Rituximab indications in dermatology, efficacy and adverse effects: a retrospective study in a tertiary care hospital in Sri Lanka and review of literature

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Abstract

Introduction and objectives: Rituximab induces B lymphocyte apoptosis by targeting CD 20 antigen and has shown efficacy in antibody mediated autoimmune diseases. It is increasingly recognized as an effective and safe treatment option for pemphigus and other autoimmune disorders.

To determine the efficacy and adverse effects of adjuvant rituximab using the lymphoma protocol (375mg/m^2 intravenously on days 0, 7, 14, 21).

Materials and methods: A retrospective cohort study was conducted using records from the Dermatology Clinic in the Teaching Hospital Kandy. Participants included 23 patients (pemphigus vulgaris, 16 (69%), pemphigus foliaceus, 1 (4.3%), epidermolysis bullosa acquisita, 1 (4.3%), bullous pemphigoid, 1 (4.3%), systemic lupus erythematosus, 3 (13%), dermatomyositis, 1 (4.3%), who received rituximab treatment between May 1, 2010, and December 30, 2016.

Main outcomes and measures: Results were analysed in two sub groups; autoimmune blistering diseases (AIBD) and connective tissue diseases (CTD). In the autoimmune bullous disorder group the primary outcomes were response to treatment at 3 months, 6 months and at the end of the study (achievement of complete remission with or without treatment) and the time to relapse. In the connective tissue disease group mean steroid dose at 3 and 6 months was used as a surrogate marker for disease activity.

Results: In the AIBD group all patients experienced remission. Complete remission rates without treatment at final follow up was 88.8% (16/18) in the immunobullous group. All patients in the connective tissues disorder group were in partial remission and on prednisolone, mean dose of 17.5 mg at 3 months and 10 mg at 6 months. Median time to relapse after the first treatment cycle was 15 months.

Introduction

Rituximab is a chimeric murine-human monoclonal IgG1 kappa antibody that targets CD20 antigen present on mature B lymphocytes and pre B cells resulting in rapid depletion of this cell population. It is composed of a murine variable region (Fab portion) that is fused onto a human constant region (Fc portion). Once rituximab binds to CD20 it causes B cell destruction by complement dependant cytotoxicity (CDC), antibody dependant cell mediated cytotoxicity (ADCC) and apoptosis[11]. CD20 is not present on stem cells and plasma cells. Consequently rituximab therapy does not cause significant reduction in total immunoglobulin levels and the B cell counts recover after 12 months of receiving a single cycle of rituximab[1].

U.S. Food and Drug Administration (FDA) approved uses for rituximab include non-Hodgkin B cell lymphomas (NHL) and rheumatoid arthritis (RA) but dermatological and non-dermatological off label uses of rituximab are rapidly expanding. Off label indications for rituximab include systemic lupus erythematosus (SLE), multiple sclerosis and pemphigus vulgaris (PV)[2]. Other new uses include intralesional rituximab[1] for recalcitrant mucosal PV and primary cutaneous B cell lymphoma[1]. There are case reports of rituximab therapy for recalcitrant, sight threatening mucous membrane pemphigoid (MMP), paraneoplastic pemphigus (PNP), recalcitrant bullous pemphigoid (BP), epidermolysis bullosa acquisita[3] (EBA) and dermatitis herpetiformis[5] (DH). Rituximab is also used as an adjuvant for stage 4 melanoma[1] and pseudolymphomas. It is increasingly used for connective tissue disorders (CTD) including dermatomyositis, cutaneous lupus erythematosus, severe vasculitis including anti neutrophil cytoplasminc antibody (ANCA) positive vasculitis and shown response of skin sclerosis in murine models of systemic sclerosis[1]. Other novel indications include severe recalcitrant atopic dermatitis (AD) and chronic graft vs host disease (cGVHD).

There are two protocols[2] for administering rituximab, the lymphoma protocol and the rheumatoid arthritis protocol, both of which had been used to treat PV; most widely used dermatological indication. Rituximab 375 mg/m^2 administered as an

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IV infusion, once a week either singly or combined with other chemotherapy regimens, is the dosage recommended for NHL. For RA, the traditional recommended dosage is 1000 mg given at the interval of 2 weeks apart (day 0 and day 14)[3]. Traditional route of administering rituximab is intravenous slow infusion over several hours. To overcome this, a new subcutaneous formulation of rituximab was formulated in combination with hyaluronidase which reduces the administration time to 5-7 minutes[4].

In this study, patients who received intravenous rituximab for a wide range of dermatological indications in the Teaching Hospital Kandy from May 2010 to December 2016 were retrospectively analysed for the efficacy and adverse effects profile. This is the largest cohort of patients who received rituximab for dermatological indications reported to date in Sri Lanka.

Methods

Study setting

We conducted a retrospective single-centre study at the Dermatology Unit of Teaching Hospital Kandy, Sri Lanka. All patients who received rituximab from May 2010 to December 2016 were included in the study. The study was approved by the institutional ethics review board.

Patients

Data was collected retrospectively from the medical records of patients who received rituximab maintained in the Dermatology Unit. Patients mainly belonged to groups of autoimmune bullous disorders (AIBD) and CTDs. Patients in the AIBD group had an established diagnosis of PV, PF, EBA or BP according to clinical histopathological and immunofluorescence criteria. Patients with CTDs met the American College of Rheumatologists (ACR) criteria for either SLE or dermatomyositis.

Initial indications for rituximab treatment were severe relapsing or recalcitrant disease that was refractory to treatment and/or a contraindication to the use of corticosteroids or other immunosuppressive therapy. Data pertaining to disease, previous therapy and response to treatment were collected.

Treatment protocol

Rituximab was administered using the lymphoma protocol of 375 mg/m^2 weekly intravenous infusions for 4 weeks (on Day 0, 7, 14 and 21). One cycle of rituximab consisted of four weekly doses. All patients received the complete 4 dose cycle of rituximab along with corticosteroid during the treatment cycle. All other immunosuppressive therapy except intravenous immunoglobulin was discontinued prior to starting rituximab. The expectation was to discontinue adjuvant treatments if there was an adequate response to rituximab. Some patients who relapsed after achieving remission with rituximab received a second cycle of rituximab. Rituximab was supplied by the Ministry of Health, Sri Lanka.

Pre-treatment assessment

Complete base line investigations including full blood count (FBC), renal function tests (RFT), liver function tests (LFT), erythrocyte sedimentation rate (ESR), CRP, mantoux test, chest X ray, ECG, 2D echocardiogram, HIV serology, hepatitis B and C serology were done. Patients were meticulously screened to be clear of all infections, especially tuberculosis, hepatitis B and C.

Monitoring

Patients were regularly reviewed for any evidence of infection, fever and the disease control. Before each dose FBC, ESR and CRP were done and in the monthly follow up FBC, RFT, LFT and ESR were monitored in addition to the clinical parameters.

Assessment of response to treatment

Response to treatment in pemphigus patients (consisted the majority in the study population) was determined according to the international consensus statement[7]. Complete remission off therapy (CR) is the absence of new or established lesions while the patient is not receiving any systemic therapy for at least 2 months. Complete remission on therapy (CROT) is the absence of new or established lesions while the patient is receiving minimal therapy. Partial remission off therapy (PR) is the presence of transient new lesions that heal within 1 week without treatment while the patient is not receiving any systemic therapy for at least 2 months. Partial remission on minimal therapy (PROT) is the presence of transient new lesions that heal within 1 week while the patient is receiving minimal therapy, including topical corticosteroids. *Relapse/flare* is the appearance of 3 or more new lesions each month that do not heal spontaneously within 1 week or the extension of established lesions in a patient who has achieved disease control. Complete and partial responses could be achieved without therapy or with minimal therapy (≤10 mg/d of prednisone and/or minimal adjuvant therapy for ≥2 months).

In patients with diseases other than pemphigus the mean prednisolone dose at 3 months, 6 months and the final follow up was used as surrogate markers of disease activity and response to treatment.

Outcome measures

We examined response to treatment, times to relapse, and adverse reactions. The primary end points were time to failure and complete remission with or without treatment. Secondary end points included adverse events, long-term follow-up, and the number of treatment cycles received.

Statistical analysis

Descriptive statistics were used to analyse basic characteristics and categorical variables. Data was analysed using SPSS, version 19.0 for Windows (SPSS, incorporated).

Results

Patients

Characteristics of the 23 study patients are presented in the Table 1. Eighteen patients (78.3%) were female and five (21.7%) were male. The mean age at diagnosis was 45 and ranged from 23 to 85 years. Sixteen patients had PV, one each for PF, BP, EBA, dermatomyositis and three patients SLE with extensive cutaneous LE. The median disease duration before rituximab therapy was 31 (2-192) months. All patients were treated with systemic therapies (corticosteroids or immuno-suppressive and immunomodulatory medications) prior to rituximab treatment. All patients were receiving corticosteroids or immunosuppressive therapies at the time of first rituximab infusion. Number of dexamethasone cyclophosphamide pulses before rituximab ranged from 8 to 30. Patients with PV and SLE constituted those who had received pulse therapy.

Treatment

First treatment cycle

In all patients rituximab was administered according to the lymphoma protocol. They received adjuvant prednisolone during and following the first cycle. This was then gradually tapered off over several months.

Table 1. Characteristics of 23 patients

Charasteristic		*Number*	*Percentage*
Sex	Male	5	21.74%
	Female	18	78.26%
Median age at diagnosis (range)		45.2 (23-85)	
Diagnosis	Pemphigus vulgaris	16	69.5%
	Pemphigus foliaceus	1	4.35%
	Bullous pemphigoid	1	4.35%
	Epidermolysis bullosa acquisita	1	4.35%
	SLE	3	13.04%
	Dermatomyositis	1	4.35%
Previous treatment before rituximab therapy			
	Corticosteroids	23	100%
	Dexamethasone-cyclophosphamide pulse therapy	16	60.87%
	Azathioprine	14	69.57%
	Mycophenolatemofetil	3	13.04%
	Intravenous immunoglobulin	6	26.09%
	Plasma exchange	4	17.39%
	Cyclophosphamide	13	56.52%
	Methotrexate	1	4.35%
	Dapsone	3	13.04%
Number of dexamethasone-cyclophosphamide pulses before rituximab (range)		8-30	
Median duration of treatment prior to rituximab therapy in months (range)		31.4 (2-192 months)	

Table 2. Indications for rituximab

Indications for rituximab	*Number*	*Percentage*
Severe disease recalcitrant to standard therapy	**23/23**	**100%**
Refractory pemphigus vulgaris	16	69.56%
Refractory pemphigus foliaceus	1	4.3%
Refractory bullous pemphigoid	1	4.3%
Refractory epidermolysisbullosaacqusita	1	4.3%
Lupus nephritis	2	8.7%
CNS lupus	1	4.3%
Refractory dermatomyositis	1	4.3%

Sixteen (94%) of patients in the pemphigus group went in to complete remission on therapy at 3 months follow up. At the final follow up 16 individuals (94%) of the pemphigus group were in complete remission without adjuvant corticosteroid treatment. Response to therapy of the pemphigus group is summarized in Figure 1.

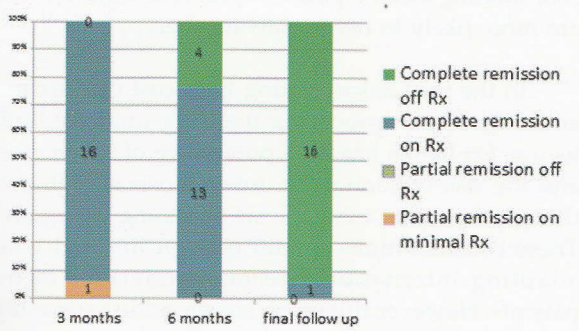

Figure 1. *Pemphigus disease activity at 3 months, 6 months and at final follow up after rituximab therapy.*

In the immunobullous disorders group mean prednisolone dose at the time of first cycle was 56.8 mg and was reduced to a mean dose of 10 mg at 3 months and 3.2 mg at 6 months after rituximab. In the connective tissue disorders group the mean prednisolone dose at the time of first cycle was 46 mg and was tapered to 17.5 mg and 10 mg at 3 months and 6 months respectively following rituximab (Figure 2).

Relapse

Pemphigus group

In the pemphigus group 15 patients (79%) who received one cycle of rituximab did not experience relapse. 89% were in complete remission off treatment and 11% were in remission with treatment at the final follow up. Four patients (21%) relapsed after the first cycle of rituximab and they received a second cycle of rituximab (lymphoma protocol) after one year.

Time to relapse ranged from 12 to 18 months and the mean time to relapse was 14.8 months.

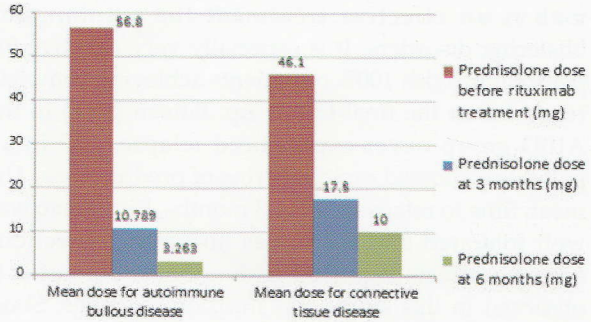

Figure 2. *Mean prednisolone dose reduction following rituximab.*

Connective tissue diseases

Patients (4) in the CTD group went in to partial remission following rituximab therapy, but it allowed tapering down of corticosteroid dose. Three patients with SLE relapsed. Rituximab did not induce durable remission in this group. Two patients who relapsed received a second cycle of rituximab (lymphoma protocol).

Table 3. Characteristics of patients who relapsed

Diagnosis	*Number of relapses*	*Second cycle rituximab*
SLE	3	1/3
Pemphigusvulgaris	4	4/4
EBA	1	1/1

Overall response to treatment

At the final follow up all patients in the pemphigus group were in complete remission off treatment and patients in the CTD group were in partial remission. The patient with EBA achieved significant reduction in disease activity and was in partial remission.

Adverse effects of treatment

No serious infections were reported during rituximab treatment for the duration of follow up. During the intravenous infusion one patient developed fever and one developed chills but they were not severe enough to discontinue treatment.

Deaths

Two patients with SLE died during the follow up. Both deaths occurred three years after receiving rituximab and they were not hospital deaths.

Discussion

Our results show that lymphoma protocol of rituximab is an effective treatment for autoimmune blistering disorders. It is especially very effective for pemphigus with 100% of patients achieving complete remission at the final follow up. Fifteen (15%) in the AIBD group never experienced relapse, and in all patients it allowed rapid tapering of prednisolone. The mean time to relapse was 14.8 months. Rituximab was well tolerated and there was no serious infectious adverse effects reported. Commonest side effects observed in this study was infusion reactions. Short term efficacy of rituximab has been established in several studies[2] and until recently long term data was unavailable. Especially data for Sri Lanka regarding safety and efficacy of rituximab is limited and this is the largest study to date on rituximab therapy in a dermatology setting. In patients with CTD rituximab failed to induce sustained remission but allowed tapering of the steroid dose in the short and medium terms. The primary indication for rituximab in the CTD group was not dermatological but clinical improvement of cutaneous lupus erythematosus was observed.

The monoclonal antibody rituximab binds to CD20 expressing B lymphocytes and removes them from the circulation for 6-12 months[4]. This is supportive of the observation in our study that relapses occurred at 14.8 months after the initial rituximab cycle when B cell counts have recovered. In most guidelines including the European Academy of Dermatology and Venereology 2015 guideline rituximab is recommended as a third line option for resistant pemphigus. Recently a landmark open label randomized trial published in the *Lancet* resulted in a paradigm shift in the management of pemphigus with evidence supporting rituximab in combination with short term steroids as a first line therapy for pemphigus[8]. This study compared rituximab combined with short term corticosteroids with prednisolone alone in 90 untreated patients and 89% of patients achieved complete remission of treatment at 24 months in the rituximab group compared to 34% in the prednisone group. Intravenous rituximab was given at a dose of 1 g on days 0 and 14 and 500 mg at months 12 and 18. Additionally patients in the rituximab group took a third of the cumulative prednisone dose that patients in the prednisone alone group took, and the number of serious side effects was lower in the rituximab group. The relapsed rate reported as 34%. The results of this study resulted in FDA granting rituximab Breakthrough Therapy Designation in March 2017 for this indication[3-4]. FDA Breakthrough Therapy Designation is intended to expedite the development and review of medicines with early evidence of potential clinical benefit in serious disease and to help ensure that patients receive access to medicines as soon as possible.

Limitations in our study include the retrospective design, the small sample size and the presence of confounding factors (patients with recalcitrant disease are more likely to need adjuvant therapy).

In the Sri Lankan setting high cost of rituximab and difficulty in procuring the drug urgently limits its use. Sri Lanka has high prevalence of tuberculosis and the risk of contracting tuberculosis is high even though the initial tuberculosis screening is negative. These considerations should be kept in mind when adapting international recommendations to our patients. However rituximab has the added advantage over cyclophosphamide in that long term malignancy risk, risk of secondary subfertility and haemorrhagic cystitis can be avoided - as a result has a place in management in younger patients with reproductive expectations.

Conclusions

Our experience shows that rituximab is an effective therapy for severe or refractory autoimmune bullous disorders. The lymphoma protocol is safe and efficacious in inducing long term remission in patients with pemphigus. In CTD group it is useful in the short term allowing tapering of corticosteroid but does not appear to induce long term remission. Patients who do not achieve remission after one cycle or patients who relapse benefit from further cycles. Rituximab when used according to the guidelines appears to be a safe therapeutic option with minimal serious side effects.

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