

ORIGINAL ARTICLE

A Single Cycle of Rituximab for the Treatment of Severe Pemphigus

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ABSTRACT

BACKGROUND

The combination of multiple cycles of rituximab and intravenous immune globulins has been reported to be effective in patients with severe pemphigus. The aim of this study was to assess the efficacy of a single cycle of rituximab in severe types of pemphigus.

METHODS

We studied 21 patients with pemphigus whose disease had not responded to an 8-week course of 1.5 mg of prednisone per kilogram of body weight per day (corticosteroid-refractory disease), who had had at least two relapses despite doses of prednisone higher than 20 mg per day (corticosteroid-dependent disease), or who had severe contraindications to corticosteroids. The patients were treated with four weekly infusions of 375 mg of rituximab per square meter of body-surface area. The primary end point was complete remission 3 months after the end of rituximab treatment; complete remission was defined as epithelialization of all skin and mucosal lesions.

RESULTS

Eighteen of 21 patients (86%; 95% confidence interval, 64 to 97%) had a complete remission at 3 months. The disease relapsed in nine patients after a mean of 18.9 ± 7.9 months. After a median follow-up of 34 months, 18 patients (86%) were free of disease, including 8 who were not receiving corticosteroids; the mean prednisone dose decreased from 94.0 ± 10.2 to 12.0 ± 7.5 mg per day ($P=0.04$) in patients with corticosteroid-refractory disease and from 29.1 ± 12.4 to 10.9 ± 16.5 mg per day ($P=0.007$) in patients with corticosteroid-dependent disease. Pyelonephritis developed in one patient 12 months after rituximab treatment, and one patient died of septicemia 18 months after rituximab treatment. These patients had a profound decrease in the number of circulating B lymphocytes but normal serum levels of IgG.

CONCLUSIONS

A single cycle of rituximab is an effective treatment for pemphigus. Because of its potentially severe side effects, its use should be limited to the most severe types of the disease. (ClinicalTrials.gov number, NCT00213512.)

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PEMPHIGUS IS A LIFE-THREATENING autoimmune blistering disease affecting the skin and mucosa. It is mediated by pathogenic autoantibodies directed against desmoglein 1 and desmoglein 3, adhesion molecules of the epidermis that are responsible for the cohesion between keratinocytes in skin and mucosa, respectively.¹⁻³ Patients with severe pemphigus require long-term treatment with corticosteroids and other immunosuppressive drugs, which can lead to serious adverse events.^{4,5}

Rituximab, a monoclonal antibody directed against the CD20 antigen of B lymphocytes, has been demonstrated to be effective in various autoimmune diseases⁶⁻¹² and in occasional cases of life-threatening pemphigus.¹³⁻²² Recently, the combination of multiple cycles of rituximab and intravenous immune globulin, another potentially active agent in pemphigus, was reported to be effective in a single-center study of 11 patients with pemphigus.²³ We report a multicenter series of 21 patients with severe pemphigus treated by a simple regimen of one cycle of rituximab. Immunologic evaluations explored the mechanism of the short-term and long-term effects of rituximab on these patients.

METHODS

PATIENTS

Thirteen centers in France participated in this prospective, open trial. The study was approved by the ethics committee of Seine-Maritime, and written informed consent was obtained from each patient.

Consecutive patients with severe mucosal erosions, superficial blisters, or both suggestive of pemphigus vulgaris or pemphigus foliaceus; a histologic picture of intraepidermal acantholysis; and deposition of IgG, complement component 3 (C3), or both on the keratinocyte membrane detected by direct immunofluorescence²⁴ were included if additional criteria were met. These were the absence of response to an 8-week course of treatment with 1.5 mg of prednisone per kilogram of body weight per day (corticosteroid-refractory cases); the occurrence of at least two cutaneous or mucosal relapses during the period when corticosteroid doses were being decreased, despite prednisone doses higher than 20 mg per day (corticosteroid-dependent cases); and contraindication to corticosteroids because of severe associated medical conditions.

TREATMENT

The patients were treated with one cycle of four weekly infusions of rituximab at a dose of 375 mg per square meter of body-surface area on days 1, 8, 15, and 22. Corticosteroids were maintained at the initial dose until the disease was controlled, and the corticosteroid dose was then reduced by 10% twice a month. Patients with contraindications to corticosteroids were treated with rituximab alone. Complete remission was defined as the epithelialization of all skin and mucosal lesions, partial remission as the epithelialization of more than 50% of lesions but not of all lesions, and relapse as the occurrence of new cutaneous or mucosal erosions.

END POINTS

The patients were evaluated clinically and biologically every month during the first year of follow-up and every other month during the second year. The primary end point was the rate of complete remission 3 months after the last infusion of rituximab. The secondary end points were the rate of complete remission during the study period, the time from the start of rituximab treatment to complete remission, the number of relapses and the length of time to each relapse, and adverse effects of treatment.

IMMUNOLOGIC EVALUATION

Blood samples were collected at each evaluation. Titers of antibodies against desmoglein 1 and desmoglein 3 were measured by a desmoglein enzyme-linked immunosorbent assay (ELISA) test (MESACUP Desmoglein Test, MBL Medical and Biological Laboratories) with 1:100 diluted serum. For determination of IgG subclass, mouse anti-human IgG1, IgG2, IgG3, and IgG4 antibodies (Sigma) and peroxidase-conjugated goat antimouse IgG (Rockland) were used. IgG reactivity of pemphigus vulgaris serum against the NH₂ terminal domains of desmoglein 3 was characterized with the use of ELISA with baculovirus-derived recombinant proteins of desmoglein 3.²⁵

The phenotype of peripheral-blood mononuclear cells was determined by three-color flow cytometry with the use of murine monoclonal antibodies against CD3, CD4, CD5, CD19, CD20, CD21, CD22, CD23, CD24, CD27, CD38, CD56, and CD86 (Coulter). The IgG, IgA, and IgM repertoire of peripheral-blood B lymphocytes was determined with the use of the immunoscope technique, a method that evaluates the diversity of the

B-lymphocyte repertoire and monitors its evolution. First, a polymerase chain reaction amplified the heavy-chain variable (HV) region of the IgG, IgA, and IgM molecules. In a second step, the lengths of the complementary determining region 3 (CDR3) were analyzed on an automatic sequencer.²⁶ The serum levels of antibodies against pneumococcal capsule polysaccharide and tetanus toxin were determined on days 0, 90, and 180.²⁷

STATISTICAL ANALYSIS

Two-sided P values less than 0.05 were considered to indicate statistical significance. Continuous variables are expressed as means \pm SD. Mean doses of prednisone were compared with the use of the nonparametric Wilcoxon test. Roche, France (the

maker of rituximab) had no role in the design of the study, in data accrual or analysis, or in manuscript preparation.

RESULTS

CHARACTERISTICS OF THE PATIENTS

Twenty-one patients (14 men and 7 women; 14 with pemphigus vulgaris and 7 with pemphigus foliaceus) were enrolled between January 2003 and December 2004 and followed through March 2007. Their mean (\pm SD) age was 53.7 \pm 15.6 years. The baseline clinical characteristics of the patients are shown in Table 1. The mean proportion of the body-surface area involved was 27%. All the patients had severe oral involvement and weight loss

Table 1. Baseline Characteristics of Patients with Pemphigus Treated with Rituximab.*

Characteristic	Corticosteroid-Refractory Disease (N=5) [†]	Corticosteroid-Dependent Disease (N=11)	Contraindication to Corticosteroids (N=5)
Sex (M/F)	2/3	7/4	5/0
Age (yr)	56.2 \pm 18.9	47.5 \pm 13.1	64.6 \pm 19.7
Type of pemphigus (no. of patients)			
Pemphigus vulgaris	4	7	3
Pemphigus foliaceus	1	4	2
Duration of mucosal lesions (mo)	21.8 \pm 30.5	81.0 \pm 82.7	12.5 \pm 7.8
Duration of cutaneous lesions (mo)	54.6 \pm 62.3	71.0 \pm 75.0	8.0 \pm 6.9
Associated medical conditions (no. of patients)			
Diabetes mellitus	1	3	2
Hypertension	0	3	2
Hyperlipidemia	0	3	2
Other [‡]	1	6	6
Previous treatment failure (no. of patients)			
Intravenous immune globulin	2	1	
Azathioprine	4	3	
Methotrexate	2	3	
Mycophenolate mofetil	0	4	
Cyclosporine	0	1	
Mean body-surface area involved (%)	30	31	17
Prednisone dose at time of rituximab infusion (mg/day)	94.0 \pm 10.2	29.1 \pm 12.4	0

* Plus-minus values are means \pm SD.

[†] Corticosteroid-refractory pemphigus did not respond to an 8-week course of treatment with 1.5 mg of prednisone per kilogram of body weight per day.

[‡] Other medical conditions included asthma in one patient with corticosteroid-refractory pemphigus; rheumatoid arthritis (one patient), myopathy (one), bone fracture (one), pyelonephritis (one), and depression (two) among patients with corticosteroid-dependent disease; and blindness, bacterial meningitis, bone tuberculosis, gram-negative pneumonia, osteonecrosis of the hip, and cardiac insufficiency, each in one patient, among those with contraindications to corticosteroids.

Table 2. Complete Remission 3 Months after Rituximab Treatment in Patients with Severe Pemphigus.*

Group	Pemphigus Vulgaris (N=14)	Pemphigus Foliaceus (N=7)	Total (N=21)
	<i>no. with remission/total no.</i>		
Corticosteroid-refractory disease	4/4	0/1	4/5
Corticosteroid-dependent disease	6/7	4/4	10/11
Contraindication to corticosteroids	2/3	2/2	4/5
Total	12/14	6/7	18/21

* Complete remission was defined as epithelialization of all skin and mucosal lesions.

of up to 10 kg. In addition, seven patients had severe involvement of one or more other mucosae, including the genital, anal, conjunctival, or pharyngeal mucosae or a combination of these. All patients with corticosteroid-refractory disease and all patients with corticosteroid-dependent disease had been treated previously with various immunosuppressive drugs, intravenous immune globulins, or both without success. The duration of all systemic therapy before study entry ranged from 4 to 168 months (mean, 70.2). Severe associated medical conditions or side effects of corticosteroids were present at baseline in 14 patients (67%). Five patients were treated with rituximab alone because they had contraindications to corticosteroid use. Corticosteroids were contraindicated in two patients because of severe diabetes mellitus, arterial hypertension, or both; in two patients because of a history of severe infection, osteonecrosis of the hip, or both; and in one patient because of old age (84 years) and poor general condition (Table 1).

RESPONSE TO RITUXIMAB TREATMENT

Eighteen of 21 patients (86%; 95% confidence interval, 64 to 94) had a complete remission at 3 months, including 12 of 14 patients with pemphigus vulgaris and 6 of 7 with pemphigus foliaceus (Table 2). Two patients with pemphigus vulgaris had a delayed complete remission on days 180 and 360 (Fig. 1). One patient with pemphigus foliaceus with lesions that initially involved the entire body surface was only slightly improved after rituximab, and treatment of this patient was considered to have failed. All the other patients (95%) had a complete remission at some time during the study period. The median delays to partial and complete remission are shown in Table 3.

Of the 20 patients who had a complete remission, 9 (6 with pemphigus vulgaris and 3 with

pemphigus foliaceus) had a relapse after a mean period of 18.9±7.9 months. Three patients with corticosteroid-dependent disease had a total of six relapses. Of the nine patients who had a relapse, three were treated with topical corticosteroids only, four with a moderately increased dose of oral corticosteroids, and two with a second course of rituximab. The second course of rituximab was chosen because one of the two patients was 84 years old and was thought to be at high risk for complications from corticosteroids, and the other had a severe relapse. Both patients had a complete remission again. After a median follow-up time of 34 months (range, 26 to 45), 18 patients (86%) were free of disease, including 8 patients (38%) who received no more corticosteroids.

The mean dose of prednisone for patients with corticosteroid-refractory disease decreased from 94.0±10.2 mg per day at baseline to 12.0±7.5 mg per day at the end of the study (P=0.04) (Fig. 1). The mean dose of prednisone for patients with corticosteroid-dependent disease decreased from 29.1±12.4 mg per day at baseline to 10.9±16.5 mg

Figure 1 (facing page). Changes in Clinical Lesions, Antidesmoglein Antibodies, and Doses of Prednisone in Patients with Pemphigus Treated with Rituximab.

Panel A shows cutaneous lesions (blue) and mucosal lesions (orange) in patients with pemphigus vulgaris; Panel B shows cutaneous lesions (blue) and no mucosal lesions in patients with pemphigus foliaceus. Arrows point to the number of days after rituximab treatment at which a relapse occurred; patients were treated on day 0. Panel C shows serum levels of anti-desmoglein 1 antibodies (blue) and anti-desmoglein 3 antibodies (orange) in patients with pemphigus vulgaris. Panel D shows serum levels of anti-desmoglein 1 antibodies (blue) and no anti-desmoglein 3 antibodies in patients with pemphigus foliaceus. Panels E and F show doses of prednisone in patients with pemphigus vulgaris and in those with pemphigus foliaceus, respectively.

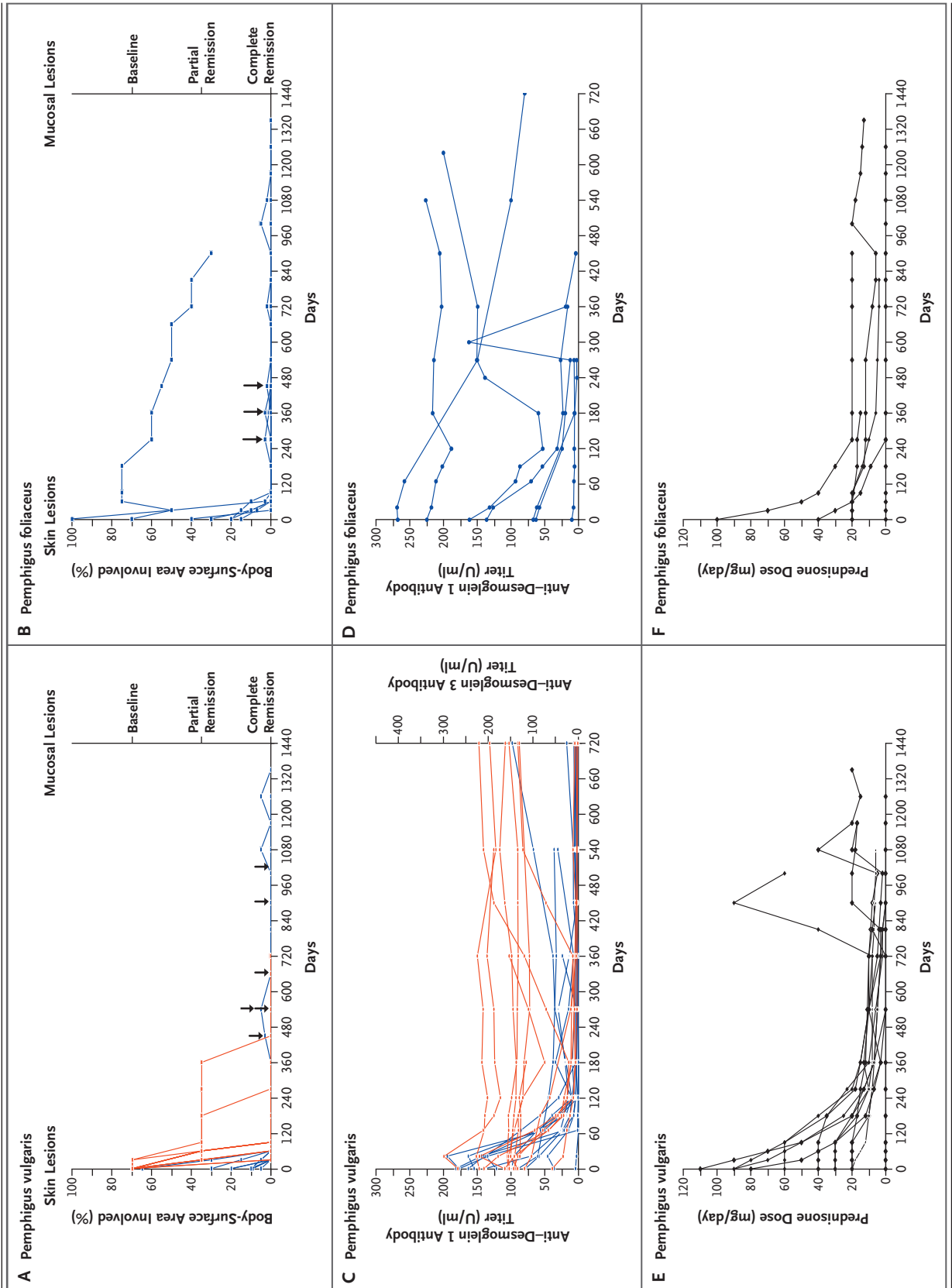


Table 3. Median Time to Partial and Complete Remission in Patients with Pemphigus Treated with Rituximab.

Type of Remission	Pemphigus Vulgaris (N=14)	Pemphigus Foliaceus (N=7)
	median no. of days to remission (interquartile range)	
Partial remission		
Cutaneous lesions	15 (15–30)	30 (30–56)
Mucosal lesions	60 (30–60)	—
Complete remission		
Cutaneous lesions	30 (30–60)	60 (60–90)
Mucosal lesions	90 (60–90)	—

per day at the end of the study ($P=0.007$). Nine patients reported minor and transient side effects during rituximab infusion: headache in three patients, asthenia in three, fever in one, chills in one, and nausea in one. In addition, two severe side effects were observed: one patient had pyelonephritis 12 months after rituximab treatment, and one patient died from septicemia 18 months after rituximab treatment. The patient who died also had rheumatoid arthritis and was concomitantly treated with the anti-tumor necrosis factor agent etanercept.

IMMUNOLOGIC EVALUATIONS

Peripheral-blood B- and T-lymphocyte subpopulations and T-lymphocyte cytokine production were analyzed longitudinally. The B-cell count decreased dramatically from a median of 275 cells per cubic millimeter (range, 29 to 752) to 0 cells per cubic millimeter (range, 0 to 1) at day 21 and remained undetectable until day 180 in all but two patients. Reappearance of B cells began between day 180 and day 270. Ninety percent of them expressed a CD19+CD27- phenotype suggestive of naive B lymphocytes. Twenty-nine percent had a CD19+CD38^{high}CD24^{high} transitional phenotype suggestive of the migration of B cells from the bone marrow to the periphery. No major changes in T cells or natural killer cells or in T-cell cytokine production were detected after rituximab treatment.

Using the immunoscope method, we followed the evolution of the repertoire of IgG, IgA, and IgM in blood B lymphocytes in two patients. Before treatment, immunoscope profiles showed some peak expansions in the immunoglobulin HV-

region genes (*IgV_H3a*, *IgV_H3b*, and *IgV_H4*), the most represented ones, reflecting in vivo antigen-driven responses. Six months later, reappearing blood B cells showed a typical gaussian distribution of the CDR3 lengths for these *IgV_H* families, similar to that found in the naive B cells of cord blood, suggesting the reconstitution of a diverse B-cell repertoire (data not shown).

Antidesmoglein autoantibody response was then analyzed. A dramatic decrease of IgG and IgG4 anti-desmoglein 1 and anti-desmoglein 3 antibodies was observed in 15 of the 18 patients who had a complete remission 3 months after rituximab treatment, whereas persistent high titers were detected in the 2 patients who had a delayed complete remission and in the 1 patient in whom treatment failed. Persistent high titers or rises in anti-desmoglein 1 and anti-desmoglein 3 antibody levels were detected in patients with relapsing disease and, surprisingly, in five patients with pemphigus vulgaris in whom a complete remission was maintained (Fig. 1). To disentangle this discrepancy, we retested serum from these patients on recombinant proteins of five extracellular (EC) domains of desmoglein 3 (EC1 to EC5). Antibodies reacting with epitopes of the EC1 to EC2 domains, which are considered the main pathogenic antibodies,^{28,29} decreased dramatically after rituximab treatment and remained undetectable until day 540, a result that was in accordance with the absence of mucosal lesions in these patients.^{30,31}

Finally, to assess the influence of rituximab on antimicrobial response, we first determined the serum level of IgG and IgM antibodies. No significant change in mean IgG levels was observed after rituximab treatment ($P=0.79$). On the contrary, mean IgM levels decreased from 1.5 ± 1.1 g per liter at baseline to 1.1 ± 0.9 g per liter on day 180 and 1.0 ± 0.7 g per liter on day 360 ($P=0.003$). We then determined that the levels of antibodies against pneumococcal capsule polysaccharide and the levels of antibodies against tetanus toxin were not significantly altered between baseline, day 21, and day 90. The two patients who had severe infections, one at 12 months after rituximab treatment and one at 18 months, had normal serum IgG levels (21 g per liter and 13.5 g per liter, respectively), despite low numbers of circulating B lymphocytes (5 per cubic millimeter and 9 per cubic millimeter, respectively) at the times of their infections.

DISCUSSION

Our study demonstrated the efficacy of rituximab for severe pemphigus; 86% of patients were in complete remission 3 months after receiving four weekly infusions of rituximab. After a 34-month follow-up period, 18 patients were free of disease, and 8 of these patients were not receiving any systemic therapy. Overall, treatment with rituximab both resulted in major clinical improvement and permitted a large decrease in the doses of corticosteroids. Our results were similar to those recently reported by Ahmed et al.,²³ who obtained a complete remission in 9 of 11 patients (82%). Our patients were treated with one cycle of four weekly infusions of rituximab, and the patients in the study by Ahmed et al. were treated with two induction cycles of rituximab, followed by consolidation therapy and six infusions of intravenous immune globulins, another potentially active agent in pemphigus.^{23,32,33} Therefore, we believe multiple cycles of rituximab may not be necessary. Accordingly, we suggest restricting the use of additional cycles of rituximab to the few relapses that cannot be adequately controlled with conventional treatments.

Two severe side effects were observed in our study: pyelonephritis developed in one patient 12 months after rituximab treatment, and one patient died from septicemia 18 months after rituximab treatment. It is important to emphasize that rituximab treatment is associated with a risk of death from severe side effects, such as pneumocystis infection, toxic epidermal necrolysis, and progressive multifocal leukoencephalopathy.^{34,35} The risk of serious infection led Ahmed et al. to propose combining intravenous immune globulins with rituximab during the first 6 months of treatment with rituximab.²³ We do not think that 6 months of treatment with immune globulins would have prevented the two serious infections observed in our study, which occurred at 12 and 18 months in patients who had no defect in IgG serum levels or in preformed antibacterial antibodies. It is not known whether the addition of intravenous im-

mune globulins to rituximab reduces the risk of serious infections.^{36,37}

Immunologic investigations demonstrated that one cycle of rituximab induced a prolonged depletion of peripheral-blood B lymphocytes, followed by the reappearance of B cells with a naive phenotype similar to that found in cord blood from neonates. Rituximab induced a modification of the repertoire of B cells, with the disappearance of the initially expanded populations and the reconstitution of a diverse B-cell repertoire that might account for its long-lasting effect.

The clinical response to rituximab in patients with pemphigus foliaceus was closely related to the evolution of anti-desmoglein 1 antibodies, which dramatically decreased in patients who had a complete remission, whereas we were surprised to observe persistently high levels of anti-desmoglein 3 antibodies in a few patients in whom pemphigus vulgaris was in complete remission. The dissociation between anti-desmoglein 1 and anti-desmoglein 3 antibody responses, as well as the absence of major modification of serum levels of antibodies against pneumococcal and tetanus-toxin antigens, suggested some specificity of rituximab for the autoreactive B-cell response.^{38,39} One hypothesis is that rituximab would differentially affect the turnover of short-life and long-life plasma cells that produce antibodies directed against desmoglein 1 and desmoglein 3.⁴⁰

Overall, our study suggests that rituximab is a very effective treatment for severe pemphigus. Larger series with a longer follow-up are needed to assess the long-term risks of this treatment.

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REFERENCES

1. Stanley JR. Pemphigus and pemphigoid as paradigms of organ-specific, autoantibody-mediated diseases. *J Clin Invest* 1989;83:1443-8.
2. Stanley JR. Cell adhesion molecules as targets of autoantibodies in pemphigus and pemphigoid, bullous diseases due to defective epidermal cell adhesion. *Adv Immunol* 1993;53:291-325.
3. Amagai M, Klaus-Kovtun V, Stanley JR. Autoantibodies against a novel epithelial cadherin in pemphigus vulgaris, a disease of cell adhesion. *Cell* 1991;67:869-77.
4. Bystryjn JC, Steinman NM. The adjunctive therapy of pemphigus: an update. *Arch Dermatol* 1996;132:203-12.
5. McDonald CJ. Cytotoxic agents for use in dermatology. *J Am Acad Dermatol* 1985;12:753-75.
6. Kazkaz H, Isenberg D. Anti B cell ther-

- apy (rituximab) in the treatment of autoimmune diseases. *Curr Opin Pharmacol* 2004; 4:398-402.
7. Stasi R, Stipa E, Forte V, Meo P, Amadori S. Variable patterns of response to rituximab treatment in adults with chronic idiopathic thrombocytopenic purpura. *Blood* 2002;99:3872-3.
 8. Narat S, Gandla J, Hoffbrand AV, Hughes RG, Mehta AB. Rituximab in the treatment of refractory autoimmune cytopenias in adults. *Haematologica* 2005;90: 1273-4.
 9. Zaja F, De Vita S, Russo D, et al. Rituximab for the treatment of type II mixed cryoglobulinemia. *Arthritis Rheum* 2002;46:2252-4.
 10. Specks U, Fervenza FC, McDonald TJ, Hogan MC. Response of Wegener's granulomatosis to anti-CD20 chimeric monoclonal antibody therapy. *Arthritis Rheum* 2001;44:2836-40.
 11. Levine TD. Rituximab in the treatment of dermatomyositis: an open-label pilot study. *Arthritis Rheum* 2005;52:601-7.
 12. Arzoo K, Sadeghi S, Liebman HA. Treatment of refractory antibody mediated autoimmune disorders with an anti-CD20 monoclonal antibody (rituximab). *Ann Rheum Dis* 2002;61:922-4.
 13. Dupuy A, Viguier M, Bedane C, et al. Treatment of refractory pemphigus vulgaris with rituximab (anti-CD20 monoclonal antibody). *Arch Dermatol* 2004;140: 91-6.
 14. Espana A, Fernandez-Galar M, Lloret P, Sanchez-Ibarrola A, Panizo C. Long-term complete remission of severe pemphigus vulgaris with monoclonal anti-CD20 antibody therapy and immunophenotype correlations. *J Am Acad Dermatol* 2004;50: 974-6.
 15. Morrison LH. Therapy of refractory pemphigus vulgaris with monoclonal anti-CD20 antibody (rituximab). *J Am Acad Dermatol* 2004;51:817-9.
 16. Wenzel J, Bauer R, Bieber T, Tuting T. Successful rituximab treatment of severe pemphigus vulgaris resistant to multiple immunosuppressants. *Acta Derm Venereol* 2005;85:185-6.
 17. Schmidt E, Herzog S, Brocker EB, Zillikens D, Goebeler M. Long-standing remission of recalcitrant juvenile pemphigus vulgaris after adjuvant therapy with rituximab. *Br J Dermatol* 2005;153:449-51.
 18. Arin MJ, Engert A, Krieg T, Hunzelmann N. Anti-CD20 monoclonal antibody (rituximab) in the treatment of pemphigus. *Br J Dermatol* 2005;153:620-5.
 19. Kong HH, Prose NS, Ware RE, Hall RP III. Successful treatment of refractory childhood pemphigus vulgaris with anti-CD20 monoclonal antibody (rituximab). *Pediatr Dermatol* 2005;22:461-4.
 20. Herrmann G, Hunzelmann N, Engert A. Treatment of pemphigus vulgaris with anti-CD20 monoclonal antibody (rituximab). *Br J Dermatol* 2003;148:602-3.
 21. Goebeler M, Herzog S, Brocker EB, Zillikens D. Rapid response of treatment-resistant pemphigus foliaceus to the anti-CD20 antibody rituximab. *Br J Dermatol* 2003;149:899-901.
 22. El Tal AK, Posner MR, Spigelman Z, Ahmed AR. Rituximab: a monoclonal antibody to CD20 used in the treatment of pemphigus vulgaris. *J Am Acad Dermatol* 2006;55:449-59.
 23. Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. *N Engl J Med* 2006; 355:1772-9.
 24. Lever WF. Pemphigus and pemphigoid: a review of the advances made since 1964. *J Am Acad Dermatol* 1979;1:2-31.
 25. Müller R, Svoboda V, Wenzel E, et al. IgG reactivity against non-conformational NH₂-terminal epitopes of the desmoglein 3 ectodomain relates to clinical activity and phenotype of pemphigus vulgaris. *Exp Dermatol* 2006;15:606-14.
 26. Lim A, Lemercier B, Werth X, Lesjean Pottier S, Huetz F, Kourilsky P. Most human peripheral blood B cells display a unique heavy chain rearrangement. *Int Immunol* (in press).
 27. Ballet JJ, Sulcebe G, Couderc LJ, et al. Impaired anti-pneumococcal antibody response in patients with AIDS-related persistent generalized lymphadenopathy. *Clin Exp Immunol* 1987;68:479-87.
 28. Anzai H, Fujii Y, Nishifujii K, et al. Conformational epitope mapping of antibodies against desmoglein 3 in experimental murine pemphigus vulgaris. *J Dermatol Sci* 2004;35:133-42.
 29. Sekiguchi M, Futei Y, Fujii Y, Iwasaki T, Nishikawa T, Amagai M. Dominant autoimmune epitopes recognized by pemphigus antibodies map to the N-terminal adhesive region of desmogleins. *J Immunol* 2001;167:5439-48.
 30. Hacker MK, Janson M, Fairley JA, Lin MS. Isotypes and antigenic profiles of pemphigus foliaceus and pemphigus vulgaris. *Clin Immunol* 2002;105:64-74.
 31. Amagai M, Komai A, Hashimoto T, et al. Usefulness of enzyme-linked immunosorbent assay using recombinant desmogleins 1 and 3 for serodiagnosis of pemphigus. *Br J Dermatol* 1999;140:351-7.
 32. Ahmed AR. Treatment of autoimmune mucocutaneous blistering diseases with intravenous immunoglobulin therapy. *Expert Opin Investig Drugs* 2004;13:1019-32.
 33. Ahmed AR, Dahl MV. Consensus statement on the use of intravenous immunoglobulin therapy in the treatment of autoimmune mucocutaneous blistering diseases. *Arch Dermatol* 2003;139:1051-9.
 34. Bermudez A, Marco F, Conde E, Mazo E, Recio M, Zubizarreta A. Fatal varicella-zoster infection following rituximab and chemotherapy treatment in a patient with follicular lymphoma. *Haematologica* 2000; 85:894-5.
 35. Quartier P, Tournilhac O, Archimbaud C, et al. Enteroviral meningoencephalitis after anti-CD20 (rituximab) treatment. *Clin Infect Dis* 2003;36:e47-e49.
 36. Lehrnbecher T. Intravenous immunoglobulins in the prevention of infection in children with hematologic-oncologic diseases. *Klin Padiatr* 2001;213:Suppl 1:A103-A105. (In German.)
 37. Sullivan KM, Kopecy KJ, Jocom J, et al. Immunomodulatory and antimicrobial efficacy of intravenous immunoglobulin in bone marrow transplantation. *N Engl J Med* 1990;323:705-12.
 38. Smith MR. Rituximab (monoclonal anti-CD20 antibody): mechanism of action and resistance. *Oncogene* 2003;22: 7359-68.
 39. Maloney DG, Smith B, Rose A. Rituximab: mechanism of action and resistance. *Semin Oncol* 2002;29:Suppl 2:2-9.
 40. Hoyer BF, Manz RA, Radbruch A, Hiepe F. Long-lived plasma cells and their contribution to autoimmunity. *Ann N Y Acad Sci* 2005;1050:124-33.

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