Original Research Article

A prospective observational study on efficacy of serial low dose infusion of rituximab (500 mg) on patients of pemphigus

Santosh K. Singh, Prasoon Sachan*

Department of Skin, Venereology & Leprology, Baba Raghav Das Medical College, Gorakhpur, Uttar Pradesh, India

*Correspondence:
Dr. Prasoon Sachan,
E-mail: sachanprasoon12@hotmail.com

ABSTRACT

Background: Rituximab (RTX) is a chimeric anti-CD20 monoclonal antibody being increasingly used in management of pemphigus. Various studies show a lack of any uniform treatment protocol. The objective of the study was to assess the effectiveness of RTX in patients of pemphigus receiving serial low doses of RTX (500 mg; maximum of 4 doses; 2 weeks apart).

Methods: It was a prospective observational review of 40 pemphigus patients to assess the proportion of patients achieving complete remission after serially receiving low dose RTX, time and number of doses required to achieve complete remission (CR), proportion of patients who responded partially or didn't respond or relapsed after achieving CR. Additionally, the study was done to find whether a correlation existed between age, gender, and site of lesion and RTX administration.

Results: 40 pemphigus patients followed up for a mean duration (MD) of 174.15 ± 95.67 days received 4 doses of RTX (500 mg) irrespective of the disease activity 0.30 (75%) attained CR on therapy with ≥3 doses of RTX 500 mg (MD= 76.39 ± 34.45 days) and azathioprine 100 mg/day. No patients relapsed after 4 doses while 3 (7.5%) patients didn't respond. Oral lesions and pemphigus vulgaris took more time for achieving CR.

Conclusion: While we reinforce the idea of using more than 3 doses of RTX 500 mg in a view to achieve prolonged remission we promote considering usage of a more cost-effective drug like azathioprine for maintaining remission especially in a poor remote tertiary center in India with limited resources. Immunological assays were not performed limiting the study.

Keywords: Rituximab, Complete remission, Pemphigus, Mean duration, Low dose

INTRODUCTION

Pemphigus is a chronic, muco-cutaneous autoimmune blistering disorder; two main variants being pemphigus vulgaris (PV) and pemphigus foliaceus (PF). PV is the most common subtype, varying between 75 to 92% of total pemphigus patients.[1,2] It is caused due to autoantibodies directed against the cell surface proteins, desmogleins. Pemphigus was traditionally associated with high mortality and morbidity. However, advent of corticosteroids dramatically changed the outlook of this invariably fatal disease and reduced the mortality rate to <10%.[3] Another milestone in the therapeutics of pemphigus in India was the use of dexamethasone cyclophosphamide pulse (DCP) therapy by Pasricha et al.[4] Despite the benefits associated with DCP therapy, it cannot be denied that even DCP therapy with or without adjuvants can lead to numerous adverse events, which account for majority of deaths in pemphigus.[5] The next major development in pemphigus treatment was the use of rituximab (RTX) by Heizmann et al.[6] This serendipitous discovery dawned upon a new era in treatment of

pemphigus. RTX, a chimeric monoclonal antibody, selectively acts on the CD20 expressing B cells, which are known to secrete autoantibodies targeting the epidermal desmogleins. In the Indian scenario, RTX was first used by Kanwar and colleagues in 2010 and the promising findings were first published in 2012.[7] Recently, Joly et al have recommended the use of RTX as first-line treatment in treatment-naïve pemphigus patients.[8] Dose and frequency of RTX administration and outcome measures vary in different studies resulting in heterogeneity of the data generated. Apart from the two meta-analyses a retrospective analysis by Heelan et al, a systematic review by Amber et al and another prospective study by Joly et al other studies are a series of much smaller number of patients.[8-12]

In this study, we assessed clinical response in 40 pemphigus patients who received serial low doses of RTX 500 mg. Logistic difficulty of following up in time as well as poor compliance led to delay between two doses of RTX in some patients, despite being planned 14 days apart. The primary objective of this study was to assess the effectiveness of bio similar RTX in a cohort of 40 patients of pemphigus in terms of following primary outcome measures: number of doses and time to achieve partial or complete remission following serial infusions of low dose RTX treatment on therapy, optimum number of doses achieving maximum efficacy, proportion of patients who relapsed after achieving complete remission on therapy following treatment and those who didn't respond even after 4 doses of RTX. Moreover, side effects and complication following serial infusions were also noted.

METHODS

This was a prospective observational study done on 40 patients of pemphigus who presented to Department of Dermatology, BRD Medical College Gorakhpur from December 2018 to June 2020 and were diagnosed as having pemphigus clinically and histopathologically. Patients were administered biosimilars RTX and the study was not sponsored.

Inclusion criteria

Patients with recalcitrant pemphigus who had either failed to respond (i.e., developed fresh crops of new lesions or had extension of old lesions), or responded but with frequent recurrences, while on long-term high dose oral prednisolone (40–60 mg/day for 12 weeks), with or without additional immunosuppressive therapy; patients with recurrent relapse after dexamethasone-cyclophosphamide/ dexamethasone-azathioprine pulse therapy, (i.e., fresh crop of lesions or extension of old lesions) after completing 9 cycles of dexamethasone-cyclophosphamide or dexamethasone-azathioprine pulse therapy; contraindications to the use of conventional therapy; unwillingness to continue conventional therapies were included.

Exclusion criteria

Patients with active or latent tuberculosis; active or chronic hepatitis B, hepatitis C, coexistent pulmonary, renal, gastrointestinal and other disseminated infections, extensive wound infections, septicemia, pregnancy, lactation, cardiac disease (EF<60%) and history of bronchospasm, angioedema; human immunodeficiency virus infection were excluded.

The patient must fulfill at least one of the inclusion criterions and none of the exclusion criterion listed above to be eligible for the study.

Treatment protocol

The age of the patient, sex, duration of disease and a detailed history were recorded. The extent of skin/mucosal involvement was clinically assessed, baseline pemphigus activity score (PAS) was calculated and the diagnosis was confirmed clinically and histopathologically. Patients were admitted and started on intravenous broad-spectrum antibiotics, dexamethasone (2 ml 12 hourly which is gradually tapered over a week), pheniramine maleate (12 hourly), ranitidine (12 hourly) and topical steroid–antibiotic ointment over body lesions.

Patients were counseled for maintenance of oral hygiene (mouth gargles and topical steroid mouth paints) and their ocular hygiene was maintained in consultation with ophthalmology department. Meanwhile complete blood counts, liver function tests, renal function tests with serum electrolytes, chest X-ray, electrocardiography and 2-dimensional echocardiography (2-D Echo), Monteux test, viral markers were done before infusion. All routine blood investigations were repeated in each visit.

On the day of infusion after assessing general condition; patients were pre medicated with hydrocortisone (100 mg), pheniramine maleate (8 mg) intravenously, and paracetamol (500 mg) orally 30 minutes prior to infusion. Injection RTX (500 mg) in 500 ml of normal saline solution was infused over 4-5 hours and subsequent doses (until 4 doses) were planned 2 weeks apart. Infusion was started at the drop rate of 8 drops per minute which is gradually doubled after every half hour with drop rate not exceeding 90 drops per minute until infusion is complete. Vitals were monitored every 30 minutes for any signs of anaphylaxis or infusion related complication such as hypotension, nausea, headache, chills, fever and rashes.

Monitoring and follow up

The patients were sequentially evaluated after each infusion. To determine the response; we calculated the pemphigus activity severity (PAS) score published by Kumar et al. It was calculated pre-infusion, 2 weeks post fourth infusion, at 3 months and 6 months after fourth dose (Table 2).

Patients were followed up every fortnightly until 2 weeks post the fourth dose which is then followed up by monthly visits with routine investigations. Criterion for remission on therapy was defined as follows.[14]

Complete remission on therapy

It is defined as the absence of new or established lesions while the patient is receiving minimal therapy. Minimal therapy is defined as less than, or equal to, 10 mg/day of prednisone (or the equivalent) and/ or minimal adjuvant therapy for at least two months.

Partial remission on therapy

It is defined as the presence of transient new lesions that heal within one week while the patient is receiving minimal therapy, including topical steroids. All patients were prescribed low dose prednisolone (10 mg once a day) for 2-3 weeks and azathioprine 1-2 mg/kg/day after first infusion of RTX. Subsequently they were completely taken off the steroids and maintained on azathioprine 1-2 mg/kg/day with routine investigations. No patient was completely switched off azathioprine until this point of follow-up in our study.

Statistical analysis

Appropriate statistical tools like Microsoft excel were used for the analysis. Descriptive analyses were conducted to determine the distributions (means and proportions for continuous and categorical variables of interest, respectively, with corresponding standard deviations for means).

RESULTS

Patients

A total of 40 patients of pemphigus were studied [pemphigus vulgaris = 33, pemphigus foliaceus = 7]. Mean (±standard deviation) age of patients was 37.51±12.84 years. There were 16 males (40%) and 24 females (60%). The interval between two doses of RTX was 2 weeks. The patients were followed up for a mean duration of 174.15±95.67 days after administration of fourth dose of RTX (Table 1 and 2).

Outcome parameters after serial low doses RTX

Treatment

RTX 500 mg was administered at a serial interval of 2 weeks although logistic difficulty led to delay between two doses of RTX in some cases despite being planned 14 days apart.

Patients were followed up for a mean duration of 174.15±95.67 days after the fourth dose of RTX (Table 2).

Table 1: Basic demographic parameters (n=40).

Demographic data	N (%)
Gender	
Males	16 (40)
Females	24 (60)
Total number of PV	33 (82.5)
Total number of PF	7 (17.5)
Percentage of patients with comorbidities*	8 (20)
Percentage of patients without comorbidities	32 (80)
Percentage of patients with previous DCP/DAP pulse	29 (72.5)
Percentage of patients without any previous DCP/DAP pulse	11 (27.5)
Average pemphigus activity severity score pre-treatment	4.6
Average pemphigus activity severity score post-treatment	0.6

*Out of 8 patients with comorbidities 3 were anaemic and 1 each had Pott's spine, hypothyroidism, obsessive compulsive disorder and 1 patient was admitted in postpartum

Table 2: Basic outcome results with respect to pre-defined parameters.

Variables	Mean±SD
Mean time for achieving CR in pemphigus vulgaris patients' (days)	90.625±69.28
Mean time for achieving CR in pemphigus foliaceus patients' (days)	45±31
Mean age of males achieving complete remission (CR) on therapy (years)	39.28±12.50
Mean age of females achieving CR on therapy (years)	36.6±13.69
Mean duration between first dose and achieving CR on therapy in males (days)	88.28±48.34
Mean duration between of first dose and achieving CR on therapy in females (days)	85.6±42.63
Mean duration of follow-up (days) after 4th dose	174.15±95.67

SD: standard deviation; CR: complete remission.

Remission

Of 40 patients, 30 (75%) attained complete remission (CR) on therapy, 7 (17.5%) patients attained partial remission (PR) non therapy while 3 (7.5%) patients didn't show any appreciable change even after 4 serial infusions of low dose RTX. Mean interval between first dose RTX administration and complete remission achieved on minimal treatment (1-2 mg/kg/day azathioprine) was 76.39±34.45 days (Table 3 and 4).

Table 3: Relapse and remission with respect to site of lesions.

Relapse and remission features	After ≥4th dose N (%)	After 3rd dose N (%)	After 2nd dose N (%)	After >3rd dose N (%)
CR (oral and cutaneous)	30 (75)	12 (30)	1 (2.5)	30 (75)
CR (cutaneous)	10 (25)	20 (50)	0	30 (75)
CR (oral lesions)	10 (25)	6 (15)	3 (7.5)	16 (40)
Relapse	0	0	0	0
PR	7 (17.5)	0	0	0
PR of oral lesions	7 (12.5)	0	0	0
Persistence cutaneous lesions	2 (5)	0	0	0

Table 4: Follow-up.

Response	2 weeks after 4th dose (on azathioprine 1-2 mg/kg/day)	At 3 months (on azathioprine 1-2 mg/kg/day)	At 6 months (on azathioprine 1-2 mg/kg/day
CR	72.5	72.5	72.5
PR	20	20	20
NR	7.5	7.5	7.5

NR: Non-responders.

Relapse

Zero of 40 (0%) patients who had achieved complete remission on therapy relapsed after receiving 4 doses of RTX and being followed up for a mean duration of 174.15±95.67 (Table 3 and 4).

Correlation between clinic demographic parameters and outcome parameters

In addition to assessment of outcome measures described earlier, we tried to find if any correlation existed between selected clinical demographic parameters and outcome parameters as detailed earlier. No correlation was observed between gender and any of the outcome parameters. Mean age and duration of achieving remission was not significantly related in either of the sex (p value 0.6 and 0.9 respectively). None of the outcome parameters were found to correlate with total disease duration.

There was no significant association between type of pemphigus (pemphigus vulgaris or foliaceus) and proportion of patients achieving remission. Time taken to achieve remission was significantly longer in pemphigus vulgaris versus pemphigus foliaceus (p value 0.40, 95% confidence interval); in an individual with both oral and cutaneous lesions; oral lesions in general took more doses for remission than the cutaneous lesions as well as number of patients in whom oral lesions persisted were more than cutaneous lesions.

Complications or adverse events

Of 40 patients, one developed pruritic urticarial rash and one patient developed sepsis during first infusion that were managed adequately. No other long-term complications were noted except for one patient developing lichenoid eruptions 2-3 weeks after fourth dose of RTX. No deaths were observed during hospital admission in the 40 patients studied.

DISCUSSION

RTX is a chimeric monoclonal antibody, which acts against the cell surface CD20 antigen (a calcium channel in cell membrane) expressed on B cells. It acts by causing direct induction of apoptosis, complement-dependent cytotoxicity, and antibody-dependent cellular cyto-toxicity.[15,16]

RTX has been used in various protocols and in combination with other immuno-modulators in treatment of pemphigus. Currently, the two commonly used protocols in India are the lymphoma protocol and the rheumatoid arthritis protocol.[13,17-19] However, several studies have investigated lower dosage in immuno-bullous disorders like the high and low-dose RTX.[20] The high-dose regimen involved administration of 2 doses of 1000 mg of RTX 2 weeks apart. Whereas, in low-dose regimen, 2 doses of 500 mg RTX was administered 2 weeks apart. Horwath et al treated patients with pemphigus with a single course of 2 infusions of RTX (500 mg each) 2 weeks apart. 53.4% patients achieved CR in 5 weeks. 46.67% patients achieved PR in a median period of 34.5 weeks.[21] A study by Kanwar et al showed that while B-cell repopulation occurred earlier in 2×500 mg group by 8 weeks with improved outcomes in patients receiving high dose i.e. 2×1000 mg RTX. Gupta et al administered 2 doses of RTX (500 mg) 2 weeks apart. At 3 months, 82% and 18% patients showed CR and PR respectively. After 6-12 months, 38% were continuing to take low doses of steroids with or without other adjuvant immunosuppressant and 4% had to be given another 2 doses of RTX and subsequently could be managed with low-dose steroids. Of the 9 patients in partial remission at 3 months, after 6-12 months 4% had to be given 2 additional doses of RTX and were in partial remission with low-dose therapy at the end

of 12 months.[23] Cianchini et al treated 42 patients of pemphigus (37 PV, 5PF) with two doses of RTX, 86% achieved a CR and discontinued steroids within six months. 14.3% patients had CR off therapy with an additional infusion of RTX six months after initial treatment. 4.76% patients experienced relapse which was treated with RTX (500 mg) without corticosteroids, which induced a new CR.[24] A meta-analysis examined 578 patients' with pemphigus from 30 studies. 76% of patients achieved complete remission (CR) after 1 cycle of RTX. In the fully adjusted analysis, high-dose RTX (near or $\geq 2,000$ mg/cycle) was associated with longer duration of CR compared with low-dose RTX (<1,500 mg/cycle).[25] Kim et al concluded that three or more infusions of RTX are more effective than two infusions for the treatment of pemphigus with lesser relapse rate.[26] Chen et al concluded that in patients with moderate to severe PV, RTX plus short term prednisolone had a steroid sparing effect and more patients achieved complete remission off prednisone. Moreover, azathioprine with its efficacy shown in RITAZERM trials by Gopulani et al can be used as a cost-effective alternative in maintenance of remission.[28] Oral lesions of pemphigus show treatment refractoriness in comparison to cutaneous lesions.[29] Interestingly, Joly et al administered 500 mg RTX at 12 and 18 months irrespective of the disease activity when they noticed fall in desmogleins levels.[30]

n our study also a total of 40 pemphigus patients [pemphigus vulgaris= 33, pemphigus foliaceus= 7] received 4 doses of low dose RTX (500 mg) 2 weeks apart serially irrespective of the disease activity. Of 40 patients, 30 (75%) patients attained complete remission on therapy with three or more doses of RTX 500 mg while 7 (17.5%) responded partially on therapy and 3 (7.5%) did not respond at all. Mean interval between first dose RTX administration and complete remission achieved on minimal immunosuppressant (1-2 mg/kg/day azathioprine) was 76.39±34.45 days. 0 of 40 (0%) patients who had achieved complete remission after four doses of RTX relapsed during the follow up for a mean duration (MD) of 154.15±91.67 days after administration of fourth dose. There was no significant association between type of pemphigus (pemphigus vulgaris or foliaceus) and proportion of patients achieving remission. Time taken to achieve remission was significantly longer in pemphigus vulgaris versus pemphigus foliaceus (p value 0.40, 95% CI); in an individual with both oral and cutaneous lesions; oral lesions in general took more doses for remission than the cutaneous lesions as well as number of patients in whom oral lesions persisted were more than cutaneous lesions all of which were comparable to the studies referred above i.e. Gupta et al, Cianchini et al, Vinay et al, Joly et al.[3,23,29]

In addition to assessment of outcome measures described earlier, we tried to find if any correlation existed between selected clinic demographic parameters and outcome parameters as detailed earlier. No correlation was observed between gender and any of the outcome parameters as well as the type of pemphigus under evaluation.

CONCLUSION

RTX is able to induce a prolonged clinical remission in patients with both pemphigus vulgaris and pemphigus foliaceus. In our study 40 pemphigus patient's complete remission on therapy after two, three and four or more doses was observed in 1 (2.5%), 12 (30%) and 30 (75%) patients. In an individual with both oral and cutaneous lesions remission of cutaneous lesions after second, third and fourth dose was observed in 0 (0%), 20 (50%) and 10 (25%)patients with CR of cutaneous lesions in 30 (75%) patients after three or more doses of RTX while remission of oral lesions after second, third and fourth dose was observed in 3 (7.5%), 6 (15%) and 10 (25%) patients respectively i.e. in 16 (40%) patients remission in oral lesions was seen after three or more doses of RTX. Partial remission on therapy was observed in 7 (17.5%) patients i.e. persistence of oral and cutaneous lesions in 5 (12.5%) and 2 (5%) patients respectively even after four or more doses of RTX thus showing that in an individual with both oral and cutaneous lesions, oral lesions took more doses for remission than the cutaneous lesions. While we reinforce the idea of using more than 3 doses of RTX 500 mg in a view to achieve prolonged remission we promote considering usage of a more cost-effective drug like azathioprine for maintaining remission especially in a remote tertiary center in India with limited resources. However, optimum duration of usage of azathioprine keeping in mind of risk versus reward ratio especially in a remote tertiary setting in a developing country like India should be critically evaluated to balance socio-economic demographic inequalities.

REFERENCES

1. Kanwar AJ, Ajith AC, Narang T. Pemphigus in North India. J Cutan Med Surg. 2006;10:21-5.
2. Sehgal VN. Pemphigus in India. A note. Indian J Dermatol. 1972;18:5-7.
3. Lever WF, Schaumburg-Lever G. Immuno-suppressant's and prednisone in pemphigus vulgaris: Therapeutic results obtained in 63 patients between 1961 and 1975. Arch Dermatol. 1977;113:1236-41.
4. Pasricha JS, Gupta R. Pulse therapy with dexamethasone-cyclophosphamide in pemphigus.

Indian J Dermatol Venereol Leprol. 1984;50:199-203.

5. Bystryn JC, Steinman NM. The adjuvant therapy of pemphigus. An update. Arch Dermatol. 1996;132:203-12.

6. Heizmann M, Itin P, Wernli M, Borradori L, Bargetzi MJ. Successful treatment of paraneoplastic pemphigus in follicular NHL with rituximab: Report of a case and review of treatment for paraneoplastic pemphigus in NHL and CLL. Am J Hematol. 2001;66:142-4.

7. Kanwar AJ, Tsuruta D, Vinay K, Koga H, Ishii N, Dainichi T, et al. Efficacy and safety of rituximab treatment in Indian pemphigus patients. J Eur Acad Dermatol Venereol. 2013;271-7.

8. Joly P, Maho-Vaillant M, Prost-Squarcioni C, Hebert V, Houivet E, Calbo S, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): A prospective, multicentre, parallel-group, open-label randomised trial. Lancet. 2017;389:2031-40.

9. 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;95:928-32.

10. Ahmed AR, Shetty S. A comprehensive analysis of treatment outcomes in patients with pemphigus vulgaris treated with rituximab. Autoimmun Rev. 2015;14:323-31.

11. Heelan K, Al-Mohammedi F, Smith MJ, Knowles S, Lansang P, Walsh S, et al. Durable remission of pemphigus with a fixed-dose rituximab protocol. JAMA Dermatol. 2014;150:703-8.

12. Amber KT, M. Hertl M. An assessment of treatment history and its association with clinical outcomes and relapse in 155 pemphigus patients with response to a single cycle of rituximab. J European Academy Dermatol Venereol. 2014;29(4):777-82.

13. Kanwar AJ, Tsuruta D, Vinay K, Koga H, Ishii N, Dainichi T, et al. Efficacy and safety of rituximab treatment in Indian pemphigus patients. J Eur Acad Dermatol Venereol. 2013;27:1-7.

14. Dedee F. Murrell et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. J Am Acad Dermatol. 2008;58(6):1043-46.

15. Weiner GJ. Rituximab: Mechanism of action. Semin Hematol 2010;47:115-23.

16. Gupta V, Khaitan BK. Therapeutic potential of biosimilars in dermatology. Indian J Dermatol Venereol Leprol. 2015;81:451-6.

17. Sharma V, Bhari N, Gupta S, Sahni K, Khanna N, Ramam M, et al. Clinical efficacy of rituximab in the treatment of pemphigus: A retrospective study. Indian J Dermatol Venereol Leprol. 2016;82:389-94.

18. Londhe P, Khopkar U, Kalyanpad Y. Intermediate doses of rituximab used as adjuvant therapy in refractory pemphigus. Indian J Dermatol Venereol Leprol. 2014;80:300.

19. Khopkar US, Chadha AA, Nitya MS, Lahoria V. Follow-up data of rituximab as adjuvant therapy in pemphigus. Indian J Dermatol. 2017;62:671-3.

20. Ahmed AR, Shetty S. The emerging role of rituximab in autoimmune blistering diseases. Am J Clin Dermatol. 2015;16:167-77.

21. Horváth B, Huizinga J, Pas HH, Mulder AB, Jonkman MF. Low-dose rituximab is effective in pemphigus. Br J Dermatol. 2012;166:405-12.

22. Kanwar AJ, Vinay K, Sawatkar GU, et al. Clinical and immunological outcomes of high- and low-dose rituximab treatments in patients with pemphigus: a randomized, comparative, observer-blinded study. Br J Dermatol. 2014;170(6):1341-9.

23. Gupta J, Raval RC, Shah AN, Solanki RB, Patel DD, Shah KB, Badheka AD, Shah KB, Aggarwal NK, Ravishankar V. Indian J Dermatol Venereol Leprol. 2017;83(3):317-25.

24. Cianchini G, Lupi F, Masini C, Corona R, Puddu P, De Pità O. Therapy with rituximab for autoimmune pemphigus: Results from a single centre observational study on 42 cases with long-term follow-up. J Am Acad Dermatol. 2012;67(4):617-22.

25. 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;95:928-32.

26. Kim JH, Kim YH, Kim MR, Kim SC. Clinical efficacy of different doses of rituximab in the treatment of pemphigus: a retrospective study of 27 patients. Br J Dermatol. 2011;165(3):646-51.

27. Chen DM, Odueyungbo A, Csinady E, et al. Rituximab is an effective treatment in patients with pemphigus vulgaris and demonstrates a steroid-sparing effect. Br J Dermatol. 2020;182(5):1111-19.

28. Gopaluni S, Smith RM, Lewin M, et al. Rituximab versus azathioprine as therapy for maintenance of remission for anti-neutrophil cytoplasm antibody-associated vasculitis (RITAZAREM): study protocol for a randomized controlled trial. Trials. 2017;18(1):112.

29. Vinay K, Kanwar AJ, Mittal A, Dogra S, Minz RW, Hashimoto T. Intralesional rituximab in the treatment of refractory oral pemphigus vulgaris. JAMA Dermatol. 2015;151:878-82.

30. Joly P, Maho-Vaillant M, Prost-Squarcioni C, Hebert V, Houivet E, Calbo S, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): A prospective, multicentre, parallel-group, open-label randomised trial. Lancet. 2017;389:2031-40.