The prompt use of rituximab could decrease adverse effects in patient with pemphigus vulgaris: a preliminary evaluation

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Paolo G. ARDUINO[1], Roberto BROCCOLETTI[1], Mario CARBONE[1], Davide CONROTTO[1], Veronica SCIANNAMEO[3], Alessio GAMBINO[2], Marco CABRAS[1], Marco CARROZZO[4], Simone BALDOVINO[5].

[1]Department of Surgical Sciences, CIR-Dental School, University of Turin, Italy;

[2]Dimeas, Politecnico of Turin, Turin, Italy

[3]Unit of Epidemiology, Regional Health Service ASL TO3, Grugliasco, Italy;

[4]Department of Oral Medicine, School of Dental Sciences, University of Newcastle upon Tyne, Newcastle upon Tyne, UK;

[5]Center of Research of Immunopathology and Rare Diseases-Coordinating Center of the Network for Rare Diseases of Piedmont and Aosta Valley, Department of Clinical and Biological Sciences, University of Turin, Turin, Italy.

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Corresponding author:

Dr. Paolo G. Arduino

Department of Surgical Sciences, Oral Medicine Section

CIR-Dental School, University of Turin

Via Nizza 230, 10126 Turin, Italy. Tel: +390116331522.

E-mail: paologiacomo.arduino@unito.it

Abstract

Background: The systemic use of corticosteroid is the treatment of choice for patients with pemphigus vulgaris (PV), but adverse effects are frequent. To date, the use of rituximab (RTX) for PV patients is usually indicated when they failed first line immunosuppressive therapies. The early use of RTX could theoretically lessen adverse effects.

Methods: We performed a single-center study on patients with predominantly oral PV, treated with systemic corticosteroid and the prompt use of 1000 mg of intravenous RTX two week apart. We evaluated the clinical response and the reported adverse effect during a period of 24 months, comparing those with a previously published series.

Results: The study group comprised 11 patients, while the control group comprised 98 patients. The average time to achieve complete clinical remission was 3.2±2.72 months. Study group took steroids for a mean time of 11.09± 2.02 months, and they are all actually disease free with no medication. Only 3 patients (27.3%) developed plain side effects. The effect of the length of the corticosteroid therapy on the side effects (also adjusted by sex, age, and clinical oral involvement) was statistically different in the two groups: the prompt use of RTX reduced of 94% the chance to have adverse effects (p=.001).

Conclusions: This is the first report of the use of RTX as first line of therapy for PV patients with predominantly oral involvement. With the proposed regimen, the adverse effects have been minimized compared with classic systemic corticosteroid-centred therapy. Multi-center randomized controlled trail are however necessary.

1. INTRODUCTION

Pemphigus is a group of potentially life-threatening and organ-specific autoimmune disorders, described with cutaneous and/or mucosal blistering. Pemphigus vulgaris (PV), usually affects first the oral mucosa and its management aims to induce and maintain clinical remission with as few as possible adverse effects. Because of the lack of international agreed recommendations, either the dosage of corticosteroids and choice of adjuvant agents usually reflect the experience of clinicians at various centers.[1-3] Recently, we confirmed that systemic corticosteroid should be considered the mainstay medication for predominantly oral involvement.[1]

Rituximab (RTX) is a chimeric monoclonal anti-CD20 antibody that targets pre-B cells and mature B cells, resulting in complement and antibody-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and apoptosis.[4] RTX has been used as first line intervention together with short-term prednisone in patients with mucosal-cutaneous PV and it was suggested to be more effective than prednisone alone, with fewer adverse events.[5] Few data are on RTX effectiveness are available for predominantly oral PV and most of the studies report different regimens; moreover, it has been not yet used as a first line intervention in oral cases.[1, 6, 7]

We have evaluated the efficacy and safety of prompt use of RTX joint with prednisone in a cohort of Italian patients with predominantly oral PV.

2. MATERIALS AND METHODS

We describe a case series of newly diagnosed PV patient treated with steroid and with the immediate use of RTX since January 2017, with a follow up to 24 months. The diagnosis was confirmed by histopathological examination and direct immunofluorescence studies. The patient group received treatment with systemic corticosteroids (typical starting dose of 1.5 mg/kg per day of prednisone, for variable lengths of time usually of 2-4 months, and then

tapered in other 8 months approximately), together with RTX (1 g IV, two infusions two week apart within 6 months from diagnosis) provided at the Center of Research of Immunopathology and Rare Diseases (S. Giovanni Bosco Hospital, Turin, Italy). We described therapeutic response and adverse effects as previously.[1]

The ethics review board of the CIR - Dental School approved the study (CIR-PO 2018/2435). Qualitative variables were described via frequencies and percentages; quantitative ones via median and interquartile range (IQR), due to the low sample size in the new group and the following lack of the normality assumption. As control group, we decided to select all PV patients reported recently by our group and treated with systemic medication.[1] Sixteen patients of this group received intravenous RTX, after standard treatment failure.

Differences were tested via chi squared test or Fisher's exact test when appropriate for qualitative variables and via the non-parametric Mann-Whitney U test for quantitative ones. Univariate and multivariate logistic regression models were computed. Odds Ratios (OR) and their 95% Confidence Interval (95% CI) were reported. Statistical analyses were performed using R version 3.4.0. The level of significance was set at 0.05.

3. RESULTS

The study group comprised 11 unrelated Caucasian patients (7 female and 4 male), with a median age of 60.00 [49.00, 68.00].

The control group comprised 95 unrelated Caucasian patients (60 female and 35 male), together with 2 female and 1 Afro-Caribbean male (F : M; 1.65 : 1), mean age 54.56 (±14.95).[1]

The oral mucosal disease severity (MDS) was assessed as moderate (buccal and gingivolabial mucosal involvement) in 2 patients, and severe (extensive oral mucosal involvement) in 9 patients. The average time to achieve complete clinical remission was

3.2±2.72 months after commencement of therapy, very similar to the control group (3.9 ± 2.72 months) (Figure 1).

Patients in the test group took corticosteroids for a mean time of 11.09 month (± 2.02) and they are all actually disease free with no medication, compared to only 41% of the control group in remission and off medication. Only 3 patients (27.3%) developed 1 or 2 more of the following adverse effects: one patient developed hypertension and hyperglycaemia; the second one hypertension, folliculitis and the third fatigue, hypertension and hyperglycaemia. These effects, however, disappeared after 6 months from the withdrawal of corticosteroid therapy. Contrarily, in the control group, sixty-nine patients (72.63%) developed detectable adverse effects from the immunosuppressive drugs.

Table 1 described the difference in adverse effects between the test and the control group. The effect of the length of the steroid therapy on the side effects (also adjusted by sex, age, and clinical oral involvement) was statistically different: the prompt use of RTX reduced of 94% the chance to have adverse effects (p=.001).

4. DISCUSSION

To date, the gold standard of therapies for oral PV is generally thought to be a relatively long-course of corticosteroid therapy. Usually, prednisone is given at 0.5 mg to 1.5 mg/Kg/day, combined with an immunosuppressive adjuvant drugs such as azathioprine or mycophenolate mofetil immediately at the start of therapy or during the tapering stage. However, the above-mentioned regimes may still cause many and potentially complex adverse effects, particularly complications due to expected prolonged use of prednisone (>4 months) or corticosteroid dose dependency above minimal therapy (>10 mg/day).[1, 4]

RTX is usually considered for PV as third-line treatment, in refractory disease or in case of contraindications to immunosuppressants.[8]

Recently, it has been reported that first-line use of TX plus short-term prednisone for patients with PV or pemphigus foliaceous could be more effective than prednisone alone, and could cause fewer adverse events.[4] Joly and co-workers used 2 infusions (1000 mg each, on day 0 and day 14) with 2 additional half-dosage infusions at months 12 and 18.

We are likely the first to report the use of RTX, together with systemic corticosteroids as first line intervention in patients with predominantly oral PV.

Notably, we avoided in the current group of patients to deliver additional RTX infusions because the results were excellent with just the first two infusions. Even more importantly, with the proposed regimen, the adverse effects have been significantly reduced.

Our experience suggests that RTX as first line therapy with prednisone can be as effective and possibly safer that traditional just corticosteroid centred therapies for predominantly oral PV.

However, further trials with larger cohorts and possibly randomized and controlled are warranted to confirm these preliminary promising data.

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Conflicts of interest

All authors have no conflict of interest to declare.

REFERENCES

1. Arduino PG, Broccoletti R, Carbone M, et al. Long-term evaluation of pemphigus vulgaris: A retrospective consideration of 98 patients treated in an oral medicine unit in north-west Italy. *J Oral Pathol Med* 2019;48:406-412.
2. Ojaimi S, O'Connor K, Lin MW, Schifter M, Fulcher DA. Treatment outcomes in a cohort of patients with mucosal-predominant pemphigus vulgaris. *Intern Med J.* 2015;45:284-292.
3. McMillan R, Taylor J, Shephard M, et al. World Workshop on Oral Medicine VI: a systematic review of the treatment of mucocutaneous pemphigus vulgaris. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015;120:132-142.
4. Cirillo N, Cozzani E, Carrozzo M, Grando SA. Urban legends: pemphigus vulgaris. *Oral Dis* 2012;18:442-558.
5. Joly P, Maho-Vaillant M, Prost-Squarcioni C, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomized trial. *Lancet.* 2017;389:20131-2040.
6. Fortuna G, Calabria E, Ruoppo E, et al. The use of rituximab as an adjuvant in the treatment of oral pemphigus vulgaris. *J Oral Pathol Med* 2019 Aug 17. doi: 10.1111/jop.12951.
7. Laftah Z, Craythorne E, Mufti GJ, du Vivier A. Clinical efficacy of rituximab in the treatment of pemphigus vulgaris: A 10-year follow-up. *J Oral Pathol Med* 2019;48:861-862.
8. Feliciani C, Cozzani E, Marzano AV, et al. Italian guidelines in pemphigus – adapted from the European Dermatology Forun (EDF) and European Academy of

Dermatology and Venerology (EADV). *Giornale Italiano di Dermatologia e Venereologia* 2018;153:599-608.