Durable Remission of Pemphigus With a Fixed-Dose Rituximab Protocol

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OBJECTIVE To assess the clinical response of patients with pemphigus to rituximab using a modified fixed-dose rheumatoid arthritis protocol (1 g intravenously on days 1 and 15, followed by 500 mg intravenously if clinically warranted at 6-month intervals or repeated full dosing).

RESULTS Median time to relapse after the first treatment cycle was 15 months (95% CI, 10.3-19.7). All patients experienced improvement. Complete remission rates with or without adjuvant treatment at final follow-up were 89% (56 patients [61%] were in complete remission without treatment and 26 patients [28%] were in complete remission during adjuvant treatment). No serious infectious adverse events occurred.

CONCLUSIONS AND RELEVANCE The fixed-dose, modified rheumatoid arthritis protocol for rituximab was efficacious and well tolerated in patients with pemphigus. Patients who do not achieve remission after 1 cycle or patients who experience relapse benefit from further cycles of rituximab. Our results need to be confirmed in larger and controlled trials.

Pemphigus and pemphigoid compose a rare group of potentially fatal dermatologic diseases that are caused by autoantibodies against adhesion molecules of the epidermal and dermoepidermal junction.1-2 These diseases may require long-term systemic treatment with corticosteroids and other immunosuppressive agents. The therapy in many cases can cause serious adverse effects, morbidity, and even mortality.3

Rituximab is a chimeric murine/human monoclonal antibody that recognizes the B-lymphocyte surface protein CD20, a transmembrane protein expressed on pre-B to mature B cells and functions to regulate B cells early in development.4 Rituximab has increasingly been reported5 to be effective in several autoimmune diseases, including autoimmune bullous dermatoses. Several areas of uncertainty remain while treating autoimmune bullous disease with rituximab. The optimal dosage regimen and predictors of response are unknown.5-6 Duration of response is also poorly characterized, and it is undetermined how long the effects last.7 Some patients achieve a fundamental change in B-cell status and do not experience subsequent relapses after the first treatment cycle6-13; others require repeated treatment.14 In addition, it is unknown whether rituximab should be used as initial therapy or as a third-line agent. However, an improved response may be observed with earlier use of rituximab or if it is used as first-line treatment.

The objective of this study was to present our experience with rituximab therapy using the fixed-dose protocol (ie, rheumatoid arthritis [RA] protocol) in autoimmune bullous dermatoses including pemphigus vulgaris and pemphigus folia-
ceus. We aimed to assess clinical response and times to relapse. We also examined responses to subsequent treatment cycles.

Methods

Study Setting
We conducted a retrospective single-center study of all patients with autoimmune bullous disease examined at Sunnybrook Health Sciences Centre, University of Toronto, who received rituximab from May 1, 2006, through August 30, 2012, with follow-up through January 31, 2013. The study was approved by the institutional ethics review board.

Patients
Data were collected retrospectively from the medical records of patients with pemphigus diseases who had received rituximab. All patients had an established diagnosis of pemphigus vulgaris or pemphigus foliaceus (included within this subgroup was 1 patient with pemphigus herpetiformis) according to clinical, immunofluorescence, and histopathologic criteria. Initial indications for rituximab treatment were severe relapsing or recalcitrant disease that was refractory to treatment and/or a contraindication to the use of corticosteroids or other immunosuppressive therapy. Data regarding disease, previous treatment, and response to treatment were collected.

Treatment Protocol
Rituximab was administered using a fixed-dose modification of the RA protocol (1 g intravenously on days 1 and 15, with a subsequent dose of 1 g or 500 mg intravenously administered 6 months or more after induction if clinically warranted). In 1 patient, the initial dose received was 1 g only on day 1; this was because an adverse reaction prohibited administration of the day 15 dose. Most patients continued to receive concomitant adjuvant corticosteroid or immunosuppressive treatment during cycle 1. The expectation was to discontinue adjuvant treatments if there was an adequate response to rituximab. We aimed to repeat treatment in patients who experienced relapse after achieving remission with rituximab. Use of rituximab was subject to financial constraints by third-party payers, such as insurance companies and the provincial health care system. A compassionate use program sponsored by the manufacturer (Roche Pharma) aided many of our patients.

Assessment of Response to Treatment
Response to treatment was determined according to the definitions of an international consensus statement. Complete remission off therapy (CR) is the absence of new or established lesions while the patient is not receiving any systemic therapy for at least 2 months. Partial remission on minimal therapy (PR) is the presence of transient new lesions that heal within 1 week while the patient is receiving minimal therapy, including topical corticosteroids. Relapse/flare is the appearance of 3 or more new lesions each month that do not heal spontaneously within 1 week or the extension of established lesions in a patient who has achieved disease control. Complete and partial responses could be achieved without therapy or with minimal therapy (<10 mg/d of prednisone and/or minimal adjuvant therapy for ≤2 months).

Outcome Measures
We examined response to treatment, times to relapse, and adverse reactions. The primary end points were time to failure and complete remission with or without treatment. Secondary end points included adverse events, long-term follow-up, and the number of treatment cycles received.

Statistical Analysis
Baseline characteristics and categorical variables were summarized using descriptive statistics and compared with the unpaired 2-tailed t test, χ², or Kruskal-Wallis test as appropriate. Progression-free survival was calculated from the date of rituximab initiation to the date of documented disease progression, relapse, or the end date of the study; survival curves were created by the Kaplan-Meier method; overall differences were compared by the log-rank test. P < .05 was considered to indicate statistical significance. The data were analyzed using SPSS, version 19.0 for Windows (SPSS, Inc).

Results

Patients
The characteristics of the 92 study patients are presented in Table 1. Eighty-four patients (91%) had pemphigus vulgaris and 8 had pemphigus foliaceus. Fifty-five patients (60%) were female. The median (range) age at diagnosis was 43 (13-77) years. The age at the start of the first rituximab treatment cycle was 47 (17-77) years. The median disease duration before rituximab treatment was 24 (0-256) months. All but 1 patient was treated with systemic therapies (corticosteroids or immunosuppressive medications) before rituximab treatment. Seventy-six patients (83%) were receiving either systemic corticosteroids or immunosuppressive therapies at the time of first rituximab infusion. Although disease scores were not prospectively determined, all patients had severe and/or refractory disease that led to rituximab therapy.

Treatment

First Treatment Cycle
After rituximab therapy all patients experienced an improvement in their disease activity. Seventy-four patients (80%) achieved CR either with or without adjuvant treatment; this included 63 individuals (68%) receiving concomitant corticosteroids and 64 patients (70%) receiving concomitant immunosuppressives. After the first cycle, there were 56 relapses (61%) (Table 2).
Median time to relapse was 15 months (95% CI, 10.3-19.7) (Figure, A). When comparing time to relapse for pemphigus vulgaris and pemphigus foliaceus, there was no statistically significant difference. The pemphigus vulgaris median time to relapse was 15 months (95% CI, 8.6-21.4), and the pemphigus foliaceus median time to relapse was 12 months (1.5-22.5; \( P = .99 \)).

**Adjuvant Treatment**

Patients who received adjuvant treatment had a shorter time to relapse (mean, 12 months; 95% CI, 8.5-15.5) compared with those who did not receive adjuvant therapy, with the median not yet reached at last follow-up (mean, 40.6 months; 95% CI, 34.2-46.9; \( P = .001 \)) (Figure, B).

### Table 1. Characteristics of 92 Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>37 (40)</td>
</tr>
<tr>
<td>Female</td>
<td>55 (60)</td>
</tr>
<tr>
<td>Age at diagnosis, median (range), y</td>
<td>43 (13-77)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>84 (91)</td>
</tr>
<tr>
<td>Pemphigus foliaceus</td>
<td>8 (9)</td>
</tr>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Mucosal only</td>
<td>20 (22)</td>
</tr>
<tr>
<td>Mucocutaneous only</td>
<td>61 (66)</td>
</tr>
<tr>
<td>Cutaneous only</td>
<td>11 (12)</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
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<tr>
<td>Corticosteroids</td>
<td>90 (98)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>58 (63)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>48 (52)</td>
</tr>
<tr>
<td>Mycophenolate sodium</td>
<td>17 (18)</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>34 (37)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Gold</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Dapsone</td>
<td>9 (10)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Duration of disease before first rituximab cycle, median (range), mo</td>
<td>24 (0-256)</td>
</tr>
<tr>
<td>Age at time of first rituximab cycle, median (range), y</td>
<td>47 (17-77)</td>
</tr>
</tbody>
</table>

### Table 2. Response to Therapy

<table>
<thead>
<tr>
<th>Cycle</th>
<th>No. of Patients (%)</th>
<th>Time Since Previous Cycle, Median (Range), mo</th>
<th>Remission CR/CROT</th>
<th>Concomitant Corticosteroids</th>
<th>Concomitant Immunosuppressive Therapies</th>
<th>Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>92 (100)</td>
<td>...</td>
<td>74 (80)</td>
<td>63 (68)</td>
<td>64 (70)</td>
<td>56 (61)</td>
</tr>
<tr>
<td>2</td>
<td>54 (59)</td>
<td>12 (5-47)</td>
<td>50 (93)</td>
<td>18 (33)</td>
<td>21 (39)</td>
<td>23 (43)</td>
</tr>
<tr>
<td>3</td>
<td>22 (24)</td>
<td>10 (1-20)</td>
<td>21 (95)</td>
<td>4 (18)</td>
<td>7 (32)</td>
<td>6 (27)</td>
</tr>
<tr>
<td>4</td>
<td>7 (8)</td>
<td>8 (4-10)</td>
<td>7 (100)</td>
<td>1 (14)</td>
<td>1 (14)</td>
<td>3 (43)</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete remission off therapy; CROT, complete remission on therapy.

### Further Treatment Cycles

The details of additional treatment cycles are reported in Table 2. Fifty-four patients (24%) received 2 or more cycles, 22 patients (59%) received 3 cycles, 7 patients (8%) received 4 cycles, and 1 patient (1%) each received 5, 6, and 7 cycles in total. There were too few cases after 4 cycles from which to draw meaningful conclusions. There was no significant variance in the time intervals between cycles 1 and 2 (\( P = .32 \)) and cycles 2 and 3 (\( P = .60 \)). However, the numbers of patients receiving corticosteroids decreased with progressive cycles (\( P < .001 \)), as did the numbers of patients receiving concomitant immunosuppressive therapies (\( P < .001 \)). For patients receiving 3 or more cycles, 95% or more gained CR with or without concomitant treatment.

### Relapse

Thirty-six patients (39%) who received just 1 rituximab cycle did not experience relapse. Thirty-five of these individuals (38%) remained in complete remission with or without treatment at last follow-up. Status at 6 months after initiation of treatment cycles demonstrated that there was a significantly lower proportion of relapses after the second and third cycles compared with the first cycle (\( P < .05 \)) (Table 2).

### No Prior Systemic Immunosuppressive Therapy

Four patients did not receive prior systemic immunosuppressive therapy, and 3 patients received prior oral corticosteroid treatment. After the first treatment cycle, 4 patients attained a CR. One patient who received only corticosteroids before rituximab experienced relapse after 7 months and received a second cycle; however, all 4 patients remained in CR at the time of the last follow-up.

### Adverse Effects of Treatment

No serious infectious adverse events were reported. Infusion reactions were reported in 15 patients (16%). In only 1 patient (1%) did this warrant cessation of treatment (chest tightness toward the end of the infusion). Overall, there were 8 occurrences (9%) of rash/pruritus, 5 occurrences (5%) of throat irritation, 2 episodes (2%) of chest tightness, and 1 each of headache (1%), dizziness (1%), and hypotension (1%). Most (61%) reactions occurred during the first treatment cycle. One patient developed bilateral paronychia after the rituximab infusion. Two patients developed biopsy-confirmed lichen planus (1 case of oral and 1 of annular lichen planus) 3 to 6 months after a rituximab infusion.
Follow-up

Median duration of follow-up after the first treatment cycle was 24 months (range, 2-78). Median follow-up duration after subsequent treatment cycles was as follows: cycle 2, 16 months (range, 1-44 months); cycle 3, 12.5 months (range, 0-36 months); and cycle 4, 10 months (range, 0-21 months).

Status at Last Follow-up
At the time of the last follow-up, 56 patients were in CR (61%), 26 were in CROT (28%), 2 experienced PR (2%), 3 developed PROT (3%), and 5 experienced relapse/flare (5%); CR rates with or without adjuvant treatment were 89%. All 5 patients (5%) who had experienced relapse had previously been in remission (2 had achieved CR and 3 had attained CROT); all were awaiting further rituximab therapy.

Long-term Follow-up
A subgroup of 15 patients had at least a 45-month follow-up (Supplement [eTable]). All had received prior systemic immunosuppressive therapy. The median duration of follow-up was 51 months (range, 45-78 months). The median time from diagnosis to rituximab administration was 40 months (range, 1-151 months), and the median time to treatment failure was 19 months (range, 6-78 months). All patients achieved CR at some point during follow-up (CR, 73%; CROT, 27%).

Overall Response to Treatment
Overall, 64 patients (70%) achieved CR during their follow-up and 26 experienced CROT (28%). The best response for 1 patient (1%) was PR and, for another patient, PROT (1%).

Deaths
Two deaths occurred during follow-up. Neither of these deaths was deemed related to rituximab therapy. The first patient had colon cancer with metastatic deposits in the liver, and the second patient had a preexisting thoracic aortic thrombus.

Discussion

Our results show that the fixed-dose modified RA protocol is effective in the treatment of pemphigus disorders. After a single first cycle, 74 patients (80%) achieved the study end points, with almost one-third achieving complete remission while not receiving treatment. Median time to relapse was 15 months (95% CI, 10.3-19.7). Thirty-six patients (39%) never experienced relapse. Patients who received adjuvant treatment had a shorter time to relapse (12 months; 95% CI, 8.5-15.5) than did those who did not receive adjuvant treatment, with the median not yet reached at last follow-up (mean, 40.6 months; 95% CI, 34.2-46.9; \( P = .001 \)).

The short-term efficacy of rituximab has been confirmed in several studies. Long-term follow-up has not been examined in as much detail. Reguiai et al showed that rituximab appeared to be a durable, effective, and well-tolerated treatment for severe pemphigus. Mean follow-up was 41 months after the first cycle and 28 months after the last. Similarly, Cianchini et al demonstrated the efficacy of rituximab with a median follow-up of 26.5 months. Recently, Colliou et al reported that rituximab therapy can induce durable remission lasting up to 6 years. This is thought to be due in part to the reshaping of the B-cell repertoire during reconstitution. They found that nearly two-thirds of patients achieved a long-term complete response with or without concomitant therapy. We again have confirmed the short-term efficacy of rituximab and, in a subgroup of patients, have demonstrated long-term efficacy.

There is increasing evidence that rituximab may be useful as a first-line therapy. Lunardon observed that rituximab therapy early in the course of disease is significantly more likely to lead to complete disease remission with no or minimal therapy. This is supported by the evidence presented by
Colliou et al in which patients with a complete response had a greater proportion of naive and transitional B cells than did those with incomplete response, suggesting a barrier to B-cell maturation. Complete responders also had a specific loss of antibodies-megline-specific cells, but not B cells, that respond to infections. If all of this information is confirmed in larger studies, this could lead the way for use of rituximab as a first-line therapy. In our study, patients who received adjuvant rituximab therapy had a shorter time to relapse. This may be explained by several reasons: (1) these patients may have more severe disease; (2) there may be a hypothetical effect of sustained immunosuppression on immunosurveillance, permitting the subsequent development of an abnormal B-cell repertoire; or (3) these patients may represent a group that for unknown reasons has abnormal barriers to B-cell maturation.

The optimal dosing regimen for rituximab in autoimmune disorders has yet to be determined. In our study, the RA protocol was adapted for use in autoimmune bullous disorders. This protocol has not been used as widely as the lymphoma protocol, but it has been reported as being efficacious and well tolerated. We used a modified version of the RA protocol in clinical practice, and in some instances, patients did not receive the full 1-g dose on days 1 and 15 but rather received doses of 1 g or 500 mg as needed 6 months or more after induction dosing. This occurred when deemed appropriate by the treating physician or by necessity when, because of financial constraints, the full dose was not affordable for the patient. Other studies have reported successful use of low-dose rituximab; in a prospective cohort study, 2 infusions of 500 mg at an interval of 2 weeks were administered in 15 patients, with more than half of the patients achieving CR.

The rate of adverse effects in our cohort was comparable to that in other reports.

In contrast to other studies specifically using the RA protocol, we observed no serious infectious adverse events. As in other reports, an infusion reaction in one of our patients prevented the completion of treatment.

The limitations of our study include the retrospective design, the small numbers of patients with disease entities other than pemphigus vulgaris, and the potential for confounding factors (eg, patients with more refractory disease likely required more adjuvant treatment). The relationship between disease severity and relapse could not be determined because severity was not measured on a consistent basis. We did not quantify immunologic factors before and after treatment in every patient. In most patients, there was a limited follow-up time. Despite these limitations, this is the largest reported series of patients who received rituximab for pemphigus diseases, and it provides information specifically on the use of the fixed-dose RA protocol.

Pemphigus vulgaris and pemphigus foliaceus are chronic autoimmune bullous disorders associated with a significant morbidity and in some cases mortality. Rituximab has provided a major advance for patients who can gain access to it. In some instances, rituximab may be curative. The future looks positive, and with increasing evidence, rituximab may become available as a first-line treatment. There is also an emerging argument for the use of rituximab as a maintenance therapy.

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Conflicts of Interest Disclosures: Drs Shear and Walsh served as consultants on an advisory board for Roche Pharma. Dr Heelan has received fellowship support from Abbott (AbbVie) Pharmaceuticals. No other disclosures were reported.

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Tungiasis
“The Greatest Curse That Has Ever Afflicted Africa”

Fabrizio Vaira, MD; Gianluca Nazzaro, MD; Stefano Veraldi, MD

Because of air travel, diseases formerly restricted to tropical and subtropical areas may also now be observed in countries with temperate climates. Among these diseases, one often underrecognized by Western dermatologists is tungiasis, an infestation caused by penetration in the skin of the gravid female of the flea Tunga penetrans. 1-3 This infestation occurs in poor communities in South America and Africa and sporadically affects travelers to endemic areas. Medical entomology claims that the South American continent was its original site. The history of this insidious flea is characterized by curious anecdotes. The first reports date back to the pre-Incan period: artists of the Moringa in the South American continent was its original site. Medical entomology claims that the South American continent was its original site. The first contact with Europeans was after the Christopher Columbus’s sailors landed in Haiti. They fought against this parasite as well as against the natives until they were “slaughtered” by both. Soon, tungiasis became a very important problem for the colonizing European troops who had no previous experience with this flea. For instance, the Spanish military expedition in Colombia (1538), led by Gonzalo Ximenez de Quezada, was stopped for a long period in Sororoca, a town infested by T penetrans. These soldiers suffered so severely that the walking was very difficult.1 Native women had compassion and showed the Spaniards how to remove the imbedded fleas. These ancient methods of extraction of the fleas from the skin are still used in some areas in South America and Africa.

The first scientific description of T penetrans and tungiasis was provided by Alexio de Abreu in 1623.4 Tungia penetrans is one of the few parasites that spread from the Western to the Eastern hemisphere. According to the tradition, the British ship Thomas Mitchell, during its 1872-1873 voyage,1 brought the flea from Brazil to Angola in bags of sand used as ballast. Tungia penetrans spread rapidly along the African West Coasts and sub-Saharan regions following the trading caravans.7 The small flea brought Africa to its knees. Indeed, towns and villages were so infested that inhabitants were often forced to leave them. Even though T penetrans did not cause death, it caused painful lesions on the feet that prevented walking. Therefore, people starved because they were unable to work in fields. Lionel Decle, at the end of the 19th century, wrote: “In this village there was not man or woman who was not covered with ulcers... my experience makes me look upon the jigger as the greatest curse that has ever afflicted Africa.”3(p571)

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Correction: This article was corrected online July 29, 2014, for errors in the byline.


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