Rituximab – A Novel Treatment for Pemphigus in Malta

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Abstract

Until recently, the main treatment for pemphigus has been systemic corticosteroids, usually administered at high doses with consequent side-effects. Lately, the biological agent rituximab has been introduced as an effective treatment for this condition.

This article describes seven cases of pemphigus successfully treated with rituximab in Malta and discusses the benefits and drawbacks of this novel treatment modality.

Key words

Pemphigus Vulgaris; Rituximab; Immunomodulation

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Introduction

Pemphigus is an uncommon but serious cutaneous immunobullous disorder, generally of the middle-aged, where blistering occurs intraepithelially, at the level of the intercellular desmosomes due to autoantibodies (typically to desmoglein 3 in mucosal-dominant disease and to desmoglein 1 and desmoglein 3 in mucocutaneous disease).[1-2] The pathogenic role of anti-desmoglein autoantibodies is evidenced by development of pemphigus vulgaris-like lesions in neonatal mice infused with anti-desmoglein IgG and occurrence of a pemphigus vulgaris-like syndrome in genetically-modified desmoglein 3 knockout mice.[3]

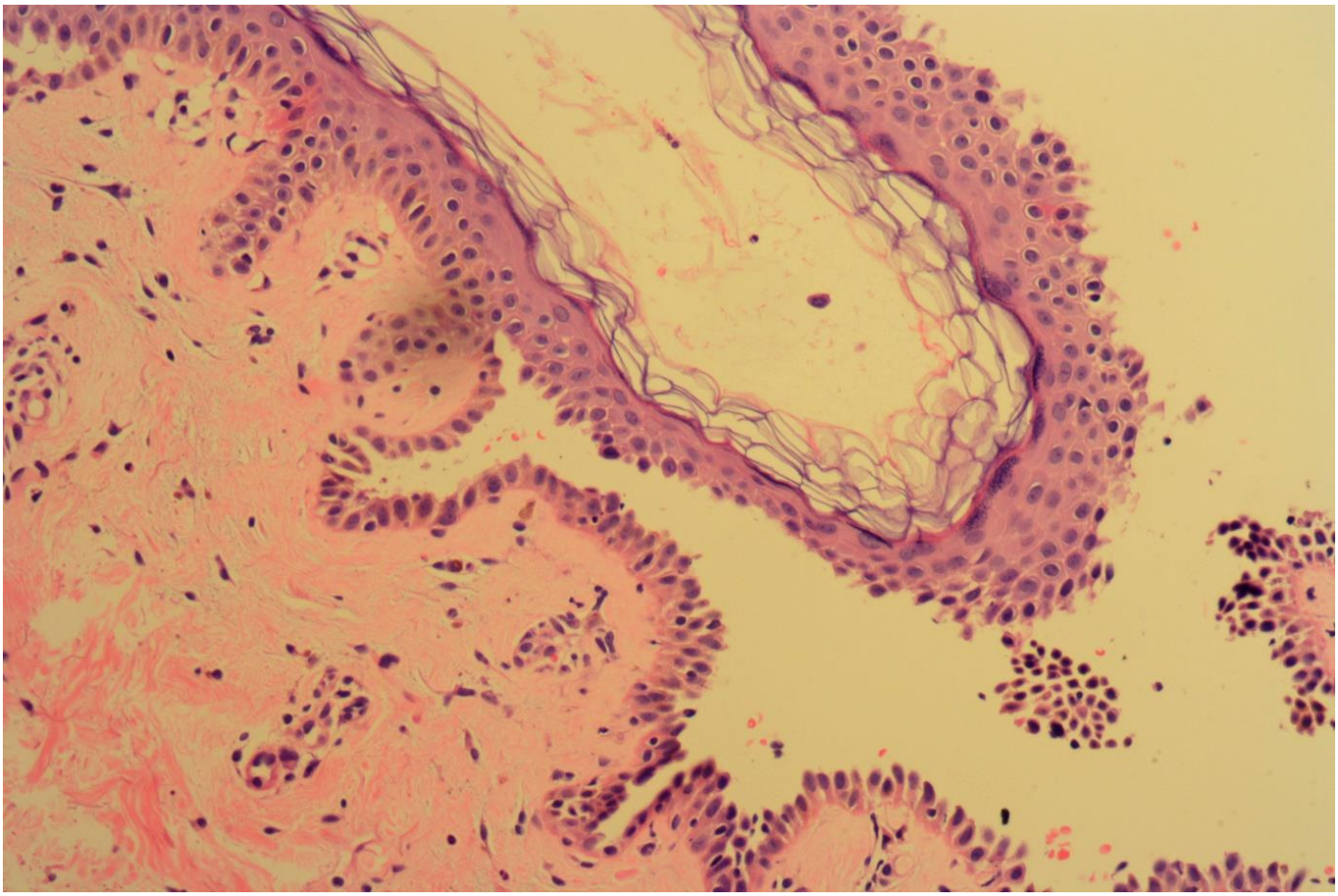
In pemphigus vulgaris, blistering may appear in both the skin and mucosae. Skin blisters and erosions occur in the majority of cases at some stage, mostly on the scalp, face, neck, back and upper chest.[4] Mucosal disease is the only manifestation in some cases. Apart from being life-threatening, pemphigus has a major impact on patients' quality of life, causing significant pain and

discomfort, especially in cases with oral involvement.

Before the advent of corticosteroids, pemphigus mortality reached 75% with many patients dying of sepsis, *Staphylococcus aureus* being the commonest pathogen on diseased skin.[5-6] Until recently, the mainstay of therapy has been systemic steroids combined with steroid-sparing agents such as azathioprine,[7] mycophenolate sodium[8] and cyclophosphamide.[9] Other treatments employed with variable efficacy include cyclosporine,[10] intravenous immunoglobulins,[11] photodynamic therapy,[12] immunoadsorption[13] and plasmapheresis.[14] There are no large randomised controlled trials comparing different treatment regimens so data is limited to that derived from retrospective studies.[8] Modern pemphigus treatment has decreased mortality to under 5%, however, the need for steroids to control disease in most cases exposes patients to significant side-effects.[9]

Rituximab is an IgG1 chimeric mouse/human anti CD-20 antibody that causes antibody-mediated B–cell lysis.[15] It has recently been shown to be effective for treating pemphigus and appears particularly useful in patients in whom traditional therapy is insufficient or inappropriate.[16] The drug has become available locally and this article describes its use in seven cases of pemphigus vulgaris in Maltese patients.

Figure 1: *H&E x40 - Histology of skin biopsy of Case 1 showing the split just above the basal layer, with tombstone morphology of the remaining basal cells and acantholytic cells in the blister lumen*



Case series

We report seven cases of pemphigus vulgaris treated with rituximab in Malta between 2013 and 2016. Four patients were male and three were female with a mean age at diagnosis of 57 years (range 44-70 years). The main presenting features were blisters, superficial ulcers and erosions on the trunk and head and neck. Five patients had painful ulcers and erosions in the oral mucosa. Other symptoms reported included hoarseness, odynophagia, nosebleeds, auditory canal erosions and crusted plaques on the trunk.

All cases were confirmed histologically, with intraepidermal clefting and acantholysis seen in all cases. Direct immunofluorescence was available in five cases, all of which showed typical intercellular C3 and IgG deposition in the epidermis. The histology of one of our patients is shown in Figure 1.

Various systemic treatments were given before administration of rituximab. These included oral and intravenous steroids, azathioprine, mycophenolate sodium, methotrexate, dapsone, intravenous immunoglobulins and colchicine.

The rituximab regimens used in our patients were once-weekly 500mg intravenous infusions for four weeks or two intravenous infusions of 1g two weeks apart. Excellent responses were reported in all cases after a few weeks. Three patients entered remission after only one rituximab cycle. Four patients had recurrences after an average of six months but the symptoms were milder in all cases. Of these patients, two went into remission after the second cycle of rituximab whilst another patient went into remission after the third cycle of rituximab. One patient had a very mild recurrence which was treated successfully with intravenous immunoglobulin. Some low-dose immunosuppressive treatment continues to be required to maintain control in all patients. This includes mycophenolate combined with low-dose prednisolone (5mg daily), azathioprine in isolation, and azathioprine combined with low-dose prednisolone (5mg daily). Improvement of cutaneous features following rituximab in one of our patients is shown in Figure 2.

***Figure 2**: Case 5 before (left) and after (right) rituximab therapy, showing resolution of extensive blistering and erosions on the back*

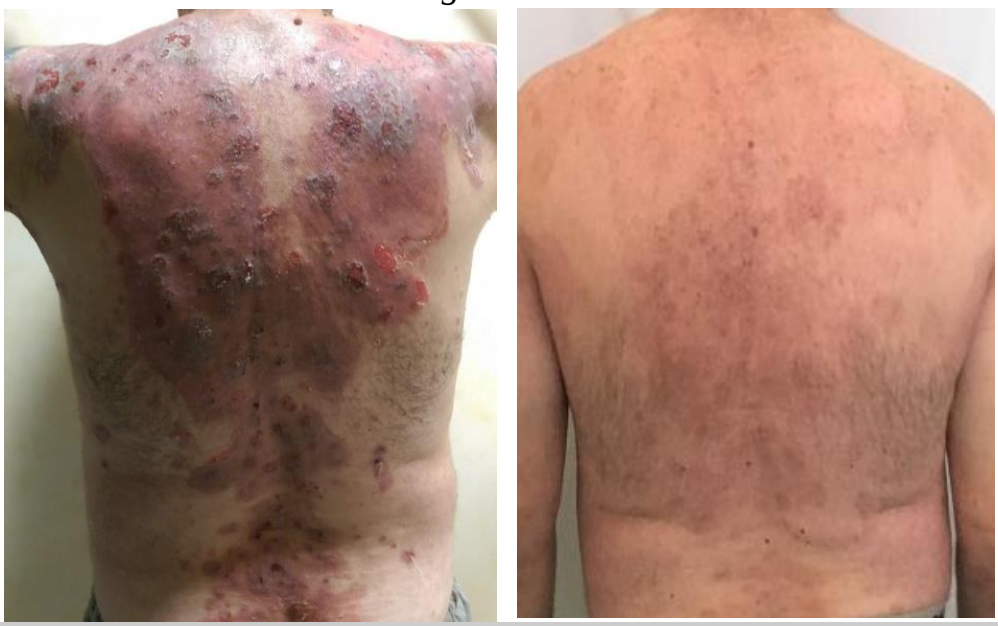


Table 1: *Details of 7 cases of pemphigus vulgaris treated in Malta with rituximab between 2013 and 2016 (IVIG – intravenous immunoglobulins)*

	Age at diagnosis (years)	**Sex**	**Symptoms at presentation**	**Histology & Immunofluorescence (IF)**	**Treatment attempted before rituximab**	**Rituximab regimen/doses used**	**Response**	**Rituximab side-effects**
Case 1	51	F	• Painful ulcers on hard palate and buccal mucosa • Nose bleeds • Persistent sore throat • Auditory canal erosions	• Suprabasal blistering with acantholytic cells in intraluminal bulla • Dilapidated brick wall appearance • IF – weak intercellular positive staining in basal layers for C3 and IgG	• Prednisolone + azathioprine • Prednisolone + iv methylprednisolone + mycophenolate sodium	- 4 once-weekly 500mg infusions - 1 g 2 weeks apart for 2 subsequent infusions	After 1st – dramatic improvement + minor recurrence after 6 months After 2nd – slight recurrence after 1 year After 3rd - remission	Minor reaction during 3rd cycle - pruritic erythema on the hands, spreading to arms and face; no systemic symptoms
Case 2	53	M	• Odynophagia • Mouth ulcers • Hoarseness • Blisters on left supraclavicular area and chest	• Intraepidermal clefting with acantholysis • Basal keratinocytes still attached to basement membrane with a tombstone appearance • Sparse chronic inflammatory cell infiltrate including a few eosinophils • IF – intercellular C3 and IgG deposition in epidermis	• Prednisolone • Prednisolone + azathioprine	- 4 once-weekly 500mg infusions, - 1 g 2 weeks apart for 1 subsequent infusion	After 1st –improvement + minor recurrence after a few weeks After 2nd – remission	Nil
Case 3	44	M	• Blisters over scalp, chest and abdomen	• Suprabasal acantholysis • IF - intercellular C3 anf IgG deposition in epidermis	• Dapsone • Dapsone + prednisolone • IVIG	- 4 once-weekly 500mg infusions - 2 500mg infusions	After 1st – improvement + flare after 9 months After 2nd – remission	Nil

Case 4	50	F	• Extensive painful oral ulcers	• Suprabasal acantholysis with basal keratinocytes remaining intact with a tombstone appearance • Superimposed viral changes within nuclei of keratinocytes implying superimposed herpes simplex • IF – IgG deposition in epithelium	• Prednisolone + azathioprine	- 4 once-weekly 500mg infusions	Remission	Nil
Case 5	63	M	• Scaly eruption over chest • Plaques on face, scalp, neck and upper trunk, limbs and thighs • Erosions in oral mucosae • Blisters on lower back	• Intraepidermal blister with partially preserved basal keratinocytes • Mild chronic inflamation with a few eosinophils • IF - equivocal IgG and C3 deposition intercellularly in the epidermis	• Topical clobetasone • Prednisolone • Azathioprine	- 1g 2 weeks apart	Recurrence with facial bullae, for which he was given IVIG, then entered remission	Nil
Case 6	69	F	• Mouth ulcers • Blisters on lower back	• Mucosal hyperplasia + suprabasilar clefting • Acantholysis • Basal keratinocytes with a tombstone appearance • IF – Not available	• Prednisolone + azathioprine	- 1g 2 weeks apart	Remission	Nil
Case 7	70	M	• Persistent lip ulcer • Blister over scar	• Submucosal epithelial split with hobnail type mucosal cells • Underlying haemorrhage • IF – Not available	• Prednisolone • Prednisolone + azathioprine • Prednisolone + colchicine • Prednisolone + IVIG • Prednisolone + IVIG + dapsone • IVIG + Dapsone	- 1g 2 weeks apart	Remission	Nil

Rituximab was well tolerated in all cases with only one patient developing a significant side-effect, namely pruritic erythema on the hands spreading to the arms and face without systemic symptoms during the third treatment cycle. The infusion was stopped and the erythema resolved without treatment within two hours.

Details of the seven cases are shown in Table 1.

Discussion

The mechanism of rituximab action is not yet fully-understood. Although it decreases production of pathogenic auto-antibodies, it does not affect levels of protective antibodies and so total antibody titre remains unchanged. One theory for this is that whereas pathogenic autoantibody-producing plasma cells are CD-20 positive and thus targeted by rituximab, protective plasma cells are CD-20 negative and hence not targeted.[17]

Rituximab entered clinical use in the 1990s, mainly to treat lymphoma and rheumatoid arthritis. Other indications include ANCA-positive vasculitis, systemic lupus erythematosus, dermatomyositis and primary Sjogren's syndrome.[15] It was first used in the context of autoimmune bullous diseases in 1999 by Heizmann et al who reported a case of paraneoplastic pemphigus successfully treated by rituximab, and is increasingly being used worldwide in the management of pemphigus.[18] Locally it was first used to treat pemphigus in 2013. Other autoimmune bullous diseases for which treatment with rituximab has been employed include bullous pemphigoid, mucous membrane pemphigoid and epidermolysis bullosa acquisita.[19]

Rituximab has a half-life of around 20 days, and is given by slow intravenous infusion.[15] The dosing protocols most commonly used are the lymphoma protocol, consisting of four weekly infusions of 375 mg/m^2 and the rheumatoid arthritis protocol, where two infusions of 1g are given two weeks apart.[2] However, there is no scientific rationale reported in the literature as to why these two protocols should be used in pemphigus. The protocols appear equivalent in terms of remission and relapse rates although remission may be more prolonged with higher rituximab doses.[20] Rituximab may be administered in conjunction with intravenous immunoglobulins, with early studies of such combination treatment reporting promising results.[16,21]

Infusion reactions have been reported in 25% of individuals receiving their first rituximab dose. Such reactions tend to be mild to moderate in nature, the severity decreasing with subsequent doses. The risk of infusion reactions may be reduced by premedication (including analgesics, antihistamines and steroids).[15] In our series, a minor cutaneous infusion reaction occurred in one patient, during her eighth infusion, despite premedication with prednisolone, chloremphenamine and paracetamol. Other more serious possible adverse events include an increased infection risk (including opportunistic pathogens), progressive multifocal leukoencephalopathy, cytopenia and cardiac events in individuals with underlying cardiac problems. The incidence of severe adverse effects does not appear to be influenced by the protocol used.[20] Paradoxical worsening of pemphigus following rituximab infusion has also been reported.[22]

Contraindications to rituximab include severe immunosuppression, active infection, uncontrolled cardiac disease and recent live vaccination. Before starting rituximab,

patients should be screened for cardiac disease, current or previous infections that could be reactivated (e.g. tuberculosis and viral hepatitis) and vaccination status (especially for pneumococcal disease and influenza) checked. Viral hepatitis is not an absolute contraindication, however, it must be looked out for, and a decision on whether or not rituximab may be prescribed taken in the light of expert hepatological advice.[15] Due to its reported adverse effects on pregnancy, women are advised to avoid pregnancy during treatment and for at least 12 months afterwards.[15,23]

Patients treated with rituximab should be monitored for signs of infection and neurological complications. Basic blood tests, including full blood count, renal profile and liver enzyme levels should be assessed regularly. It is also recommended that serum immunoglobulins and lymphocyte subsets are checked prior to each subsequent dose.[15]

Despite not being a new drug per se, specific long-term complications, if any, of rituximab use in pemphigus, have yet to be described. Currently, dermatologists are using the drug in patients unresponsive to conventional therapy or in patients in whom conventional therapy is contraindicated because of adverse effects.[16] It may also be used as a first-line treatment, although the exact place of rituximab in the routine management of pemphigus has yet to be determined.[2] Undoubtedly a major drawback of the drug is its cost, which, like other biological agents, is much higher than that of conventional treatment. In fact, the current drug cost of four 500mg doses of rituximab is estimated to be €5710.00 (€1427.50 x4) *(Mr. Joe Sciberras, Senior Pharmacist, Sir Paul Boffa Hospital, personal communication)*.

Apart from controlling relapses of pemphigus,[21] rituximab may also produce long-term disease remission. A study in India on 25 patients (21 with pemphigus vulgaris and four with pemphigus foliaceus) reported a complete remission rate of 88% following rituximab, complete remission defined as absence of lesions for two months. Furthermore, this study reported a decrease in the cumulative corticosteroid dose of 69.6% when compared to patients treated with prednisolone alone.[2] Another study[20] reported complete remission rates of 76%, with a mean time of 5.8 months to remission and a mean duration of 14.5 months of remission; relapse rates were reported to be 40%. However, it is important to consider original disease severity when interpreting such statistics. In our cases rituximab clearly had a major suppressive effect on disease activity. It was well tolerated apart from a minor cutaneous reaction in one patient.

Conclusion

The results of rituximab therapy of pemphigus are promising. The drug appears to be generally well tolerated and may produce long-term remission, reducing the need for systemic steroids in affected patients. Further experience should help define the place of rituximab in the management of pemphigus.

Acknowledgement

Dr. David Pisani, for kindly providing us with copies of histology slides, and for his help in their interpretation.

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