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Case series of two different dose regimen Rituximab therapy for severe Pemphigus

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Abstract. Rituximab is a monoclonal antibody approved for treatment of adults with severe and refractory pemphigus vulgaris. Concerns about side effects and high costs of conventional doses have rised the hypothesis that low-dose rituximab regimen may be cost-effective with a better safety profile. Here we report our experience of seven patients with extensive/recalcitrant pemphigus, who either were steroid dependent, had contraindications or refused conventional treatment. Two patients received conventional rituximab (1000 mg 2 weeks apart) while five received ultra low-dose rituximab (200 mg 2 weeks apart). At 3 months, the two patients treated with high Rituximab regimen showed respectively a complete remission off therapy (CROT) and a complete remission on minimal therapy (CRMT), while among the five patients treated with ultra low-doses, three achieved CROT, one achieved CRMT and one a partial remission off therapy (PROT). All patients treated with ultra low-dose rituximab achieved complete depletion of cd19+ and cd19/45+ B lymphocytes after three months and all patients except one male manteined the zeroing after 6 months. No serious side effect was documented with low dose regimen except for a case of diziness. Our data suggest that ultra low-dose rituximab can be effective even in patients with extensive/recalcitrant pemphigus, with a lower probability of side-effects respect to higher dose regimen and may act as a steroid sparing strategy.

Keywords: Rituximab, Pemphigus, low-dose therapy, ultra low-dose regimen.

INTRODUCTION

Pemphigus includes a group of rare autoimmune bullous diseases characterized by flaccid blisters and erosions of the mucous membranes and skin. This sometimes life-threatening condition, is characterized by the presence of IgG autoantibodies against the desmosomal adhesion proteins, desmoglein 3 and/or desmoglein 1, on epidermal keratinocytes, that are responsible of intraepithelial blister formation.

The severity of the disease is based on its progressive course which is accompanied by an increased body catabolism with loss of body fluids and proteins and secondary bacterial and viral infections which may lead to sepsis and heart failure.

Rituximab is a chimeric monoclonal antibody approved for treatment of adults with severe and refractory pemphigus vulgaris. Recent studies have focused on assessments of efficacy and safety of low-dose rituximab (<2 gram in each cycle)[2-8].

We reported our experiences based on a case series of seven patients treated with Rituximab at rheumatologic dose regimen (1000) and ultra-low (200) dose regimen.

MATERIALS AND METHODS

Seven patients with extensive pemphigus were selected (Table 1), who either had recalcitrant pemphigus, were steroid dependent, had relapsed after pulse therapy, had contraindications to conventional treatment or wanted to avoid conventional treatment and its side effects. Two doses of conventional rituximab (1000 mg) or ultra low-dose rituximab (200 mg) were given 2 weeks apart and patients were regularly followed up every 2 weeks for the first month and then every three months. Complete blood counts, liver function tests, renal function tests, flow cytometry assessments of B-cell subtypes, skin biopsy, direct immunofluorescence and desmoglein levels were checked before and after rituximab administration. Pre-rituximab chest X-ray, electrocardiograph, oculistic evaluation and computed bond mineral density were also obtained. Clinical response was defined by the criteria outlined in the consensus statement on definitions of endpoints and therapeutic response for pemphigus [1] Complete remission off therapy (CROT) was defined as complete epithelialization and absence of new or established lesions while the patient is off all systemic therapy for at least 2 months while complete remission on minimal therapy (CRMT) was defined as the absence of new lesions while the patient is receiving minimal doses of systemic therapy. Partial remission off therapy (PROT) was defined as the presence of transient new lesions that healed within 1 week without treatment and while off all systemic therapy. Minimal therapy was defined as prednisone up to 10 mg/day or azathioprine up to 1.25 mg/kg/day. Relapse was defined as the appearance of at least three new lesions in 1 month that did not heal spontaneously within 1 week or the extension of established lesions in a patient who had previously achieved disease control.

RESULTS

We recruited seven patients with an average age of 63.1 years old, three were males and four females (Table 1). All of them undergoing and failed previous systemic corticosteroid therapy (Metilprednisolone 1 mg/kg/die or multiple boluses of 1 gr) and/or systemic immunosuppressant (Azathioprine or Mycophenolate). Two male patients were treated with two doses of Rituximab at rheumatologic regimen (1000 mg) two weeks away. One male patient and three female patients were treated with two ultra-low doses of Rituximab (200 mg) two weeks away. At 3 months, the two patients treated with Rituximab at rheumatologic regimen (1000 mg) showed respectively a complete remission off therapy (CROT) and a complete remission on minimal therapy (CRMT). At 3 month, the five patients treated with ultra-low doses of Rituximab (200 mg) achieved respectively: three patients a complete remission off therapy (CROT), one patient a complete remission on minimal therapy (CRMT) and one patient a partial remission off therapy (PROT) (Table 2; Graphic 1).

Two patients showed adverse events, in detail, one patient treated with Rituximab 1000 mg showed defect of vision like visual blurring and one patient treated with Rituximab 200 mg developed dizziness (Table 2).

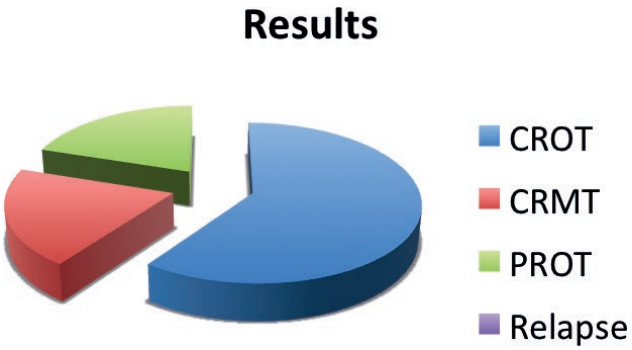
Flow cytometry assessments of B-cell subtypes displayed a lasting maintenance of the zeroing of linf B cd19 + and cd19 / 45 + at three months and at 6 months in all patient except one male patient treated with 200 mg (Table 2; Graphic 2).

Table 1. Population dermographic characteristics

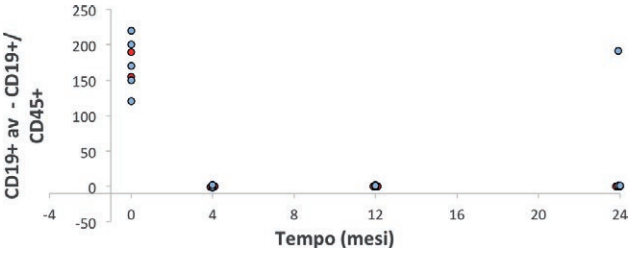
Patients	Age	Sex	Desease	Previous therapy	Dose T0	Dose T1 (2w)
1	82	M	Pemfigo	CS	1000	1000
2	32	M	Pemfigo	CS, AZT	1000	1000
3	74	M	Pemfigo	CS	200	200
4	66	F	Pemfigo	CS	200	200
5	55	F	Pemfigo	CS, MMF, AZT	200	200
6	64	F	Pemfigo	CS, Dapsone, MMF, evIG	200	200
7	69	F	Pemfigo	CS, RTX	200	200

Table 2. Results of efficacy and safety in patients undergoind Rituximab at conventional and ultra low-dose regimen.

Patients	Age	Sex	Dose T0	Results (12w)	Cd19+ Cd19+/ Cd45+% (4 W)	Cd19+ / Cd19+/ Cd45+% T2 (12w)	Cd19+ / Cd19+/ Cd45+% T3 (24w)	Aes
1	82	M	1000	CROT	0/0	0/0	0/0	-
2	32	M	1000	CRMT	0/0	0/0	0/0	EP
3	74	M	200	CROT	2/0	2/0	1/0	headache
4	66	F	200	PROT	0/0	0/0	191/10	dizziness
5	55	F	200	CROT	0/0	0/0	0/0	-
6	64	F	200	CROT	0/0	1/0	1/0	-
7	69	F	200	CRMT	0/0	1/0	1/0	-



Graphic 1. Results at week 12, in patients undergoing two doses of low-dose Rituximab (200 mg). CROT complete remission off therapy; CRMT: complete remission on minimal therapy; PROT: partial remission off therapy.



Graphic 2. Manteinance of zeroing cd19+ and cd19+/45+ B lymphocytes since first week, manteined after 3 and 6 months from the first infusion.

DISCUSSION

Rituximab has been approved as a treatment for moderate-to-severe Pemphigus Vulgaris (PV). By depleting B cells, rituximab decreases circulating anti-desmoglein autoantibodies. However, the optimal dosage has not been standardized. Since the B-cell burden in autoimmune blistering skin diseases is much lower than that in lymphoproliferative disorders, lower dosage regimens, as low as a single infusion of 200 mg has been reported to be effective for PV (Ailabac et al [4]). Schoergenhofer et al. [5] showed that CD20+ cells were depleted by 68%, 74%, and 97% at 1 h after the infusion of rituximab at the doses of 0.1, 0.3, and 1 mg/m2, respectively, and the CD20+ cell counts gradually returned to baseline in 1–9 months. Therefore, the authors extrapolated that 100 mg Rituximab may be sufficient to fully suppress CD20+ cells for 3 months.

In our series low-dose Rituximab regimen was associated with a good and prolonged clinical response with zeroing of cd19+ and cd19+/45+ B lymphocytes since first week, manteined after 3 and 6 months from the first infusion (Graphic 2). No serious side adverse events was reported, and only one male developed diziness.

Our data show that this strategy can be effective even in patients with extensive and recalcitrant pemphigus, with a lower probability of side-effects, thus potentially reducing the negative consequences deriving from long-term use of corticosteroids and other immunosuppressive drugs.

Instead higher Rituximab doses “at rheumatologic regimen”, may be necessary in very severe cases with high levels of anti-desmoglein 3 antibodies, which are considered predictive of therapy failure.

Such preliminary hypothesis need to be confirmed on larger and possibly randomized prospective clinical trials.

CONCLUSIONS

Our results suggest that ultra low-dose rituximab can be a well-tolerated and effective adjuvant therapy in recalcitrant and/or severe pemphigus which may also act as a steroid-sparing strategy, avoiding long-term side effects of chronic corticosteroids intake.

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