First-line Treatment of Pemphigus Vulgaris With a Combination of Rituximab and High-Potency Topical Corticosteroids

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Pemphigus vulgaris is a rare autoimmune disease characterized by skin and mucous membrane blisters and erosions due to autoantibodies targeting desmogleins 1 and 3, which are major components of desmosomes. The severity of the disease can be assessed by measures such as the Harman score or by newer scales, such as the Pemphigus Disease Area Index score (PDAI) or Autoimmune Bullous Skin Disorder Intensity Score. To date, except in cases with very limited lesions that can be treated by topical corticosteroid monotherapy, first-line treatment is based on high-dose systemic corticosteroids (1.0 or 1.5 mg/kg/d) according to the severity of the disease, but this treatment is complicated by a high rate of severe adverse effects, such as infections, osteoporosis, myopathy, and diabetes mellitus. Thus, adjuvant immunosuppressive therapies including corticosteroid-sparing agents are often warranted.

A single cycle of rituximab has shown excellent effectiveness in patients with refractory pemphigus vulgaris, as demonstrated by a greater than 80% rate of short-term complete remission, a dramatic corticosteroid-sparing action, and few severe adverse effects. The mechanism of action of rituximab in pemphigus vulgaris is based on prolonged inhibition of specific antidesmoglein B-cell response.

However, to our knowledge, even though rituximab is considered a major promising treatment of pemphigus vulgaris, its efficacy in first-line treatment without systemic corticosteroids has not been assessed. We report herein a series of 5 patients who received successful treatment with a combination of rituximab and topical corticosteroids as first-line therapy.

Report of Cases

Five women in their 50s, 60s, or 70s had pemphigus vulgaris (PDAI score, 15-84 at diagnosis) and contraindications to systemic corticosteroid treatment received rituximab with high-potency topical corticosteroids as first-line treatment. All patients experienced a favorable response, with a mean time to healing of skin and mucosal lesions of 15 weeks. Two patients, with 42- and 48-month follow-up evaluations, did not experience relapse. Three patients developed 2 to 4 relapses, with effective retreatment achieved using rituximab and topical corticosteroids. No severe adverse effects were observed.

IMPORTANCE The main component of the first-line treatment of pemphigus vulgaris is high doses of systemic corticosteroids, but adverse effects of these drugs are frequent and sometimes severe. Rituximab has shown effectiveness as a corticosteroid-sparing agent or in case of relapse. To our knowledge, the effectiveness of rituximab as a first-line treatment without systemic corticosteroids has not been evaluated.

OBSERVATIONS Five women in their 50s, 60s, or 70s with pemphigus vulgaris (Pemphigus Disease Area Index score, 15-84 at diagnosis) and contraindications to systemic corticosteroid treatment received rituximab with high-potency topical corticosteroids as first-line treatment. All patients experienced a favorable response, with a mean time to healing of skin and mucosal lesions of 15 weeks. Two patients, with 42- and 48-month follow-up evaluations, did not experience relapse. Three patients developed 2 to 4 relapses, with effective retreatment achieved using rituximab and topical corticosteroids. No severe adverse effects were observed.

CONCLUSIONS AND RELEVANCE Considering the high rate of severe adverse effects induced by prolonged administration of high doses of systemic corticosteroids, new therapeutic options are warranted in the treatment of pemphigus vulgaris. The combination of rituximab and topical corticosteroids could be considered in mild to severe cutaneous disease. Larger long-term studies are needed to evaluate the optimal treatment strategies according to the severity of the disease and the benefit-risk ratio of rituximab.

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Table. Clinical Characteristics, Treatment, and Follow-up of the 5 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>F (70s)</th>
<th>F (50s)</th>
<th>F (70s)</th>
<th>F (70s)</th>
<th>F (60s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Skin (large folds), oral and genital mucosa</td>
<td>Skin (trunk, back, thighs), oral mucosa</td>
<td>Skin (hands, feet, nails, trunk); oral, epiglottal, genital, anal, and conjunctive mucosa</td>
<td>Skin (trunk, face, scalp); oral, conjunctive, genital, and anal mucosa</td>
<td>Skin (large folds, trunk, thighs), oral and anal mucosa</td>
</tr>
<tr>
<td>At diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PDAl score (maximum score, 250)</td>
<td>15 (skin; 10; mucosa, 5)</td>
<td>19 (skin, 9; mucosa, 10)</td>
<td>36 (skin, 14; mucosa, 22)</td>
<td>84 (skin, 26; mucosa, 58)</td>
<td>39 (skin, 17; mucosa, 22)</td>
</tr>
<tr>
<td>Indirect immunofluorescence titer</td>
<td>1:640</td>
<td>1:320</td>
<td>1:320</td>
<td>1:1280</td>
<td>1:80</td>
</tr>
<tr>
<td>ELISA value, AU/mL</td>
<td>Dsg 1, 42; Dsg 3, 172</td>
<td>Dsg 1, 120; Dsg 3, 179</td>
<td>Dsg 1, &gt;100; Dsg 3, &gt;100</td>
<td>Dsg 1, &gt;100; Dsg 3, &gt;100</td>
<td>Dsg 1, 48; Dsg 3, 30</td>
</tr>
<tr>
<td>Contraindications to systemic corticosteroids</td>
<td>Hypertension, glucose intolerance</td>
<td>Diabetes mellitus</td>
<td>Depressive disorder</td>
<td>Diabetes mellitus, hypertension</td>
<td>Depressive disorder, overweight, social difficulties</td>
</tr>
<tr>
<td>Rituximab regimen</td>
<td>375 mg/m², 4 wk</td>
<td>1 g, 2 doses</td>
<td>1 g, 2 doses</td>
<td>1 g, 2 doses</td>
<td>1 g, 2 doses</td>
</tr>
<tr>
<td>Associated topical treatment</td>
<td>Clobetasol propionate, 5 g/d</td>
<td>Clobetasol propionate, 10-20 g/d</td>
<td>Clobetasol propionate, 20 g/d; methylprednisolone mouthwashes</td>
<td>Clobetasol propionate, 15 g/d; methylprednisolone mouthwashes</td>
<td>Clobetasol propionate, 10 g/d; methylprednisolone mouthwashes</td>
</tr>
<tr>
<td>Treatment-related adverse effects</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Time to disease control after first rituximab dose, wk*</td>
<td>Oral mucosa, 6; skin, 12</td>
<td>Skin and mucosa, 2</td>
<td>Skin and mucosa, 4</td>
<td>Skin, 3; mucosa, 5</td>
<td>Skin and mucosa, 1</td>
</tr>
<tr>
<td>Time to complete remission after first infusion, wk</td>
<td>20</td>
<td>16</td>
<td>12</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>At remission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indirect immunofluorescence titer</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
<td>1:160</td>
<td>Negative</td>
</tr>
<tr>
<td>ELISA value, AU/mL</td>
<td>Dsg 1, 3; Dsg 3, 72</td>
<td>Dsg 1, &lt;1; Dsg 3, 7</td>
<td>Dsg 1, 10; Dsg 3, 25</td>
<td>Dsg 1, 3; Dsg 3, 80</td>
<td>Dsg 1, 2; Dsg 3, 2</td>
</tr>
<tr>
<td>Time to onset and treatment of relapses, No.</td>
<td>4 Relapses; time between (1) 1st rituximab dose and 1st relapse, 12 mo; (2) 1st and 2nd relapses, 11 mo; (3) 2nd and 3rd relapses, 22 mo; (4) 3rd and 4th relapses, 21 mo; each relapse treated with 1 infusion of rituximab, 500 mg</td>
<td>2 Relapses; time between (1) 1st rituximab dose and 1st relapse, 22 mo; (2) 1st and 2nd relapses, 16 mo; each treated with 2 infusions of rituximab, 1 g</td>
<td>3 Relapses; time between (1) 1st rituximab dose and 1st relapse, 14 mo; (2) 1st and 2nd relapses, 15 mo; (3) 2nd and 3rd relapses, 23 mo; each treated with 2 infusions of rituximab, 1 g</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Follow-up after the first rituximab dose/follow-up since the last infusion, mo; status of disease at last follow-up</td>
<td>78/12; Complete remission</td>
<td>63/3; Complete remission</td>
<td>63/1; Partial remission with clobetasol propionate 10 g/wk</td>
<td>48/NA; Complete remission</td>
<td>42/NA; Complete remission</td>
</tr>
</tbody>
</table>

Abbreviations: AU, arbitrary unit; Dsg, antidesmoglein; ELISA, enzyme-linked immunosorbent assay; NA, not available; PDAI, Pemphigus Disease Area Index.

* Disease control was the time between the first infusion of rituximab and the end of the appearance of new lesions and the beginning of healing.

traindications to use of systemic corticosteroids, such as diabetes mellitus, hypertension, obesity, depressive disorder, and elderly age, a consensual decision of our medical staff was off-label use of rituximab combined with topical corticosteroids using a fixed-dose regimen (1-g infusions on day 1 and day 15) in 4 patients and 4 weekly infusions of 375 mg/m² in 1 patient. Premedication included a single infusion of methylprednisolone, 100 mg, as recommended by the manufacturer. All patients also received daily applications of 5 to 20 g of clobetasol propionate and methylprednisolone mouthwashes (20 mg or 3 times a day) followed by a progressive withdrawal of treatment within a few weeks after significant improvement. The mean time after the first infusion to achieve complete (n = 4) or nearly complete (n = 1) healing of the disease (ie, absence or near absence of active lesions according to a Physician's Global Assessment [PGA] score of 0 or 1) was 15 weeks (range, 12-20 weeks). A dramatic decrease of the circulating desmoglein autoantibodies identified by indirect immunofluorescence and enzyme-linked immunosorbent assay (ELISA) was observed in all cases during remission. The median follow-up was 63 months (range, 42-78 months). Two patients did not experience relapse during 42 and 48 months of follow-up. Three patients experienced several relapses, with a mean time to the first relapse of 16 months after the first cycle of rituximab. Relapses were successfully treated with rituximab and topical corticosteroids, with follow-up evaluations at 1, 3, and 12 months since the last infusion (Table). No adverse effects related to rituximab occurred during the study period, and no diabetes mellitus induced or worsened by topical corticosteroids was described.
Discussion

Considering the high rate of severe adverse effects induced by systemic corticosteroids, new therapeutic strategies are warranted for treatment of pemphigus vulgaris. As shown in several trials and many case reports and series, rituximab has emerged as the most effective treatment for pemphigus vulgaris in refractory cases. Hematologic and rheumatologic regimens have similar effectiveness in autoimmune diseases, including pemphigus vulgaris. However, the efficacy of rituximab as first-line treatment remains to be evaluated. A French prospective, randomized trial is being conducted to compare 2 first-line strategies for the treatment of pemphigus vulgaris: the classic high doses of corticosteroids alone vs lower doses and shorter durations of corticosteroids combined with rituximab (clinicaltrials.gov identifier: NCT00784589), but the efficacy of rituximab without concomitant systemic corticosteroids has not been assessed.

We report herein a series of 5 patients with pemphigus vulgaris of moderate severity successfully treated with a combination of rituximab and high-potency topical corticosteroids as first-line therapy without use of systemic corticosteroids because of various comorbidities. In a study conducted by Joly et al, 5 of 21 patients received rituximab without corticosteroids because of contraindications, and 4 of 5 were in complete remission at 3 months, as were the 16 patients receiving corticosteroids.

During the time to the initiation of the healing effects of rituximab in our patients with mild pemphigus vulgaris, we used short-term topical corticosteroids to limit the extension of the lesions and promote healing. Topical corticosteroid use has not been assessed in a blinded manner in the treatment of pemphigus vulgaris, in contrast with bullous pemphigoid, but may be considered in very mild disease with low levels of autoantibodies. In France, topical corticosteroids are available at a low cost (10 g of clobetasol propionate costs €2.28 [US $2.95] and 20 tablets of prednisolone for mouthwashes costs €4.88 [US $6.32]) and are reimbursed at 65% through Social Security.

In 4 of our patients, the lesions began to heal 1 to 5 weeks after the first infusion and were in complete remission within 3 to 4 months. This time to achieve complete remission is similar to that in previously published studies with rituximab and to the time to heal observed with systemic corticosteroids with or without mycophenolate mofetil. Systemic circulation of topical corticosteroids and methylprednisolone infusion given as premedication could have played a role in the improvement of our patients, but that improvement probably was a minor and short-term effect. Indirect immunofluorescence showed a dramatic decrease of circulating antibodies in complete remission, with negative results in 4 patients and a low titer (1:160) in the patient who had the highest titer at diagnosis. In contrast, as previously shown, the results of antiglomerular basement membrane ELISA did not always parallel the clinical status, with a persistence of positive ELISA results (especially antiglomerular basement membrane 3 ELISA) in clinical remission in 3 patients.

In our series, the patients’ tolerance of rituximab was excellent and no severe treatment-related adverse effects occurred, even in the 3 patients in their 70s. We did not observe any topical corticosteroid–related diabetes mellitus. This outcome is in accordance with the good safety profile of rituximab reported in pemphigus vulgaris, with an incidence of less than 10% of severe adverse effects. However, a significantly higher rate of rituximab-related mortality was recently described in patients with autoimmune blistering diseases compared with patients with other autoimmune diseases (10.4% vs 2.4%), especially in patients receiving systemic corticosteroids, other immunosuppressive agents, or both given with rituximab. Furthermore, some unexpected cases of progressive, multifocal leukoencephalopathy and Pneumocystis jiroveci pneumonia have been described in patients with autoimmune diseases.

In our series, 3 of 5 patients experienced relapses, with a mean time for the first relapse of 16 months after the first cycle of rituximab. Our results are similar to those of previously published studies reporting a rate of relapse of 40% to 60% and a median relapse-free remission of 19 months. A limitation to our study could be the lack of systematic monitoring of circulating CD19-positive B-cell levels during the treatment, especially in cases of relapse.

Conclusions

Concomitant use of rituximab and high-potency topical corticosteroids could be considered as treatment for pemphigus vulgaris in some patients with contraindications to use of high doses of systemic corticosteroids. However, larger long-term studies are needed to evaluate the optimal strategies according to the benefit-risk ratio of rituximab and the severity of the disease. Such studies are especially needed to evaluate which patients could benefit from rituximab without systemic corticosteroids and which ones would need short-term systemic corticosteroids to obtain the most rapid healing possible and thus reduce the risk of infectious complications.
Acquisition, analysis, or interpretation of data: Ingen-Housz-Oro, Valery-Aline Cosnes, Ortonne, Hie, Wolkenstein, Chosidow.

Drafting of the manuscript: Ingen-Housz-Oro, Paul.

Critical revision of the manuscript for important intellectual content: Valery-Aline Cosnes, Ortonne, Hie, Wolkenstein, Chosidow.

Administrative, technical, or material support: Cosnes, Ortonne, Hie, Paul.

Study supervision: Cosnes, Wolkenstein, Chosidow.

Conflict of Interest Disclosures: None reported.

REFERENCES


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