Manuscript title: RITUXIMAB TREATMENT OF PEMPHIGUS FOLIACEUS- A RETROSPECTIVE STUDY OF 12 PATIENTS

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“This study has been approved by our Institutional Review Board.”
Pemphigus foliaceus (PF) is a chronic autoimmune blistering disease related to pathogenic serum auto-antibodies against desmoglein-1. Initial treatments for PF include systemic corticosteroids, immunosuppressants and dapsone.\textsuperscript{1} Rituximab, a chimeric monoclonal antibody that targets the CD-20 molecule on B-cells, has been shown to be effective in severe and refractory cases of pemphigus.\textsuperscript{2} Meta-analysis have tried to analyse its efficacy in PF, but results are based on heterogeneous case series and reports. Our aim was to evaluate the clinical response to rituximab in a series of patients with PF.

The medical records of 12 patients with PF treated with rituximab from January 2007 to May 2017 were reviewed. Mean patient age was 55.75±12.4 years, and the median disease duration was 46 months (range 2 months-11 years). All the patients had been treated according to the European Guidelines.\textsuperscript{1}

After the first infusion of rituximab, 6 patients (50%) showed a complete response (CR) off and 5 patients (42%) a partial response. Relapses occurred in 6 patients (50%) after a median of 12 months (range 7-55 months).

Adverse events were reported in 4 cases (33.3%). We did not observe a trend towards infection if immunosuppressive drugs or doses of prednisone higher than 10 mg/day were used as comedication (p=0.627). Cumulative rituximab dose, dose per cycle or the number of cycles of rituximab and sex were not associated with a greater risk of infection (p=0.4777, p=69654, p=0.5758 and p=0.5301 respectively) (Table 1).

Rituximab is considered to be effective in pemphigus, with an estimated CR rate of 76-87\% after the first cycle.\textsuperscript{2-4} The largest published series of PF found a CR rate of 50\%,\textsuperscript{5} which was lower than the response rates in pemphigus vulgaris (PV), but was identical to our series. These lower response rates could be the result of the selection of the most severe and complicated patients, with a longer disease duration.
Relapses occurred in 6 patients (50%), similar to the reported results for patients with PV (40%-67%), but they occurred earlier. Contrary to other case series, we were unable to find any trends towards CR with the number of cycles, but none of our patients received more than two cycles of rituximab.

Adverse events were reported in four patients (33.3%). This rate was higher than in other studies in PV (24%) but lower than the 42% found in the largest case series of PF. Patient 5 developed tuberculous meningitis, but had been treated with prednisone and immunosuppressants before receiving rituximab, and it is difficult to determine if this infection could only be attributed to rituximab. As well as in the series of de Sena Nogueira Maehara, we were unable to show that the cumulative dose or the number of cycles of rituximab were associated with a risk of infection, but contrary to them we did not observe an association of infections with sex.

In conclusion, rituximab seems to be effective as a third-line therapy for patients with PF. However, CR rates in severe patients with PF with longer disease duration might be lower than expected.
ABBREVIATIONS

Pemphigus foliaceus (PF)

Rituximab (RTX)

Complete response (CR)

Pemphigus vulgaris (PV)
   and treatment – guided by the European Dermatology Forum (EDF) in
   cooperation with the European Academy of Dermatology and Venereology

2. Ahmed AR, Shetty S. Autoimmunity Reviews A comprehensive analysis of
   treatment outcomes in patients with pemphigus vulgaris treated with rituximab.

   systematic review and meta-analysis of different regimens. Acta Derm Venereol.

   pemphigus: results from a single-center observational study on 42 cases with

5. de Sena Nogueira Maehara L, Huizinga J, Jonkman MF. Rituximab therapy in
   pemphigus foliaceus: report of 12 cases and review of recent literature. Br J
Table 1. Patient characteristics and outcomes after treatment with rituximab.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex/Age</th>
<th>Previous therapies</th>
<th>Duration of disease before rituximab (months)</th>
<th>Rituximab protocol (1&lt;sup&gt;st&lt;/sup&gt; cycle)</th>
<th>Time to disease control (weeks)*</th>
<th>End point*</th>
<th>Minimal therapy*</th>
<th>R&lt;sup&gt;it&lt;/sup&gt;uximab protocol (2&lt;sup&gt;nd&lt;/sup&gt; cycle)</th>
<th>Time to relapse (months)</th>
<th>End point*</th>
<th>Complications; total dose of rituximab (g) until complications</th>
<th>Follow-up (months)&lt;sup&gt;#&lt;/sup&gt;</th>
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<td>1</td>
<td>M/38</td>
<td>Pred, Aza, MFA, IVIG</td>
<td>44</td>
<td>LP</td>
<td>24</td>
<td>CR off</td>
<td>No</td>
<td>11</td>
<td>LP</td>
<td>No</td>
<td>CR off</td>
<td>21&lt;sup&gt;†&lt;/sup&gt;</td>
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<tr>
<td>2</td>
<td>M/48</td>
<td>Pred, MFA, Dap</td>
<td>27</td>
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<td>20</td>
<td>PR on</td>
<td>Pred/Dap</td>
<td>13&lt;sup&gt;‡&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>Staphylococcus aureus skin infection; 2.92</td>
<td>61</td>
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<td>3</td>
<td>F/65</td>
<td>Pred, Aza</td>
<td>65</td>
<td>RAP</td>
<td>10</td>
<td>PR on</td>
<td>Pred/Aza</td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>5</td>
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<td>Pred&lt;sup&gt;^&lt;/sup&gt;</td>
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<td>Pred 100</td>
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<td>7</td>
<td>PR on</td>
<td>Pred</td>
<td></td>
<td></td>
<td></td>
<td>Tuberculous meningitis; 1.95</td>
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<td>8</td>
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<td>Pred 7.5</td>
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<td>72&lt;sup&gt;‡&lt;/sup&gt;</td>
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<td>Pred, Aza, Dap</td>
<td>50</td>
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<td>CR off</td>
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</table>

Aza, azathioprine; Chloro, chloroquine; CPM, cyclophosphamide; CR off, complete response off therapy; Dap, dapsone; F, female; Gold, gold salts; IVIG, high-dose intravenous immunoglobulin; LP, lymphoma protocol; M, male; MFA, mycophenolic acid; MMF, mycophenolate mofetil; Mp, methylprednisolone; Nico, nicotinamide, Pred, prednisone; PR off, partial response off therapy; PR on, partial response on minimal therapy; RAP, rheumatoid arthritis protocol; Tetra, tetracyclines.

*As defined by an international consensus statement for patients with pemphigus.

† Relapse was controlled with low doses of prednisone and with full doses of dapsone.

‡ Relapse was controlled with low doses of prednisone and with full doses of dapsone.

Lost to follow-up.

^ Patient 4 was diagnosed with pemphigus vulgaris that evolved into pemphigus foliaceus. Only the data since the diagnosis of pemphigus foliaceus are included, but he had previously been treated with other immunosuppressants that are not listed in the table.

‡ Relapse was controlled with low doses of prednisone and with full doses of dapsone.

† Lost to follow-up.

The patient did not achieve control of the disease despite treatment with rituximab, prednisone and azathioprine and was lost to follow-up.

The patient died due to an unrelated cause, and at that time was on complete response off therapy.