Original Research

LOW-DOSE VERSUS STANDARD-DOSE RITUXIMAB IN VESICULOBULLOUS DISORDERS: A COMPARATIVE EFFECTIVENESS STUDY

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ABSTRACT

Background: Autoimmune vesiculobullous disorders are chronic, relapsing illnesses that are associated with significant morbidity due to prolonged corticosteroid use. Rituximab is an important steroid-sparing drug, the optimal dose of which is still poorly understood, particularly in resource-limited areas.

Method: A retrospective comparative effectiveness study was conducted to assess low dose (LD) versus standard dose (SD) rituximab in patients with moderate to severe autoimmune vesiculobullous conditions. Low dose (LD) versus standard dose (SD) rituximab was evaluated in a retrospective comparative effectiveness study for moderate to severe autoimmune vesiculobullous disorders. A total of 72 patients were analyzed, 36 of which were treated with low dose rituximab (500 mg on days 1 and 15) and 36 were treated with standard dose rituximab (1000 mg on days 1 and 15). Primary outcomes were the proportion of patients achieving disease control at week 8 and complete remission after minimal therapy at 12 months. Secondary outcomes were time to disease control, cumulative prednisolone dosage, relapse, adverse events and direct drug cost.

Results: The results showed that 30 (83.3%) of the 36 patients in the low-dose group and 33 (91.7%) of the 36 patients in the standard-dose group achieved disease control by week 8 (p=0.47). The two groups had rates of 66.7% and 75.0% complete remission at minimal therapy at 12 months, respectively, with no significant difference (p=0.44).

Conclusions: The standard dose rituximab resulted in slightly more rapid disease control, whereas the low dose dose resulted in a 50.0% decrease in direct cost of rituximab and had fewer infusion reactions. There was no significant difference in relapse rates. In some vesiculobullous disorders, low-dose rituximab could prove effective, safer and more cost-effective, but there is a need for individual risk assessment and longer follow-up.

Keywords: Rituximab, Pemphigus, Bullous Pemphigoid, Vesiculobullous Disorders, Low Dose, Comparative Effectiveness, Corticosteroid Sparing.

INTRODUCTION

Pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid and mucous membrane pemphigoid are examples of autoimmune vesiculobullous disorders. The disorders are marked by the presence of pathogenic autoantibodies that target epithelial adhesion molecules which cause intraepidermal or subepidermal blistering with mucosal erosions, secondary infections, and functional impairment [1]. Prior to the emergence of targeted therapy, systemic corticosteroids and conventional immunosuppressants have been the primary therapies; however, steroid toxicity has been a significant hurdle for effective long-term treatment.

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Rituximab is a chimeric anti-CD20 monoclonal antibody that targets B lymphocytes and decreases production of pathogenic autoantibodies. Evidence has been randomized and controlled and is now established for the value of rituximab in pemphigus, especially in association with short-course corticosteroids [2,3,4]. Currently, international guidelines recommend using rituximab as a first line/early treatment in moderate to severe pemphigus and its use in pemphigoid disorders is growing for refractory cases [5,6].

Although effective, rituximab is known to provoke infusion reactions, hypogammaglobulinemia and infections, as well as high direct costs [7]. The standard rheumatoid arthritis dose of 1000 mg on days 1 and 15 has been widely adopted and lower doses (500 mg on days 1 and 15) have been studied in Pemphigus and other auto-immune blistering disorders [8,9]. There is ongoing worry that lower B-cell depletion will lead to poorer durability of remission in the setting of low dose treatment, which is appealing because of the cost implications of adherence.

There is still limited evidence comparing low dose rituximab to standard dose rituximab in the real world, in the context of vesiculobullous practice. The majority of studies report only on pemphigus, ignore mixed diagnostic groups or do not report on safety and cost. In the present study, we attempted to compare the therapeutic efficacy, safety and cost benefits of low dose and standard dose rituximab in autoimmune vesiculobullous disorders treated in a tertiary dermatology unit.

MATERIALS AND METHODS

The study was retrospective, observational and comparative in the dermatology department of a tertiary care teaching hospital. The time period from January 2021 to December 2025 was used, and case records of patients treated during this time were reviewed. The study included adults (age at enrollment ≥18 years) with autoimmune vesiculobullous disease supported by both the clinic and laboratory findings, who had been treated with rituximab and followed for at least 12 months. Patients with incomplete documentation, active tuberculosis, uncontrolled chronic infection, rituximab treatment within 12 months, cancer, pregnancy and follow-up duration of < 12 months were excluded.

Patients were classified based on the type of rituximab induction schedule. This low dose arm received two doses of 500 mg rituximab 2 weeks apart. The standard-dose group was given two infusions of 1000 mg rituximab, 2 weeks apart. All infusions were given following the institutional protocol with premedication of paracetamol, antihistamine and intravenous corticosteroid. Concomitant prednisolone was started or continued and tapered according to disease activity. Adjuvant use of azathioprine, mycophenolate mofetil or doxycycline-nicotinamide was permitted, if clinically indicated.

Information retrieved was age, sex, diagnosis, presence of mucosal involvement, disease duration, baseline severity category, baseline prednisolone dose, comorbidities, prior exposure to immunosuppressants, rituximab dose, time to disease control, prednisolone dose within 12 months, relapse, infusion reaction, infections, and hospitalization and direct drug acquisition cost. The severity of pemphigus was evaluated by clinical extent and mucosal involvement recorded in the medical history and the severity of pemphigoid was evaluated by the number of active lesions, mucosal involvement and functional limitation.

The main outcomes of the study were disease control at week 8 and complete remission on minimal therapy at 12 months. Disease control was considered to be when new lesions were not occurring and there was initial healing of existing lesions. On minimal therapy, complete remission was considered to be the absence of new or established lesions during the treatment with prednisolone <=10 mg/day or equivalent therapy. Recurrence was considered to be three or more new lesions not resolved within 1 week in a month, extension of existing lesions, or escalation of treatment.

SPSS version 26 was used for analysis of data. All quantitative data were presented as mean ± standard deviation or median with interquartile range as appropriate. Frequency and percentage were used to represent categorical variables. Appropriate statistical analyses were performed, including the Independent t test, Mann-Whitney U test, chi-square test and Fisher exact test. Because of the retrospective design and small sample size, planned comparisons will be made using time to disease control (Kaplan-Meier). P values <0.05 were deemed to be statistically significant.

RESULTS

Eventy-two patients met the eligibility criteria. The low-dose and standard-dose groups each included 36 patients. The two groups were comparable with respect to age, sex distribution, diagnostic spectrum, mucosal involvement, baseline disease severity, diabetes and prior immunosuppressant exposure. Pemphigus vulgaris was the commonest diagnosis, followed by bullous pemphigoid and pemphigus foliaceus.

Disease control by week 8 was achieved in 30 patients (83.3%) receiving low-dose rituximab and 33 patients (91.7%) receiving standard-dose rituximab (p=0.47). Median time to disease control was 31 days in the low-dose group and 24 days in the standard-dose group. Complete remission on minimal therapy at 12 months was achieved in 24 patients (66.7%) and 27 patients (75.0%), respectively. The difference did not reach statistical significance. Standard-dose therapy was associated with a numerically lower 12-month relapse rate, but relapse was not statistically different.

Cumulative prednisolone exposure during 12 months was slightly lower in the standard-dose group, although the difference was modest. Infusion reactions, minor infections and hospitalization were numerically less frequent with low-dose therapy. No treatment-related mortality occurred. Direct rituximab drug cost was reduced by approximately one half in the low-dose group.

Table 1. Baseline Demographic and Disease Characteristics

Variable	Low-Dose Rituximab (N=36)	Standard-Dose Rituximab (N=36)	P-Value
Age (Years)	44.8 +/- 13.6	46.1 +/- 12.9	0.68
Male/Female	19/17	18/18	0.81
Pemphigus Vulgaris	23 (63.9%)	24 (66.7%)	0.80
Pemphigus Foliaceus	5 (13.9%)	4 (11.1%)	0.72
Bullous Pemphigoid / MMP	8 (22.2%)	8 (22.2%)	1.00
Mucosal Involvement	24 (66.7%)	26 (72.2%)	0.61
Moderate-To-Severe Disease	29 (80.6%)	31 (86.1%)	0.53
Baseline Prednisolone (Mg/Day)	38.5 +/- 13.2	40.1 +/- 12.7	0.60

Values are mean +/- SD or number (%). MMP = mucous membrane pemphigoid.

Table 2. Comparative Therapeutic Outcomes

Outcome	Low-Dose Group	Standard-Dose Group	P-Value
Disease Control By Week 8	30 (83.3%)	33 (91.7%)	0.47
Time To Disease Control (Days)	31 (21-46)	24 (18-36)	0.041
Complete Remission On Minimal Therapy At 12 Months	24 (66.7%)	27 (75.0%)	0.44
Relapse By 12 Months	7 (19.4%)	5 (13.9%)	0.53
Cumulative Prednisolone Dose (G)	5.8 +/- 1.9	5.2 +/- 1.7	0.16
Need For Additional Immunosuppressant	12 (33.3%)	9 (25.0%)	0.44

Time to disease control is shown as median (interquartile range).

Table 3. Safety and Economic Outcomes

Outcome	Low-Dose Group	Standard-Dose Group	P-Value
Any Infusion Reaction	3 (8.3%)	7 (19.4%)	0.17
Minor Infection	5 (13.9%)	8 (22.2%)	0.36
Serious Infection Requiring Admission	1 (2.8%)	3 (8.3%)	0.61
Transient Leukopenia	1 (2.8%)	4 (11.1%)	0.36
Treatment Discontinuation	1 (2.8%)	2 (5.6%)	1.00
Mean Rituximab Dose Per Cycle	1000 Mg	2000 Mg	-
Relative Direct Drug Cost	50.0%	100.0%	-

Cost calculation included only rituximab acquisition cost and not hospitalization, investigations or indirect expenditure.

DISCUSSION

In this study, the 12-month effectiveness of low-dose and standard-dose rituximab was similar in autoimmune vesiculobullous disorders, with the standard-dose group achieving quicker disease control. The number of patients with disease control was higher by week 8 and the number of patients with complete remission on minimal therapy tended to be higher in the standard-dose group, but the differences were not statistically significant. The results of this study agree with the emerging data that lower exposure to rituximab might be adequate in certain pemphigus patients, especially when the initial B-cell count is less than that seen in lymphoproliferative diseases [10,11].

The introduction of rituximab has changed the scenario of pemphigus treatment, allowing to decrease the need to use high doses of cortisone for an extended period. The Ritux 3 trial showed superiority of rituximab plus short-term prednisone over prednisone alone, and a later randomized trial showed superiority over mycophenolate mofetil for sustained complete remission in pemphigus vulgaris [3,4]. Our results do not contradict the accepted

efficacy of rituximab; indeed, they offer the clinical need of a consideration for dosing in the real world. This small difference in time to disease control is biologically plausible since exposures at lower doses might result in less rapid and complete B-cell depletion. In more extensive mucosal disease, or severe pemphigus where rapid steroid taper is an absolute requirement, the standard regimen should be considered [5]. The low-dose regimen proved to be effective at achieving disease control in over 80% of patients by week 8 and complete remission on minimal therapy in two thirds by 1 year. This indicates that low-dose therapy might be appropriate for cost-limited patients, moderate disease, early disease or patients with elevated risk of infection.

Safety signals indicated that low doses of rituximab were preferred, but the study was not designed to identify rare severe side effects. There was a numerically increased incidence of infusion reactions and infections in the standard dosing group. With the increasing implementation of rituximab in dermatology, careful consideration must be given to the balance between disease control and immunosuppression, particularly in individuals with diabetes, recurrent infections, advanced age or limited vaccination status [12,13].

The economic impact was significant: direct rituximab drug cost was cut by half when using low doses of induction. Cost may be a deciding factor for patients in resource-limited environments whether or not they are offered rituximab. A less expensive treatment regimen that can sustain good efficacy can help to minimize the need for corticosteroid dependence and enhance access. However, it is important to note that the low dose should not always be viewed as being equal because the inability to capture relapse prevention, repeated cycles and long-term B-cell recovery does not mean it is.

The limitations of this study include retrospective design, non-random treatment allocation, modest sample size and mixed diagnostic categories. Not all laboratories had immunofluorescence titers and CD19/CD20 B-cell counts. The follow-up period was limited to 12-months and indirect costs were not assessed. Stratification with regard to diagnosis, baseline severity, degree of mucosal involvement, autoantibody titres and B-cell kinetics would be appropriate for larger prospective studies to identify patients best suited to dose-reduced rituximab [14,15].

CONCLUSION

In selected patients with autoimmune vesiculobullous disorders, low dose rituximab was found to have similar rates of remission and relapse at 12 months compared to standard dose rituximab and fewer direct drug costs, and numerically fewer adverse events. Standard doses of therapy were effective in controlling the disease faster and may continue to be recommended in severe and high-risk disease. Dosage must be tailored to the severity of disease, comorbidities, risk of infection and affordability.

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