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Rituximab as first line adjuvant in pemphigus: retrospective analysis of the long-term outcomes in a single center

Running head: First line rituximab in pemphigus

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Rituximab has been widely used for treatment-refractory pemphigus, but the experience as first line steroid-sparing agent is limited.[1,2] In this retrospective study we assessed if early use of rituximab in the disease course would improve the long-term clinical outcome.

All pemphigus vulgaris and pemphigus foliaceus patients evaluated between January 2008 and December 2016 at our institute and systematically treated with rituximab were included. Group A encompassed patients who received rituximab as a first line steroid-sparing adjuvant within 6 months of diagnosis without any conventional immunosuppresants. Group B consisted of patients with disease activity who received rituximab after failing corticosteroids/conventional immunosuppressants or for relapse after them. Patients in both groups were treated with two infusions of 1000 mg rituximab, two weeks apart. Patients who relapsed or failed to achieve clinical remission (CR)[3] in 6 months were re-treated with a single infusion (1000mg) of rituximab.. In addition, patients in both groups received oral corticosteroids with a starting dose of prednisolone between 0.5 to 1 mg/kg with invariably a quick taper and withdrawal of the corticosteroids within 6 months depending on the severity of the disease and clinical judgement.

The primary aim was to compare the efficacy between the two groups in terms of achieving CR off treatment. The secondary outcomes were CR on minimal therapy, relapse rate, requirement of repeat infusions and rituximab-related adverse events.[3]

The baseline characteristics of the two groups are summarized in **Table 1**. In group A, 7/9 (estimated cumulative rate 87.5%) patients and 12/20 (66.2%) patients in group B achieved CR off therapy (p=0.01). After accounting for the effect of disease duration, the hazard ratio between the two groups was still statistically significant (HR: 6.10, 95% CI: 1.52 - 24.44, p=0.01).

When both minimal therapy and off therapy was considered, CR was achieved by 8/9 (estimated cumulative rate 100%) patients in group A and 19/22 (92.9%) patients in group B without any statistically significant difference (**Table 2**). Relapse was seen in 4/9 (44.4%) and 7/22 (31.8%) patients in group A and B respectively. Five/9 (55.6%) patients in group A and 6/22 (35.5%) patients in group B were administered repeated infusions of rituximab, with three (33.3%) and two (9.1%) patients respectively receiving two or more repeat infusions. No significant difference was found between the two groups regarding the time to first relapse (p=0.33).

In our study CR off treatment was more likely to be achieved by patients receiving rituximab earlier in the disease (<6 months) and as first-line steroid sparing adjuvant. Even when accounting for prolonged disease durations, our results were still significant. Given the limits of our sample size, we were unable to account for additional potential cofounders such as disease subtype or the use of different adjuvant therapies. However, previous analyses have failed to show any effect of these confounders on clinical outcomes.[4] Thus, it is unlikely they contributed to the difference in our observed responses. Noteworthy, despite the differences in early outcome, there was no difference between the groups in any of the secondary end points. The higher requirement of repeat infusions in group A is skewed by its small sample size and two of the patients requiring re-treatment for failure to achieve CR. A prospective multicentre study encompassing 91 pemphigus patients has shown that first-line use of rituximab in combination with short-term prednisone allows to achieve CR off treatment in a three times greater portion of patients than using prednisone alone and was associated with significantly fewer grade 3 and 4 side effects.[5] These findings support the use of rituximab with low dose corticosteroids as first-line regimen in pemphigus.

81 **Abbreviation**

82 CR: complete remission

83 HR: hazard ratio

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Table 1. Demographics and clinical characteristics of the included patients

		Group A (N=9)		Group B (N=22)		P**
		N*	%	N*	%	
Sex	M	3	33.3%	8	36.4%	1
	F	6	66.7%	14	63.6%	
Age (years)	*Mean, SD*	*62.5*	*17.9*	*54.8*	*16.7*	0.66
Age at diagnosis (years)	*Mean, SD*	*62.2*	*18.0*	*51.3*	*16.4*	0.24
Disease duration prior to rituximab (weeks)	*Mean, SD*	*15.1*	*7.1*	*180.8*	*142.5*	**<0.001**
Type of pemphigus	PV	4	44.4%	15	71.4%	0.22
	PF	5	55.6%	6	28.6%	
Previous treatments	Azathioprine	-	-	14	66.7%	-
	MMF			5	23.8%	
	Cyclophosphamide			1	4.8%	
	Methotrexate			1	4.8%	
	Dapsone			2	9.5%	
	Others			1	4.8%	
Number of previous treatments	0	-	-	1	4.8%	-
	1			16	76.2%	
	2 or more			4	19.0%	
Baseline cutaneous severity (ABSIS)	*Mean, SD*	9.7	10.7	7.7	7.5	1
Baseline mucosal severity*	None	5	55.6%	6	28.6%	0.23
	Mild (<5% area involved)	1	11.1%	10	47.6%	
	Moderate (5%-30% area involved)	2	22.2%	3	14.3%	
	Severe (>30% area involved)	1	11.1%	2	9.5%	
Dsg 1	Negative	3	33.3%	6	27.3%	0.69
	0 - 99	2	22.2%	9	40.9%	
	100+	4	44.4%	7	31.8%	
Dsg 3	Negative	4	44.4%	6	27.3%	0.55
	0 - 99	3	33.3%	7	31.8%	
	100+	2	22.2%	9	40.9%	

PV: pemphigus vulgaris; PF: pemphigus foliaceus; SD: standard deviation; Dsg: Desmoglein ELISA values in U/ml ; MMF: mycophenolate mofetil;

* Numbers may not add up to the total due to missing data

** Fisher's exact test or Mann-Whitney U test for categorical and continuous variables, respectively

Table 2. Cumulative rates and hazard ratios of patients achieving complete remission (CR) and of patients remaining in CR, overall and by kind of rituximab treatment

	Group A	Group B	P*	HR, A vs. B (95% CI)	P**
CR off therapy, % (95% CI)	87.5% (64.6 - 100)	66.2% (43.7 - 88.7)	**0.01**	**6.10 (1.52 - 24.44)**	**0.01**
N patients	9	20			
N events	7	12			
Max time, weeks	128.1	414.9			
Median time to achieve CR, weeks (95% CI)	39.7 (30.4 - 49.0)	72.3 (0 - 184.7)			
CR on minimal therapy and off therapy, % (95% CI)	100% (NC)	92.9% (80.6 - 100)	0.46	1.03 (0.35 - 3.07)	0.96
N patients	9	22			
N events	8	19			
Max time, weeks	119.7	213.9			
Median time to achieve CR, weeks (95% CI)	30.9 (13.8 - 47.9)	29.7 (26.5 - 32.9)			
Patients remaining in CR, % (95% CI)	33.3% (0 - 70.9)	61.1% (38.6 - 83.6)	0.33	1.19 (0.28 - 5.04)	0.82
N patients	8	19			
N events	4	7			
Max time, weeks	127.4	396.0			
Median survival time, weeks (95% CI)	51.9 (19.4 - 84.3)	NC			

CI: confidence interval, HR: hazard ratio, NC: not computable

* Log-rank test

** P-value from Cox regression models including disease duration prior to rituximab as adjustment variable