

Original Research Article

A prospective observational study on efficacy of modified rheumatoid arthritis protocol of rituximab (2000 mg) on patients of pemphigus

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ABSTRACT

Background: Rituximab (RTX), an anticluster of differentiation 20 antibody, targets B lymphocytes, has been shown in open series studies to be effective in treating pemphigus. The objective was to evaluate whether a modified rheumatoid arthritis protocol, in which the patient received four doses of 500 mg of rituximab at an interval of two weeks was safe and effective in pemphigus management.

Methods: It was a prospective observational study in which 46 pemphigus patients included and four doses of 500 mg of RTX at an interval of two weeks given and number of doses required for complete remission (CR), proportion of patient respond partially or doesn't respond or relapsed after CR.

Results: We enrolled 46 patients in the study, 8 with pemphigus foliaceus (PF) and 38 with pemphigus vulgaris (PV). 20 were male and 26 were female followed up for 15±4.24 months (12-18). All patient responded to therapy. CR of 23 patient after 2 dose OF 500 mg RTX ,of 18 patient after 3 dose, 5 patient partial remission (PR) after 4 doses. All patient were on 100 mg OD azathioprine. PR, all have oral lesions got CR after 3 weeks of 4th dose. 3 patients relapsed MD 11±2.8 months (9-13 months) and given additional dose of 500 mg RTX and got resolved in 3 weeks.

Conclusions: We found modified rheumatic arthritis protocol for RTX was shown to be effective in treatment of pemphigus patient and relapse cases with additional dose. Immunological assay were not performed to limit the study.

Keywords: Pemphigus, Rituximab, B lymphocyte, Complete remission

INTRODUCTION

Pemphigus stems from the Greek pemphix, which means blister, is group of chronic blistering epithelial diseases in which the production of IgG autoantibodies against extracellular domains of cell membrane proteins of keratinocytes results in acantholysis (the loss of cell-cell adhesion between keratinocytes).¹ In pemphigus, IgG autoantibodies are characteristically directed against desmoglein 1 and 3, which are part of the cadherin family that are found in desmosomes, which are the structures primarily responsible for maintaining intercellular adhesion in stratified squamous epithelia such as the skin and oral mucosa, two main variants being PV and PF.²⁻⁴

Initially pemphigus has high mortality but with advent of corticosteroid the mortality rate reduced to <10%.⁴ Another milestone in the therapeutics of pemphigus in India was the use of dexamethasone cyclophosphamide pulse (DCP) therapy by Pasricha et al.⁵ The next development in pemphigus treatment was the use of RTX by Heizmann et al.⁶ RTX is a murine human chimeric monoclonal antibody targeted against CD20. It acts by destruction of autoreactive B cells, its effect lasting six to nine months. Sustained remission after repopulation of B cells has been documented.⁷ This study aimed to assess the effectiveness of RTX and confirm the effectiveness of the modified rheumatoid arthritis protocol in patients with pemphigus.

METHODS

We had performed this study in dermatology department of B. R. D medical college, Gorakhpur. This was a prospective observational study. In this we had included 46 patient of pemphigus who attended OPD. We performed this study from July 2019 to January 2021 and were diagnosed as having pemphigus clinically and histopathologically. Patients were administered RTX and the study was not sponsored.

Inclusion criteria

Confirmed diagnosis of pemphigus based on the presence of clinical and histological features of acantholysis via skin or mucosal biopsy, patients with included refractory disease, pemphigus disease area index (PDAI) >15, patients with steroid dependence, patients with contraindication to use of conventional therapy, patients with severe disease with unwillingness for conventional therapies were included in the study.⁸

Exclusion criteria

History of a severe allergic or anaphylactic reaction to humanized or murine monoclonal antibodies or known hypersensitivity to any component of rituximab, patients with lack of peripheral venous access, pregnant or lactating, or intending to become pregnant during the study, patients with known active infection of any kind, latent tuberculosis, active or chronic hepatitis B, hepatitis C, coexistent pulmonary, renal, gastrointestinal and other disseminated infections, extensive wound infections, septicemia, history of alcohol or drug abuse recently, history of live or attenuated vaccine within 28 days and history of or current cancer including solid tumors, hematologic malignancies and carcinoma *in situ*.

The patient fulfilling at least one of the inclusion criterions and none of the exclusion criterion listed above were eligible for the study.

Method and management 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 PDAI was calculated and the diagnosis was confirmed clinically and histopathologically. Baseline investigation like complete hemogram, liver function tests, renal function tests, chest X-ray, Mantoux test, HRCT chest (when indicated), screening test for HBsAg, anti-HBc, anti-HCV, HIV 1 and 2, ECG and dine. The patient was premedicated with injection hydrocortisone 100 mg IV stat, injection pheniramine maleate 22.75 mg IV stat, tablet paracetamol 500 mg PO, 30 min prior to RTX infusion.

RTX was administered using a modification of the rheumatoid protocol consisting of 500 mg of RTX in 500

ml of normal saline 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 was gradually doubled after every half hour with drop rate not exceeding 90 drops per minute until infusion was 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. Patient were kept on azathioprine (2 mg/kg body weight).

The patients were sequentially evaluated after each infusion. To determine the response we calculated the score PDAI.⁸ It was calculated pre-infusion, 2 weeks post infusion, at every subsequent visit after fourth dose.

Complete remission was called when PDAI=0.

Partial remission was called when there was decrease in PDAI score but not reached to zero.

All patients were prescribed 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.

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

Total 46 patients were enrolled in the study 26 (56.5%) female and 20 (43.4%) male from July 2019 to February 2020 and followed up to February 2021. Mean (\pm standard deviation) age of patients was 39.5 \pm 15.5 years. The patients were followed up for a mean duration of 15 \pm 4.2 months after administration of fourth dose of RTX. Various demographic data is in Table 1.

Review of patients with pemphigus treated with RTX showed that 100% of PV patient responded to therapy with 86.84% having CR. Success rates were even better with PF with 100% responding to therapy and 100% having CR (Table 2).

Follow up and relapse

All the 46 patients were followed up for mean duration 15 \pm 4.2 months. All were kept on azathioprine (1-2 mg/kg weight) and mean PDAI score decreased from 80 to 1.46 in 10 weeks. Gradually PR patient moved to CR in 4 to 8 weeks they all had oral lesion (Table 3). After RTX, CR was attained within 5-9 weeks with a mean time of 7 weeks. Seven patients attained CR after two dose, another

15 after 3 dose and after 4th dose 19 patients got CR. Remaining five (four women and one man) patients got PR and all have oral lesion. After one months of follow up all PR patient got CR. Remission period ranged from 12-18 months, the mean duration of remission was 15 months. This variation probably reflected the difference in the follow up period for each patient. Out of 46 patients in the study, 43 were in CR till the end of the study period. Three (6.52%) patients relapsed during the study period two at nine months, one patient at 13 months after RTX and they were given additional dose of 500 mg

of RTX and kept on azathioprine and got CR after 4 weeks (Table 3).

No life threatening immediate adverse effects were noted in any patient. However, 4 patients developed bradycardia and hypotension and 5 patient developed shivering initially during the infusion, which was successfully managed by decreasing the infusion rate. 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 46 patients studied.

Table 1: Basic demographic parameters (N=46).

Demographic data	N (%)
Gender	
Male	20 (43.48)
Female	26 (56.52)
Total number of PV	38 (82.6)
Total number of PF	8 (17.39)
Percentage of patients with comorbidities	9 (19.57)
Percentage of patients without comorbidities	37 (80.43)
Average PDAI pre-treatment	80
Average PDAI post-treatment	1.46

Table 2: Comparison of remission in pemphigus vulgaris and pemphigus foliaceus.

Pemphigus	CR (%)	PR (%)	Total
Vulgaris	33 (86.84)	5 (13.84)	38
Foliaceus	8 (100)	0	8
Total	41 (89.13)	5 (10.87)	46

Table 3: Follow up.

Responses	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)	Between 9 to 18 months (on azathioprine 1-2 mg/kg/day)
CR	89.13	100	100	0
PR	10.87	0	0	0
NR	0	0	0	0
Relapse	0	0	0	3

DISCUSSION

Pemphigus is a chronic autoimmune blistering disease with antibodies against desmoglein antigens produced by autoreactive B cells. RTX binds to the CD20 cell surface receptor of B cells and destroys them.⁷ RTX is now being used as an adjuvant to pemphigus refractory to conventional treatment and also as a first line therapy. In our study, we had evaluated the effectiveness of RTX in both refractory and naïve patients.

There was a female predominance in our study. Studies by Singh et al and Sehgal have shown a male

preponderance.^{9,10} Mascarenhas et al and Kanwar et al had female predominance, while Kanwar et al in another study found no sex preponderance in pemphigus.¹¹⁻¹³

RTX had 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.¹⁴⁻¹⁷ However, several studies have investigated lower dosage in immunobullous disorders like the high and low-dose RTX.¹⁸ 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.¹⁹ 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, that is, 2×1000 mg RTX.²⁰ 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.²¹ Cianchini et al treated 42 patients of pemphigus (37 PV, 5 PF) 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.²² A meta-analysis examined 578 patients' with pemphigus from 30 studies. 76% of patients achieved 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).²³ Kim et al concluded that three or more infusions of RTX were more effective than two infusions for the treatment of pemphigus with lesser relapse rate.²⁴ 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 CR off prednisone.²⁵ 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.²⁶ Oral lesions of pemphigus show treatment refractoriness in comparison to cutaneous lesions.²⁷ 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.²⁸

In our study also a total of 46 pemphigus patients (PV=38, PF=8) received 4 doses of RTX (500 mg) 2 weeks apart serially irrespective of the disease activity. Of 46, 41 (89.13%) patients attained complete remission on therapy with three or more doses of RTX 500 mg while 5 (10.87%) responded partially on therapy. Mean interval between first dose RTX administration and CR achieved on minimal immunosuppressant (1-2 mg/kg/day azathioprine) was 5±2 weeks. Three of 46 (6.52%) patients who had achieved CR after four doses of RTX relapsed during the follow up for a mean duration (MD) of 11±2.8 months after administration of fourth dose. There was no significant association between type of pemphigus (PV or PF) and proportion of patients

achieving remission. Time taken to achieve remission was significantly longer in PV versus PF ($p=0.0006$, 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, Gupta et al, Cianchini et al, Vinay et al and Joly et al.^{4,21,27,28}

CONCLUSION

RTX is able to induce a prolonged clinical remission in patients with both pemphigus vulgaris and pemphigus foliaceus. In our study also a total of 46 pemphigus patients [pemphigus vulgaris=38, pemphigus foliaceus=8] received 4 doses of RTX (500 mg) 2 weeks apart serially irrespective of the disease activity. Of 46, 41 (89.13%) patients attained complete remission on therapy with three or more doses of RTX 500 mg while 5 (10.87%) responded partially on therapy. 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.

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