

ORIGINAL ARTICLE

# Treatment of Pemphigus Vulgaris with Rituximab and Intravenous Immune Globulin

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ABSTRACT

**BACKGROUND**

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Pemphigus vulgaris is a potentially fatal autoimmune mucocutaneous blistering disease. Conventional therapy consists of high-dose corticosteroids, immunosuppressive agents, and intravenous immune globulin.

**METHODS**

We studied patients with refractory pemphigus vulgaris involving 30% or more of their body-surface area, three or more mucosal sites, or both who had inadequate responses to conventional therapy and intravenous immune globulin. We treated the patients with two cycles of rituximab (375 mg per square meter of body-surface area) once weekly for 3 weeks and intravenous immune globulin (2 g per kilogram of body weight) in the fourth week. This induction therapy was followed by a monthly infusion of rituximab and intravenous immune globulin for 4 consecutive months. Titers of serum antibodies against keratinocytes and numbers of peripheral-blood B cells were monitored.

**RESULTS**

Of 11 patients, 9 had rapid resolution of lesions and a clinical remission lasting 22 to 37 months (mean, 31.1). All immunosuppressive therapy, including prednisone, could be discontinued before ending rituximab treatment in all patients. Two patients were treated with rituximab only during recurrences and had sustained remissions. Titers of IgG4 antikeratinocyte antibodies correlated with disease activity. Peripheral-blood B cells became undetectable shortly after initiating rituximab therapy but subsequently returned to normal values. Side effects that have been associated with rituximab were not observed, nor were infections.

**CONCLUSIONS**

The combination of rituximab and intravenous immune globulin is effective in patients with refractory pemphigus vulgaris.

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**P**EMPHIGUS VULGARIS IS A POTENTIALLY fatal blistering mucocutaneous autoimmune disease that affects the skin and the oral cavity and other mucosal surfaces. The lesion is characterized by intraepidermal vesicles with acantholysis and an intact basal layer.<sup>1</sup> Serum samples from patients with pemphigus vulgaris contain antibodies against desmoglein 3, which have been shown to be pathogenic.<sup>2-4</sup>

The risk of death in patients with pemphigus vulgaris has been substantially reduced by treatment with systemic corticosteroids.<sup>5</sup> Current therapy consists of high doses of corticosteroids plus immunosuppressive agents.<sup>6</sup> This combination frequently causes long-term immunosuppression, the consequences of which are now the most common cause of death in patients with pemphigus vulgaris.<sup>7</sup> Patients who do not have a response to corticosteroids plus immunosuppressive agents or who have severe side effects from this therapy have been successfully treated with intravenous immune globulin,<sup>8,9</sup> which can be used as monotherapy and can produce long-term remissions.

We report a study of 11 patients with severe pemphigus vulgaris that was resistant to corticosteroids plus immunosuppressive agents and intravenous immune globulin. We treated these patients with rituximab (Rituxan, Genentech), a humanized monoclonal antibody against the B-cell antigen CD20 that depletes antibody-producing B cells, plus intravenous immune globulin.<sup>10,11</sup> We assessed the response to treatment, the duration of clinical remission, toxic effects, and immune correlates of the response.

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## METHODS

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### PATIENTS

Patients were eligible for the study if they met the following criteria: pathological findings of a lesion showing intraepidermal vesicles, suprabasilar acantholysis, and an intact basal layer; involvement by pemphigus vulgaris of at least 30% of the body surface, three or more mucosal surfaces, or both; deposition of the IgG of the patient on the surface of keratinocytes in perilesional tissue as shown by direct immunofluorescence; and the presence, at the time of initiation of rituximab therapy, of antibodies that bind to the surface of keratinocytes, as determined by indirect immunofluorescence with the use of monkey esophagus. Additional eligibility criteria were a

lack of response to long-term, high-dose prednisone plus at least three or more immunosuppressive agents and a minimal response to intravenous immune globulin when given as described below, or acute relapse whenever intervals between intravenous infusions of immune globulin were increased<sup>9</sup>; a failure of dapsone, oral methotrexate, or other immunosuppressive agents used in combination with intravenous immune globulin to induce a sustained remission; and the ruling out of coexisting illnesses on the basis of normal findings for blood counts, serum chemical measurements, urinalysis, and computed tomographic scans of the neck, chest, abdomen, and pelvis. All patients gave written informed consent, and an institutional review board of New England Baptist Hospital approved the study.

### THERAPY

Patients were treated with an infusion of rituximab (375 mg per square meter of body-surface area) once a week for 3 weeks. In the fourth week, intravenous immune globulin, 2 g per kilogram of body weight, was given. This treatment was repeated for a second cycle. In months 3, 4, 5, and 6, patients received a single infusion of rituximab plus a single infusion of 2 g of intravenous immune globulin per kilogram at the start of the month. Thus, during a 6-month period, each patient received a total of 10 infusions of rituximab and 6 infusions of intravenous immune globulin. If by then the patient was clinically free of disease, seven additional infusions of intravenous immune globulin were given.<sup>9</sup>

The time to first improvement was defined as the time from the start of therapy to the healing of earlier lesions and the cessation of the development of new lesions. Complete improvement was defined as the time from the start of therapy to complete clearing or clinical resolution and healing of all lesions, with complete reepithelialization. The time to discontinuation of all systemic immunosuppressive therapy after the start of rituximab therapy was recorded. The duration of follow-up was the time between the start of treatment and the last office visit.

### IMMUNOLOGIC RESPONSES

Serum samples were collected from all patients before each infusion of rituximab and intravenous immune globulin. The titers of antibodies against keratinocyte cell-surface antigen were measured

with the use of an indirect immunofluorescence assay with monkey esophagus.<sup>1,12</sup> The secondary antibodies in this assay were fluorescein-conjugated goat antihuman IgG, IgG1, and IgG4 antibodies. The phenotypes of peripheral-blood mononuclear cells were determined by flow cytometry with the use of murine monoclonal antibodies (10  $\mu$ g per milliliter) against CD4 (SIM4), CD8 (OKT8), CD16 (B73.1), CD32 (Coulter Immunotech), CD19 (Exalpha), and CD20 (IF5.3), followed by fluorescein-conjugated goat antimouse IgG.<sup>13</sup>

## RESULTS

### CHARACTERISTICS OF THE PATIENTS

Eleven patients were enrolled and treated (Table 1). All patients had been and were being treated with conventional therapy, consisting of high-dose corticosteroids and immunosuppressive agents. The highest dose of prednisone ranged from 60 to 240 mg daily (mean, 125). All patients had received four to eight immunosuppressive agents (mean, four), including 1.5 to 2.0 mg of cyclophosphamide per kilogram per day for at least 6 months (6 patients) and 2 to 3 g of mycophenolate mofetil per kilogram per day for at least 6 months (11 patients), and none had a remission. The duration of conventional therapy ranged from 20 to 132 months (mean, 55.7). All patients had a clinical response to subsequent therapy with intravenous immune globulin. Attempts to prolong the intervals between cycles resulted in a recurrence in seven patients. Four patients had recurrences during treatment with intravenous immune globulin. Initially, intravenous immune globulin was used as monotherapy for 4 to 22 months (mean, 12.2). Since relapses occurred with intravenous immune globulin, all patients with relapses received dapsone with methotrexate and intravenous immune globulin. This triple therapy was used for 12 to 36 months (mean, 16.5). The total previous duration of therapy with intravenous immune globulin ranged from 18 to 81 months (mean, 32.6). The duration of all systemic therapy before study entry, including intravenous immune globulin, ranged from 31 to 219 months (mean, 68.8).

### RESPONSE TO THERAPY WITH RITUXIMAB AND INTRAVENOUS IMMUNE GLOBULIN

All patients had improvement between the third and sixth infusions of rituximab (mean, halfway

between the fourth and fifth infusions). Complete clearance of lesions was achieved between the seventh and ninth infusions. Of the 11 patients, 9 received 10 infusions of rituximab and had a sustained remission. Two patients had a relapse after initial therapy; one patient received one additional course of rituximab, and the other re-

**Table 1. Characteristics of the Patients.**

Characteristic	Patients (N=11)
Male sex (no.)	5
Age at onset (yr)	
Median	38
Range	15–68
Involvement (no.)	
Skin*	
30 to 40% of body-surface area	5
41 to 60% of body-surface area	5
Oral cavity	11
Penis	3
Vagina	3
Conjunctiva	2
Pharynx	11
Larynx	7
Nose	8
Anus	5
Drug therapy before intravenous immune globulin therapy (no.)	
Prednisone	11
Mycophenolate mofetil	11
Azathioprine	10
Dapsone	9
Methotrexate	9
Cyclophosphamide	6
Thalidomide	1
Gold	1
Colchicine	1
Tacrolimus	1
Cyclosporine	1
Intravenous immune globulin (no.)	
10–20 cycles	5
21–60 cycles	4
>60 cycles	2
Duration of disease before rituximab therapy (no.)	
30–48 mo	3
49–96 mo	6
>96 mo	2

\* The affected body-surface area of one patient was not recorded.

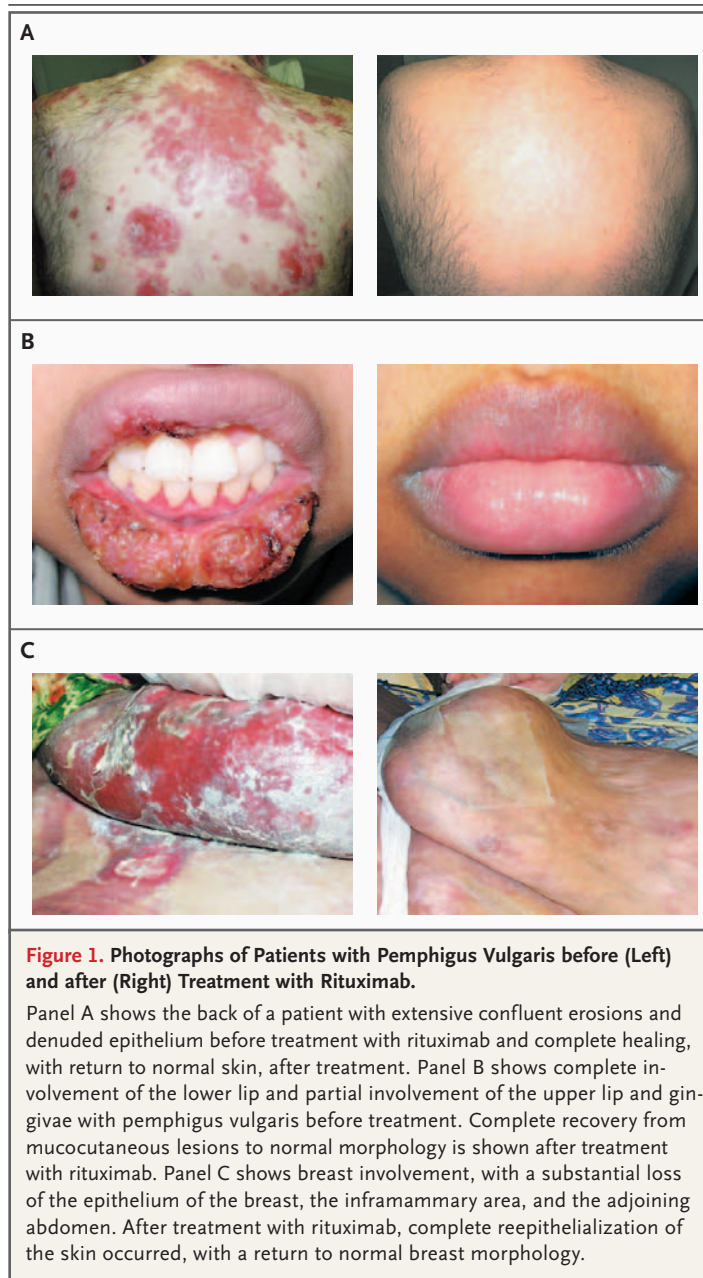
ceived two additional courses. Tapering of immunosuppressive therapy was begun as soon as rituximab therapy had been initiated and was discontinued by the end of the second cycle in all patients. All patients were observed for the following side effects that have been associated with rituximab and intravenous infusions of immune globulin: allergic reactions, nausea, vomiting, rigors, chills, fever, cytokine-release syndrome, and infections. None of these side effects were observed in any of the patients.

The duration of follow-up after the discontinuation of rituximab therapy was 15 to 37 months (mean, 32.5). Sustained clinical remissions lasted for 22 to 37 months of observation (mean, 31.1) (Table 2) for nine patients. These patients discontinued all conventional immunosuppressive therapy and were free of pemphigus lesions during the period of remission.

Patient 10 had a recurrence 6 months after the 10th infusion of rituximab. The patient was given an additional infusion of rituximab once a week for 3 consecutive weeks without any added drugs. A complete resolution was observed within 6 weeks. Twenty-four months later, the patient remained disease-free and received no systemic therapy. Patient 11 also had a recurrence 6 months after the 10th infusion of rituximab. The patient was given an infusion of rituximab once a week for 3 consecutive weeks and had a complete clinical resolution. Eight months later, a second, wide-

spread recurrence developed. The patient again was given an infusion of rituximab once a week for 3 consecutive weeks, and a complete clinical resolution of disease was observed. The patient remained free of disease and received no systemic therapy for 15 months. Five patients who had been unable to work because of the disease and the treatment were able to resume full employment. Figure 1 shows representative photographs documenting the disease at baseline and after treatments.

Variable	Value
Time to first improvement	
No. of patients	11
Median — wk (range)	4 (3–6)
Time to complete remission	
No. of patients	9
Median — wk (range)	9 (7–9)
Duration of complete remission	
No. of patients	9
Median — mo (range)	31 (22–37)
Recurrence	
No. of patients	2
Time to first recurrence — mo	
Patient 10	12
Patient 11	12
Duration of most recent remission — mo	
Patient 10	24
Patient 11	15



### TITERS OF ANTIKERATINOCYTE CELL-SURFACE AUTOANTIBODIES

Autoantibodies to keratinocyte cell-surface antigen, or desmoglein, can be of the IgG1 or IgG4 subclass. IgG4 is pathogenic, whereas IgG1 is nonpathogenic.<sup>2-4,12</sup> The titers of IgG1 and total IgG antikeratinocyte cell-surface antibodies were identical in our patients (data not shown). Hence, total IgG titers are reported. The mean titer of total IgG and IgG4 antikeratinocyte cell-surface antibodies in the 11 patients was 1:1280 (range, 1:5120 to 1:320) before the start of rituximab

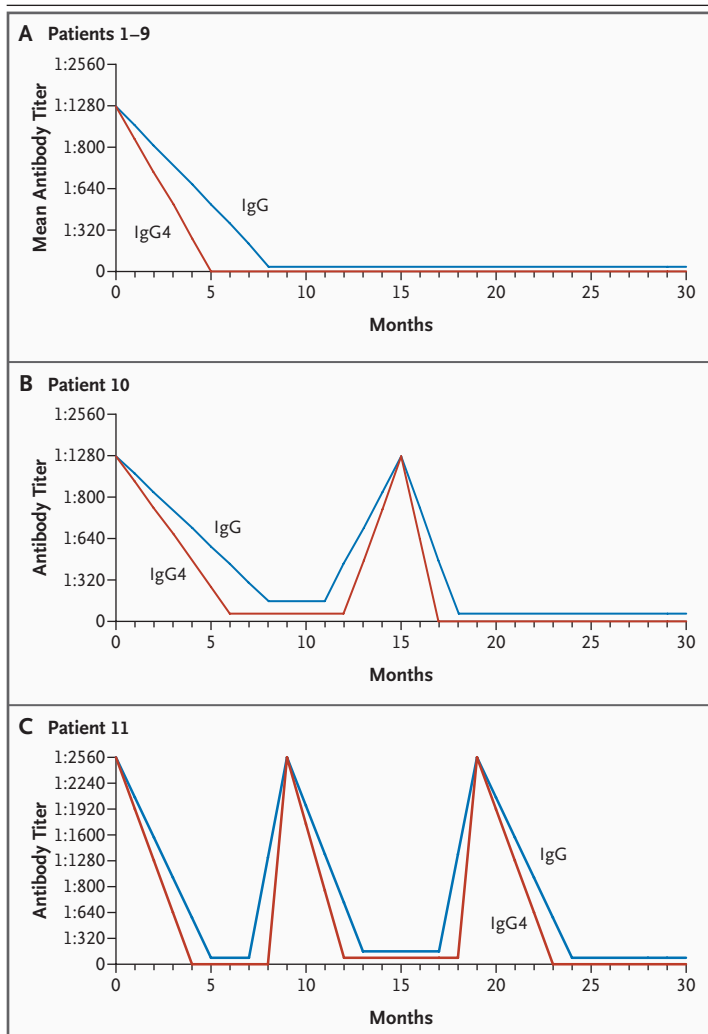
treatment (Fig. 2A). In nine of the patients, there was a rapid decrease in the levels of IgG4 antibodies; levels became undetectable within a mean of 4.6 months (range, 2.5 to 5.3). The total IgG levels decreased more slowly, reaching a mean titer of 1:40 by 7 months and remaining at that level in all patients who had a sustained response.

The increases and decreases in titers of IgG and IgG4 antikeratinocyte cell-surface antibodies in the two patients with recurrences (Fig. 2B and 2C) correlated directly with disease activity. The IgG4 titers remained undetectable during the follow-up period after the final discontinuation of rituximab.

### SUBGROUP ANALYSIS OF PERIPHERAL-BLOOD LYMPHOCYTES

Lymphocytes from patients were analyzed longitudinally for the expression of specific T-cell and B-cell markers and Fc receptors. There were no significant changes from baseline in CD4+ or CD8+ T cells or Fc-receptor-positive cells.

The percentage of B cells in peripheral blood was lower than normal because all patients were receiving multiple immunosuppressive agents before rituximab therapy. Within 2 weeks after the start of rituximab therapy, CD20+ B cells were undetectable in all patients and remained so throughout the treatment. A return to normal levels was observed 8 to 18 months (mean, 11.2) after the discontinuation of rituximab treatment, and B cells remained at normal levels during the follow-up period in the nine patients with sustained remission (Fig. 3A). In Patient 10, the percentage of B cells rapidly declined to undetectable levels after the infusions of rituximab but returned to 14 percent of peripheral-blood mononuclear cells at the time of recurrence (Fig. 3B). Treatment of this recurrence with rituximab resulted in a rapid decline in CD20+ B-cell levels, and they remained at undetectable levels for the subsequent 6 months. The levels returned to 13 percent in 9 months and remained at that level thereafter. A similar relationship between the two recurrences of disease and B-cell levels was observed in Patient 11.



**Figure 2.** Relationship between Titers of Serum Antikeratinocyte Antibodies and Rituximab Therapy in Patients with Pemphigus Vulgaris.

Panel A shows the mean titer of total IgG and IgG4 antikeratinocyte cell-surface antibodies at various intervals in nine patients who were treated according to the study protocol and had no recurrences. Panel B shows the titers in Patient 10, who had one relapse, and Panel C shows the titers in Patient 11, who had two relapses. Log scales are used.

### DISCUSSION

We report the clinical course of 11 patients with refractory, widespread, and prolonged pemphigus vulgaris who were treated with rituximab and intravenous immune globulin. Before treatment was

initiated, all patients had limited or incomplete responses to conventional treatment and had had numerous relapses and remissions associated with multiple side effects and hospitalizations. No observable side effects were associated with the use of rituximab and intravenous immune globulin, and therapy with these two agents resulted in sustained and complete remission in 9 of 11 patients and eventually in complete control of the disease in all 11 patients. All patients ultimately were able to discontinue all treatment. Control of the pemphigus was correlated with a reduction in titers of pathogenic IgG4 antikeratinocyte antibodies.

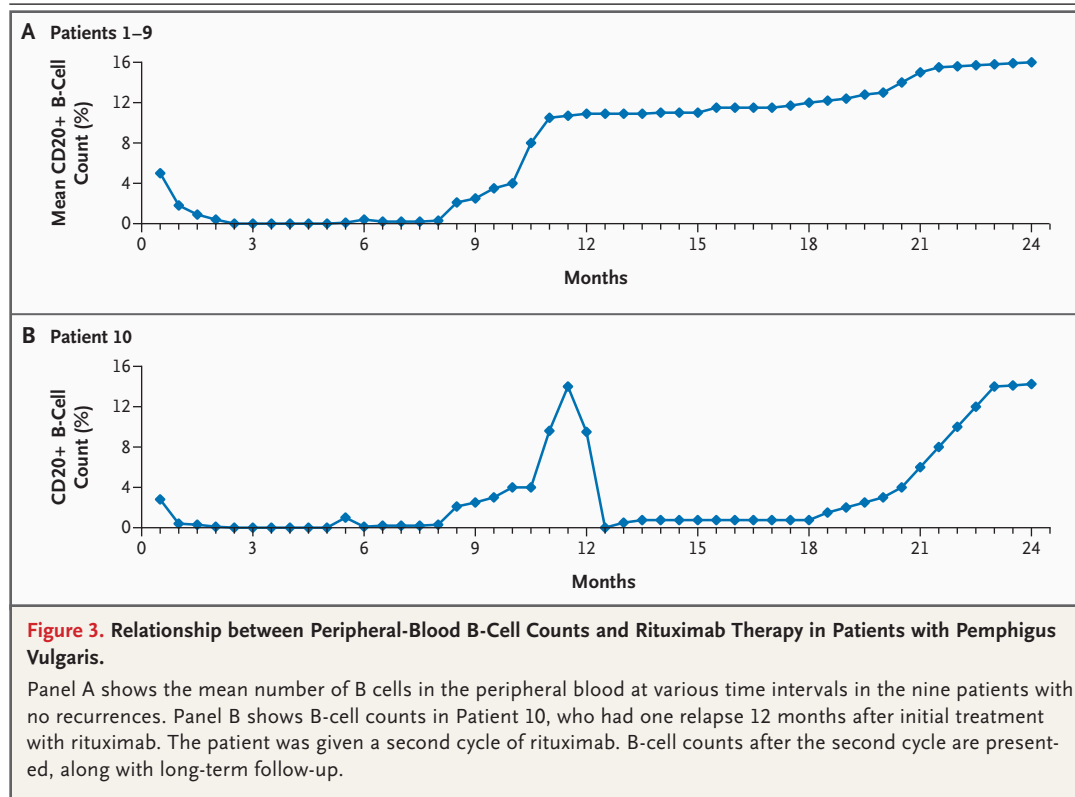
We treated the patients with a combination of intravenous immune globulin and rituximab to provide protection from reduced immunoglobulin levels,<sup>14-17</sup> which rituximab can cause; to eliminate pathogenic B cells and the production of pathogenic autoantibodies; and to try to reconstitute normal immunity.<sup>10</sup> Intravenous immune globulin alone can produce long-term clinical and serologic remissions in patients with pemphigus vulgaris.<sup>9</sup> However, it did not do so in our patients. For this reason, we believe that the dramatic and rapid clinical responses we observed can be attributed to rituximab and possibly to synergistic effects of intravenous immune globulin. The long-

term remissions in these patients could be due in part to the transient elimination of B cells by rituximab in combination with the regulatory effects of intravenous immune globulin.

The regimen of two induction cycles followed by consolidation therapy was designed to eliminate pathogenic antibody-producing B cells and then to destroy memory B cells that might have escaped the induction treatment. Although rituximab reduced peripheral-blood CD20+ B cells to undetectable levels within 2 weeks, these cells returned to normal levels within 10 to 12 months but without the reappearance of pathogenic autoantibodies in most patients.

Despite aggressive treatment, two patients had recurrences. We speculate that these relapses were due to the reappearance of pathogenic memory B cells, which were subsequently eliminated by rituximab monotherapy. Our finding that the levels of antikeratinocyte IgG4 antibodies correlated with disease activity better than did the levels of IgG antibodies is consistent with published reports that IgG4 antibodies against keratinocyte cell surfaces are pathogenic in pemphigus vulgaris.<sup>2-4,12</sup>

Previous experience with rituximab therapy for patients with pemphigus vulgaris is limited. Sev-



enteen patients have been reported to have received rituximab therapy for refractory pemphigus.<sup>18-26</sup> Most were treated with a regimen used for lymphomas, which is limited to infusions of rituximab once a week for 4 consecutive weeks.<sup>11</sup> In addition, conventional immunosuppressive therapy was used concomitantly with rituximab and was maintained in most patients. Nine of the 17 patients (53%) were disease-free at a 6-month follow-up. Serious systemic infections developed in five of the patients (29%), and one patient died of septicemia. Long-term follow-up data are limited, and conventional immunosuppressive therapy was not systematically evaluated.

Treatment with rituximab has been used for other autoimmune diseases,<sup>26-37</sup> although these studies did not involve a combination of intravenous immune globulin and rituximab or a planned regimen of induction and consolidation with rituximab that was similar to ours. Furthermore, the rapid and lasting responses seen in our study have not been observed in most other studies.

There were no clinically significant side effects of therapy in our study, including infection. Most acute side effects of rituximab are mild, transient, and infusion-related. The cytokine-release syndrome can develop in patients receiving rituximab for lymphoma and is most common in patients with bulky adenopathy or bone marrow involvement.<sup>38,39</sup> Although none of the patients in our study had these serious side effects, the long-term consequences of rituximab therapy in patients with autoimmune diseases are unknown. We conclude that refractory pemphigus vulgaris can respond to a regimen of intravenous immune globulin and 10 infusions of rituximab during a 6-month period.

No potential conflict of interest relevant to this article was reported.

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