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Title:
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Date:
2018-02-01

Citation:
Robinson, A. J., Vu, M., Unglik, G. A., Varigos, G. A. & Scardamaglia, L. (2018). Low-dose rituximab and concurrent adjuvant therapy for pemphigus: Protocol and single-centre long-term review of nine patients. Australasian Journal of Dermatology, 59 (1), pp.e47-e52. https://doi.org/10.1111/ajd.12571.

Low-dose Rituximab and concurrent adjuvant therapy for pemphigus: Protocol and single-centre long-term review of nine patients

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Short running title:

Low-dose Rituximab for pemphigus, protocol and review

Acknowledgements:

The authors would like to thank Dr. Yew Yik Weng for advice and assistance with statistical analysis.

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ajd.12571

Received Date : 22-Apr-2016
Revised Date : 22-Aug-2016
Accepted Date : 23-Aug-2016
Article type : Small Case Series

ABSTRACT:

Pemphigus is an autoimmune B-cell mediated blistering disease, associated with significant morbidity and mortality. Rituximab has proven effective for treatment of steroid-refractory pemphigus, although there is controversy regarding the optimum dosing protocol. Additionally, effective disease control often requires long-term immunosuppression, even in disease-free periods. We present a case series of single-centre long-term follow up of nine patients with pemphigus, treated with two 500mg doses of Rituximab separated by 14 days along with concurrent adjuvant therapy. In all patients, low-dose Rituximab resulted in B-cell depletion, along with a reduction in blistering disease. Three of these patients required repeat dosing cycles, due to either relapsed disease or incomplete disease control following the first dosing cycle, and have remained disease free out to as long as 154 weeks thus far. Six patients developed minor infections throughout the course of their treatment, but no major complications were observed.

INTRODUCTION:

Pemphigus is a B-cell mediated autoimmune blistering disease, caused by pathogenic

antibodies directed against Desmoglein 1 and 3 and associated with significant morbidity and mortality. Pemphigus vulgaris (involving blistering of the skin and mucous membranes), and pemphigus foliaceous (which involves solely the skin) have been described, and due to due to the similarities in both the pathogenesis and management of

these conditions, most studies have focused on investigating these conditions as a group .

First line therapy for pemphigus is usually systemic corticosteroids (along with potent topical steroids) for initial disease control, with the early introduction of adjuvant corticosteroid-sparing agents such as azathioprine or mycophenolate mofetil[3]. With this difficult to manage condition, many patients require long-term immunosuppression for effective disease control, even in symptom-free periods.

Rituximab (a monoclonal antibody directed against CD20, a surface antigen on B lymphocytes) has proven efficacious for management of pemphigus, including in patients with disease refractory to management with other systemic therapies[4,2]. Although a single cycle of Rituximab has been shown to be effective for induction of remission in pemphigus, there is ongoing controversy regarding the most appropriate dose[2] and the the clinical utility of Rituximab is often limited by the high cost of this medication[5].

Rituximab dosing for off-label immunological indications such as pemphigus is often based on dosing previously used in randomised controlled trials (RCTs) for other conditions, reflected in the names of the two most commonly used protocols. Rituximab was initially investigated for use in pemphigus using the “lymphoma” protocol (involving four infusions of 375mg/m^2, each separated by one week)[4]. Given the lack of a malignant B cell clone in pemphigus and the similarities in pathogenesis with other autoimmune diseases, a fixed-dose protocol has subsequently been developed, similar to the protocol used for rheumatoid arthritis (involving two infusions of 1g, two weeks apart)[2]. Despite the common use of these doses, the initial selection of these doses for the above mentioned RCTs was arbitrary and not clearly based on pharmacologic considerations[6]. This combined with other factors including large inter-individual dose exposure and pharmacodynamic differences, has led to numerous trials and case series examining the effect of smaller doses for treatment of various diseases, even for severe conditions such as ANCA-

associated vasculidities [7]. A “low-dose” protocol has subsequently been shown to be effective for pemphigus, involving two infusions of 500mg Rituximab, separated by two weeks [8].

Despite multiple studies and meta-analyses investigating the optimum Rituximab dose for management of pemphigus, controversy still exists in this area. In the largest and most comprehensive meta-analysis to date [2], higher doses of Rituximab were shown to be associated with longer duration of complete remission compared to lower doses, but there was significantly higher associated cost, and no superiority in other outcomes measured.

MAIN TEXT:

We present a case series of nine patients with pemphigus from a single-centre long-term retrospective review, all treated with low-dose Rituximab in an outpatient setting, along with concurrent adjuvant therapy. All patients in this series had disease refractory to management with prednisolone and other non-biologic adjuvants. Approval for this study was granted following review by the Melbourne Health Human Research Ethics Committee, and patients were recruited sequentially having received Rituximab from 2012 through to 2015. All patients consented to their anonymised data being used for this report, which was collected through a retrospective review of all clinical notes and pathology results. Diagnosis of pemphigus vulgaris or pemphigus foliaceus was confirmed in all patients by integrating clinical history, serology and histopathology. All patients were treated initially with prednisolone, along with the use of various adjuvants (such as MMF or azathioprine), as steroid sparing agents. Patients in this series were treated with two 500mg infusions of Rituximab, each separated by two weeks, in an outpatient setting, using the protocol described in this Table 1. All patients were monitored on a regular basis following therapy. Clinical monitoring and serology of each patient varied depending on assessment of clinical need at the time of review. End points for review were as defined in a previously published consensus statement [9], and were collated for each patient, as

shown in Table 2.

Demographics, comorbidities and previous therapies used for all patients in this series are outlined in Table 2, along treatment response and clinical endpoints. Patients were followed up for a period between 4 and 154 weeks post-Rituximab treatment. All patients were found to have significant depletion of circulating B cells following Rituximab treatment, reaching a nadir of zero for B cell counts (using a standard three colour flow cytometry assay to identify CD19+ CD2- B cells; data not shown). A wide inter-individual variation was observed in clinical responses seen to Rituximab (in terms of time to early and late end points, relapse rate along with the prednisolone and adjuvant doses required for disease control), which did not appear to correlate with serology or disease severity. Similar wide variation in pemphigus disease responses to Rituximab has also been observed in other studies [2,8,11,12].

Three of the nine patients in this series relapsed and were treated with additional cycles of Rituximab (2x500mg doses), resulting in subsequent disease control. For all relapsed patients, B cell repopulation (data not shown) and serological evidence of relapse was observed prior to or concurrent with clinical relapse. These observations suggest a role for close serological and B cell monitoring of patients treated with Rituximab, in order to identify patients at higher risk of further relapse, who might then benefit from closer clinical monitoring and increased adjuvant doses. Data for end points of patients treated with repeat cycles is shown in Table 3.

Figure 1 shows a graphical representation of the clinical progress of patient 4 (as referenced in Table 2 above), who received a total of 3 cycles of low-dose Rituximab (2x500mg per cycle), before finally achieving durable clinical remission. Figure 1a shows disease activity versus circulating B cells and serological indices, whilst Figure 1b shows concurrent therapy with prednisolone and mycophenolate mofetil, in addition to the three cycles of Rituximab. Mean times to both early and late end points appeared to be reached sooner in patients receiving additional cycles of Rituximab (151$\pm$131 days for EEP cycle 1 compared to 58$\pm$56 days for EEP cycle 2, and 288$\pm$218 days for LEP cycle 1 compared to 110$\pm$100 days for LEP cycle 2; data expressed as mean $\pm$ standard deviation). Additionally, Patient 4 required less concurrent prednisolone and MMF to achieve disease control with each subsequent Rituximab cycle, as shown in Figure 1a, and Table 2. A similar observation of an apparent increase in magnitude of response in subsequent

dosing cycles of Rituximab has been observed in a previous study , suggesting that repeat cycles may provide additional benefit for depleting the pathogenic B cell population responsible for disease.

Multiple studies have demonstrated the efficacy of Rituximab in pemphigus, with various dosing protocols. In the largest meta-analysis to date, involving data from 578 patients over 30 studies, higher dose Rituximab was found to be associated with a significantly longer duration of complete remission, but only a trend towards a shorter time to disease control and lower relapse rate (without statistical significance), compared to lower dose Rituximab protocols [2]. Our data additionally supports the practical approach of using low-dose Rituximab combined with adjuvant therapy for inducing disease control and maintaining remission in pemphigus. Given the prohibitive cost of Rituximab, the observations of wide inter-individual variation, and the observation of an apparent greater magnitude of effect on repeat dosing cycles, we recommend the use of the low-dose Rituximab protocol described, in patients refractory to management with non-biologics alone. Additionally, we recommend combining Rituximab with prednisolone and an adjuvant such as MMF, which can be modulated based on patients individual clinical response. In those patients who do subsequently relapse, further low-dose Rituximab cycles can then be employed to facilitate disease control and re-induce remission. This approach represents a practical and cost effective method for using this effective but costly medication.

CONCLUSION:

Low-dose Rituximab, with concurrent use of adjuvants such as prednisolone and mycophenolate mofetil is a safe and effective means of inducing and maintaining remission in pemphigus, and re-dosing in the event of relapse is an efficient means of achieving ongoing disease control. For many patients, the prohibitive cost of Rituximab is a limiting factor in its utility for management of pemphigus. The low-dose approach described in this and other studies, combined with other adjuvants, represents a practical protocol to assist in access to Rituximab for patients refractory to management with other systemic agents. Further research with larger multi centre randomised controlled trials is

necessary to better understand the optimum dosing of Rituximab in pemphigus and which patients are likely to respond or relapse, along with the optimum adjuvant protocols for long-term management of this difficult condition.

References:

1. Reguiai Z, Tabard T, Maizières M et al. Rituximab treatyment of severe pemphigus: long-term results including immunologic follow-up. *J Am Acad Dermatol*. 2012; 67(4): 623-9.

2. Wang HH, Liu CW, Li YC et al. Efficacy of rituximab for pemphigus: a systematic review and meta-analysis of different regimens. *Acta Derm Venereol*. 2015; 95(8):928-32.

3. Martin LK, Werth VP, Villaneuva EV et al. A systematic review of randomized controlled trials for pemphigus vulgaris and pemphigus foliaceus. *Am Acad Dermatol.* 2011; 64(5):903-8.

4. Joly P, Mouquet H, Roujeau JC et al. A single cycle of rituximab for the treatment of severe pemphigus. *N Engl J Med.* 2007; 357(6):545-52.

5. Heelan K, Hassan S, Bannon G et al. Cost and Resource Use of Pemphigus and Pemphigoid Disorders Pre- and Post-Rituximab. *J Cutan Med Surg*. 2015; 19(3):274-82.

6. Maloney DG, Liles TM, Czerwinski DK et al. Phase I clinical trial using escalating single-dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2B8) in patients with recurrent B-cell lymphoma. *Blood* 1994; 84(8): 2457-66

7. Turner-Stokes T, Sandhu E, Pepper RJ et al. Induction treatment of ANCA-associated c=vasculitis with a single dose of rituximab. *Rheumatology* 2014; 53(8): 1395-403.

8. Horváth B, Huizinga J, Pas HH et al. Low-dose rituximab is effective in pemphigus. *Br J Dermatol*. 2012; 166(2):405-12.

9. Murrell DF, Dick S, Ahmed AR et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. *J Am Acad Dermatol.* 2008; 58(6):1043-6.

10. Cho HH, Jin SP and Chung JH Clinical experiences of different dosing schedules of rituximab in pemphigus with various disease severities. *J Eur Acad Dermal Venereol.* 2014; 28(2): 186-91.

11. Kanwar AJ, Vinay K, Sawatkar GU et al. Clinical and immunological outcomes of high- and low-dose rituximab treatments in patients with pemphigus: a randomized, comparative, observer blinded study. *Br J Dermatol.* 2014; 170(6):1341-9.

12. de Sena Nogueira Maehara L., Huizinga J. and Jonkman MF. Rituximab therapy in pemphigus foliaceus: report of 12 cases and review of recent literature. *Br J Dermatol* 2015; 172(5): 1420-3.

13. Leshem YA., Hodak E, David M et al. Successful treatment of pemphigus with biweekly 1-g infusions of rituximab: A retrospective study of 47 patients. *J Am Acad Dermatol* 2013; 68(3): 404-11.

Figure legends:

Table 1: Protocol for low-dose Rituximab for the treatment of pemphigus.

Table 2: Patient data and endpoints.

PV: Pemphigus vulgaris; PF: Pemphigus foliaceus. “Disease history” represents weeks between diagnosis and first cycle of Rituximab. MMF: Mycophenolate mofetil; Aza: Azathioprine; IVIG: Human intravenous immunoglobulin; Mtx: Methotrexate; Pred: Prednisolone. GORD: Gastro-Oesophageal reflux disease; NAFLD: Non-alcoholic fatty liver disease; OP: Osteoporosis; T2DM: Type 2 Diabetes mellitus. Co-med: Comedication at the time of first Rituximab cycle. EEP: Early end point; DC: Disease control; EC: End of consolidation phase. LEP: Late end point; PR ON: Partial remission on minimal therapy; CR ON: Complete remission on minimal therapy; CR OFF: Complete remission off all

therapy. DSG1: Desmoglein 1; DSG3: Desmoglein 3; AIS: Anti-intercellular substance antibody. FU: Follow up; Total FU indicates number of weeks patients were followed up post-cycle 1. CPred: Cumulative prednisolone taken post-cycle 1; Cx: Complications; HSV: Herpes simplex virus; URTI: Upper respiratory tract infection; CMV: Cytomegalovirus. n/a: Not applicable.

Table 3: Patient data and endpoints for patients receiving additional cycles of Rituximab.

D0: Day zero of cycle. MMF: Mycophenolate mofetil; Pred: Prednisolone. FTA: Patient failed to attend follow up appointments. EEP: Early end point; DC: Disease control; EC: End of consolidation phase. LEP: Late end point; CR ON: Complete remission on minimal therapy; CR OFF: Complete remission off all therapy. DSG1: Desmoglein 1; DSG3: Desmoglein 3; AIS: Anti-intercellular substance antibody.

Figure 1: Clinical progress graph for patient 4.

Data is shown for patient 4 (see Table 2), who received three total cycles of Rituximab, each 2x500mg. Figure 1a shows disease activity (in red), over time, along with circulating B cells (in purple, x10e9), along with Desmoglein 1 serology (orange), and Desmoglein 3 serology (grey). Figure 1b shows daily prednisolone dose (green, in miligrams) and daily Mycophenolate mofetil dose (blue, in milligrams, given over two divided doses), over time. Purple arrows indicate dates on which this patient received Rituximab infusions. AD: Active disease; DC: Disease control; PR ON: Partial remission on minimal therapy; CR ON: Complete remission on minimal therapy; CR OFF: Complete remission off all therapy.

Figure 1a

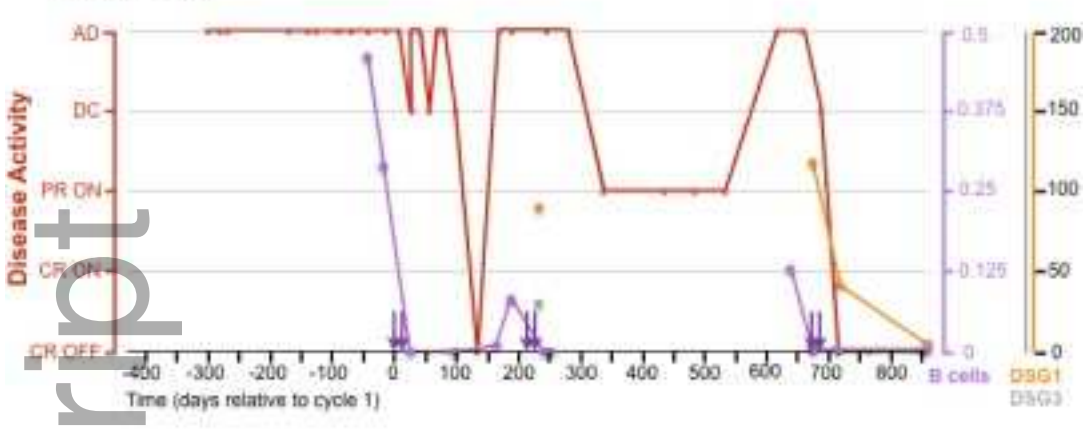
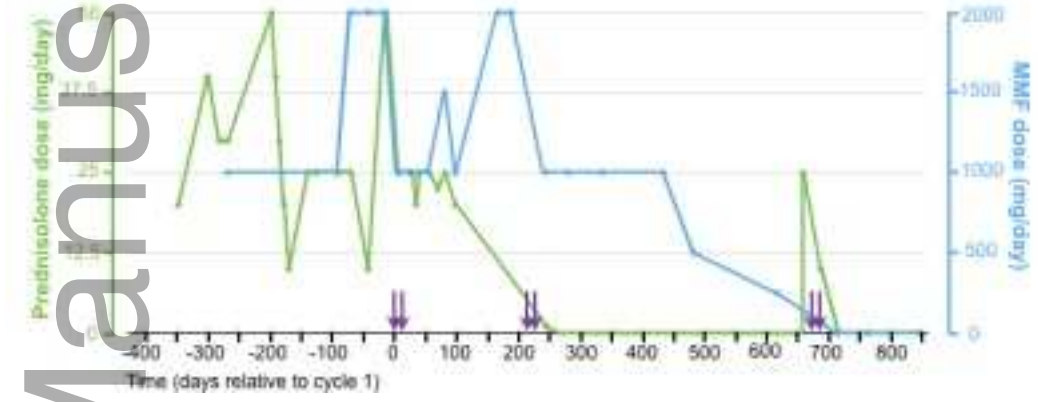


Figure 1b



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