.25%) were in complete remission, six (22.22%) were in partial remission and five (18.51%) were non responders. Disease severity was limited and could be a factor in non responders.

51 patients were treated by RA protocol. 33 (64.70%) were in complete remission, 13 (25.49%) were in partial remission, four (7.84%) were failures and one was a non responder.

Amongst the patients treated with RA protocol, relapse occurred in 25 (49.01%) patients. After second cycle 16 (64%) were in complete remission and 9 (36%) were in partial remission. Third cycle was given to five patients, four patients (80%) went into complete remission and one patient (20%) was in partial remission. The patient in partial remission received 4th cycle but no follow up was provided.

After the first cycle the relapse rate in MMP patients treated by RA protocol was 49.01% and 37.5% in patients treated by LP protocol. Patients in relapse were given second cycle. In LP protocol patients, 16 of 27 (59.25%) were in complete remission and 16 of 25 (64%) patients were in complete remission treated by RA protocol. Further comparison could not be done because of limitation of data provided. A statistical comparison between the two protocols showed no statistical significance.

Limitation in follow up data provided only two comparisons. Results after first cycle showed that 55 of 72 (76.38%) patients were in complete remission in lymphoma protocol and 33 of 51 (64.70%) patients were in complete remission in rheumatoid arthritis protocol.

4.1. Treatment of relapse

A relapse of MMP was reported in 52 (41.93%) patients in this cohort, amongst these patients 19 had received RTX as monotherapy, 17 had received RTX with immunosuppressants and three were on immunosuppressants only at time of relapse. In 10 patients data regarding treatment of relapse was not provided [3]. In three patients no further treatment was given for their relapse [21,22].

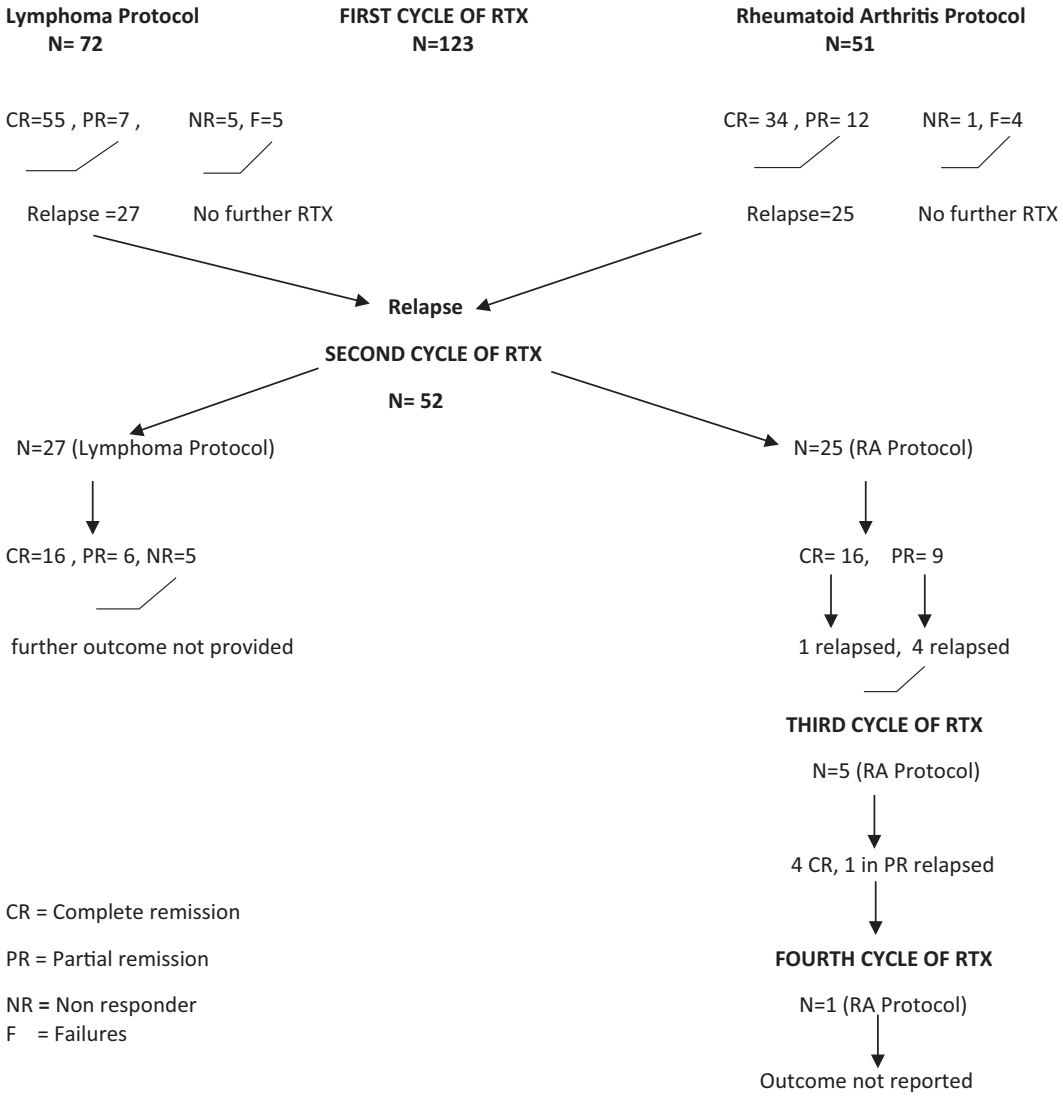

Fig. 1. Shematic diagram comparing clinical outcomes in mmp patients treated with lymphoma protocol compared to rheumatoid arthritis protocol.

Table 3
Statistical comparison of rituximab as monotherapy versus rituximab with combination therapy in MMP patients in complete response.

Type of therapy (number of patients)	Complete Remission	Partial Remission	No response	Failure	Time to response (Months)	95% Confidence Interval	P value
RTX monotherapy (24)	15	3	1	5	3.5 (range 2–5)	3.1433–3.7966	0.0415
RTX + Combination therapy (100)	74	17	5	4	4 (range 0.5–8)	3.6279–4.3720	

Out of those 39 patients on whom data for treatment of relapse was available, 36 patients received a second cycle of RTX [15,16,43,41,45], and the remaining three patients were treated with only immunosuppressants [43]. Amongst the 36 patients, who received a second dose of RTX, five patients (13.88%) were treated with a third cycle of RTX, and one patient received a fourth cycle of RTX.Authors did not provide the duration between each subsequent cycle in patients who received multiple cycles of RTX. 23 patients were in complete remission, seven patients were in partial remission and six patients had no response. Amongst the three patients who received immunosuppressants, two achieved partial remission and one was a non-responder. The cumulative data on treatment of relapses demonstrates that with repeated RTX infusions, 23 of 36 (63.8%) achieved complete remission, seven of 36 (19.44%) had partial remission and six of 39 (15.38%) were non responders.

5. B cell depletion and repopulation

There were five studies in which $CD20^{+}$ B cells correlation with

Table 4
B cells depletion versus repopulation at time of relapse.

Study (Reference No)	Percentage of patients in whom B cells were measured at time of relapse	B cells depleted at time of relapse	B cells detectable at time of relapse
[44]	60%	66%	33%
[26]	33%	50%	50%
[21]	40%	40%	60%
[22]	38%	data not provided	33%
[43]	64%	55%	44%

relapse was presented [44,21,22,26,43]. Table 4 demonstrates percentage of patients in whom CD20$^+$ B cells were reported and detected vs depleted. Correlations between B cell depletion and repopulation provided in 28 patients (22.6%). In 13 (46.42%) patients relapse occurred when B cell were repopulated. In 15(53.57%) patients relapse occurred when B cell were not detected in the peripheral blood.

6. Discussion

This analytical review describes a cohort of 124 MMP patients treated with RTX, due to failure of conventional therapy in producing a sustained clinical remission. A single cycle of RTX resulted in complete remission in 89 (71.77%) patients and partial remission in 20 (16.12%) patients in a mean time of 5.12 months (range 1–18). Six patients (4.82%) were non responders and nine (7.25%) were failures to RTX therapy. Additional cycles were given to patients in partial remission and patients who experienced relapse.

The clinical efficacy of RTX is likely attributable to CD20$^+$ B cell depletion and the cellular and molecular changes produced in the microenvironment. By modulating multiple autoimmune and inflammatory pathways and influencing T and B cells interactions, RTX may reduce production of pathogenic autoantibodies [46,47].

The data in this analysis demonstrated that a statistically significant higher rate of remission was reported in MMP patients treated with the LP protocol as compared to RA protocol. However the validity of this observation is uncertain, because disease severity and other important clinical features were not identical in the two groups. Notably, in Anca-associated Vasculitis (AAV), the LP and RA protocol appear to have similar outcomes [48]. Further studies comparing the two regimens are needed to ascertain their comparative effectiveness in MMP. Similarly, the higher efficacy of RTX monotherapy versus RTX combination therapy shown in this study is likely driven by differences in study populations and confounding by indication.

In this cohort, relapses occurred in 41.93% of the patients within 10.5 months after the last infusion of RTX. Relapses after RTX therapy are of significant concern in patients with autoimmune bullous diseases. Meta-analysis of pemphigus vulgaris (PV) patients treated with RTX reported relapse rates of 50% and higher [24]. In another analysis of treatment of PV patients with RTX, it has been demonstrated that the longer the follow up, the higher the relapse rate [49]. Indeed, relapse rate of 80–85% were observed in MMP patients treated with RTX with five year follow up. These patients received a single course of RTX and no subsequent maintenance therapy [21]. In comparison, relapse rates of patients on conventional immunosuppression has ranged from 30 to 40% [44]. It is important to note that B-cell depletion after rituximab lasts on average 6 months, which may account for a significant number of relapses after RTX in our study. Data from rheumatoid arthritis (RA) and ANCA-associated vasculitis (AAV) suggests that after B-cell reconstitution, the rate of relapse increases significantly [50,51]. Therefore, these conditions are frequently treated with maintenance doses of rituximab for persistence of B-cell depletion and to prevent relapses. Howevever it should be noted that the dose and frequency of RTX retreatment in these conditions varies widely from 500 mg every 6 months to 1000 mg two weeks apart every 4–6 months without clear differences in outcomes [52,53], although head to head comparisons of these regimens are limited.

The frequent lack of data on CD20$^+$ B cell counts at flare limit our understanding of incomplete remission and relapse after RTX. During a mean follow up of 36 months, 52 patients (41.93%) had relapses. Levels of CD20+ B cells were available on 28 patients only. Amongst these 28, relapse occurred in the absence of repopulation of B cells in 14 patients (50%) and in 14 patients(50%) it occurred after repopulation. RTX is effective in depleting 100% of CD 20+ B cells in the peripheral blood. However the level of B cell depletion is less in the lymph nodes, spleen and bone marrow [54]. Data from RA and AAV demonstrate that relapse with absence of peripheral B-cells can occur but the relapse rate increases after B-cell repopulation. For example, a study in AAV demonstrated that RTX retreatment at a fixed interval (500 mg every 6 months) was similarly effective to "tailored" retreatment based on B-cell repopulation and/or a rise in the ANCA titer in maintaining disease remission. While there were numerically more relapses with the tailored approach, there were numerically fewer serious infections and patients used 50% less RTX. These observations further emphasize the need for further studies to determine the best maintenance treatment strategy in MMP.

The mechanism by which some MMP patients do not respond to RTX is not known. He et al. observed that IgA secreting plasma cells were resistant to RTX [55]. Lambert et al. studied two patients with IgA dominant MMP observing that RTX depleted IgG bearing CD20$^+$ B cells while IgA plasma cells were unaffected [43]. Recently in a study in which a patient with MMP, nonresponsive to anti CD20$^+$ B cell depleting agents responded to bortezomib, suggested that cells of the immune system other than CD20$^+$ B cells can play a pivotal role in autoantibody production [41]. Moreover, patients can progress to scarring despite treatment with RTX. However, [56], the ability of RTX to arrest progression of scarring, depends on the mucosa involved and the degree of existing scarring and severity of disease present, prior to RTX therapy.

Our understanding of the safety of RTX in MMP is relatively limited. Maley et al. reported less adverse effects with RTX compared to immunosuppressive therapy. In one study from France, the addition of RTX to patients with MMP, already on high dose corticosteroids and immunosuppressive agents, resulted in an infection rate of 12% and mortality rate of 8%, attributed to the combination therapy [57]. Data from RA, where RTX is commonly used in combination with methotrexate, suggests that the rate of serious infections is approximately 4 per 100 patient years [58]. In addition, B-cell depletion has been linked to hypogammaglobulinemia, which may lead to an increased risk of infection [59,60]. Therefore, monitoring immunoglobulin levels during RTX therapy may help inform the risk-benefit ratio of re-treatment. The COVID pandemic has brought to light additional risks of RTX therapy. Treatment with B-cell depleting agents have been found to have an increased risk of COVID-related death across a variety of disease states [58]. Further compounding this risk are findings that patients receiving RTX have decreased immune response to COVID vaccination [61]. Strategies such as vaccination between RTX doses or with B-cell reconstitution and pre-exposure prophylaxis with tixagevimab/cilgavimab, particularly in patients with negative or low-titer COVID spike antibodies, may decrease the risk of RTX treatment [62]. When RTX is used in MMP patients, particularly with concomitant CS and ISA, careful monitoring for systemic infection and efforts to reduce this risk are warranted [63]. Additional adverse effects with RTX include late onset neutropenia, leukopenia, serum sickness and other allergic reactions.

While a randomized clinical trial would be required to fully understand the efficacy and safety of RTX in MMP, the rarity of the disease may make it challenging to recruit a sufficient number of patients. The goal of a clinical trial is to have similarities in at least some variables like length of follow up, protocol used and relapse data which will help in providing a better understanding of the time to achieve remission and relapses.

The data in this analysis has several significant limitations. There was a lack of uniformity in the assessment of disease, severity and reporting in the included studies. Most importantly, majority of the authors did not specifically define remission and partial remission. Similarly, features of disease relapse were not well defined with regard to scarring or new blister and erosion formation. Most patients had multiple mucosal involvement. There was a lack of information on whether all sites of involvement respond uniformly, or some responded sooner or more completely than others. Inconsistency in treatment protocols, lack of monitoring of therapy, significant absence of CD20$^+$ B cell studies and absence of autoantibody studies further limit our findings. The most significant limitation was the lack of long-term follow-up in some of the studies. An important or clinical limitation of the studies

used in the analysis is a lack of information on immediate and late onset adverse events, notably infections. Hence the full effect of RTX on the clinical course of MMP cannot be truly ascertained. Unique protocols that have a defined use of RTX, based on B cell biology have produced long term sustained clinical remission in MMP and PV patients [64–66], have been ignored and neither emulated or compared to LP or RA protocol.

In the future physicians who treat MMP patients with RTX, capturing and reporting full data on the clinical course,outcomes with long-term follow-up is critical to better understand the role of RTX and the most effective protocols. This is particularly important in patients with potentially trachea-bronchial involvement, which can occur after a significant time interval of other mucosal involvement. One of the major focus of this review is to highlight the fact that limited or incomplete data leaves many unanswered questions for both patients and physicians. Healthcare practices and policies vary enormously from one country to another and one continent to another. Groups that create guidelines should be aware of this fact and clearly define the audience they address and the patients whose treatment they advocate. The role and the need for maintenance RTX to prevent disease relapse requires further study. Nonetheless RTX is a significant addition to the armamentarium of the therapeutic agents that can be used to treat mucous membrane pemphigoid.

7. Conclusion

In this cohort of 124 patients with MMP the response to RTX was analyzed. 58% of patients were treated with Lymphoma protocol and 42% patients were treated with Rheumatoid Arthritis protocol. In a mean period of 5.71 months (range 1–18), 89 patients (71.77%) achieved clinical remission. 5 patients (4.03%) were non responders and 9 patients (7.25%) were failures. A comparison between Lymphoma protocol and RA protocol demonstrated a statistically better outcome with Lymphoma protocol. 52 patients (41.93%) relapsed in a follow up period of 36 months (range 0,5–72). An important limitation was the lack of data on immediate and late onset adverse effects. In conclusion rituximab appears to be a safe and effective treatment for MMP patients who fail conventional immunosuppressive therapy. Despite its beneficial outcome, relapses are common and may respond well to additional cycles. The unmet need is the lack of a specific RTX protocol to treat MMP and guidelines to monitor RTX therapy. Unless comprehensive all inclusive data is provided, treating MMP patients remains a tremendous burdensome challenge.

Take home message

Rituximab has been used to treat patients with mucous membrane pemphigoid using the LP and RA protocols. In spite of a limited follow up, 71.77% were in complete remission. 4% were non responders and 7% were failures. Relapse occurred in 42% patients. Results of LP were better than RA protocol.

A protocol that can give better clinical outcomes in MMP patients is needed. Careful evaluation of which mucosal site respond better needs to be studied.

Guidelines for management and monitoring therapy are required.

In patients non responsive to conventional therapy or who develop significant or catastrophic side effects to them, use of RTX is suggested.

Funding source

This study was supported in part, by an unrestricted educational grant from the Dysimmune Disease Foundation (DDF). The DDF was not involved in the conduct of the research or preparation of the manuscript. DDF has no role in study design, data collection, analysis or interpretation. DDF was not involved in writing the manuscript or in its submission.

Submission declaration

This manuscript is not under consideration for submission elsewhere. The manuscript is approved by all the authors.

If accepted this manuscript will not be published elsewhere in the same form.

Authorship

All the authors have made substantial contributions to the conception and design of the study, collection, analysis and interpretation of data and in the drafting, revisions and final approval of this manuscript.

Declaration of Competing Interest

All the authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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