

# Refractory pemphigus vulgaris treated with rituximab and mycophenolate mofetil\*

Stephanie Del Rio Navarrete Biot<sup>1</sup>  
Ricardo Barbosa Lima<sup>1</sup>  
Luiz Paulo José Marques<sup>1</sup>

Joanna Pimenta de Araujo Franco<sup>1</sup>  
Henrique Novo Costa Pereira<sup>1</sup>  
Carlos José Martins<sup>1</sup>

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**Abstract:** The main treatment for pemphigus vulgaris are systemic corticosteroids and immunosuppressive agents, but due to adverse reactions and therapeutic failure, new drugs such as rituximab and mycophenolate mofetil have been used. In this case report are described two cases of severe pemphigus vulgaris refractory to various treatments, with resolution after use of rituximab and mycophenolate mofetil, associated with corticosteroids. A higher-than-usual dose of rituximab was employed, without the occurrence of serious adverse reactions. Mycophenolate mofetil was added as adjunctive therapy due to lack of response to azathioprine.

**Keywords:** Antibodies, monoclonal; Immunosuppressive agents; Pemphigus

## INTRODUCTION

Pemphigus vulgaris (PV) is a potentially fatal autoimmune bullous disease with a mortality rate around 5%.<sup>1</sup> The main treatment are systemic corticosteroids associated with immunosuppressants, but due to adverse reactions and treatment failure new therapeutic drugs have been prescribed, such as rituximab<sup>2</sup> and mycophenolate mofetil (MMF).<sup>3,4</sup> Rituximab is an anti-CD20 monoclonal antibody that causes the depletion of B lymphocytes and B pre-lymphocytes. Initially developed for the treatment of non-Hodgkin lymphoma, it has been shown to be an excellent option for autoimmune diseases like PV.<sup>2</sup> MMF is a relatively new immunosuppressant.<sup>3</sup> It acts by specifically inhibiting activated T lymphocytes, with a more selective action, and with the advantage of being less mutagenic regarding azathioprine.<sup>4,5,6</sup> Its use is approved for the prevention of solid organs allograft rejection and for lupus nephritis. Several studies point out its efficacy in the treatment of PV.<sup>4,8</sup> In this current study two cases of severe PV are reported, refractory to diverse treatments, with clinical resolution after use of rituximab and MMF combined with corticotherapy.

## CASE REPORTS

Case 1 – Male, 47 years old, with diagnosis of PV and using prednisone 120mg/day for one month. At the examination he presented eroded and crusted lesions disseminated on the skin and erosions in the oral mucosa. Diagnosis of PV was histologically confirmed. Treatment was begun with pulses of methylprednisolone IV and oral prednisone between pulses. The patient progressed rapidly with severe worsening and infusions of intravenous immunoglobulin combined with prednisone and oral azathioprine were introduced (Figure 1A). After a period of improvement new lesions appeared and pulses of cyclophosphamide IV were administered, continuing with oral prednisone. Again there was improvement but after the fourth pulse a severe relapse occurred. Plasmapheresis was performed as well as a new pulse of cyclophosphamide with good response, but after seven days there was onset of new lesions (Figure 1B). At this point, treatment with rituximab was initiated. Prednisone was maintained and MMF was added. After the second cycle there was complete resolution of the clinical picture with hospital discharge, main-

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<sup>1</sup> Universidade Federal do Estado do Rio de Janeiro (UNIRIO) – Rio de Janeiro (RJ), Brazil.

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**FIGURE 1 (CASE 1):** A: extensive erosion of lesions on the trunk and limbs, in the first phase of exacerbation of the disease before beginning treatment with intravenous immunoglobulin. B: dorsolumbar region after plasmapheresis, before beginning treatment with rituximab. C: dorsolumbar region after the end of second cycle of rituximab, three months after the first infusion

taining prednisone and MMF (Figure 1C). The patient was hospitalized for eight months and presented severe complications like infections and sepsis, before the initiation of rituximab, making use of several schemes of antibiotic therapy. During the outpatient clinic follow-up the MMF dose was maintained and the dose of prednisone was progressively reduced in the course of one year, until suspension. At this point, oral lesions appeared which persisted even after increase of prednisone. A new infusion of rituximab was started and the dose of MMF was increased, with resolution of lesions. One year after the last cycle of rituximab, the patient remains with the disease controlled with MMF 2.5g/day and prednisone 10mg on alternate days. The therapeutic steps with drugs, doses, intervals and duration, are described in table 1.

Case 2 - Female, 46 years old, with hypertension and diabetes, both difficult to control, presented bullous lesions and erosions, with purulent secretion, disseminated on the scalp, face, trunk and limbs. Diagnosis of PV was confirmed histologically. She was hospitalized and submitted to treatment with antibiotic therapy, pulses of methylprednisolone IV and pulses of cyclophosphamide IV, with monthly intervals, besides oral prednisone and azathioprine. She achieved almost complete remission of lesions after the second pulse of cyclophosphamide, with hospital discharge. After the fifth pulse she presented leucopenia and after the sixth pulse there was relapse of the disease (Figure 2A). The patient was hospital-

ized again and rituximab infusions were administered with two-week intervals, maintaining oral prednisone and azathioprine. There was improvement in the trunk lesions, but worsening of the facial ones, even after the third infusion of rituximab (Figures 2B and 3A). As a consequence, together with the fourth infusion the prednisone dose was increased and azathioprine replaced with MMF, with progressive improvement and hospital discharge after two months of hospitalization (Figure 3B). Since then the prednisone dose was progressively reduced and two years after hospital discharge, the patient remains with the disease under control with MMF 1g/day and prednisone 5mg/day (Figure 3C). The therapeutic steps, with drugs, doses, intervals and duration, are described in table 2.

## DISCUSSION

Rituximab is indicated mainly for patients with PV refractory to at least two therapeutic modalities.<sup>2,9</sup> The most used schemes are the four infusions per week at a dose of 375mg/m<sup>2</sup> and the one of two infusions of 1g with two-week interval. They are approved, respectively, for the treatment of B cell non-Hodgkin lymphomas, and for rheumatoid arthritis refractory to therapy with anti-TNF $\alpha$ .<sup>10</sup> The most common collateral effects are related to infusion (headache, fever, nausea, vomiting, pruritus, hypotension). Severe effects such as sepsis and opportunistic infections are rare.<sup>9</sup> In a study of 103 patients with PV

TABLE 1: Therapeutic phases - case 1

Phases	Medications	Period
1st	2 cycles of pulse therapy with MPD 1g IV, for 3 days, with weekly interval and PDN 60 mg/day, between pulses.	2 weeks
2nd	3 cycles of infusions of IVIG 2g/kg/cycle, divided in 4 days, with intervals of 2 to 3 weeks, PDN 120mg/day and AZA 150mg/day.	9 weeks
3rd	4 pulses of CPP 500mg/m <sup>2</sup> IV, with interval of 3 weeks between pulses and PDN 120mg/day.	9 weeks
4th	3 sessions of PPH with 1 pulse of CPP on fourth day, and PDN 120mg/day	2 weeks
5th	RTX, 2 cycles of 4 weekly infusions of 375mg/m <sup>2</sup> , with 4-week intervals between cycles, PDN 120mg/day and MMF 2g/day. Hospital discharge after 8 months.	12 weeks
6th	Outpatient clinic treatment with MMF 2g/day and progressive reduction of PDN dose for 1 year, until suspension, when relapse of lesions occurred, refractory to reintroduction of PDN 80mg/day.	12 weeks
7th	New hospitalization for administration of RTX, 1 cycle of two infusions of 1g, with a two-week interval, PDN 80mg/day and MMF 2.5g/day. Hospital discharge after 4 weeks.	4 weeks
8th	Outpatient clinic treatment with progressive reduction of PDN dose. One year after the last RTX infusion, the disease remains controlled with MMF 2.5mg and PDN 10mg on alternate days.	12 weeks

Note: MPD = methylprednisolone; PDN = prednisone; IVIG = intravenous immunoglobulin; AZA = azathioprine; CPP = cyclophosphamide; PPH = plasmapheresis; RTX = rituximab; MMF = mycophenolate mofetil.



FIGURE 2 (CASE 2): A: erosions in dorsolumbar region after relapse of the disease, during pulse therapy with cyclophosphamide plus prednisone and azathioprine orally. B: improvement of lesions in dorsolumbar region, after the third rituximab infusion

who were treated with rituximab, Schmidt and collaborators reported complete remission in 77% and partial remission in 21% of the patients. Severe collateral effects occurred in 14% of the patients.<sup>2</sup> In the two cases reported in this work a greater number of infu-

sions of rituximab were necessary until the resolution of lesions, with no occurrence of adverse reactions.

MMF is considered by some authors the best corticosteroid-sparing drug for bullous diseases.<sup>4,5</sup> The recommended dose is 35mg-45mg/kg/day, adminis-



FIGURE 3 (CASE 2): A: erosions on face and scalp, after the third rituximab infusion. B: healing of lesions on the face three weeks after the fourth rituximab infusion, increase of prednisone dose and introduction of MMF. C: face and scalp 18 months after the end of rituximab infusions

TABLE 2: Therapeutic phases - case 2

Phases	Medications	Duration
1st	Pulse therapy with MPD 1g/day IV, for 3 days, and 6 pulses CPP 500mg/m <sup>2</sup> IV, with monthly intervals and PDN 30mg/day and oral AZA 150mg/day between pulses. Hospital discharge after second pulse of CPP. Following pulses in a day-hospital schedule.	22 weeks
2nd	New hospitalization for administration of RTX, 4 infusions of 1g, with 15-day interval, continuing PDN 30mg/day and AZA 150mg/day up to the 4th infusion. With the 4th infusion, PDN was increased to 80mg/day and AZA was replaced by MMF 1.5g/day. Hospital discharge after 2 months.	9 weeks
3rd	Outpatient clinic treatment with MMF 1.5g/day and progressive decrease of PDN dose. Two years after the last RTX infusion, the disease remains controlled with MMF 1g/day and PDN 5mg/day.	24 weeks

Note: MPD = methylprednisolone; CPP = cyclophosphamide; PDN = prednisone; AZA = azathioprine; RTX = rituximab; MMF = mycophenolate mofetil.

tered every 12 hours with meals. The dose should be gradually increased to avoid gastrointestinal effects.<sup>3,4,5</sup> The drug is presented in 500mg capsules and there is another form, sodium mycophenolate, presented in 360mg capsules, equivalent to 500mg of MMF.<sup>4</sup>

In a study with 36 cases of patients with PV and pemphigus foliaceus treated with rituximab, the most used concomitant drugs were prednisone and MMF, in 53% and 50% of the cases, respectively.<sup>10</sup>

The high cost and the *off-label* condition are factors that limit its provision by Unified Health System (SUS - Sistema Único de Saúde). In the reported cases, rituximab was supplied by the hospital unit and the MMF by the nephrology sector, until obtained by SUS with a judicial warrant.

The reports in the literature and the results obtained in the described cases indicate that rituximab and MMF are safe, effective drugs, with lasting results, revealing themselves as valuable therapeutic options for severe and refractory PV.<sup>1-10</sup> □

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**MAILING ADDRESS:**

*Stephanie Del Rio Navarrete Biot  
Rua Mariz e Barros, 775 - Tijuca  
20270-004 - Rio de Janeiro - RJ  
Brazil  
E-mail: tupibiot@hotmail.com*

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