OBSERVATION

Rituximab for Patients With Refractory Mucous Membrane Pemphigoid

Christelle Le Roux-Villet, MD; Catherine Prost-Squarcioni, MD, PhD; Marina Alexandre, MD; Frédéric Caux, MD, PhD; Francis Pascal, MD; Serge Doan, MD; Marie-Dominique Brette, MD; Isaac Soued, MD; Éric Gabison, MD, PhD; Françoise Aucouturier, MD; Rémi Letestu, MD, PhD; Liliane Laroche, MD, PhD; Hervé Bachelez, MD, PhD

Background: Mucous membrane pemphigoid (MMP) still represents a potentially life- and sight-threatening disease. In a subset of patients with severe MMP, conventional immunosuppressants are ineffective or contraindicated.

Observations: Twenty-five patients with severe refractory MMP, including 5 with mucous membrane–dominant epidermolysis bullosa acquisita, received 1 or 2 cycles of rituximab (375 mg/m² weekly for 4 weeks). Twenty-one of the patients were receiving concomitant therapy with dapsone and/or sulfasalazine therapy, which was maintained during rituximab cycles. Complete responses in all affected sites (ocular and/or extraocular) were obtained in 17 patients (68%) by a median time of 12 weeks after the first cycle, and 5 additional patients responded completely after a second cycle, yielding an 88% complete response rate. In all but 1 of the 10 patients with ocular lesions, their eyes became noninflammatory within a mean of 10 weeks. Among the 3 patients (12%) who developed severe infectious complications, 2 (8%) died; they had been receiving concomitant conventional immunosuppressants and high-dose corticosteroids and were hypogammaglobulinemic. Treatment with immunosuppressants was discontinued for all other patients, and no other infection was observed. Ten patients experienced relapse after a mean of 4 (range, 1-16) months after achieving complete responses.

Conclusions: Rituximab appears to have rapid and dramatic efficacy in patients with severe, refractory MMP. The occurrence of severe infections in patients receiving concomitant conventional immunosuppressants supports using rituximab without other immunosuppressants. Controlled prospective studies are warranted to define an optimal treatment protocol.


IN 1999, AN INTERNATIONAL CONSENSUS meeting defined the heterogeneous group of diseases called mucous membrane pemphigoid (MMP), which encompasses autoimmune, chronic, inflammatory, and subepithelial blistering diseases that predominantly affect mucous membranes (MMs). Formerly called cicatricial pemphigoid, MM-dominant epidermolysis bullosa acquisita (EBA), or MM-dominant linear IgA bullous dermatosis, these entities share the common immunohistological features of linear deposition of immunoglobulins and/or complement fragments in the epithelial basement membrane zone (BMZ). Mucous membrane pemphigoid is associated with major morbidity, potentially leading to definitive functional sequelae and/or death in the case of laryngeal, conjunctival, tracheal, and/or esophageal involvement. For patients with moderate forms of MMP involving only oral mucosa and/or skin and whose scars have mild adverse impact, usual treatments include topical corticosteroids, dapsone, sulfasalazine, and tetracyclines, used either alone or in combined regimens. However, patients with severe involvement or those responding poorly to the usual treatments require alternative systemic immunosuppressive/immunomodulatory therapies, for example, systemic corticosteroids, cyclophosphamide, cyclosporine, and/or intravenous immunoglobulins (IVIg). But MMP is sometimes refractory to appropriately administered single or combined immunosuppressive regimens. Therefore, effective innovative therapies are needed for patients with severe forms of MMP.

See Practice Gaps at end of article

Rituximab, a genetically engineered chimeric murine-human anti-CD20 monoclonal antibody targeting B lymphocytes, has
been successfully used to treat B-cell lymphomas and auto-immune antibody-mediated diseases, including myasthenia gravis, autoimmune hemolytic anemia, systemic lupus erythematosus, idiopathic thrombocytopenic purpura, and rheumatoid arthritis. Concerning autoimmune skin diseases, rituximab has shown striking efficacy against refractory forms of pemphigus. Indeed, rituximab induced long-lasting remissions in patients with pemphigus vulgaris or foliaceus and in those with paraneoplastic forms. But rituximab remains poorly investigated in patients with MMP, with only a few cases reported in the literature and a recent series of 6 ocular pemphigoid cases. We describe herein our experience with rituximab therapy for 25 patients with severe refractory forms of MMP.

METHODS

PATIENTS

A subset of patients seen for diagnosis and treatment of an autoimmune blistering disease between July 2002 and January 2008 in 2 dermatology departments, belonging to the French Reference Center for Autoimmune and Toxic Acquired Bullous Dermatoses, was diagnosed as having severe refractory MMP. After being validated by a local expert committee, rituximab was prescribed for some of those patients with contraindications for conventional immunosuppressants or in whom conventional immunosuppressants were ineffective, and informed consent was obtained for all patients.

Mucous membrane pemphigoid was diagnosed according to the previously established consensus definition, for example, an autoimmune subepithelial blistering disease with linear deposition of IgG, IgA, and/or C3 along the epithelial BMZ, clinically characterized by predominant MM involvement. All patients had skin lesion or perilesion biopsy specimens taken from at least 1 site: skin and/or buccal, anal, genital, orotonal, or conjunctival MM. Histological examination and direct immunofluorescence (IF) assays were performed using standard procedures. The in vivo ultrastructural location of BMZ immune deposits was determined by direct immunoelectron microscopy (IEM), and Western blotting on dermal extracts was performed as previously described. Rat esophagus and human split skin were used as substrates for indirect IF. Commercially available BP180-NC16a and BP230 enzyme-linked immunosorbent assay (ELISA) kits (Medical and Biological Laboratories Ltd, Nagoya, Japan) were used to test the serum samples. HLA class II was genotyped using polymerase chain reaction, as previously reported. Serum antinuclear antibodies were also sought to confirm the diagnosis of vesiculobullous systemic lupus erythematosus. B-cell counts were performed using multicolor staining including CD19, CD20, CD45, and CD2 (Becton Dickinson, San Jose, California). Data were acquired on FACS (fluorescence activated cell sorting) Canto II flow cytometer (Becton Dickinson). The minimal number of events stored was 20,000 lymphocytes to reach a sensitivity ranging from $10^3$ to $10^4$ in samples with no detectable B-cell population. A significant B-cell population was defined as a cluster of at least 20 cells with CD19 and CD20 coexpression; CD2 was used as an exclusion marker for T and natural killer cells. Physicians considered MMP severe when active and/or cicatricial lesions were present in the pharynx, larynx, or esophagus and/or there was a conjunctival Tauber grade of III/IV. A scoring system (eTable 1; http://www.archdermatol.com), based on a slightly modified version of a previously approved MMP score, was devised to assess lesion extension at the patient’s first consultation and during follow-up. The modifications include evaluation of all the potentially affected MM, particularly anal and traheal, and discrimination between active lesions (erythema, erosions, and edema) and cicatricial lesions (scars, synechiae, and stenoses). Ocular lesions were specifically graded according to the scoring system devised by Tauber et al. Each of the 8 sites examined was graded (range, 0 [negative] to 20) to give each patient a clinical score based on the sum of the active and cicatricial lesion scores at each consultation (range, 0-160).

RESULTS

PATIENT CHARACTERISTICS

Rituximab was given to 25 patients with MMP (16 women and 9 men), aged 17 to 89 years (mean, 66 years) (eTable 2). Mucous membrane pemphigoid had lasted a mean of 32 (range, 1-156) months before diagnosis. A median of 3 (maximum, 6) sites were involved. Their mean total severity score at baseline was 23.7 (range, 11-46), with mean active lesion and mean cicatricial lesion scores of 13 (range, 5-24) and 10.8 (range, 0-36), respectively. Cicatricial lesions included stenosis of the upper aerodigestive tract (8 nasal, 1 laryngeal, and/or 2 tracheal) in 8 patients and/or severe cicatricial ocular involvement (Tauber grade III/IV) in 11 patients. Among the latter, patient 16 had severe cicatricial lesions that had healed, leaving severe scarring, and inactive (noninflam-
matory) ocular involvement, so rituximab efficacy was expected only against his extraocular lesions. Previous treatments prescribed were dapsone and/or sulfasalazine for 21 patients; prednisone for 10, IVIg for 3, and 1 or several immunosuppressant(s) for 20. Immunosuppressants included cyclophosphamide for 17 patients, cyclosporine for 2, azathioprine for 2, mycophenolate mofetil for 7, or methotrexate for 1.

Rituximab was given as salvage therapy for severe active lesions of the upper aerodigestive tract and/or conjunctiva in 19 patients, including 2 with tracheal lesions. Five of the patients had severe conjunctiva and larynx involvement. For 6 other patients with buccal and/or anal MM and/or skin involvement, many treatments had previously been tried unsuccessfully. Even patients without severe eye or larynx involvement complained of the dramatic impact of MMP on their quality of life because of pain and persistent pruritus, bleeding, and/or aesthetic consequences.

Among the 21 patients who were taking dapsone, sulfasalazine, and/or topical corticosteroids, all continued rituximab therapy until the lesions healed, except the 2 patients with intolerance to sulfasalazine. Dapsone (1 mg/kg/d) was prescribed to 3 other patients after CR had been obtained with rituximab alone and there was 1 final patient with anemia, which contraindicated its use. Dapsone and/or sulfasalazine intensification for relapsing disease did not provide sufficient improvement.

For all patients, systemic therapy was started at the time of MMP diagnosis and lasted a median of 32 months before rituximab was prescribed (eTable 2). Although the median follow-up after initiating rituximab treatment was shorter than that for systemic therapy, for a majority of patients (15 of 25 [60%]), follow-up with rituximab was longer than the duration of conventional therapy. In either case, the relapse rate was similar, regardless of whether the rituximab period was longer or shorter than conventional therapy.

IMMUNOLOGICAL DATA

Each patient’s biopsy specimen, obtained from 1 or several sites (buccal mucosa for 10 patients, skin for 9, conjunctiva for 2, nose or bronchus for 3, and genital mucosa for 3), was subjected to standard histological analysis, direct IF, and IEM. Routine histological staining revealed subepithelial bullae in conclusive cases. Direct IF detected linear IgG, IgA, and/or C3 deposits on the BMZ of all patients except patient 7; patient 8 had only predominant IgA deposits.

Direct IEM revealed immune deposits within the lamina densa alone or associated with deposits within the lamina lucida of 4 and 12 patients, respectively, including patient 7 whose specimen had been negative on direct IF, while immune deposits in hemidesmosomes were observed in 3 patients (eTable 3). Four patients had immune deposits in the anchoring fibril zone, in accordance with a diagnosis of MM-dominant EBA. Direct IEM could not be performed for patient 24, who was receiving systemic corticosteroids, but immunoblotting on dermal extracts showed that this patient’s serum samples reacted with a 290-kDa antigen that comigrated with type VII collagen, leading to an additional diagnosis of MM-dominant EBA.

Indirect IF on rat esophagus was positive for 4 of the 25 patients (16%), 3 of whom had MM-dominant EBA. Autoantibodies were detected by indirect IF on salt-split skin samples for 11 of the 25 patients (44%), with labeling of the roof or floor of the cleavage for 6 and 5 patients, respectively, and 4 of the 5 patients with labeling of the floor of the cleavage had MM-dominant EBA; only patient 14 had floor labeling and immune deposits in the lamina densa consistent with autoantibodies directed against laminin 5. Results of NC16a and BP230 ELISAs were positive for 5 (24%) and 3 (14%), respectively, of the 21 patients tested.

Among the 24 patients in whom HLA class II molecules were studied, the DQB1*0301 allele was found in 21 (88%). Serum antinuclear autoantibodies were detected in 10 patients and were negative in 10, but no patient fulfilled American College of Rheumatology criteria for systemic lupus erythematosus.

RESPONSE TO RITUXIMAB

After 1 cycle of 4 rituximab infusions, 18 of our 25 patients (72%) were considered responders: 17 had a CR (68%) within a median of 12 (range, 2-32) weeks (Table and Figure) after the first infusion, and patient 6 achieved only PR (4%). Clinical improvement, attested by the decreased active lesion score, was noted for 16 of the 25 patients (64%) as early as the fourth infusion, when patient 15 had already attained a CR. Notably, the mean active lesion score declined from 13 at baseline to 8.8 at the time of the fourth infusion. Moreover, no evidence of disease progression during this first month was observed in any patient other than patient 8, who eventually attained a CR. The other 7 patients (patients 1-3, 11-13, and 17) had NR with a follow-up of at least 4 months after the first rituximab infusion; none of them had evidence of disease progression.

A second cycle of 4 rituximab infusions was administered to the 8 patients who had not achieved CR after the first cycle, i.e., patient 6 with PR and 7 patients with NR. After this second cycle, 5 of the 8 patients (patients 3, 6, 12, 13, and 17) obtained a CR; patient 11 had a PR and remaining patients 1 and 2 still had NR after 2 rituximab cycles.

The overall response rate (CR + PR) was 72% (68% + 4%) after the first rituximab cycle and 92% (88% + 4%) after the second cycle. Among the 23 responders (CR or PR), 6 (26%) required 2 rituximab cycles to obtain a response. Remarkably, 5 of the 7 patients with NR after the first cycle became responders (4 CR and 1 PR) after the second cycle. Two rituximab cycles were administered to 16 of 25 patients (64%): 8 who experienced relapse and 8 with NR to the first cycle.

Considering only the subgroup of 10 patients with ocular disease, 90% had white and noninflammatory eyes after the first rituximab cycle and 100% after the second cycle. All but patient 3 had white and noninflammatory eyes by a median of 10 weeks after the first infusion. However, for patients 1 and 2, who had severe eye and laryngeal involvement at baseline, no perceivable change in laryngeal involvement could be detected despite 2 ritux-
imab cycles (NR after 2 cycles), even though their inflammatory ocular lesions had healed.

**BIOLOGICAL MONITORING**

The median absolute lymphocyte count was 1150/µL (range, 130-2490/µL) at baseline and 1110/µL (range, 440-2300/µL) [to convert to \(10^9/L\), multiply by 0.001] 4 months after the first infusion. The mean peripheral blood CD20-positive B-lymphocyte count was 58/µL (range, 1-300/µL) before starting rituximab therapy. The peripheral blood B-cell level was determined for the 10 patients who experienced relapse (Table); no B lymphocytes were detectable in 4 of the patients but were found in the 6 others. Intriguingly, relapses occurred concomitantly with or 1, 5, and 6 months after circulating B-lymphocyte reappearance in 1 patient or in 1, 1, and 3 patients, respectively. However, peripheral blood B lymphocytes reappeared in all 9 patients tested who did not have a relapse. The mean time to circulating B-lymphocyte reappearance, in tested patients, was 9 (range, 3-14) months. No correspondence could be established between the onset of clinical relapse and recovery of peripheral blood B cells. No patient be-

**Table. Response to Rituximab (RTX)**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Combined Drugs</th>
<th>Response</th>
<th>Follow-up, mo</th>
<th>Treatment(s) After Failure or Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>DDS, SAZ – NR NR NA NA 17 NA NA ND IVIg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>DDS – NR CR 4b 18 25 No NA ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>DDS – CR NA 1.75 17.25 19 No NA ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>DDS, SAZ – CR NA 2 45 47 No NA ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>DDS – PR CR 3b 6 12 No NA ND NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>DDS – CR NA 3 21 24 No NA ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>DDS – CR NA 5 5 10 No NA ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>DDS – CR NA 3 22 25 No NA ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>– CYC, Pred CR NA 2 3 5 Yes 4 No5 Died</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>DDS, SAZ – NR PR NA NA 30 NA NA ND</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>DDS, SAZ – NR CR 6b 10 26 No NA 6d NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>DDS – NR CR 3.5b 18.5 22 No NA 10d NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>DDS MMF, Pred CR NA 3 46 49 No NA 10 NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>SAZ – CR NA 0.5 71.5 72 Yes 5 Noe RTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>DDS – CR NA 8 41 49 Yes 12 6 RTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>DDS, SAZ – NR CR 6b 3 24 No NA 12 NA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>DDS, SAZ – CR NA 2 22 24 Yes 18 12 RTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>DDS – CR NA 3 46 49 Yes 15 10 RTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>DDS – CR NA 4 42 46 Yes 5 Noe RTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21e</td>
<td>– MTX CR NA 3 15 18 Yes 12 6 RTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>22e</td>
<td>DDS, SAZ AZA CR NA 4 22 26 Yes 8 8 RTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>23e</td>
<td>– CSA, CR NA 1.5 2.5 4 Yes 4 Noe Died</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24e</td>
<td>DDS, SAZ – CR NA 5 5 10 Yes 10 9 RTX</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25e</td>
<td>DDS Pred CR NA 3 9 12 No NA 14 NA</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AZA, azathioprine; CR, complete response; CSA, cyclosporine; CYC, cyclophosphamide; DDS, dapsone; IS, immunosuppressant; IVIg, intravenous immunoglobulins; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not applicable; ND, not done; NR, no response; PR, partial response; Pred, prednisone; SAZ, sulfasalazine; TNF, tumor necrosis factor; –, not given.

a These agents were prescribed successively.

b After second cycle.

c No reappearance of B lymphocytes at the time of relapse.

d After the second infusion of RTX.

e Mucous membrane pemphigoid epidermolysis bullosa acquisita forms.

**Figure.** Flowchart of clinical responses to rituximab (RTX) for 25 patients with severe mucous membrane pemphigoid (MMP). CR indicates complete response; IS, immunosuppressants; NR, no response; and PR, partial response.

©2011 American Medical Association. All rights reserved.
RITUXIMAB ADVERSE EVENTS

The only immediate rituximab adverse effect was mild transient blood pressure diminution, which did not require treatment discontinuation. Three patients (12%) developed severe infectious complications 4 months after rituximab initiation: undocumented pulmonary infection in a context of previous severe pulmonary tuberculosis and therapeutic pneumothorax (patient 10), severe pyelonephritis (patient 14), and Pneumocystis jirovecii pneumonia (patient 23). Two patients (8%) died (patients 10 and 23) despite intensive anti-infectious therapy. The 3 patients with the severe infectious complications had attained a CR after only 1 rituximab cycle. When the disease relapsed with laryngeal and tracheal involvements and edema under high-dose prednisone and immunosuppressants in patients 10 and 23, their drug doses were further increased, which probably contributed to their infectious complications and deaths. The 3 patients (Nos. 10, 14, and 23) had hypogammaglobulinemia (5.8 [patient 10], 4.7 [patient 14], and 4.1 g/L [patient 23]) at the time of infection onset, and it had already been present when rituximab therapy was started in patients 10 and 14. After stopping therapy with mycophenolate mofetil and systemic corticosteroids, patient 14 rapidly recovered a normal γ-globulin level without IVIg therapy. Immunosuppressant therapy had been maintained in combination with rituximab for these patients because of their severe MMP with initial laryngeal or subglottic edema. In response to these very early observations, immunosuppressant treatment was subsequently discontinued when rituximab therapy was started.

FOLLOW-UP

Of the 22 patients who achieved a CR, 10 developed signs of relapse at a mean of 4 (range, 1-16) months after CR (Figure and Table), all of whom had received only 1 rituximab cycle. Eight of these 10 patients then received a second cycle of 4 rituximab infusions, and a response was again observed in all 8 (7 CR and 1 PR).

After 1 or 2 rituximab cycles and a median follow-up after the first infusion of 24 (range, 4-72) months, CR and PR persisted in 19 (76%) and 2 (8%) patients, respectively, resulting in an overall response rate of 84%, with 2 NRs and 2 deaths completing those outcomes. Among the 21 patients with a CR or PR, 14 (66%) required 2 rituximab cycles.

COMMENT

Mucous membrane pemphigoid covers chronic, MM-dominant, subepithelial autoimmune bullous diseases. These entities are characterized by progressive fibrosis and scarring, potentially leading to life-threatening airway obstruction, permanent partial or total vision loss due to ocular sequelae, or esophageal stenosis associated with major feeding difficulties.1 The fibrosis-scarring course follows an inflammatory stage (postbullous lesions, erythema, and edema), with acceleration of the fibrosis-scarring cycle, once the former has reached an advanced stage.

For these severe forms, first-line treatment consists of systemic corticosteroids, immunosuppressants, and/or IVIg, according to the consensus conference.1 However, some patients respond poorly to these therapies; others have contraindications to them or experience adverse events requiring their permanent withdrawal. Moreover, a similar strategy has been applied to patients with less severe disease that responded poorly to dapsone.1 In our national referral center, a large subset of patients with MMP falls into these categories.

For all these reasons, innovative therapeutic strategies targeting the key effector mechanisms of the disease are warranted. Pertinently, rituximab obtained striking efficacy against refractory forms of pemphigus, an intraepidermal autoimmune bullous disease in which the direct pathogenicity of autoantibodies has been demonstrated, as in MM-dominant EBA (20% of our patient cohort). Indeed, rituximab induced long-lasting remission in patients with pemphigus vulgaris or foliaceus and those with paraneoplastic forms.10,21

So far, few published case reports have described the benefit of rituximab for patients with refractory EBA or MMP (7 and 4 cases, respectively)20-22,24: 8 CRs and 3 PRs were obtained within 2 to 7 months after 1 rituximab cycle. Most often, when it was specified, improvement was observed as early as the first month after the first rituximab infusion, and it was sufficient to allow dose reduction of other combined agents. One patient required additional rituximab infusions to remain lesion free. Two additional patients with MMP, treated with a combination of immunoadsorption and rituximab, achieved 1 CR and 1 PR.25 Among those reported cases, patient 1, patient who contracted fatal Pseudomonas pneumonia after rituximab was administered.24 Those observations suggested rituximab efficacy against EBA and MMP. However, the use of concomitant immunosuppressants and/or corticosteroids in those reports did not allow accurate assessment of rituximab’s intrinsic effects. Recently, Foster et al20 reported the benefit of combining rituximab (12 infusions in 6 months) and IVlg (2 g/kg/mo), which halted disease progression in 6 patients with severe ocular pemphigoid, in contrast to a group of 6 patients who became totally blind despite maximal immunosuppressive regimens.

Herein, we report, to our knowledge, the first experience using this innovative agent to treat a series of 25 patients with severe and/or refractory MMP, including 5 instances of MM-dominant EBA. All these patients had severe disease, involving at least 2 sites. The DQB1*0301 allele was found in 18 of the 19 patients (90%) with MMP with immune deposits within hemidesmosomes, inferior lamina lucida, and/or lamina densa by IEM (formerly called cicatricial pemphigoid). These observations are in accordance with an article on HLA in cicatricial pemphigoid.22

Moreover, rituximab efficacy was evaluated using a standardized system to score all involved areas, which
is used daily in our center. Until now, most published case and series reports describing therapies used to treat MMP referred only to ocular lesions, and few data are available on other MM sites. Indeed, we found no published data on overall clinical evaluation of skin and MM. In particular, immunosuppressant efficacy against all extracocular locations has not been described in detail.

Rituximab was administered in accordance with literature recommendations. Our results strongly support its dramatic efficacy, usually when used without any other immunosuppressants to treat severe refractory MMP, as an overall response rate of 92% (CR, 88%; and PR, 4%) was obtained after 1 or 2 cycles. Moreover, rituximab was again successful against relapses, thereby further supporting the efficacy of this strategy for refractory MMP. Rituximab enabled 19 patients to totally discontinue the use of immunosuppressants and corticosteroids.

One of the challenges of treating patients with MMP is the need for rapidly beneficial agents to avoid blindness. With classic treatments, time to ocular CR was often as long as 12 months (intravenous cyclophosphamide) or a minimum of 5 (IV Ig) or 2 to 4 (combined cyclophosphamide and prednisone) months. With rituximab, median time to CR in all sites was as short as 3 months, comparable to that observed for pemphigus. Notably, ocular remission achieved within a median of 10 weeks, comparable to that observed with combined cyclophosphamide and prednisone.

Patients 1 and 2 were considered to have NR because their laryngeal involvement remained rituximab resistant, as opposed to the healing of their eye lesions. Per- tinently, these 2 patients had not received any immunosuppressant treatment previously.

We wondered whether a subset of the 25 patients was less likely to respond or to relapse more frequently. Laryngeal disease was particularly resistant: among the 6 cases of NR, 4 had persistently active laryngeal lesions. In contrast, the autoantibody type(s) (IgA and/or IgG) deposited, their ultrastructural location (lamina densa or anchoring fibril zone), or their detection by indirect IF or ELISA did not seem to affect the response to rituximab.

The development of severe infectious complications in 3 of our patients (12%), with death of 2 (8%), might raise some concerns about rituximab safety. However, it is worth noting that these patients with MMP had extremely severe disease, with long histories of immuno-suppressant exposure prior to rituximab, which was administered concomitantly with high-dose corticosteroids and immunosuppressants.

Variable degrees of rituximab-associated infectious risk have been reported. The results of a recent study suggested that combining rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone to treat lymphoma increased the frequency of interstitial pneumonia. Conversely, no significant infectious risk increase was observed in randomized studies on indolent lymphoid malignant neoplasms treated with combined rituximab and chemotherapy regimens. Some patients with refractory autoimmune diseases, who were treated with combined rituximab and immunosuppressants, developed infectious complications. Schmidt et al analyzed serious infectious adverse effects in autoimmune diseases: 31% of 35 patients in several series of mixed autoimmune bullous diseases, 17% of 18 patients with systemic lupus erythematosus and 9% of 161 patients with rheumatoid arthritis. Pertinently, no infectious complication has been reported for patients in whom rituximab was initiated alone, without systemic corticosteroids or other immunosuppressants. Conventional systemic treatment failure due to severe adverse events is sometimes observed in patients with MMP. To our knowledge, no study comparing the infectious risk of conventional immunosuppressants vs rituximab is available. The infectious risk of rituximab monotherapy might not be higher than that of immunosuppressants and corticosteroid regimens.

Taking all these observations together, we think that rituximab has high efficacy as an alternative therapy for patients with severe, refractory forms of MMP and that it should be prescribed without immunosuppressants, rather than combined with intensive immunosuppression. In the absence of confirmatory studies, rituximab cannot be the first-line drug for MMP. Only future prospective studies and registries might be able to accurately evaluate rituximab’s safety profile, an optimal regimen, and its risk to benefit ratio in the setting of severe MMP.

Accepted for Publication: January 26, 2011.
Published Online: March 21, 2011. doi:10.1001/archdermatol.2011.54

Author Affiliations: Departments of Dermatology (Drs Le Roux-Villet, Prost-Squarcioni, Alexandre, Caux, Pascal, and Laroche), Pathology (Dr Prost-Squarcioni), Histology (Dr Prost-Squarcioni), Otorhinolaryngology (Dr Soued), and Hematology Laboratory (Dr Letestu), Hôpital Avicenne, Assistance Publique–Hôpitaux de Paris (AP-HP), Université Paris 13, Bobigny, France; Departments of Dermatology (Dr Bachelez), Stomatognathic (Dr Pascal), and Immunology (Dr Aucouturier), Hôpital Saint-Louis, AP-HP, Université Paris Diderot, Paris, France; Department of Ophthalmology (Drs Doan and Gabinson), Hôpital Bichat–Claude-Bernard, AP-HP, Université Paris Diderot, Paris; Department of Otorhinolaryngology (Dr Brette), Hôpital Lariboisière, AP-HP, Université Paris Diderot; INSERM U976 (Dr Bachelez); and French Referral Center for Autoimmune and Toxic Acquired Bullous Dermatoses (Drs Le Roux-Villet, Prost-Squarcioni, Alexandre, Caux, Pascal, Doan, Brette, Soued, Aucouturier, Gabinson and Laroche), AP-HP, Paris, Bobigny, Boulogne-Billancourt, and Créteil, France.

Correspondence: Christelle Le Roux-Villet, MD, French Referral Center for Autoimmune and Toxic Acquired Bullous Dermatoses, Department of Dermatology, Hôpital Avicenne, 125 route de Stalingrad, 93009 Bobigny CEDEX, France (christelle.le-roux@avc.aphp.fr).

Author Contributions: Drs Le Roux-Villet and Prost-Squarcioni contributed equally to this work. Drs Le Roux-Villet, Prost-Squarcioni, Bachelez, and Laroche had full access to all of the data in the study and take full responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Roux-Villet, Prost-Squarcioni, and Bachelez. Acquisition of data: Roux-Villet, Prost-Squarcioni, Alexandre, Caux, Pascal, Doan, Brette, Soued, Gabinson, Aucouturier, and Letestu. Analysis and interpretation of data: Roux-Villet, Prost-Squarcioni, Caux, Laroche, and Bachelez. Drafting of the manuscript: Roux-Villet, Prost-Squarcioni, Letestu, and Bachelez. Critical re-
vision of the manuscript for important intellectual content: Prost-Squarciion, Alexandre, Caux, Pascal, Doan, Bret, Soued, Gabison, Aucouturier, Larocco, and Bachelez. Obtaining funding: Aucouturier. Administrative, technical, or material support: Letestu. Study supervision: Roux-Vil tet, Prost-Squarciion, and Bachelez.

Financial Disclosure: Dr Bachelez received consultant fees from Abbott, Cephalon-Zeneus, Janssen-Cilag, Merck-Sero, Schering-Plough, and Wyeth Pharmaceuticals.

REFERENCES


