Rituximab in recalcitrant pemphigus: a case series experience

Jennifer Marchetti Cautela
Andrea Conti
Stefania Borsari
Camilla Reggiani
Maurizio Coppini
Giovanni Pellacani

Head & Neck Department, Dermatologic Unit, “Azienda Ospedaliero Universitaria Policlinico di Modena”, Modena, Italy

Address for correspondence:
Andrea Conti
Head & Neck Department, Dermatologic Unit
Azienda Ospedaliero Universitaria Policlinico di Modena
41124 Modena, Italy
E-mail: a.conti.dermo@gmail.com

Summary

Rituximab, an anti-CD20 monoclonal antibody, has been successfully used for treatment of severe autoimmune blistering diseases. Autoimmune blistering diseases involve the skin and mucous membranes of middle-aged women and men, typically occurring after the age of 50 years, although some cases have been reported in younger adults and children. Systemic steroids, in combination with immunosuppressive agents, are the mainstay of therapy in bullous diseases and have dramatically improved the prognosis, but still there are cases of recalcitrant patients, in which none of these combination therapies seem to work. In non responsive diseases, the use of rituximab seems to be a valid therapeutic option.

We discuss a case series of 9 patients with recalcitrant severe bullous diseases not responding or having contraindications to conventional therapy treated with rituximab from 2004 to 2014. We observed 4 serious infections resolved after adequate therapy, even though 1 patient had to stop rituximab therapy and switch to intravenous immunoglobulins therapy. Complete clinical remission was achieved in all patients after rituximab therapy, with a free-disease period ranging from 36 to 48 months.

KEY WORDS: rituximab; monoclonal antibody; anti-CD 20; pemphigus; pemphigus vulgaris; pemphigus foliaceous.

Introduction

Rituximab is a chimeric monoclonal antibody of the IgG class, directed at a specific CD20 B cell surface antigen. It induces a transient depletion of CD20+ B cells in peripheral blood within a few hours and it is complete by 2-4 weeks after infusion, with repopulation occurring 5-13 months after infusion. B cell reconstitution after the rituximab therapy is associated with new VDJ and VJ recombinations, creating a new B cell antibody repertoire that, theoretically, would eliminate the autoreactive clones (1-4).

The first report of rituximab in the treatment of pemphigus was published in 2002, and since then, many studies have shown favorable results, especially in those patients resistant to conventional therapy (5-8). Systemic steroids represent the standard therapy in combination with steroid-sparing immunosuppressive agents, such as azathiprine, mycophenolate mofetil, methotrexate, cyclophosphamide or immunomodulators like diamino-diphenyl sulfone or intravenous immunoglobulin (IVIg) (9-12). These combination therapies have improved the prognosis, but side effects and complications due to long-term steroid and immunosuppressive therapy cannot be ignored and are responsible for the reported 5% mortality (13).

In those particular patients with severe active autoimmune blistering disease, such as pemphigus vulgaris (PV) and pemphigus foliaceous (PF), not responding to standard therapies, the Italian Drug Agency (AIFA) approved the use of rituximab (14).

There are two officially approved dosages of rituximab: in the lymphoma protocol, patients received four intravenous (IV) weekly infusions of rituximab at the dose of 375 mg/m² (1 cycle) otherwise in the rheumatoid arthritis (RA) protocol consisted of two IV infusions of 1,000 mg each 15 days apart, along with methotrexate (15).

In PV the most used protocol in the literature is a 375 mg/m² IV infusion of rituximab once weekly for 2-4 consecutive weeks (13). Another option is 375 mg/m² IV of rituximab once weekly for 8 consecutive weeks with 1 cycle of 2 mg/kg IVIg during weeks 4 and 8, followed by a monthly dose of rituximab and IVIg cycles for 4 consecutive months (13-15).

Few randomized controlled trials (RCT) are available and most of the accessible evidences derive from case series and case reports: that is because the rarity of the disease, its variability in cutaneous and mucocutaneous extension and, overall, the fewness of standardized tools capable of assessing the disease activity (16).

Furthermore, there are patients who are resistant to
Rituximab in recalcitrant pemphigus: a case series experience

conventional therapy; in these cases, the use of rituximab has been shown to be beneficial, leading to a fast clinical improvement and a longer remission of the disease (10-12).

Materials and methods

From 2004 to 2014 9 patients (4 women and 5 men), aged 45 to 68 years affected by severe autoimmune bullous disease referring to our Dermatologic Department were treated with rituximab. Eight patients had PV with severe mucocutaneous and mucous involvement and 1 had PF. All of them received steroids and/or immunosuppressive agents previously with no response and/or had contraindications to the se and/or experienced one or multiple adverse reactions due to the prolonged corticosteroid intake (Table 1).

According to the principles of the Declaration of Helsinki, in this case series, patients with a clinical and histopathological diagnosis of mucous or mucocutaneous PV or PF were recruited, prior written and informed consent.

The inclusion criteria were severe refractory disease, severe contraindications to conventional immunotherapy and the presence of severe adverse effects due to long-term corticosteroid therapy. Contraindications were: active or severe infections, heart failure or uncontrolled heart disease, pregnancy and breastfeeding.

According to safety information and to the Product Information Leaflet, before starting the treatment, all patients were screened for previous viral infections such as HIV or hepatitis B or C, a X-chest ray and the QuantiFERON TB Gold test® (QFT-G, Cellestis Limited, Carnegie, Victoria, Australia) were performed to screen latent tuberculosis infection and paraneoplastic markers were detected. If all these conditions

Tabella 1 - Demographic and clinical characteristics of enrolled patients.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Sex</th>
<th>Age (yrs)</th>
<th>Diagnosis</th>
<th>Previous Therapies</th>
<th>RTX</th>
<th>Other Therapies</th>
<th>Adverse Reactions</th>
<th>Maintenance Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>65</td>
<td>PV</td>
<td>Prednisone, MET, CYC</td>
<td>1 cycle (4 EV infusions)</td>
<td>Plasmapheresis</td>
<td>None</td>
<td>Prednisone 0.3 mg/kg/die</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>61</td>
<td>PV</td>
<td>Prednisone, AZA, P /</td>
<td>3 cycles (12 EV / infusions)</td>
<td>None</td>
<td>Bacterial Pneumonia</td>
<td>Prednisone 0.2 mg/kg/die</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>58</td>
<td>PV</td>
<td>Prednisone, MET, CYC</td>
<td>1 cycle (4 EV infusions) + 1 extra EV infusion</td>
<td>/</td>
<td>None</td>
<td>Prednisone 0.5 mg/kg/die - 0.20 mg/kg/die every other day</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>45</td>
<td>PF</td>
<td>Prednisone, MET</td>
<td>1 cycle (4 EV infusions) + 1 extra EV infusion</td>
<td>/</td>
<td>None</td>
<td>Prednisolone 0.10 mg/kg/die</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>68</td>
<td>PV</td>
<td>Prednisone, MET, AZA, P, CYC</td>
<td>1 cycle (4 EV infusions)</td>
<td>/</td>
<td>None</td>
<td>Prednisolone 0.05 mg/kg/die every other day</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>59</td>
<td>PV</td>
<td>Prednisone, AZA, CYC, P /</td>
<td>2 EV infusions</td>
<td>/</td>
<td>Staphylococcal and P. Aeruginosa Sepsis (interrupted after 2 infusions)</td>
<td>/</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>66</td>
<td>PV</td>
<td>Prednisone, AZA, IVIG, P, CYC, P, Photo</td>
<td>1 cycle (4 EV infusions)</td>
<td>CSA 2 mg/kg/die</td>
<td>Staphylococcal Sepsis</td>
<td>Prednisolone 0.5 mg/kg/die</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>45</td>
<td>PV</td>
<td>Prednisone, MET, CYC, IVIG, MMF</td>
<td>1 cycle (4 EV infusions)</td>
<td>MTX, CSA 2 mg/kg/die</td>
<td>None</td>
<td>Prednisolone 0.20 mg/kg/die</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>55</td>
<td>PV</td>
<td>CYC, Prednisone, MET</td>
<td>1 cycle (4 EV infusions)</td>
<td>/</td>
<td>S. Haemoliticus Sepsis and CMV Infection</td>
<td>Prednisolone 0.5 mg/kg/die</td>
</tr>
</tbody>
</table>

Clinical Data Legend: IVIG intravenous immunoglobulins; MTX methotrexate; MMF mycophenolate mofetil; HD high dose; CSA cyclosporin A
were found negative, the patients could be treated with rituximab.

The lymphoma protocol was used, in which patients received four weekly IV infusions of rituximab at the dose of 375 mg/m² after premedication with hydrocortisone sodium succinate (200 mg IV), chlorphenamine maleate (10 mg IV) and calcium gluconate (94 mg IV). Blood pressure and heart rate were strictly monitored every 30 minutes until the end of every infusion.

All patients were evaluated for the occurrence of severe adverse reactions. Serious adverse reactions to rituximab are rare and in general its adverse effects are mostly mild and transitory and are associated with infusion reactions, such as fever, chills, bronchospasm, urticaria, nausea, vomiting and hypotension (17, 18).

Clinical response to rituximab was assessed according to the consensus statements for pemphigus (19).

Outcomes were classified as “complete remission”, which is the absence of mucosal and skin lesions for at least 2 months and “partial remission” where transient new lesions, generally healing in 1 week, can be found. These outcomes can be achieved off therapy, or, on minimal therapy, defined as less than 10 mg/day of prednisone (or its equivalent) and/or minimal adjuvant therapy (systemic immunosuppressant, IVIg, dexamethasone) for at least 2 months. Relapse has been defined as the appearance of 3 or more new lesions that did not heal spontaneously in 1 week or by the extension of established lesions in a patient who had previously achieved disease control.

Treatment failure was defined as the inability to control the disease activity with full therapeutic doses of systemic treatment (20).

Results and discussion

Table 1 shows the clinical data of these patients, including age, sex, diagnosis, previous therapies, maintenance therapies and adverse reactions occurring during therapy.

Therapy was well tolerated in 5 patients, 4 patients developed severe infections (3 a septicemia and 1 bacterial pneumonia). Bacterial pneumonia occurred between third and fourth IV rituximab infusion in patient 2; that condition lead to the temporary suspension of the treatment and to the need to an antibiotic therapy for 10 days with IV piperacillin and tazobactam (2.5 g 3 times a day) and claritromycin 500 mg 2 times a day. At a later stage, along with the resolution of the pneumonia it was possible to continue with the fourth IV rituximab infusion.

Patient 7 developed Staphylococcal sepsis between third and fourth IV rituximab infusion and he was treated for 10 days with IV piperacillin and tazobactam (4.5 g 3 times a day), IV meropenem (1000 mg 3 times a day) and doxycyclin (100 mg 2 times a day).

Patient 6 contracted staphylococcal and P. Aeruginosa sepsis had been treated for 15 days with antibi-

otic therapy with IV sulbactan and ampicillin (3 gr 3 times a day) in association with IV gentamicin 240 mg (1 time a day), then vancomycin 1 gr twice a day in association with ciprofloxacin 200 mg twice a day, then meropenem 1000 mg 3 times a day in association with gentamicin 80 mg 3 times a day. Due to this important adverse reaction, rituximab was suspended and he had been introduced to IVIg (a cycle of 1 g/kg in 3 days), with a good response.

A staphylococcal (S. Haemolyticus) sepsis followed by a citomegalovirus sepsis, occurred in patient 9; he has been treated for 20 days with IV daptomycin 500 mg/die and IV clindamycin 600 mg/die and IV ganciclovir 5 mg/kg. As the patient responded and his physical conditions improved, the cycle of rituximab was completed with remission of the symptoms.

Two patients experienced relapse 1 year after the rituximab therapy, the first (patient 7) had been treated with prednisone 0.5 mg/kg/die and cyclosporine A 2 mg/kg/die with partial clinical remission. In the other patient (patient 8), methotrexate was added to the prednisone therapy at the dose ranging from 10 to 15 mg once a week. Since there was no significant benefit, methotrexate was suspended and cyclosporine A was added at the dose of 2 mg/kg/die with clinical remission.

After the first cycle of IV infusions of rituximab and an initial clinical response, patient 1 had to switch to several cycles of plasmapheresis with a persistent remission until her death, occurred for abdominal aneurysmal rupture.

In our experience, 2 non responders patients (patients 5-9) to systemic corticosteroids, after 1 cycle (4 IV infusions) of rituximab, started again to respond to low doses of systemic corticosteroids. The median of long term clinical remission for our 3 patients was 48 months.

Two patients (patients 3 and 4) needed an additional IV infusion of rituximab at the dose of 375 mg/m² to achieve a complete remission, with a maintenance low dose corticosteroid therapy.

One patient (patient 2) required more cycles (3 cycles of rituximab, that is 12 IV infusions in total) to attain complete remission, still ongoing and 1 (patient 6), due to the severe adverse reaction, had to discontinue the therapy and switch to IVIg.

2 patients (patients 7-8), after 1 cycle of rituximab, started to respond to lower doses of corticosteroids but needed to add cyclosporine A to their therapy to attain partial remission at a dosage of 2 mg/kg/die.

Patient 1 had a minimal response to rituximab, that implied a switch to plasmapheresis with the achievement of a complete clinical remission on minimal therapy.

Due to the important and severe reaction, patient 6 had to stop the IV rituximab infusions and switch to IVIg, with a complete remission.

The noticeable aspect is that therapy with rituximab helped non-responders to corticosteroids patients to respond to low doses of corticosteroids and achieving a clinical remission. This amazing recovery of patients in their steroids response has already been described in literature (21).
Rituximab in recalcitrant pemphigus: a case series experience

Clinical remission was achieved on minimal therapy in 5 patients with a disease free period of 48 months. Two patients (patients 7 and 8) who added cyclosporine A to their therapy reached a clinical remission for 36 months.

In a recent systematic review it has been concluded that immunosuppressant in general and cyclosporine specifically, could help decreasing the risk of relapse by 29% and can be used as a sparing steroids agent (22, 23).

In our experience we evidenced that in almost 50% of the patients, severe adverse reactions occurred, such as sepsis and bacterial pneumonia, which is a higher rate comparable to other studies, this could be due to the fact that all the patients had an important immunosuppressive therapy prior the beginning of rituximab.

CD20 evaluation in the follow up has not been considered, but it could certainly be interesting to monitor it in the follow up of patients in the future in order to prevent or predict a potential relapse of the disease and eventually associate it with changes in the antibodies titers.

Long-term efficacy and safety results still need further studies to completely and deeply understand the consequences of rituximab therapy in patients with autoimmune diseases, since they are unknown at the moment.

Since its first Food and Drug Administration (FDA) approval in 1997 for the treatment of non-Hodgkin lymphomas and RA, rituximab has been reported responsible of severe adverse reactions only in a minority of patients.

A retrospective study from the German Registry of Autoimmune diseases found that 12.2% of patients experienced mild to severe infectious complications, including pneumonia, sepsis and cellulitis, leading to death in 1.9% of the patients (24).

The meta-analysis of Feldman et al. based on 153 patients affected by pemphigus who received rituximab infusions, showed that 7% developed serious infections with 2 fatalities (25).

Severe infections such as lethal pneumocystis pneumonia (PCP) and bacterial sepsis have also been described (26, 27).

It was found, on a meta-analysis of published prospective and retrospective studies on rituximab in pemphigus, encompassing 153 patients, that the overall efficacy (complete healing of lesions regardless of systemic therapy) was 65% (25).

Schmidt et al. and Gurcan et al. analyzed 130 patients with rituximab treated pemphigus and showed that 90% achieved complete remission during the first year (28, 29).

Reguià et al. observed a complete remission in 70 and 85%, respectively after 3 and 9 months after a single cycle of rituximab treatment (30).

In a prospective trial presented by Joly et al. it was pointed that a single cycle of lymphoma dosage was adequate to obtain complete clinical remission (4).

Ahmed et al. reported a remission lasting from 22 to 34 months in 9 patients out of the 11 treated with two cycles of rituximab consistent of 3 weekly IV infusion of rituximab and IVIg the fourth week, followed by a monthly IV infusion of rituximab and IVIg for 4 consecutive months (10).

As shown by Leshem et al., in those patients who could not achieve complete remission with 1 rituximab cycle, additional cycles of rituximab were beneficial leading to 62.5% (with 1 extra cycle) and 80% (with 2 extra cycles) remission (31).

Cianchini et al. had shown that 86% of patients achieved a complete remission after 6 months: 29 of them in complete remission off therapy and 7 in complete remission on minimal therapy. Six patients achieved partial remission on therapy and received an extra IV infusion of 500 mg of rituximab after 6 months from the previous one, 4 months later a complete remission was reached (32).

Although the rates of disease remission are uncertain, 23% of these patients in the meta-analysis achieved complete remission off all systemic immunosuppressant therapy.

The rate of serious adverse events and severe infections between rituximab and control treatment was not significantly different on a Cochrane systematic review (20).

Conclusions

Rituximab has to be considered as a valid therapeutic option in patients affected by bullous diseases resistant to conventional therapy and/or had contraindications to these and/or experienced one or multiple adverse reactions due to the prolonged corticosteroid intake.

It has a high response rate and is well tolerated. Its tolerability do not change after subsequent infusions, even in those patients who developed infections, the antibiotic response rate was excellent and did not change the clinical response to rituximab.

Patients who do not achieve remission after rituximab treatment or who relapsed after achieving remission, may benefit from additional cycles.

The use of rituximab in bullous diseases is an evolving work in progress.

Whether this control is long term, life long, or of limited duration is not yet known and it is interesting debating if it should be used as a first line therapy, that could spare the corticosteroid intake and obtain a better clinical outcome in those patient affected by severe cutaneous or mucocutaneous pemphigus, or it has to be considered as the treatment of last resort, as it is considered nowadays.

Disclosure

The Authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. Leandro MJ, Cambridge G, Ehrenstein MR, Edwards JC. Reconstitution of peripheral blood cells after de-
J. Marchetti Cautela et al.


