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Original Article

Retrospective review of rituximab treatment in pemphigus disease in a single tertiary dermatology centre

單一第三級皮膚科中心內利妥昔單抗治療天皰瘡的回顧性研究

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Pemphigus is a rare autoimmune blistering disorder. Rituximab is a useful therapy to avoid prolonged steroid use and its resultant side effects. We reviewed pemphigus patients that were treated with Rituximab at our centre. We found that Rituximab was effective and well tolerated with a nadir of Pemphigus Disease Activity Index and anti-desmoglein level at 6 months. Most patients only had clinical relapse of disease after 15 months.

天皰瘡是一種罕見的自身免疫性水皰病。利妥昔單抗是一種有用的療法，可用以避免類固醇的長時間使用及其產生的副作用。我們回顧了本中心接受過利妥昔單抗治療的天皰瘡患者，發現利妥昔單抗有效且耐受性良好，天皰瘡疾病活動指數和橋粒芯糖蛋白抗體水平俱在 6 個月時達至最低點。大多數患者的疾病臨床復發都是在 15 個月之後。

Keywords: Desmogleins, pemphigus, rituximab, steroids

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Introduction

Pemphigus is a rare autoimmune blistering disorder characterised clinically by mucocutaneous blisters and erosions and histopathologically by intraepidermal acantholysis. The two major subgroups of pemphigus are pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Pemphigus patients have circulating autoantibodies directed against desmogleins. PF is caused by anti-desmoglein-1 (anti-DSG1) antibodies and in PV, anti-desmoglein-3 (anti-DSG3) antibodies. Clinically, PF lesions are confined to the skin with minimal to no involvement of mucous membranes whereas in PV there is usually significant mucous membrane involvement.

The mainstay of treatment include systemic glucocorticoids in combination with adjuncts such as azathioprine, mycophenolate mofetil and dapsone. However, the prolonged use of systemic glucocorticoids is associated with multiple side effects.

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Rituximab, a chimeric monoclonal antibody, which selectively depletes CD20 expressing B cells, has proven effective as treatment for adults with pemphigus.[1]

This retrospective study presents the experience of rituximab use in pemphigus patients in a tertiary hospital.

Methods

Data was collected on pemphigus patients treated with rituximab that presented to the National University Hospital, Singapore between 2015 and 2019.

Data was collected on the demographics and treatment of patients prior to rituximab. The Pemphigus Disease Activity Index (PDAI), anti-DSG1 and anti-DSG3 levels were recorded at baseline, 8-week, 6-month, and 1-year post-rituximab. If a patient had repeated cycles of rituximab, data was recorded at the same time points.

Patients were treated with rituximab using the rheumatoid arthritis protocol (two 1000 mg infusions separated by 2 weeks).

All patients treated with rituximab were treated with oral steroids and/or steroid sparing agents prior. Decision to use rituximab depended on the severity and chronicity of the pemphigus, the patients response to conventional systemic therapy as well as to avoid complications from chronic corticosteroid use. The time lapse from diagnosis of pemphigus and treatment with rituximab varied depending on clinical presentation and progress.

Clinical relapse was defined clinically as patients that had an increase in their PDAI and the reappearance of at least 3 new lesions in a month that did not heal spontaneously within 1 week.[2]

Patients who only had serological without a concordant clinical relapse were not given repeat rituximab.

Results

There was a total of 12 patients treated with rituximab who presented during this time. All patients had histological and serological proven pemphigus.

Of the 12 patients, 9 patients had PV, 2 patients had PF and 1 patient had a skin biopsy consistent with PV, however, the patient's serology and clinical presentation were more consistent with PF and was managed as PF.

There were 21 separate cycles of rituximab given. All patients were treated with prednisolone prior to rituximab, regardless of cycle. Other prior systemic adjuvant medications included colchicine, azathioprine, mycophenolate and dapsone.

Five patients had a clinical and serological relapse of pemphigus that required repeat rituximab. Of these, 3 patients required 1 additional cycle and 2 patients required more than 1.

Clinical relapse was associated with serological relapse (anti-DSG levels) in the majority (20/21) of rituximab cycles. One patient showed a serological without clinical relapse and was not retreated with rituximab.

A mean of 13.2 months (10-20 months) lapsed between initial and repeat rituximab. One patient required repeat rituximab at 10 months while the remainder only required repeat rituximab from beyond 15 months.

Table 1 shows the demographics of patients and their medication prior to 1st cycle of rituximab.

All except 2 patients were able to taper their prednisolone doses over a period of 2 weeks to 3 months post-rituximab. The rapidity and overall duration of taper depended on starting prednisolone dose as well as residual disease activity. The 2 patients that required a long taper of 6 to 8 months had high PDAI prior to rituximab (PDAI 60 and 116).

Of the 12 patients, 1 patient and 2 patients, respectively, have yet to reach their 1 year and 6 months follow-up, leaving 9 patients that have reached their 1 year follow up. The 3 patients defaulted follow up due to various logistic reasons such as the COVID-19 pandemic; on review of their clinical records, they remain in clinical remission.

Table 2 shows the mean PDAI at baseline, 8 weeks, 6 months and 1 year post-rituximab.

Figure 1 shows the mean anti-DSG levels of patients at baseline, 8 weeks, 6 months and 1 year post-rituximab. Tables 3 to 5 show the PDAI, anti-DSG1, and anti-DSG3 trend at baseline, 8 weeks, 6 months and 1 year post-rituximab for each participant respectively.

Significant side effects of rituximab occurred in 3/12 patients.

One patient passed away 2 months after rituximab. He presented with a preliminary diagnosis of viral fever but discharged against medical advice. He passed away 3 days after discharge however we were unable to ascertain his cause of death from the records available as he passed away without presenting to our hospital.

Another patient had a flare of herpes zoster immediately after receiving her 1st cycle of

Table 1. Demographics of patients

Patient	Age	Gender	Diagnosis	Race	Medication
1	54	Male	PV	Indian	Prednisolone 20 mg, Colchicine
2*	51	Female	PV	Indian	Prednisolone 60 mg, Azathioprine
3*	63	Female	PV	Bengali	Prednisolone 50 mg
4	72	Male	PV	Chinese	Prednisolone 70 mg
5*	40	Female	PV	Maldivian	Prednisolone 50 mg, Mycophenolate mofetil
6*	52	Female	Histo-PV; Sero-PF	Burmese	Prednisolone 35 mg, Azathioprine
7	74	Female	PV	Malay	Prednisolone 30 mg
8*	70	Female	PV	Malay	Prednisolone 30 mg, Azathioprine
9	58	Female	PV	Chinese	Prednisolone 20 mg
10	48	Female	PV	Chinese	Prednisolone 40 mg, Azathioprine
11	61	Female	PF	Chinese	Prednisolone 60 mg, Azathioprine, Dapsone
12	72	Male	PV	Chinese	Prednisolone 40 mg, Azathioprine

*Patients that required repeat cycles of rituximab

PV: Pemphigus vulgaris, PF: Pemphigus foliaceus

Table 2. Mean Pemphigus Disease Area Index (PDAI)

Mean PDAI (baseline)	Mean PDAI (8 weeks)	Mean PDAI (6 months)	Mean PDAI (1 year)
24.23 (0-116)	2.84 (0-12)	0.57 (0-3)	4.92 (0-16)

rituximab which resolved with conventional therapy. She received her 2nd cycle of rituximab without complications.

The last patient had a prolonged inpatient stay after rituximab due to methicillin-resistant *staph. aureus* bacteraemia, a provoked lower limb deep vein thrombosis with pulmonary embolism and adrenal insufficiency likely secondary to chronic steroid exposure.

In this patient, most of her complications could be attributed to chronic systemic steroid exposure and morbid obesity with consequent immobility.

Table 6 shows a summary table of adverse events.

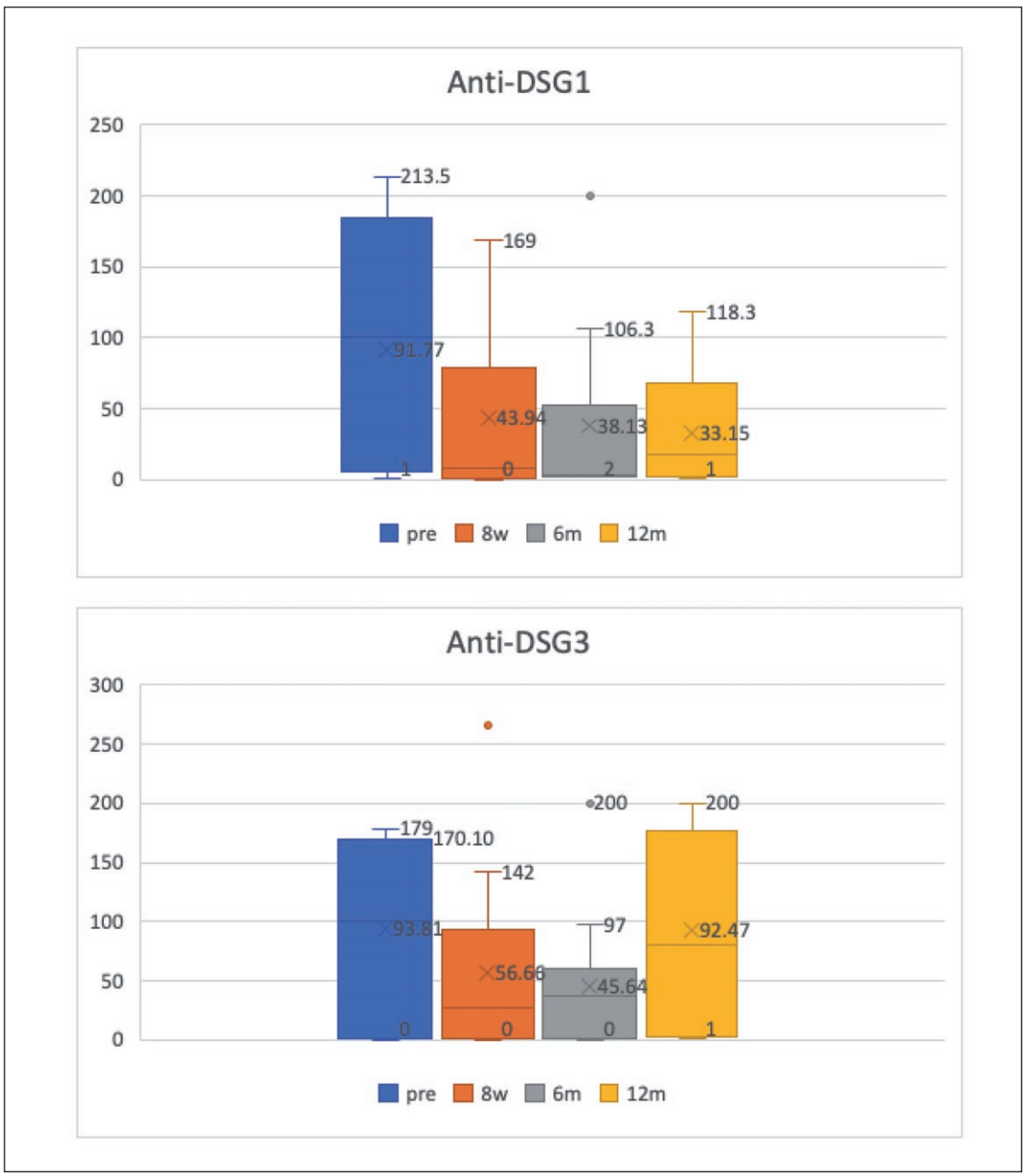

Figure 1. Trend of anti-desmoglein-1 (anti-DSG1) and anti-desmoglein-3 (anti-DSG3) levels prior to rituximab, 8 weeks, 6 months and 12 months after rituximab. It shows a decreasing trend in anti-DSG levels, with a nadir at 6 months.

Discussion

This study showed that rituximab was an effective treatment for patients with recalcitrant pemphigus.

All patients showed a decrease in their mean PDAI and anti-DSG levels after administration of rituximab. The nadir for PDAI and anti-DSG levels was consistent at the 6-month mark. This demonstrates that rituximab induces both clinical and serological remission in pemphigus patients.

This is consistent with previous studies which show that circulating anti-DSG levels and disease activity decline after rituximab.[1,3,4] Anti-DSG levels declined to a nadir of 6-month similar to previous studies.[5,6]

However, what is less clear is how long the anti-DSG level depletion is expected to last. In our own study population, all patients showed a mean increase in their anti-DSG levels at the 1-year mark. Still, the mean anti-DSG levels at 1-year were lower than at baseline. Previous studies have been heterogenous as some studied populations showed consistently low anti-DSG levels for up to 24 months.[5] However, there is significant heterogenicity in the way that rituximab was administered, rapidity of steroid taper and use of maintenance rituximab. All the patients seen at our centre tapered their prednisolone in accordance with improvement in clinical presentation and did not receive additional doses of rituximab unless they had a serological and clinical flare.

Table 3. Pemphigus Disease Activity Index trend

Patient	Pre	8 weeks	6 months	1 year
1	1	0	0	0
2 Cycle 1	60	2	0	11
2 Cycle 2	9	0	0	0
3 Cycle 1	116	9	0	2
3 Cycle 2	5	1	1	Flare <1 year
3 Cycle 3	3	0	0	0
4	61	2	Deceased	–
5 Cycle 1	0	0	–	16
5 Cycle 2	16	0	0	Flare <1 year
5 Cycle 3	1	–	–	2
5 Cycle 4	2	0	–	8
5 Cycle 5	8	–	–	–
6 Cycle 1	1	1	3	16
6 Cycle 2	16	10	0	0
7 Cycle 1	40	12	0	5
8 Cycle 1	2	2	–	3
8 Cycle 2	13	1	0	0
9	15	1	1	1
10	57	10	3	11
11	63	3	0	–
12	20	0	–	–

Additionally, previous studies that aimed to correlate the level of anti-DSG levels and disease activity have been mixed[7-11] but have mainly showed poor correlation between anti-DSG level and disease activity. This discordance was seen in 1 of our patients who had a serological relapse but no clinical relapse. However, although anti-DSG level does not correlate with contemporaneous disease activity, the overall trend of anti-DSG antibody level did reflect changes in disease activity as measured by PDAI.[9]

Rituximab is generally well-tolerated with minimal adverse side effects[12] such as flushing, itch and nausea reported in our patients. Infective complications occurred in the minority of our patients. The single patient who demised is of concern, though we lack detail on the precise cause of death.

The strength of this study is that Singapore is an international hub with a resultant broad mix of ethnicities, including patients from neighbouring countries that seek medical care in Singapore. Our sample size of 12 patients over 6 years is sizeable considering that pemphigus is a rare auto-immune blistering disease.

However, there are a few limitations of this study. We are unable to draw any conclusion as to which patients will have long-term quiescent disease

Table 4. Anti-desmoglein-1 trend

Patient	Pre	8 weeks	6 months	1 year
1	3.62	1	2	2
2 Cycle 1	203	157.6	19.2	22
2 Cycle 2	14	2	2	1
3 Cycle 1	171.6	10.4	2.05	13.36
3 Cycle 2	13.36	4.08	–	–
3 Cycle 3	7.42	2.15	–	3
4	213.5	83.78	–	–
5 Cycle 1	197	1.49	–	25.23
5 Cycle 2	25.23	–	–	–
5 Cycle 3	1.72	–	–	1.65
5 Cycle 4	1.65	0	–	89
5 Cycle 5	1	–	–	–
6 Cycle 1	146.2	117.5	106.3	100
6 Cycle 2	100	–	53	62
7 Cycle 1	200	4.9	2.87	22.53
8 Cycle 1	152.9	66.17	–	118.3
8 Cycle 2	144	–	28	–
9	2	0	2	2
10	29	17	2	2
11	200	169	200	–
12	100	66	–	–

Table 5. Anti-desmoglein-3 trend

Patient	Pre	8 weeks	6 months	1 year
1	172.6	100	60	200
2 Cycle 1	179	266.4	40.8	100
2 Cycle 2	123	95	97	47
3 Cycle 1	>200	46.4	36.9	175.51
3 Cycle 2	175.51	128.72	–	–
3 Cycle 3	143.2	64.9	–	100
4	22.09	4.11	–	–
5 Cycle 1	136.6	7.1	–	167.59
5 Cycle 2	167.59	–	–	–
5 Cycle 3	100.3	–	–	178
5 Cycle 4	178	53	–	1
5 Cycle 5	89	–	–	–
6 Cycle 1	0.73	1.46	0.79	1
6 Cycle 2	1	–	1	2
7 Cycle 1	178	9.3	11.5	59.46
8 Cycle 1	0.58	0.13	–	3
8 Cycle 2	0.75	–	0	–
9	100	0	52	60
10	100	142	200	200
11	2	2	2	–
12	100	86	–	–

Table 6. Summary table of adverse events

Adverse event	Number
Death#	1
Herpes zoster	1
Bactaraemia*	1
Deep vein thrombosis/pulmonary embolism*	1
Adrenal insufficiency*	1

#Discharged against medical advice with a presumptive diagnosis of viral fever

*All 3 occurred in the same patient was is likely attributable to her chronic corticosteroid use as well as morbid obesity with resultant immobility

as some patients responded well to a single cycle of rituximab. Additionally, we did not consistently measure anti-DSG levels at defined intervals beyond 1 year to predict a clinical relapse.

On closer examination of the 5 patients that required repeat cycles of rituximab, all showed an expected decrease in anti-DSG levels with a nadir at 6 months similar to patients that did not relapse. There was no significant difference in the mean baseline PDAI activity and anti-DSG levels between the relapsed and single dose rituximab groups.

There may be other factors that contribute to clinical relapse. Mignard et al[13] showed that higher baseline

PDAI as well as high anti-DSG levels at the 3 months mark had a higher occurrence of relapse after rituximab. Saha et al[14] concluded that high anti-DSG 3, younger age at disease onset and mucosal involvement predicted for increased disease duration. Kushner et al[15] showed that patients treated with lymphoma dosing and older age may be associated with better prognosis (complete remission off therapy) whereas BMI greater or equal to 35 may be a negative prognostic factor.

This study showed that rituximab was effective and well tolerated for pemphigus patients in our centre with a nadir of PDAI and anti-DSG level at 6 months. Most patients treated with rituximab only had relapse of pemphigus after 15 months.

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