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Comparing Clinical Outcomes of Steroid-Sparing Therapy With Rituximab Versus Rituximab Alone in Pemphigus

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ABSTRACT

Background: Previous clinical trials have demonstrated that rituximab therapy combined with conventional steroid-sparing therapy (SST) has increased rates of disease control for mucous membrane pemphigoid compared with rituximab alone. However, limited data is available regarding the role of SST with rituximab therapy in pemphigus.

Objective: This study aimed to examine clinical outcomes in pemphigus patients treated with rituximab with SST versus without the addition of SST.

Methods: A retrospective chart review was performed for adult pemphigus patients in the Southeastern US at Emory between January 1, 2011, and December 31, 2021. Primary outcomes, including time to remission, time to prednisone dose of 10 mg or less, time to cessation of prednisone therapy, and time to relapse after a rituximab cycle, were compared between patients on SST and patients without SST.

Results: Following rituximab therapy, there was no difference in time to remission, time to prednisone dose of 10 mg or less, time to cessation of prednisone therapy, or time to relapse for patients with or without SST.

Limitations: Our study is limited by its retrospective decline, setting at a single academic center, and inclusion of a high proportion of patients with moderate disease.

Conclusions: The use of SST with rituximab dosing did not improve clinical outcomes related to time to remission, reduction in prednisone dosing, or relapse. These data provide further evidence for the use of rituximab in the majority of pemphigus patients without the need for SST.

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INTRODUCTION

Pemphigus is a rare autoimmune blistering disease that is associated with significant morbidity and mortality. Rituximab demonstrated superiority over oral steroid monotherapy and steroid-sparing agent mycophenolate in prior clinical trials and is FDA-approved as first-line therapy for pemphigus.[1,2] Despite improved efficacy, rates of relapse remain high with estimates of 40-50%.[3] While the use of rituximab therapy with conventional steroid-sparing therapy (SST) in patients with mucous membrane pemphigoid showed improved disease control, limited data are available regarding the role of SST as an adjunct to rituximab therapy in pemphigus.[4] A small retrospective study demonstrated decreased relapse rates when severe pemphigus patients were maintained on low-dose SST following rituximab.[5] However, it is unclear whether SST following rituximab offers better outcomes for non-severe pemphigus patients, particularly given the added risk of adverse effects such as infection. Here, we examined a larger, more diverse cohort of pemphigus patients to determine the difference in clinical outcomes including time to remission, relapse, tapering to minimal therapy of prednisone, and adverse events for patients on or off SST at the time of rituximab dosing.

MATERIALS AND METHODS

A retrospective analysis was performed for adult pemphigus patients treated with rituximab at the Emory Clinic between October 2011 and December 2021. Patients included in the analysis had clinically, histologically, and/or serologically confirmed pemphigus. Pemphigus Disease Area Index (PDAI) scores and endpoints were determined by the same provider (RJF) at the time of the visit. Remission (including partial and complete remission) and relapse (3 or more new lesions a month without resolution within one week) were defined by consensus statement.[6] Data are presented as mean (SD) and differences in observed variables were assessed using one-way ANOVA and Fisher's exact tests for numerical and categorical covariates, respectively. A P-value ≤ 0.05 was considered statistically

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TABLE 1.

Descriptive Statistics and Clinical Characteristics			
	Steroid-sparing therapy* N=37	No steroid-sparing therapy N=82	*P*
Age (mean ± SD)	53.3 ± 16.2	52.1 ± 15.5	0.710
Gender (#, %)	--	--	0.842
Male	14 (37.8)	33 (40.2)	--
Female	23 (62.2)	49 (59.8)	--
Race (#, %)	--	--	0.655
White	15 (40.6)	35 (42.7)	--
Black	14 (37.8)	26 (31.7)	--
Asian	6 (16.2)	11 (13.4)	--
Other (Hispanic, Middle Eastern)	2 (5.4)	10 (12.2)	--
Pemphigus subtype (#, %)	--	--	0.268
Pemphigus vulgaris	25 (67.6)	63 (76.8)	--
Pemphigus foliaceous	12 (32.4)	17 (20.7)	--
Other pemphigus†	0 (0)	2 (2.5)	--
Disease duration, years (mean ± SD)	6.3 ± 8.8	2.8 ± 4.5	0.006
Prednisone dose at time of infusion, mg (mean ± SD)	19.3 ± 12.8	24.0 ± 17.9	0.237
Pre-rituximab PDAI (mean ± SD)‡			
Activity	15.3 ± 16.6	16.7 ± 14.2	0.670
Damage	1.9 ± 2.4	1.7 ± 2.4	0.718
Baseline PDAI banding, *Boulard 2016* (#, %)	--	--	0.227
None (0)	0 (0)	1 (1.2)	--
Moderate (1-15)	23 (62.2)	37 (45.1)	--
Significant (16-45)	6 (16.2)	24 (29.3)	--
Extensive (>45)	3 (8.1)	3 (3.7)	--
Baseline PDAI banding, *Shimizu 2014* (#, %)	--	--	0.805
Mild (0-8)	13 (35.1)	22 (26.8)	--
Moderate (9-24)	13 (35.1)	29 (35.4)	--
Severe (>24)	6 (16.2)	14 (17.1)	--
Baseline PDAI banding, *Hébert 2018* (#, %)	--	--	0.199
PDAI 0-15	23 (62.2)	38 (46.3)	--
PDAI 16+	9 (24.3)	27 (32.9)	--

Abbreviations: PDAI, Pemphigus Disease Area Index
*Steroid-sparing therapy consisted of mycophenolate, methotrexate, azathioprine, or dapsone
†Includes pemphigus erythematosus and paraneoplastic pemphigus
‡Due to missing data, SST n=32 and no SST n=65

significant. For survival-type endpoints, we estimated survival distributions using Kaplan-Meier's method, with comparisons between treatment groups utilizing the log-rank test.

RESULTS

Of 119 pemphigus patients included in this study, 37 received rituximab with SST, and 82 received rituximab without SST. SST consisted of mycophenolate, methotrexate, azathioprine, cyclosporine, dapsone, sulfasalazine, 6-thioguanine, or intravenous immunoglobulin. Mean age (53.3 ± 16.2 vs 52.1 ± 15.5, *P*=0.710) and sex distribution (62.2% vs 59.8% female, *P*=0.842) did not differ between the SST and no-SST groups (Table 1). Pemphigus vulgaris was the most common diagnosis in both groups (67.6% vs 76.8%, *P*=0.268; Table 1). Prior to rituximab therapy, patients who received SST had a longer duration of disease (6.31 ± 8.8 years vs 2.81 ± 4.5 years, *P*=0.006). The average PDAI activity score for patients with and without SST was 15.3 ± 16.6 and 16.7 ± 14.2 (*P*=0.670), respectively, with no difference in disease severity per published disease severity classification scores (Table 1).[7-9] There was no difference between prednisone dose at the time of rituximab treatment between patients on and off SST. Following rituximab therapy, there was no difference in time to remission (*P*=0.507; Figure 1A), time to prednisone dose of 10 mg or less (*P*=0.743; Figure 1B), time to cessation of prednisone therapy (*P*=0.289; Figure 1C), or time to relapse (*P*=0.430; Figure 1D). No significant difference was noted in the number of serious adverse events between groups.

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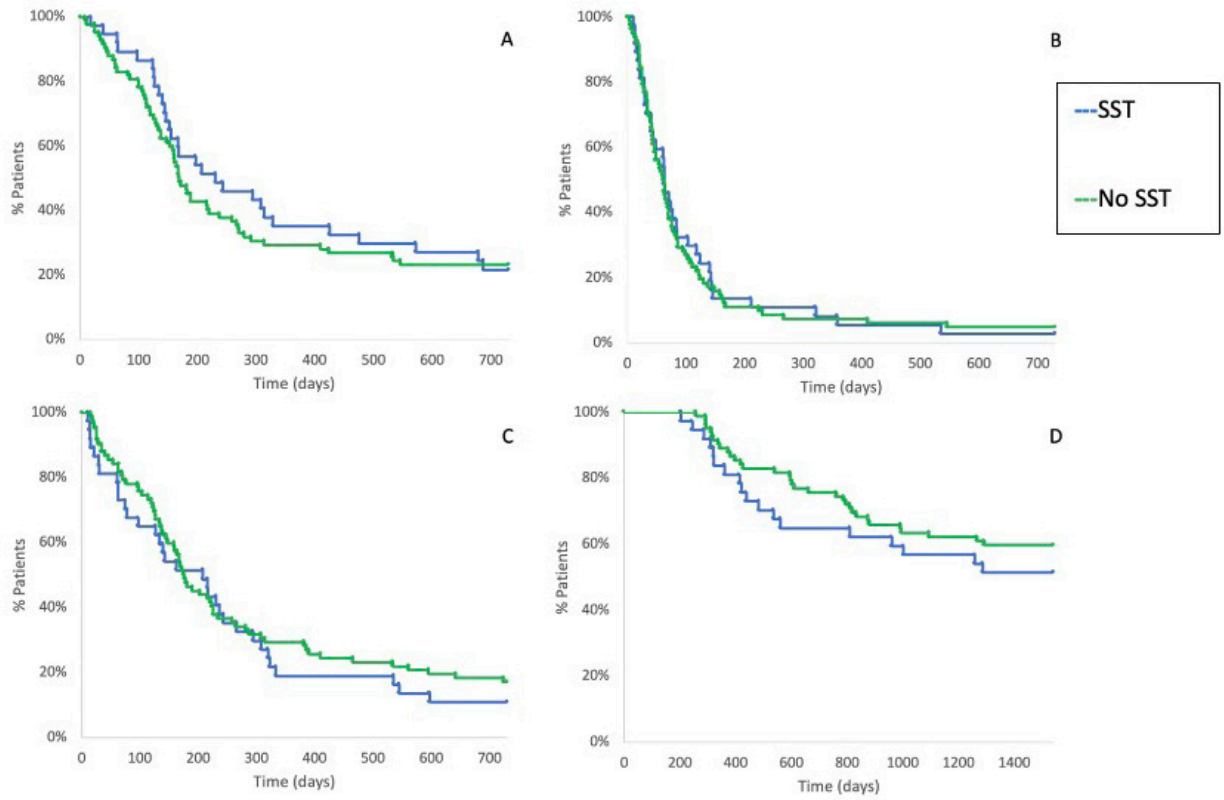
FIGURE 1. Kaplan-Meier regression curves from time of rituximab dosing demonstrate no statistical difference in (A). Time to remission (B). Time to prednisone dose ≤ to 10 mg (C). Time to cessation of prednisone therapy (D). Time to relapse.



CONCLUSION

Our results indicate that the use of SST with rituximab dosing did not improve clinical outcomes related to time to remission, reduction in prednisone dosing, or relapse. While the cohort on SST had a longer disease duration, it is not clear whether continuing SST with rituximab dosing confers any additional benefit. These data provide further evidence for not adding and/or discontinuing SST with rituximab therapy in most patients with pemphigus. Limitations include a high proportion of patients with moderate disease, a retrospective analysis, and a single academic center. Further clinical trials are needed to confirm the appropriate rituximab dosing schedule for induction of long-term remission.

DISCLOSURES

The authors have no conflicts of interest to declare.

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