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SHORT COMMUNICATION

First-line Combination Therapy with Rituximab and Corticosteroids is Effective and Safe for Pemphigus

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Pemphigus is a life-threatening autoimmune blistering disease. Systemic corticosteroids have been the mainstay and first-line treatment with success. However, long-term use of corticosteroids results in significant morbidities and mortalities. Much effort has been focused on searching alternative or corticosteroids-sparing agents. Rituximab (MabThera™; Roche, Basle, Switzerland), a chimeric anti-CD20 monoclonal antibody has been shown to be effective for refractory pemphigus with acceptable side effects (1, 2). Herein, we reported our successful experience with rituximab and corticosteroids as first-line combination therapy for pemphigus.

CASE SERIES

Nine moderate-to-severe pemphigus patients were retrospectively collected at a referral centre in Taiwan from 2009 to 2011. Three cases were pemphigus foliaceus and the others 6 were pemphigus vulgaris (Table I). Four pemphigus vulgaris paients had severe disease and others had moderate disease according to the Pemphigus Severity Scale (3). All patients were having 1st episodes, thus receiving rituximab and corticosteroids as first-line combination therapy. The starting dose of systemic corticosteroids was 1.0 mg/kg/day prednisolone. It was doubled if the disease was not controlled after 1 to 2 weeks. Rituximab infusion began within the 1st week of corticosteroid therapy with a dose of 500 mg/infusion for 4 weekly infusions. Usually, a remarkable efficacy could be observed at about 4 weeks after the start of rituximab treatment. The dose of prednisolone was then tapered rapidly with each dose lasting for only 2–4 weeks. Usually, prednisolone could be discontinued after 4–6 months. We also gave prophylactic co-trimoxazole for pulmonary *Pneumocystis jiroveci* infection. All patients were closely followed for at least one year, including clinical disease activity, side effects, and complications, as well as laboratory parameters. Treatment response was accessed based on the consensus statement of the International Pemphigus Committee (4).

The mean dose and duration of corticosteroids were 4,636 mg (range 2,280–7,460 mg) and 20.5 weeks (range 16–24), respectively (see Table I). All patients got complete remission (CR) with treatment (CRon) at a mean time of 16.5 weeks (range 14–23) and eventually achieved the status of CR without any treatment (CRoff) when the prednisolone was discontinued. No side effects and complications were encountered in this study. B-cell repopulation was available in 8 patients with a mean time of 35.8 weeks (range 26–49). Relapse occurred in 8 patients, mean time was 42.6 weeks (range 32–60). Relapse occurred after CR in a mean duration of 27.1 weeks (range 17–45). B-cell repopulation always

Table I. *Data summary of the patients and the trestment outcomes*[a]

Case	Age/Sex	Disease	Severity	P cumulative dose and duration mg (weeks)	Treatment response[b]	Duration of CR (weeks)	Time to (weeks)				Treatment for R	Duration of follow-up, weeks
							DC	CR	B	R		
1	36/F	PF	Moderate	4,200 (22)	CRoff	17	1.5	19	26	36	RTX	129
2	48/M	PV	Severe	7,410 (24)	CRoff	25	2	18	40	43	AZA	122
3	36/M	PV	Moderate	3,010 (16)	CRoff	24	2	14	26	38	RTX	107
4	79/M	PV	Moderate	3,610 (19)	CRoff	45	1	15	42	60	RTX+P	95
5	56/M	PF	Moderate	4,270 (19)	CRoff	28	3	23	39	51	RTX	90
6	72/M	PF	Moderate	2,280 (19)	CRoff	18	2	14	NA	32	RTX+P	62
7	69/F	PV	Severe	4,050 (20)	CRoff	38	2	14	49	NA	NA	61
8	41/F	PV	Severe	7,460 (24)	CRoff	25	3	15	26	40	AZA	61
9	50/F	PV	Severe	5,440 (22)	CRoff	24	3	17	39	41	AZA	63
Mean	54			4,636 (20.5)		27.1		16.5	35.8	42.6		

[a] The re-elevation of titres of serum autoantibodies based on the indirect immunofluorescence (IIF) studies was only observed in 2 patients. Because re-elevation of values of IIF was infrequent in our study and serial data of anti-desmoglein antibody were not available, we did not include these data into the Table. [b] According to the consensus statement of the International Pemphigus Committee, CRoff means no development of new lesions and healing of all established lesions for at least 2 months while patients are not receiving any treatment. Therefore, patients who fullfilled with the criteria were classified as complete remission even if they got a relapse later.

AZA: azathioprine; B: B-cell repopulation; CR: complete remission; CRoff: complete remission without any treatment; DC: disease control; NA: non-applicable; P: prednisolone; PF: pemphigus foliaceus; PV: pemphigus vulgaris; R: relapse of disease; RTX: rituximab.

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preceded the occurrence of relapse. For the treatment of the relapses, 3 patients received rituximab monotherapy with a dose of 500 mg/infusion for 4 weekly infusions. Two patients received combination therapy with rituximab and prednisolone, with an accumulation dose of 1,680 mg and duration of 12 weeks. The other 3 patients received oral azathioprine with a dose of 100 mg/day. All of the relapses resolved rapidly and all patients achieved CR again within 3 months. One patient, who did not have relapse of disease, remained disease-free for one year after the first-line combination therapy.

DISCUSSION

Although rituximab has been shown to be useful in refractory pemphigus patients, the role of rituximab as first-line treatment for pemphigus is not yet determined. In this case study, we demonstrated the efficacy and safety of rituximab and corticosteroids as first-line combination therapy for pemphigus. In a previous report (5), one-year cumulative doses of prednisolone, alone or combined with azathioprine, mycofenolate, or cyclophosphamide as first-line therapy of pemphigus, were 11,631 mg, 7,712 mg, 9,798 mg, and 8,276 mg, respectively, i.e. much higher than that of our regimen (mean 4,636 mg). Moreover, CR rates in these 4 treatment groups were all 70–80%, lower than that of our regimen (100%). Accordingly, one can point out that rituximab and corticosteroids as first-line combination therapy has an outstanding efficacy and steroid-sparing effect compared to other commonly-used regimens.

As to the complications of rituximab treatment, it has been reported to cause thrombocytopenia, neutropenia (6), and interstitial pneumonitis (7) in patients with haematologic malignancies. Serious infections, including fatal bacterial pneumonia (8) or systemic viral infection (9), have been observed in patients with autoimmune blistering diseases receiving rituximab at a frequency of around 30% (9). Although no definite risk factors have been identified, these severe adverse effects are thought to be associated with underlying malignancies and high-dose adjuvant immunosuppression (9). Despite no complications being encountered in this study, we had experienced such side effects in other rituximab-included regimens. Thus, a close monitoring of patients is suggested.

For a high relapse rate in this study, the dose of rituximab did influence the effectiveness in treating patients with pemphigus (10, 11). However, it might not be the case in our series. Because the total dose of rituximab we used was equal to that of bi-weekly 1 g infusion (12), the regimen had been shown to be effective with a low relapse rate. The main cause might be the lower cumulative dose and shorter duration of prednisolone in our study, motivated by our wish to reduce corticosteroid-related morbidities and mortalities. Also, consistent with the previous findings that rituximab used early in the course of disease has better outcome (13), the severity of the relapses in our study were quite mild and easily controlled by treatment modifications.

In our experience, first-line combination therapy with rituximab and corticosteroids is relatively effective and safe for moderate-to-severe pemphigus compared to more conventional regimens. Further evaluation by a larger randomised, controlled trial is required, however.

The authors declare no conflict of interest.

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