Background: Treatment of pemphigus vulgaris can be challenging. Systemic steroids associated with other immunosuppressant agents are the mainstay of therapy and have dramatically reduced morbidity and mortality from pemphigus vulgaris. In some patients, however, these agents are not able to control the disease or have severe adverse effects. Rituximab (MabThera; Roche, Basel, Switzerland), a chimeric monoclonal anti-CD20 antibody, induces depletion of B cells in vivo and has shown efficacy in patients with refractory antibody-mediated autoimmune disorders. We report 10 cases of pemphigus vulgaris and 2 cases of pemphigus foliaceous treated with rituximab—to our knowledge the largest series of patients so far—and review the existing literature on the topic.

Observation: The 12 patients were selected for treatment with the anti-CD20 antibody. Rituximab was administered intravenously at a dosage of 375 mg/m² once weekly for 4 weeks. The treatment was well tolerated, and all 12 patients showed a good clinical response during an 18-month follow-up period, along with a consensus decline of the serum antidesmoglein titers. No infectious complications were observed.

Conclusions: Rituximab is able to induce a prolonged clinical remission in patients with both pemphigus vulgaris and pemphigus foliaceous after a single course of 4 treatments. The preliminary experiences worldwide make rituximab a promising therapeutic option for patients with autoimmune diseases. The high costs and the limited knowledge of long-term adverse effects, however, limit its use to selected patients with treatment-resistant or life-threatening disease.

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EMPHIGUS VULGARIS (PV) AND pemphigus foliaceous (PF) are autoimmune blistering diseases that affect the skin and mucous membranes, mediated by circulating autoantibodies directed against desmogleins, which are desmosomal proteins responsible for keratinocyte adhesion. Pemphigus foliaceous is caused by autoantibodies directed against desmoglein 1 (Dsg1), whereas in PV the autoantibodies heat desmoglein 3 (Dsg3) with or without concomitant damage to Dsg1. The binding of autoantibodies results in loss of cell-cell adhesion and blister formation. Systemic steroids, in combination with immunosuppressive agents, are the mainstay of therapy in PV and have dramatically improved the prognosis, but adverse effects and complications from long-term immunosuppressive therapy still contribute substantially to morbidity and mortality from this disease. Furthermore, a number of patients are resistant to conventional therapy. For these patients, alternative treatments (eg, pulse administration of high-dose steroids or cyclophosphamide, plasmapheresis, photopheresis, intravenous immunoglobulins, mycophenolate mofetil, immunoabsorption) have been used.

More recently, rituximab (MabThera; Roche, Basel, Switzerland), a chimeric murine-human anti-CD20 monoclonal antibody directed against pre-B lymphocytes and mature B lymphocytes, has been used in a small number of patients affected with severe PV and PF after the failure of conventional and alternative therapies. Rituximab induces depletion of B cells in vivo and has been shown to be effective and well tolerated in several autoimmune antibody-mediated conditions.

We report 10 cases of recalcitrant or rapidly progressive PV and 2 cases of widespread PF treated with rituximab, discuss the indications for and adverse effects of this therapy, and provide a review of the existing literature on the topic.

METHODS

Patients with an unequivocal diagnosis of mucocutaneous PV or PF according to clinical, histopathologic, and immunofluorescence criteria and level of antidesmoglein antibodies were considered for treatment with rituximab if they had recalcitrant or rapidly progressive disease that was not controlled by conventional therapy and had severe adverse effects from long-term steroid therapy.
The severity of the disease was assessed according to the revised severity index for pemphigus described by Ikeda et al. Each item in the severity index was scored from a minimum of 0 to a maximum of 3 and included: (1) the ratio of the affected area of skin to the total skin area as a percentage (0, none; 1, <5%; 2, 5%-15%; and 3, >15%); (2) the presence or absence of the Nikolsky phenomenon (0, none; 1, only focal; 2, positive; and 3, distinct); (3) the number of newly developed blisters per day (0, none; 1, occasional blisters; 2, 1-5 blisters; and 3, >5 blisters), and (4) the presence or absence of oral lesions as a percentage (0, none; 1, <5%; 2, 5%-30%; and 3, >30%). Consequently, the severity of a case was rated by the total of the scores and considered to be mild if the score was less than 5, moderate if 5 to 7, and severe if higher than 7.

Circulating levels of anti-Dsg3 and anti-Dsg1 IgG antibodies were measured in serum samples by a commercially available enzyme-linked immunosorbent assay (Medical & Biological Laboratories, Nagoya, Japan) based on recombinant human desmogleins produced in a baculovirus expression system. All sera, stored at –20°C until use, were assayed in duplicate, using a cutoff in quantity of 14 and 7 U/mL for anti-Dsg1 and anti-Dsg3 antibodies, respectively.

Rituximab was administered in 4 weekly infusions at a dosage of 375 mg/m², with a premedication of oral paracetamol, 500 mg, and chlorphenamine maleate, 10 mg. Follow-up examinations were performed weekly for the first month and monthly thereafter, and included assessment of the skin and mucous membranes, photographic documentation, routine blood tests, peripheral B-cell count, and antidesmoglein antibodies level measurement.

The primary efficacy criteria were the resolution of the mucocutaneous lesions and the subsequent control of the disease with low-dose immunosuppressive agents. Complete response was defined as the absence of lesions for at least 1 month and no treatment with glucocorticoids or adjuvants or treatment with 5 mg or less of prednisone per day. Partial response was defined as the presence of 1 to 5 new oral or cutaneous blisters per week with treatment with 10 mg or less of prednisone and no adjuvants. Disease control was defined as the suppression of new blisters, together with the beginning of healing of the existing lesions and the Nikolsky phenomenon potentially present. Long-lasting complete response was defined as no treatment with glucocorticoids or adjuvant therapies for 6 months and being free of lesions.

REPORT OF CASES

Twelve patients (5 men and 7 women, aged 27-63 years) underwent rituximab treatment. Of these, 10 patients had PV with severe mucocutaneous involvement and 2 had PF. Patient 11 had PF induced by hydroxychloroquine prescribed for concomitant rheumatoid arthritis. All of the patients had refractory disease and had experienced severe adverse effects from long-term steroid therapy (Table).

In all the cases, the prednisone dosage before the beginning of the rituximab infusions was at least 40 mg/d. Steroid-sparing immunosuppressive therapy had already been administered in at least 2 different ways, in all but 2 cases (patients 8 and 11, whose clinical conditions were characterized by psychosis).

The prednisone dosage was reduced to 25 mg/d soon after the first rituximab infusion and was maintained until the end of the fourth infusion; then a dosage of 12.5 mg/d was continued with a subsequent gradual decrease according to the clinical conditions. Concomitant immunosuppressive therapies were stopped at the beginning of the first infusion in 9 patients: only patients 1 and 5 continued treatment with azathioprine and patient 2 with cyclophosphamide, respectively (see “Comment” section).

RESULTS

All patients had a positive response after treatment (Figure 1 and Figure 2). All the patients experienced disease control for 1 month after the end of the rituximab infusions. Patients 3 and 7 showed an early complete response 1 month after the completion of the treatment. Two months after therapy, 4 patients had complete response (patients 3, 4, 7, and 8) and 8 patients had a partial response. Six months after the end of the infusions only 3 patients had a partial response (patients 5, 10, and 12), whereas the other 9 had a complete response. Four patients experienced a long-lasting complete response for up to a year (patients 1, 2, 3, and 4). No relapses were recorded during follow-up. In 1 case (patient 5), 1 additional infusion of rituximab was given after 6 months. No serious adverse effects occurred after the infusion of rituximab; the only adverse effect was mild tachycardia during the infusion in patient 8.

Patients were given maintenance therapy with prednisone, beginning with 12.5 mg/d and thereafter in tapering doses. Two patients were also administered azathioprine, 100 mg/d, for 2 months in patient 1 and for 6 months in patient 5, and 1 patient was given cyclophosphamide, 50 mg/d, for 2 months.

Changes in anti-Dsg1 and anti-Dsg3 levels, consistent with the clinical response, are shown in Figure 3 and Figure 4, respectively. The antibody titer showed a slow but progressive decline over a 6-month period. In patient 3, a rapid decrease of anti-Dsp3 was observed 1 month after starting the treatment, with a consensual rapid clinical improvement; the patient remained stable 6 months after starting the treatment.

All patients underwent close surveillance for occurrence of infections, but none of them had such a complication. A slight decrease in the serum immunoglobulin level, not exceeding 20% of the basal value, was observed in all patients. As expected, the B-cell count in the peripheral blood dropped to 0 after the first infusion and remained undetectable for at least 6 months in all the treated patients.

After reviewing the literature, we found 17 case reports describing a total of 22 patients with PV and 3 with PF who had been treated with rituximab. Clinical characteristics, treatments, and outcomes for these patients are available in an eTable [http://archdermatol.com]).

COMMENT

The treatment of PV can be a challenge. Steroids are the first-line therapy, but long-term administration may lead to serious adverse effects. To control the disease, adjuvant therapy with other immunosuppressive agents, such as azathioprine, cyclophosphamide, or mycophenolate mofetil, are added as steroid-sparing agents, even though, to date, evidence on the best therapeutic regimen is scanty. In some patients, combined immunosuppressive regimens fail, and to date, treatment options have been limited.

Rituximab is a chimeric murine-human anti-CD20 monoclonal antibody that binds to the CD20 antigen on
pre-B, immature, and mature B cells. Because CD20 is not expressed on stem cells and plasma cells, depletion of the B-cell subpopulation is transient and does not affect immunoglobulin synthesis. Rituximab has become part of the standard therapy for patients with CD20-expressing B-cell lymphoma and is currently under investigation for other indications, including autoimmune diseases, in particular, lupus erythematosus and rheumatoid arthritis.

In the literature, we found 17 case reports describing 22 patients with PV and 3 with PV who were treated with rituximab and followed up for 3 to 36 months. Three patients underwent an additional infusion, and 2 patients had multiple infusions of rituximab without serious adverse effects. In 20 cases there was a complete response, followed by a relapse in 1 patient in whom a second course of rituximab cleared the lesions, obtaining a new complete response. Only 1 patient with severe PF did not show a clinical response.

A recent article by Ahmed et al reported the outcome of a combined treatment with CD20 and intravenous immunoglobulin treatment for 11 patients with PV. The patients were treated with 1 infusion of rituximab, 375 mg/m² weekly for 3 weeks, followed in the fourth week by an intravenous immunoglobulin infusion, 2 g/kg. This cycle was then repeated. At the start of each of the followings of rituximab, these cases are not comparable with our series and those in the existing literature. However, the authors reported a good clinical response with no adverse effects or infections during a mean follow-up period of 31.1 months.

In previously reported cases, we noticed that a variety of immunosuppressive drugs were used as adjuvant therapy after rituximab administration (available in the eTable [http://archdermatol.com]). It is very difficult to compare drugs and dosages to clarify their single role in inducing the clinical response, but because of the concomitant use of intravenous immunoglobulin infusions and the repeated administrations of rituximab, these cases are not comparable with our series and those in the existing literature. However, the authors reported a good clinical response with no adverse effects or infections during a mean follow-up period of 31.1 months.

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We treated 12 patients with recalcitrant PV or PF with rituximab, one of the largest series of patients reported to date. All tolerated the treatment well. Nine exhibited a complete response 6 months after 1 course of 4 infusions of rituximab, and only 1 patient was given an additional single dose 6 months after the first course.

All but 3 received maintenance therapy with low-dose steroids without other immunosuppressive agents. This is quite a different feature compared with those of

![Figure 1: Severity index (according to Ikeda et al) of patients with pemphigus.](https://jamanetwork.com/)

![Figure 2: Case 5. A, Before rituximab therapy; B, 2 months after the end of rituximab administration.](https://jamanetwork.com/)
the previously reported cases, in which the several drugs used during follow-up after rituximab infusion made it difficult to compare the real efficacy of rituximab in inducing the clinical response. In patients 1 and 2, a concomitant immunosuppressive therapy was continued with azathioprine and cyclophosphamide, respectively, for 2 months, whereas in patient 5, treatment with azathioprine was continued for 6 months because of the severity of the disease and then was stopped after the second infusion of rituximab. The evolution of clinical and serological responses in these 3 cases did not show much difference compared with the other 9 cases; therefore, in our opinion, these results indicate that rituximab makes PV and PF more responsive to low-dose steroid therapy.

In most of our patients, a clinical response was observed 6 to 10 weeks after the completion of treatment. This outcome can be explained by assuming that rituximab depletes from peripheral blood and peripheral lymphoid organs the CD20⁺ B cells that are precursors of long-lived autoantibody-forming plasma cells and that these cells are not immediately replaced. This depletion lasts for 6 months or more in most patients, well beyond the persistence of rituximab itself. The extent of depletion of B cells from peripheral lymphoid organs is not known. Because long-lived plasma cells that are CD20⁺ survive and continue to produce antibodies, the levels of serum immunoglobulins do not fall substantially during the treatment. In 2 reported cases of patients treated with rituximab, the Dsg1 and Dsg3 levels correlated with clinical response to the therapy, whereas antibody levels against herpes simplex virus 1 and 2 and varicella-zoster virus were not significantly affected. To explain the fall in levels of specific autoantibodies, 1 hypothesis is that rituximab acts on distinct B-cell subsets and that different sensitivity to rituximab depends on factors derived from the cellular microenvironment.

In only 2 of our patients did we observe that a more rapid response manifested during the rituximab course. Similar cases showing an early clinical improvement have been described. We can hypothesize that this favorable response to rituximab therapy may be due to a late response to previous immunosuppressive therapy or to other immunological mechanisms, including a high percentage of CD20⁺ cells in the total amount of autoantibodies producing B cells. In fact, a late response may be observed: in the literature we have found several other cases that are similar to our case 5.

In most of the cases reported, the clinical response paralleled the serum decrease of autoantibodies measured by indirect immunofluorescence. In 13 patients, the levels of anti-Dsg1 and anti-Dsg3 were measured, and those levels were not always correlated with the clinical response. In fact, in some patients the clinical improvement was not accompanied by a simultaneous decrease of antibodies measured by indirect immunofluorescence. In 13 patients, the clinical response paralleled the serum decrease of autoantibodies measured by indirect immunofluorescence. In 13 patients, the levels of anti-Dsg1 and anti-Dsg3 were measured, and those levels were not always correlated with the clinical response. In fact, in some patients the clinical improvement was not accompanied by a simultaneous decrease of antibodies measured by indirect immunofluorescence. In 13 patients, the clinical response paralleled the serum decrease of autoantibodies measured by indirect immunofluorescence. In 13 patients, the levels of anti-Dsg1 and anti-Dsg3 were measured, and those levels were not always correlated with the clinical response. In fact, in some patients the clinical improvement was not accompanied by a simultaneous decrease of antibodies measured by indirect immunofluorescence.
imab administration, but the age of the patient at the time of infusion does not seem to be an important feature.

In 4 of the cases of pemphigus reported in the literature, serious infections occurred following rituximab treatment. In the case reported by Salopek et al.9, sepsis from *Pseudomonas aeruginosa* and *Staphylococcus aureus* developed shortly after the first infusion of rituximab in an immunocompromised patient who had previously experienced similar episodes, so it is unlikely that rituximab had caused this complication. Dupuy et al9 described the occurrence of hip pneumonia in another patient 12 weeks after the first infusion of rituximab, but this complication was a relapse of an already existing condition.9 Dupuy et al9 also describe a community-acquired pneumonia in 2 cases, azathioprine in 1 case, and cyclosporine A plus mofetil mycophenolate in 1 case), and in the fatal case there was concomitant administration of cyclophosphamide.

These data seem to show that therapy with rituximab does not cause an increase in the rate of opportunistic infections in patients with serious and refractory PV or PF, keeping in mind that all these patients had experienced years of immunosuppressive therapy with high dosages of multiple drugs. We believe that only the addition of immunosuppressive drugs other than steroids could increase the risk of infectious adverse effects, but this choice does not seem to influence the clinical response of the disease or the incidence of relapses. However, the possibility of multiple courses of rituximab can be considered in refractory cases: the tolerability profile does not change, as Kong et al.10 have shown.

Finally, rituximab is a chimeric murine-human molecule, so there are some concerns about the long-term adverse effects of infusion of foreign protein, and a prior sensitivity to murine proteins has to be ruled out before administering this monoclonal antibody.

In conclusion, rituximab can be considered an important treatment option in patients with widespread recalcitrant or life-threatening PV. This drug has a good safety and tolerability profile and has shown a positive and long-lasting response in patients with PV after a single course. These characteristics make it a therapy that is potentially able to modify the natural history of PV. Unfortunately, rituximab is very expensive, and its long-term effects are still unknown. Although its use is currently limited to selected cases of PV, controlled clinical trials with a greater number of patients are urgently needed.

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Author Contributions: Study concept and design: Cianchini, Didona, and Puddu. Acquisition of data: Cianchini, Frezzolini, Ruffelli, and Didona. Analysis and interpretation of data: Cianchini, Corona, Frezzolini, and Ruffelli. Drafting of the manuscript: Cianchini, Frezzolini, and Ruffelli. Critical revision of the manuscript for important intellectual content: Cianchini, Corona, Didona, and Puddu. Statistical analysis: Corona and Frezzolini. Administrative, technical, and material support: Cianchini, Corona, and Ruffelli. Study supervision: Cianchini, Corona, Didona, and Puddu.

Financial Disclosure: None.

Additional Information: The eTable is available at http://www.archdermatol.com.

REFERENCES


### eTable. Overview of the Published Cases

<table>
<thead>
<tr>
<th>Source</th>
<th>Sex/Age, y</th>
<th>Disease Duration, y</th>
<th>Cycles of Rituximab, No.</th>
<th>Previous Treatments</th>
<th>Response</th>
<th>Follow-up, mo</th>
<th>Remission</th>
<th>Relapse</th>
<th>Maintenance Therapya</th>
<th>Infections</th>
</tr>
</thead>
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<tr>
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<td>1</td>
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<td>15</td>
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(continued)
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<th>Disease Duration, y</th>
<th>Cycles of Rituximab, No.</th>
<th>Previous Treatments</th>
<th>Response</th>
<th>Follow-up, mo</th>
<th>Remission</th>
<th>Relapse</th>
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<th>Infections</th>
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<tr>
<td>Wenzel et al12</td>
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<td>Schmidt et al13</td>
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<td>Arin et al15</td>
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</tbody>
</table>

Abbreviations: C, complete; EP, extracorporeal photopheresis; HD, high-dose; IAd, immunoadsorption; Ig, immunoglobulins; IV, intravenous; MI, multiple infusions; NR, not reported; P, partial; PLA, plasmapheresis.

After rituximab administration.

The patient had pemphigus foliaceous.

Follow-up of the case reported by Herrmann et al.