Pemphigus vulgaris: rituximab therapy - case series on three patients

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Sri Lanka Journal of Dermatology, 2010, **14**, 28-30

Abstract

Pemphigus vulgaris (PV) is an immunobullous disorder caused by pathogenic autoantibodies against Desmogleins. Many therapies have been designed to reduce autoantibody production. Systemic corticosteroids and immunosuppressive agents have greatly improved the prognosis of patients. However these have limitations due to resistant disease states or side effects. Rituximab is a new biologic agent that has been introduced to treat PV. It is a chimeric anti-CD20 monoclonal antibody. It destroys cells of B cell lineage thus inhibiting antidesmoglein antibody production. Three patients with PV were treated with Rituximab once per week for four weeks. All patients showed favorable response with minimal side effects.

Introduction

Systemic corticosteroids with or without immunosuppressive drugs remains the mainstay of treatment of pemphigus vulgaris[1, 2, 3]. The introduction of these agents has greatly improved the prognosis of PV; however, the morbidity and mortality is still significant. Numerous drugs and regimes are available at present but controlled trials for these are few[1].

Rituximab, a chimeric monoclonal anti CD20 antibody which depletes B cells has shown promising results even in treatment resistant patients[3,4,5]. It also has number of side effects but severe side effects are rare. Patients should be closely monitored during therapy and should be followed up thereafter.

Method and results

Patients

All three were females (patients A, B, and C) and all of them had confirmed diagnosis with direct immunofluoresence studies. Patient A was 31 years old and had PV since 2004. She was treated with systemic steroids and immunosuppressants. She had residual localized disease which did not give long standing remission even with second-line treatments (intravenous immunoglobulin and plasmapheresis). Patient B was 63 years old with PV for 3 years. She responded well to conventional treatment. While on oral steroids she developed haematemesis. Her steroid therapy was stopped by the physicians. She developed severe relapse of disease two weeks later. Patient C was 39 years old with PV for 1½ years. She responded partially to conventional therapy, but developed recurrences whenever the dose of prednisolone was reduced. She had significant side effects with steroid therapy, including hypertension, steroid induced diabetes mellitus, severe obesity, dyslipidaemia and iatrogenic Cushing's syndrome.

Treatment

All three patients received infusions of 500 mg of Rituximab weekly for four weeks. Pre-medication included 100 mg of intravenous methylprednisolone, 10 mg of intravenous chlorpheniramine one hour before infusion and two oral doses of 1 g paracetamol twelve hours apart. Steroid dose was reduced to maintenance dose of 12.5 mg prednisolone daily and all other immunosuppressive drugs were discontinued.

All three patients had full blood count, hepatitis B screening, ECG, liver and renal functions tests performed before initiation of therapy. Patient B had to be kept in the ward throughout the treatment duration due to the severity of the disease. Patients A and C were given Rituximab dose as in-patients and were discharged from the ward after 24 hours observation. Patients were followed up in the clinic monthly after treatment.

Response to treatment

Two months following Rituximab therapy patients A and C were disease free and the dose of prednisolone was reduced further (Figure 1).

Patient B who had severe disease achieved control of disease activity by the end of first month. She is now in partial remission developing 1-2 small lesions per week. Her prednisolone dose remains unchanged (Figure 2).

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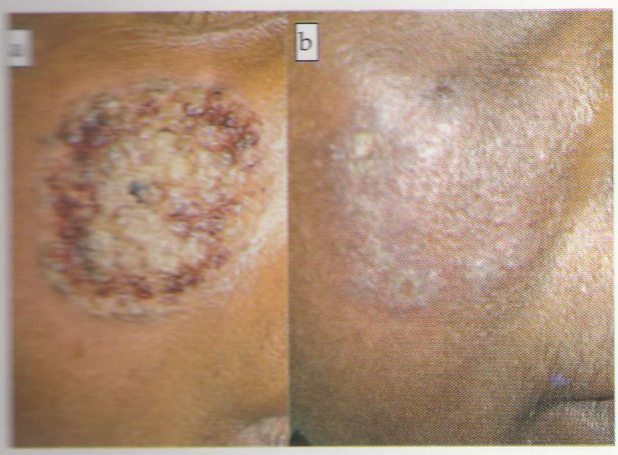

Figure 1. *A resistant facial lesion of patient A: a – before Rituximab therapy; b – two months after completion of therapy.*

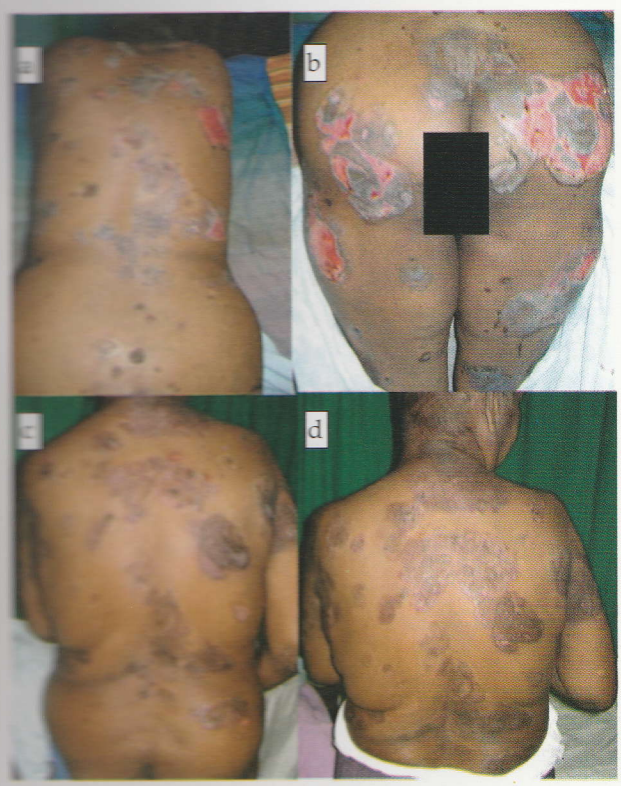

Figure 2. *Patient B: a,b – second week on Rituximab therapy; c – one month after completion of therapy, d – two months after completion of therapy.*

Adverse events

Patient A experienced transient hypotensive episodes during the second and third infusions. These were managed with stopping the infusion and restarting along with normal saline infusion simultaneously. Patient B developed a febrile reaction during third infusion which was treated symptomatically. None of the patients developed severe infusion related reactions.

Patients A and B have now been followed for five months each, and patient C for 3 months. Patient B had developed widespread tinea corporis which was treated with oral Itraconazole. None of the patients had severe bacterial or viral infections.

Discussion

Pemphigus vulgaris is an autoimmune bullous skin disease characterized by antibodies to the desmosomal cadherin desmoglein-3 which have been shown to be directly pathogenic. However T cells, other auto-antibodies and various cytokines are involved in the process of acantholytic blister formation[6].

Rituximab, is an anti-CD20 chimeric monoclonal antibody which was initially approved for the treatment of non-Hodgkin's B cell lymphoma and later for resistant rheumatoid arthritis. It has since then been added to the treatment options of pemphigus vulgaris[2,3,4,5,7]. CD20 molecule is expressed on surface of cells of B cell lineage, i.e. from pre-B to immature plasma cells and minority of mature plasma cells[2, 3, 7]. Rituximab destroys CD20 positive cells of the B cell lineage. Mature plasma cells continue to produce autoantibodies for few weeks. Therefore it takes few weeks to achieve remission. Since it does not affect bone marrow stem cells there is no depletion of other bone marrow derived cell lines[2, 3, 7]. Rituximab therapy is associated with prolonged B cell suppression. Since bone marrow stem cells are spared B cell recovery occurs in about 6-9 months. However disease relapse was rare. It was noted that B cell recovery is not associated with reappearance of pathogenic autoantbodies[2, 3, 7].

In most of the reported cases of PV treated with Rituximab, steroids with or without immuno-suppressants have been used concomitantly. The probable reason for necessity of the other drugs may be related to complex pathogenic mechanism of disease[2, 3, 4, 5].

Rituximab has been used to treat PV when there is a failure of conventional therapy or in cases with significant side effects or contraindications to conventional therapy[2]. Absolute contraindications are allergy to drug or its components, pregnancy and breastfeeding. Hepatitis B carrier state, cardiac arrythmias, angina pectoris, heart failure and active infection are relative contraindications[2, 3, 7, 8].

Majority of side effects due to Rituximab are mild transient and infusion related. These include chills

and fever, nausea, vomiting, diarrhea, heartburn, muscle or back pain, flushing, night sweats, tiredness, burning or tingling in the hands or feet and runny nose[8, 2, 3, 7].

Serious adverse effects include severe infusion-related reactions, arrhythmias, hypersensitivity, and pulmonary toxicity. These are very rare and most frequently occur during the infusion of first dose of the drug. These reactions are caused by release of massive amount of cytokines. These infusion related adverse effects can be minimized by premedication with paracetamol, antihistamines and corticosteroids[8]. Resuscitation facilities should be available at treatment setting for management of reactions.

Hypotension during infusion is a common problem which can be controlled by reducing the infusion rate and the use of intravenous fluids. This problem can be minimized by withholding any antihypertensive therapy 12 hours before infusion[8].

Prolonged immunosuppression is associated with the risk of viral infections like Hepatitis-B reactivation and progressive multifocal leukoencephalopathy (caused by JC virus). There are rare reports of severe bacterial infections which can be fatal[2, 4]. Most of the reported severe infections occurred when patients continued immunosuppressive drugs following Rituximab therapy. Thus maintenance therapy with steroids only will be a safer option as suggested by Cianchini et al[3].

The protocol being used to treat PV patients is most case reports was similar to that used to treat non-Hodgkin's lymphoma (375 mg/m^3 body surface area per dose) which may not be the ideal protocol in the setting of immune mediated disease[2]. Ahmed et al have used combination treatment of Rituximab and intravenous immunoglobulin successfully but cost for this regime is extremely high[7].

Rarity of disease and high cost of the drug are obstacles to perform randomized controlled trials. Recent literature review revealed 136 reported cases of Rituximab therapy for PV. 95% of those have shown either complete or partial remission. However further studies are needed to establish an ideal Rituximab regime[5].

The dose of rituximab used for our patients was slightly lower than the required dose calculated according to body surface area. This was unavoidable because Rituximab 100 mg vials were not available. Even with this slightly lower dosage regime all three patients showed good response.

In our patients there were transient milder infusion related events only. Patients are still being followed up and there were no fatal or serious infections up to now. Antidesmoglein antibody titres and B cell counts were not performed in our patients due to unavailability of facilities. These would have been very valuable to assess the disease activity and response to therapy.

Rituximab was found to be an effective and relatively safe alternative treatment option in management of these 3 difficult cases of PV even though the cost was high.

References

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