Effect of a Single-Cycle Alternative Dosing Regimen for Rituximab for Recalcitrant Pemphigus

A Case Series of 9 Patients

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Background: There is increasing evidence that a single cycle of rituximab (375 mg per square meter of body surface area once weekly for 4 weeks) is efficacious in patients with severe pemphigus. The approved protocol in rheumatoid arthritis is 1 g on days 1 and 15. We report herein on the efficacy and safety of this latter protocol for rituximab in 9 patients with pemphigus.

Observations: Nine patients with recalcitrant pemphigus were treated with prednisone, immunosuppressive agents, and/or intravenous immunoglobulin. Rituximab, 1 g, was infused on days 1 and 15. Each patient was observed for a minimum of 6 months. Reepithelialization of at least 50% of the affected areas occurred in all patients within 16 weeks. Three of 6 patients (50%) discontinued intravenous immunoglobulin therapy. A significant decrease in the pemphigus severity score and the mean dosage of prednisone was observed at 3 and 6 months. Relapses were observed in 4 patients between 5 and 13 months after rituximab treatment; these patients completed a second cycle of rituximab. There were no serious adverse effects observed during the follow-up period.

Conclusions: A single cycle of rituximab, 1 g on days 1 and 15, is an effective treatment for pemphigus. Further studies are needed to determine the efficacy and safety of repeated treatment courses in patients who experience recurrences.


Pemphigus is a rare, life-threatening, autoimmune, blistering disease affecting the skin and mucous membranes. This group of diseases is mediated by antibodies directed against desmogleins 1 and 3 and results in the loss of cell-cell adhesion of keratinocytes through acantholysis. Patients with severe pemphigus often require long-term, high-dose corticosteroid therapy to maintain disease control. However, adverse effects frequently accompany this dosing regimen, such as glaucoma, metabolic abnormalities, and hypothalamic-pituitary-adrenal axis suppression. Thus, immunosuppressive agents (eg, azathioprine sodium, cyclophosphamide, and methotrexate sodium) and intravenous immunoglobulin (IVIG) therapy are often used concomitantly as corticosteroid-sparing agents. Despite the use of these potent drugs, there are patients whose disease is resistant to therapy and others who are intolerant of these agents.

Rituximab is a chimeric murine-human monoclonal antibody that targets the CD20 antigen found on B cells and results in rapid depletion of this cell population. It is approved for the treatment of non-Hodgkin B-cell lymphoma and rheumatoid arthritis; in addition, rituximab has been shown to be effective in other autoimmune diseases, such as systemic lupus erythematosus, multiple sclerosis, and pemphigus. In published studies of pemphigus, the dosing schedule for rituximab is similar to that indicated for non-Hodgkin B-cell lymphoma, namely, 1 cycle of 4 weekly infusions of rituximab at a dose of 375 mg per square meter of body surface area (BSA). In contrast, rituximab has been approved for rheumatoid arthritis at a dosage of 1000 mg on days 1 and 15. We hypothesized that the 2-dose protocol would be effective and safe in the treatment of pemphigus. We report herein on the efficacy and safety of rituximab therapy in 9 patients with recalcitrant pemphigus who were treated using this alternative protocol.

REPORT OF CASES

PATIENTS

Patients with a confirmed diagnosis of severe pemphigus vulgaris or pemphigus
foliaceus were eligible to receive rituximab if they met at least one of the following conditions: (1) relapsing disease that was resistant to treatment, including the use of systemic corticosteroids, immunosuppressive agents, and/or IVIG; (2) contraindication to the use of systemic corticosteroids; or (3) recalcitrant disease that affected more than 50% of the BSA. Patients were assessed according to a pemphigus severity score11 (Table 1). Outpatient medical records were reviewed to identify demographic information, the extent of disease involvement, and the use of corticosteroids, immunosuppressive agents, and IVIG.

All patients had a confirmed diagnosis of pemphigus vulgaris or pemphigus foliaceus. Diagnoses were based on severe mucosal erosions, superficial blisters, and/or erosions on the skin that formed a histologic picture of intradermal acantholysis and/or deposition of IgG complement component 3 on the keratinocyte membrane, which was detected by direct immunofluorescence. Indirect immunofluorescence studies were performed for most patients at diagnosis. This type of study uses monkey esophagus for the substrate and applies antihuman IgG–fluorescein isothiocyanate conjugate. Serial dilutions are performed if the initial dilution (1:40) is positive for circulating IgG autoantibodies directed against the cell surface of keratinocytes or if the patient is known to have had positive test results previously. Eligible patients were identified by the treating dermatologist (S.W. and N.H.S.). This study was approved by the Sunnybrook Health Sciences Centre and Women’s College Research Ethics Board.

TREATMENT REGIMEN

Rituximab, 1 g, was administered as an intravenous infusion on days 1 and 15 along with methylprednisolone sodium succinate, 100 mg, before each infusion, according to previous recommendations.6 All patients received the treatment in a local hospital or in an outpatient infusion center between January 1 and August 31, 2008. Therapy with corticosteroids, other immunosuppressive agents, and IVIG was maintained during rituximab treatment. When rituximab infusion was completed, these treatments were decreased or discontinued if a remission occurred.

END POINTS

Each patient was observed for a minimum of 6 months. The extent of disease was evaluated at 1, 3, and 6 months after rituximab treatment was completed. Primary end points were a change in the pemphigus severity score, the dosage of corticosteroids used (ie, prednisone), whether IVIG therapy was discontinued, the time from the start of rituximab treatment to partial or complete remission, the number and length of relapses, and the adverse effects of treatment, including infections. Secondary end points were whether the immunosuppressive agents (other than corticosteroids) were decreased and results of an immunological evaluation of the pemphigus antibody. Partial remission was defined as the epithelialization of more than 50% of the lesions; complete remission was defined as the epithelialization of all skin and mucosal lesions.

STATISTICAL ANALYSIS

Basic descriptive statistics were used to characterize the patient population. The percentage of change in the prednisone dosage at 1, 3, and 6 months after rituximab infusion was calculated. Single-sample paired t tests were performed to determine the significance in mean values between treatment time frames. All statistical tests were performed using Microsoft Excel 2003 software (Microsoft Corp).

PATIENT CHARACTERISTICS

Nine patients (6 men and 3 women; 8 with pemphigus vulgaris and 1 with pemphigus foliaceus) were included in this study (mean [SD] age, 41.3 [11.5] years). Patient characteristics are given in Table 2. Two patients had skin lesion involvement of more than 50% of their BSA. Two patients had had recalcitrant, severe oral mucosal lesions for more than 2 years. Three patients experienced at least 2 cutaneous or mucosal relapses while corticosteroid dosages were being decreased. The use of corticosteroids was contraindicated in 1 patient owing to uncontrolled hypertension and osteopenia.

Before rituximab treatment, 8 of the 9 patients were treated with high dosages of prednisone (mean [SD] dosage, 38.1 [49.7] mg/d). Immunosuppressive agents used included mycophenolate mofetil hydrochloride (6 patients), azathioprine (1 patient), methotrexate and mycophenolate mofetil (1 patient), and cyclophosphamide (1 patient). Intravenous immunoglobulin was administered monthly in 6 patients.

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Table 1. Pemphigus Severity Scorea

<table>
<thead>
<tr>
<th>Score</th>
<th>No. of Sites Involved</th>
<th>Prednisolone Equivalent, mg/d</th>
<th>Immunosuppressive Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>≤15</td>
<td>AZT, ≤100 mg/d; MMF, ≤1 g/d; MTX, ≤15 mg/wk; dapsone/tetracycline/gold at any dosage</td>
</tr>
<tr>
<td>2</td>
<td>2 or 3</td>
<td>16-49</td>
<td>AZT, &gt;100 mg/d; MMF, &gt;1 g/d; MTX, &gt;15 mg/wk; IVIG</td>
</tr>
<tr>
<td>3</td>
<td>4 or 5</td>
<td>50-89</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>≥6</td>
<td>≥90</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AZT, azathioprine sodium; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil hydrochloride; MTX, methotrexate sodium.

a The pemphigus severity score is calculated from the sum of each score for the number of sites involved, dosage of prednisolone, and dosage of immunosuppressive agents. Adapted from Herbst and Bystryn.11

b Involved sites included the face/neck, upper torso, lower torso, arms, legs, oral mucosa, and genital mucosa. Maximum score, 10.
We found a significant decrease ($P = .05$) in the average pemphigus severity score at 3 and 6 months compared with the mean score at baseline (Figure 1). Partial remission occurred in all patients between 4 and 16 weeks (mean [SD], 7.5 [3.1] weeks) after rituximab treatment (Table 3). Complete remission was seen in 4 patients between 16 and 24 weeks (18.0 [4.0] weeks).

**TREATMENT RESPONSE**

We found a significant decrease ($P < .05$) in the average pemphigus severity score at 3 and 6 months compared with the mean score at baseline (Figure 1). Partial remission occurred in all patients between 4 and 16 weeks.

**MEDICATION REDUCTIONS**

Eight patients were taking prednisone at baseline (mean [SD] dosage, 58.1 mg/d). The mean percentages of decrease in the prednisone dosage were 39% at 1 month (mean [SD] dosage, 35.1 [22.3] mg/d), 67% at 3 months (21.7 [11.9] mg/d), and 74% at 6 months (15.6 [3.7] mg/d) (Figure 2). One patient’s prednisone dosage was increased at 6 months because of disease recurrence at 5 months. We noted a significant ($P < .05$) decrease in the mean prednisone dosage at 3 and 6 months compared with baseline.

### Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>Diagnosis</th>
<th>Disease Duration, mo</th>
<th>Prednisone Dosage at Baseline, mg/d</th>
<th>Immunosuppressive Agent, Dosage</th>
<th>Monthly IVIG Therapy</th>
<th>Involvement</th>
<th>Pemphigus Severity Score, Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/47</td>
<td>PV</td>
<td>36</td>
<td>30</td>
<td>MMF, 3 g/d</td>
<td>Yes</td>
<td>Oral, genital</td>
<td>Scalp, chest, axilla, groin, arms, legs</td>
</tr>
<tr>
<td>2/M/42</td>
<td>PV</td>
<td>9</td>
<td>160</td>
<td>MMF, 3 g/d</td>
<td>Yes</td>
<td>Oral</td>
<td>Scalp, chest, axilla, groin, arms, legs</td>
</tr>
<tr>
<td>3/M/41</td>
<td>PV</td>
<td>38</td>
<td>15</td>
<td>MMF, 3 g/d</td>
<td>Yes</td>
<td>Oral (severe)</td>
<td>Diffuse, BSA, &gt;50%</td>
</tr>
<tr>
<td>4/F/45</td>
<td>PV</td>
<td>72</td>
<td>100</td>
<td>MMF, 3 g/d</td>
<td>Yes</td>
<td>Oral</td>
<td>Diffuse, BSA, &gt;70%</td>
</tr>
<tr>
<td>5/M/29</td>
<td>PV</td>
<td>40</td>
<td>35</td>
<td>AZT, 150 mg/d</td>
<td>Failed</td>
<td>Oral</td>
<td>Chest, back</td>
</tr>
<tr>
<td>6/M/45</td>
<td>PF</td>
<td>57</td>
<td>15</td>
<td>MMF, 3 g/d</td>
<td>Yes</td>
<td>Oral</td>
<td>Diffuse, BSA, &gt;70%</td>
</tr>
<tr>
<td>7/M/21</td>
<td>PV</td>
<td>40</td>
<td>60</td>
<td>MMF, 3 g/d</td>
<td>Failed before</td>
<td>Oral</td>
<td>Diffuse, BSA, &gt;70%</td>
</tr>
<tr>
<td>8/F/40</td>
<td>PV</td>
<td>114</td>
<td>Discontinued before rituximab</td>
<td>MMF, 3 g/d</td>
<td>Failed before</td>
<td>Oral</td>
<td>Diffuse, BSA, &gt;70%</td>
</tr>
<tr>
<td>9/M/62</td>
<td>PV</td>
<td>24</td>
<td>50</td>
<td>CYT, 75 mg/d</td>
<td>Yes</td>
<td>Oral</td>
<td>Scalp, face, back</td>
</tr>
</tbody>
</table>

Abbreviations: AZT, azathioprine sodium; BSA, body surface area; CYT, cyclophosphamide; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil hydrochloride; MTX, methotrexate sodium; PF, pemphigus foliaceus; PV, pemphigus vulgaris.

* Patients 2 and 4 were admitted to the burn unit before treatment.

### Table 3. Clinical Response to Rituximab Treatment

<table>
<thead>
<tr>
<th>Responsea</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 mo</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>4</td>
</tr>
<tr>
<td>Partial</td>
<td>4</td>
</tr>
<tr>
<td>At 12 mo</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>3</td>
</tr>
<tr>
<td>Partial</td>
<td>3</td>
</tr>
<tr>
<td>Severe recurrenceb</td>
<td></td>
</tr>
<tr>
<td>At 5 mo</td>
<td>1</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>2</td>
</tr>
<tr>
<td>At 13 mo</td>
<td>1</td>
</tr>
</tbody>
</table>

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**Figure 1.** Pemphigus severity score before and after rituximab treatment. A significant decrease ($P < .05$) was observed in the mean score (red curve) of 9 patients at 3 and 6 months compared with the mean score at baseline.

**Figure 2.**
Six patients received monthly IVIG therapy prior to rituximab treatment. Two patients discontinued IVIG therapy at 3 months and 1 patient at 5 months. Three patients continued monthly IVIG treatments during the follow-up period.

Patients received immunosuppressive agents, such as mycophenolate mofetil (Figure 3A), azathioprine and cyclophosphamide (Figure 3B), and methotrexate (Figure 3C). The use of these agents was generally reduced after the prednisone dosage was decreased. The dosage of mycophenolate mofetil was decreased in 2 patients at 3 and 6 months. The cyclophosphamide dosage was decreased in one patient (75 mg/d at 1 month reduced to 50 mg/d at 3 months), and the methotrexate sodium dosage was decreased in another (22.5 mg/wk at baseline reduced to 5 mg/wk at 6 months). The dosage of azathioprine was decreased in a third patient at 6 months. All other patients remained on the same dosage of these agents after undergoing a decrease in their prednisone dosage.

**IMMUNOLOGICAL EVALUATION**

The peripheral-blood B-lymphocyte (CD19+ B-lymphocyte) count was examined in 3 patients. The rate of B cells in all 3 patients decreased dramatically to undetectable levels (<1000/µL [to convert to cells × 10⁹ per liter, multiply by 0.001]) at 4 weeks and remained undetectable during the follow-up period. In addition, the circulating antipemphigus antibody level was measured in 3 patients at baseline and 6 months. Two patients' titers became negative at 3 and 6 months after rituximab treatment. One patient had a flare at 5 months; his titer was 1:320 at baseline, 1:80 at 3 months, and 1:160 at 6 months after treatment.
RECURRENT AND ADVERSE EFFECTS

Four patients experienced disease recurrence: 1 at 5 months, 2 at 12 months, and 1 at 13 months. All 4 patients completed a second cycle of rituximab intravenous infusion, 1 g, on days 1 and 15. One of our 9 patient developed bacterial pneumonia 7 months after rituximab treatment; his condition improved after standard antibiotic therapy. No other adverse effects, including infusion reactions, were noted.

To our knowledge, this is the first report to describe the use of an alternative dosing regimen for rituximab in patients with pemphigus. In previously published reports, rituximab was administered intravenously at a dosage of 375 mg per square meter of BSA once weekly for 4 infusions per course.6-8 The 2-dose regimen was administered to our patients because it was an approved dosing regimen for rheumatoid arthritis (1 g administered on days 1 and 15), it was more convenient for patients because it decreased the number of clinic visits they needed to attend to receive their infusion, and the cost of the rituximab was decreased, on average, by about 35%.12

Rituximab has been shown to provide clinical benefit in patients with pemphigus vulgaris or pemphigus foliaceus that is treatment resistant, widespread, or both.10-14 A recent review article summarized the case reports in the literature to December 2008.10 In all, 136 patients with pemphigus were treated with rituximab. In 79 of the 103 patients with pemphigus vulgaris (77%), rituximab treatment resulted in the healing of all lesions; in 41 (40%), all immunosuppressants were discontinued. Thirteen patients (13%) had a relapse that required a second course of rituximab treatment. In our report of 9 patients, all had a partial response initially between 4 and 16 weeks after rituximab treatment. At 6 months, 4 patients (44%) had a complete response and 4 (44%) had a partial response; 1 patient (11%) had a recurrence at 5 months. At the end of the observation period (a minimum of 6 months), 3 of the 9 patients (33%) were in complete remission, 3 (33%) were in partial remission, and 4 (44%) had a recurrence requiring a second cycle of rituximab. The relapse rate is similar to the study by Joly et al,9 who described 9 of 21 patients (43%) who experienced disease relapse after a mean (SD) of 18.9 (7.9) months.

In our study, the dosage of prednisone was decreased 74% compared with baseline at 6 months after rituximab treatment. In addition, of the 6 patients who were receiving IVIG therapy prior to rituximab, 3 patients discontinued therapy after 6 months. For 6 of the 8 patients receiving mycophenolate mofetil, no change in dosage was noted at the end of the observation period. Azathioprine treatment was decreased in 1 patient.

We observed no serious adverse effects during the study period. One patient developed pneumonia at 7 months, which resolved with a course of oral antibiotics. Reported adverse effects of rituximab in the treatment of pemphigus include 1 patient who developed pyelonephritis8 and 1 death from septicemia at 18 months.8 Another report13 describes 2 deaths in a cohort of 25 patients who received rituximab for refractory mucous membrane pemphigoid. One patient was receiving cyclophosphamide and prednisone, and the other was receiving azathioprine, cyclosporine, and prednisone. The authors hypothesized that there was an increased risk of death associated with continuing immunosuppressive treatment following administration of rituximab. In our patient population, the prednisone dosage was decreased on completion of the rituximab infusions. Treatment with other immunosuppressive agents is usually continued until some improvement is observed. We did not find that continuation of immunosuppressives resulted in increased adverse events. However, it is still important to monitor for potential adverse effects of immunosuppressive therapy, such as serious infections and late-onset neutropenia. We may not have observed any serious adverse effects because of the small number of patients studied or because of our simplified protocol.

In conclusion, a single cycle of rituximab administered as 1 g on days 1 and 15 is an effective and safe treatment for patients with recalcitrant pemphigus. A larger study is needed to assess the long-term benefits and risks of this treatment and to determine the optimal dosing regimen (2 doses vs 4 doses) of rituximab for patients with pemphigus. Further studies are also needed to establish criteria for subsequent infusions of rituximab. Our study provides encouraging results for the use of an alternative regimen that requires only 2 infusions.

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Author Contributions: Drs Matsukura and Shear and Ms Knowles had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Matsukura, Knowles, Walsh, and Shear. Acquisition of data: Matsukura, Knowles, and Shear. Analysis and interpretation of data: Matsukura, Knowles, and Shear. Drafting of the manuscript: Knowles and Shear. Critical revision of the manuscript for important intellectual content: Matsukura, Knowles, Walsh, and Shear. Statistical analysis: Matsukura and Knowles. Administrative, technical, or material support: Matsukura and Knowles. Study supervision: Knowles and Shear.

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REFERENCES


Notable Notes

It's been 50 years since the tragic death of Marilyn Monroe (1926-1962). As a tribute to the legendary screen star, I draw your attention to one of her most popular films, “The Seven Year Itch.” Itch, in dermatology, describes a skin sensation that causes a desire to scratch. Another meaning of itch is having a restless craving for something, such as the urge for infidelity, as is portrayed in the movie. When a word, such as itch, has 2 or more related meanings, it is called a polyseme. Polysemes differ from other homonyms, which are, by definition, words that sound the same but have different meanings. An example of such a homonym can be found in the trite pun, “Dermatologists tend to make rash decisions.” Rash in this case means to be imprudently hasty, and the word is semantically distinct from its dermatologic homonym, the skin rash.

Another polyseme is the word inflamed, which has several related meanings, such as when the skin becomes inflamed or when one’s passions are inflamed. For the classic film “Some Like It Hot,” Ms Monroe recorded the title song, with the following opening lyrics (although it was not used in the movie):

“I got a fever, an inflammation
That’s what I got
You turn the heat on me
Some like it hot”

Ms Monroe’s sultry rendition of the song leaves no doubt as to the meaning of the words hot and inflammation in these verses. Other examples of dermatology-related polysemy are as follows:

1. Skin can weep and so can eyes.
2. A skin rash can erupt and so can a volcano.
3. One can have a physical scar or an emotional one.

By now, you should be more knowledgeable in recognizing polysemy. Can you detect the 2 examples that appear in my final paragraph, one of which was cited above?

This article only begins to scratch the surface of the topic under discussion. Yet it pays tribute to some of Ms Monroe’s cinematic achievements as well as to her “lesson” on the semantics of dermatology. And on that note, I’ll end this note!

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