Clinical and Immunologic Factors Associated With Bullous Pemphigoid Relapse During the First Year of Treatment
A Multicenter, Prospective Study

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IMPORTANCE Although predisposing factors for bullous pemphigoid (BP) have been recently established, no clinical or immunologic factors have yet been identified to predict disease outcome.

OBJECTIVE To identify risk factors for BP relapse during the first year of treatment.

DESIGN, SETTING, AND PARTICIPANTS Multicenter prospective study of 120 consecutive patients with newly diagnosed BP in 8 French dermatology departments. Baseline and 6 follow-up visits were planned to record disease activity and collect blood samples for measurement of serum anti-BP180 and anti-BP230 levels by means of enzyme-linked immunosorbent assay (ELISA).

MAIN OUTCOMES AND MEASURES The end point was clinical relapse within the first year of therapy. Associations of clinical and immunologic (including serum levels of anti-BP180 and anti-BP230 autoantibodies) parameters with clinical relapse were assessed using univariate and multivariate analyses.

RESULTS During the 1-year follow-up, 35 patients (29.2%) experienced relapse, whereas anti-BP180 and anti-BP230 ELISA results were similar at baseline between patients who did and did not experience relapse. Factors at baseline independently associated with relapse were extensive disease at inclusion (hazard ratio [HR], 2.37 [95% CI, 1.2-4.8]) and an associated dementia (HR, 2.09 [95% CI, 1.0-4.2]). Use of superpotent topical corticosteroids alone (by 100 patients [83.3%]) induced a dramatic, early decrease in serum levels of anti-BP180 and anti-BP230 autoantibodies. Mean early decreases in autoantibody levels between baseline and day 60 were lower in patients with relapse compared with patients with ongoing remission (−10.0% and −45.2%, respectively, for anti-BP180 levels [P < .001] and –11.8% and –35.4%, respectively, for anti-BP230 levels [P = .046]). A higher serum level of anti-BP180 at day 150, with a cutoff of 23 U/mL, provided 84.2% sensitivity, 44.8% specificity, 33.3% positive predictive value, and 89.7% negative predictive value for the occurrence of relapses between days 150 and 360.

CONCLUSIONS AND RELEVANCE The pronounced decrease in the level of anti-BP180 autoantibodies and, to a lesser extent, those directed against BP230 confirmed the use of superpotent topical corticosteroids alone as a reference BP treatment. Furthermore, our study suggests that neurological diseases play a major role in BP, not only as a predisposing but also as a prognostic factor.

Published online November 13, 2013.
Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disease of the skin in European countries, including France. In BP, the autoantigens targeted are 2 hemidesmosomal proteins of the epidermal basement membrane zone (BMZ), BP180 and BP230. The NC16a domain of the BP180 ectodomain has been identified as the immunodominant domain. Using a commercially available enzyme-linked immunosorbent assay (ELISA), anti-BP180 autoantibodies are detected in 79% to 93% of BP cases, and serum levels at diagnosis have been correlated with disease activity. Anti-BP230 autoantibodies are detected by means of ELISA in 57% to 63% of BP cases.

Several large case-control studies have attempted to define predisposing factors for BP. Factors associated with BP were neurological disorders, chronic use of spironolactone or psycholeptics, unipolar or bipolar disorders, and bedridden condition. An association between neurological diseases and development of BP has been described. However, to our knowledge, no clinical or immunologic factors have been identified to predict the outcome of patients with good-prognosis BP (defined by long complete remission after cessation of therapy) or poor-prognosis BP (defined by recurrent disease requiring maintenance therapy for years). In this matter, the usefulness of anti-BP180 or anti-BP230 ELISA results for monitoring patients with BP during treatment also remains unclear. In contrast, we recently showed that a high anti-BP180 titer at the time of cessation of therapy and after a mean duration of treatment of 11.5 months was associated with BP relapse during the 12 months after the cessation of therapy. To identify risk factors for early BP relapse within the first year of treatment, we conducted an additional prospective, multicenter, open study enrolling 120 new patients with BP. To address this question, we (1) performed a longitudinal study linking the evolution of anti-BP180 and anti-BP230 ELISA values with disease relapse and (2) analyzed the clinical characteristics of patients with BP before starting therapy, including number of new blisters daily and associated medical conditions.

**Methods**

**Study Patients and Design**

This prospective, multicenter, observational study was conducted in 8 French dermatology departments (Reims, Rouen, Limoges, Thionville, Dijon, Besançon, Mulhouse, Chalons). Among these, 3 belong to the French Referral Center for Autoimmune Bullous Diseases (Reims, Rouen, Limoges). Consecutive patients with newly diagnosed BP were included in this prospective study using the same inclusion criteria as in previous large clinical studies from our group. The diagnosis of BP was made on the basis of the following criteria: clinical features typical of BP with the presence of at least 3 of 4 well-established criteria of Vaillant et al., subepidermal blisters on skin biopsy, and deposits of IgG and/or C3 in a linear pattern along the epidermal BMZ by direct immunofluorescence. Exclusion criteria were receipt of a BP treatment for more than 7 days, relapse of previously diagnosed BP, age younger than 18 years, pregnancy, and expected survival after BP diagnosis shorter than 6 months. The study was approved by the Ethics Committee of the University Hospital of Reims; patients or their relatives received an information letter and gave oral consent.

Those patients with BP who were included were observed for 1 year. Six visits were planned, at baseline and then on days 60, 90, 150, 210, 270, and 360, to record disease activity and treatment modalities. Blood samples were collected at each visit for the measurement of anti-BP180 and anti-BP230 values by means of ELISA. Because of the high mortality rate and early occurrence of most relapses, the follow-up period was limited to 12 months.

**Baseline and Follow-up Measurements**

Clinical data recorded at baseline were sex, age, associated medical conditions (neurological disorders: dementia, stroke, Parkinson disease, multiple sclerosis; malignat neoplasm; other diseases), and concomitant treatments. The type of neurological disorders was prospectively assessed by physical examination and inquiring of the patient, general practitioner, or related neurologist (if applicable). When necessary, cognitive impairment was evaluated using the Mini-Mental State Examination (MMSE), and the patient was evaluated for possible dementia when the MMSE score was lower than 17 points. Baseline clinical examination included the number of new blisters daily for 12 consecutive days, localization of skin or mucous membrane blisters and erosions, and Karnofsky score. Extensive BP was defined as the occurrence of at least 10 new blisters daily. The first-line treatment used was recorded (superpotent topical corticosteroid [CS], ie, clobetasol propionate cream, 20-30 g per day; methotrexate; other systemic therapy).

Serum anti-BMZ autoantibodies were detected by means of standard indirect immunofluorescence or indirect immunofluorescence using salt-split human skin as substrate. Serum anti-BP230 and anti-BP180-NC16a autoantibody concentrations were detected using specific commercially available ELISAs following the manufacturer’s instructions. Data were expressed as units per millimeter of serum, and the recommended 9-μU/mL cutoff value was used in both anti-BP180 and anti-BP230 ELISAs.

At each visit, the presence of pruritus or erythematous, eczematous, or urticarial plaques and the number of new blisters daily were recorded on standardized forms. Treatments for BP were also recorded, as were the occurrence and date of relapse if it eventually occurred or the date of early study release and its cause (death, loss to follow-up, serious adverse reaction, other reason). Relapse was defined as the reappearance of at least 3 new blisters daily along with pruritus and/or erythematous, eczematous, or urticarial plaques.

**Statistical Analysis**

Quantitative variables were reported as mean and standard deviation, and qualitative data, as number and percentage. Comparisons among groups were performed using the χ² test, Fisher exact test, Student t test, or Wilcoxon rank test, as appropri-
ate. Univariate analysis of baseline factors associated with relapse was performed using the Kaplan-Meier method and the log rank test. Factors with \( P < 0.10 \) in these analyses were included in a Cox stepwise regression with entry and removal limits set at \( P = 0.10 \). Variations in anti-BP180 and/or anti-BP230 ELISA results during follow-up were compared according to the occurrence of cutaneous relapses with variance analysis for repeated measures, allowing us to take into account the dependency of measures in each patient. The sensitivity and specificity of BP autoantibodies for the occurrence of relapse were calculated, and a receiver operating characteristic (ROC) curve was calculated to determine a cutoff value with optimal sensitivity and specificity. Whatever the test used, \( P < 0.05 \) was considered significant. All statistical analyses were performed using SAS software, release 9.3 (SAS Inc).

### Results

**Characteristics of Patients at Baseline**

Between November 2009 and May 2012, 120 patients with BP were included. The baseline clinical characteristics are given in Table 1. One hundred eight patients had lesions on the lower limbs (90.0%), 101 on the upper limbs (84.2%), 89 on the trunk (74.2%), and 20 on the head and neck (16.7%) (always in generalized BP in these latter cases). Standard indirect immunofluorescence and indirect immunofluorescence on salt-split skin showed anti-BMZ antibodies in 72 (75.5%) samples from 60 of 82 patients (73.2%) and 37 of 49 patients (75.5%), respectively. Serological analysis of specific autoantibodies showed that 108 patients (90.0%) had positive anti-BP180 ELISA values (mean [SD], 92.1 [56.1] U/mL) and 72 (60.0%) positive anti-BP230 ELISA values (mean [SD], 44.3 [46.5] U/mL) at baseline.

**Clinical Outcome**

The first-line treatments included superpotent topical CSs alone (n = 100), oral methotrexate associated with an initial course of topical CS (n = 14), and other systemic therapies including leflunomide (n = 3) and oral CS (n = 1). Two patients did not receive any treatment because of very low clinical activity. The mean (SD) follow-up was 278 (132) days (median, 358 days; range, 1-392 days). Twenty-five patients (20.8%) died during the study, 7 (5.8%) were lost to follow-up, and 13 (10.8%) dropped out of the study because of either serious adverse events (n = 6) or a decision of the investigator or the patient's relatives (n = 7). All the living patients at month 2 (108 of 120) achieved disease control between day 0 and day 60. Thirty-five of the 120 patients (29.2%) experienced at least 1 relapse after initial disease control during the study period. The mean (SD) delay of relapse from baseline was 153 (97) days (median, 126 days; range, 26-378 days). The overall relapse-free survival (i.e., the proportion of patients with relapse-free disease) within the first year of treatment is shown in Figure 1A. Thirty-one of the 35 patients who experienced relapse were still receiving therapy at the time of relapse, including topical CSs (n = 24), oral methotrexate (n = 6), or doxycycline associated with topical CSs (n = 1). Four other patients experienced relapse after a scheduled treatment withdrawal. All patients with BP relapse were treated with superpotent topical CSs, leading to disease control in all cases.

**Serological Outcome**

Longitudinal variations in anti-BP180 and anti-BP230 ELISA levels are shown in Figure 2. The most important decrease was observed between day 0 and day 60, especially for anti-BP180 ELISA result. Mean anti-BP180 and anti-BP230 ELISA levels decreased from 92.1 and 44.3 U/mL at baseline to 55.9 and 32.1 U/mL, 39.8 and 28.8 U/mL, and 24.3 and 23.3 U/mL at months 2, 5, and 12, respectively. Variations in mean anti-BP180 and anti-BP230 ELISA levels according to the occurrence of a clinical relapse are shown in Figure 2B and Figure 2D, respectively. During the whole follow-up period, anti-BP230 ELISA levels were not significantly different between patients with relapse and ongoing remission, whereas anti-BP180 ELISA values tended to be higher in patients with relapse compared with patients with ongoing remission (\( P = 0.24 \) and \( P = 0.09 \), respectively; variance analysis for repeated measures). Mean early decreases in anti-BP180 and anti-BP230 ELISA levels between baseline and day 60 were lower in patients with relapse compared with

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (N = 120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female to male sex ratio</td>
<td>1.35</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>81.1 (10.7)</td>
</tr>
<tr>
<td>No. of daily new blisters, mean (SD)</td>
<td>18 (30)</td>
</tr>
<tr>
<td>Patients with extensive disease, No. (%)*</td>
<td>53 (44.2)</td>
</tr>
<tr>
<td>Mucosal involvement, No. (%)b</td>
<td>9 (7.5)</td>
</tr>
<tr>
<td>Associated neurological disorders, No. (%)</td>
<td>57 (47.5)</td>
</tr>
<tr>
<td>Dementia</td>
<td>36 (30.0)</td>
</tr>
<tr>
<td>Parkinson disease</td>
<td>17 (14.2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>16 (13.3)</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>7 (5.8)</td>
</tr>
<tr>
<td>Other</td>
<td>7 (5.8)</td>
</tr>
<tr>
<td>Karnofsky score, mean (SD)</td>
<td>59.6 (20)</td>
</tr>
<tr>
<td>Drug intake, No. (%)c</td>
<td>23 (19.2)</td>
</tr>
<tr>
<td>Psycholeptics</td>
<td>6 (5.0)</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>8 (6.7)</td>
</tr>
<tr>
<td>First-line therapy, No. (%)</td>
<td>100 (83.3)</td>
</tr>
<tr>
<td>Superpotent topical CS alone</td>
<td>14 (11.7)</td>
</tr>
<tr>
<td>Methotrexate + short course of topical CS</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Other*</td>
<td>2 (1.7)</td>
</tr>
</tbody>
</table>

Abbreviation: CS, corticosteroid.

* Patients with more than 10 new blisters daily.

b Restricted to oral mucosa in all cases.

c No patients received immunosuppressive therapy.

d Including only 1 patient with a concurrent, active malignant neoplasm (chronic lymphocytic leukemia).

e Leflunomide (3 patients) and oral CSs (1 patient).
Figure 1. Relapse-Free Survival Curves of Patients With Bullous Pemphigoid During the 1-Year Follow-up Period

Kaplan-Meier curves estimating the overall relapse-free survival of patients with BP (A) and the relapse-free survival according to associated dementia determined at baseline (black curve, patients with associated dementia; blue curve, patients without associated dementia) (B) and disease extent at disease entry before treatment (black curve, patients with extensive disease; blue curve, patients with nonextensive disease) (C).
patients with ongoing remission (−10.0% and −45.2%, respectively, for anti-BP180 levels \( P < .001 \) and −11.8% and −35.4%, respectively, for anti-BP230 levels \( P = .046 \)). For later clinical relapses, mean anti-BP180 ELISA levels at day 150 tended to be higher in patients who experienced relapse between day 150 and day 360 than in patients in ongoing remission (\( P = .07 \)). An ROC curve was calculated to determine a cutoff value for the prediction of clinical relapses after day 150. The cutoff value of 23 U/mL provided 84.2% sensitivity, 44.8% specificity, 33.3% positive predictive value, and 89.7% negative predictive value for the occurrence of clinical relapses between day 150 and day 360 (Figure 3). For all patients who experienced relapse, whatever the date of relapse, the longitudinal study did not highlight any significant variation in the mean (SD) anti-BP180 (61.3 [56.2] and 59.2 [59.3] U/mL; \( P = .69 \)) or anti-BP230 (25.8 [33.4] and 33.1 [47.1] U/mL; \( P = .23 \)) ELISA levels at the 2 visits preceding the relapse (Figure 4).

Factors Associated With Relapse During the 1-Year Follow-up

Univariate and multivariate analyses of potential relapse-predictive factors at baseline are shown in Table 2. In univariate analysis, clinical features associated with relapse were head and neck involvement (\( P = .046 \)) and extensive BP (\( P = .006 \)). The mean (SD) number of daily new blisters at baseline was higher in patients with relapse vs patients with ongoing remission (27.8 [40.5] and 14.1 [23.7], respectively; \( P = .001 \)). In contrast, mean anti-BP180 ELISA values at baseline were almost identical in the 2 groups (92.1 [57.6] and 92.2 [55.7] U/mL, respectively; \( P = .95 \)). Association with dementia and a lower frequency of anti-BP230 ELISA positivity at baseline had \( P < .10 \) in univariate analysis (\( P = .07 \) and \( P = .097 \), respectively) and were also included in the multivariate model. In multivariate analysis, factors independently associated with relapse were extensive disease at baseline (hazard ratio [HR], 2.37 [95% CI, 1.2-4.8]; \( P = .01 \) and an associated dementia (HR, 2.09 [95% CI, 1.0-4.2]; \( P = .04 \)). The relapse-free survival curves during
Discussion

The present study is the first, to our knowledge, to prospectively assess, in a large series of patients with BP, disease control, treatment modalities, and variations in levels of anti-BP180 and anti-BP230 autoantibodies systematically measured before starting therapy and at regular intervals during a 1-year follow-up. Our results clearly illustrate that levels of both anti-BP180 and anti-BP230 autoantibodies decreased after the initiation of therapy, with an initial steep decrease between days 0 and 60, especially for anti-BP180 autoantibodies. Of interest, this marked decrease in anti-BP180 level corresponded to the early therapeutic response, mainly with superpotent topical CSs alone (clobetasol 20-30 g daily during the first month) used by most (83%) of our studied patients. Treatment with initial high doses of topical CSs was continued for 2 weeks after disease control was achieved and then tapered until discontinuation, with a mean duration of treatment of 9 to 12 months. During follow-up, the decrease in the level of anti-BP180 autoantibodies remarkably paralleled topical CS dosage, which controlled not only the local inflammation but also the systemic immunologic responses similarly to systemic therapy. Of note, under superpotent topical CS treatment, only low quantities of CSs penetrate the systemic circulation. Such concentrations still display anti-inflammatory properties while avoiding immune-suppressant effects. Thus, and importantly, our study demonstrates for the first time the efficiency of superpotent topical CS treatment with regard to mainly anti-BP180 and, to a lesser extent, anti-BP230 autoantibody production, hence confirming its use as a reference first-line treatment for BP. Indeed, superpotent topical CSs are at least as effective as systemic CSs, and their use decreases 1-year mortality in BP. However, discrepancies among countries as...
regards BP mortality are a well-established fact; for instance, it ranges from 11% in the United States to 19% in the United Kingdom and up to 41% in France. Studies trying to work out the origin of these variations highlighted a higher rate of chronic inflammatory diseases associated with BP in France, such as pneumonia, pulmonary embolism, and neurological disorders, but not sex ratio.17 Besides these therapeutic considerations, variations in levels of anti-BP180 autoantibodies during follow-up were expected because levels of these autoantibodies tend to (1) fluctuate in parallel with disease activity along the time course, (2) decrease after successful therapy, and (3) increase during relapses. However, although we occasionally observed an increase in the level of anti-BP180 autoantibodies, mean anti-BP180 values remained stable before relapses, whatever the time of the relapse. Meanwhile, compared with patients with BP who did not experience relapse, a small decrease (no more than approximately 20%) in anti-BP180 levels between days 0 and 60 was associated with relapse. In addition, determination of anti-BP180 antibody level at day 150 is also of interest in clinical practice because of its negative predictive value; i.e., when anti-BP180 antibody titer is less than 23 U/mL, the probability of nonrelapse is elevated (90%). Thus, systematic determination of the levels of anti-BP180 antibodies at days 0, 60, and 150 is useful for monitoring patients with BP during the first year of treatment because antibody fluctuations measured at these particular end points may predict outcome. Besides, anti-BP230 levels decreased in parallel with disease response to treatment but more slowly than anti-BP180 levels. This is in keeping with the fact that the median anti-BP230 level was not significantly different between patients with and without relapse after the end of treatment.15 As for anti-BP180, anti-BP230 values did not significantly increase before relapse. In previous reports, autoantibody increase and relapse seemed to occur almost simultaneously. These differences might be related to the delay between autoantibody detection and time of relapse. Thus, with the knowledge that anti-BP230 ELISA results are positive in only 60% of patients with BP, this ELISA does not sound valuable for the diagnosis and monitoring of patients with BP.

In the present study, all patients with BP who had dementia displayed a high level of anti-BP180 antibodies. Association between BP and neurological disorders has been well established. Patients with BP who have significantly increased risk for dementia, stroke, Parkinson disease, and multiple sclerosis. In turn, dementia and Parkinson disease are 2 independent risk factors for BP. Of interest, neurological isoforms of both BP180 and BP230 have been demonstrated in the central nervous system. The 2 isoforms of BP230 share the same sequence in their NH2-terminal portion, which may be recognized by anti-BP230 antibodies from patients with BP. Then, an autoimmune response initially directed against a neuronal isoform of BP230 may secondarily trigger an autoimmune response against the epithelial isoform of BP230 according to the epitope-spreading phenomenon, explaining the fact that the presence of the neurological disorder precedes BP onset. However, expression of anti-BP230 antibodies at time of diagnosis was not associated with neurodegenerative disease in our study, unlike that of anti-BP180 antibodies, especially with dementia. Indeed, at baseline, all 36 patients with BP who had associated dementia had a positive anti-BP180 ELISA result (100% vs 84.1% in patients without dementia; P = .02), suggesting that patients with BP who have dementia might represent a specific cluster among all patients with BP. Thus, a possible epitope-spreading phenomenon involving anti-BP230 autoantibodies may potentially exist.

### Table 2. Univariate and Multivariate Comparisons of Patients With or Without Relapse

<table>
<thead>
<tr>
<th>Variable</th>
<th>Relapse (n = 35)</th>
<th>No Relapse (n = 85)</th>
<th>P Value</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extensive BP, No. (%)</td>
<td>20 (59)</td>
<td>33 (39)</td>
<td>.006</td>
<td>2.37 (1.2-4.8)</td>
<td>.01</td>
</tr>
<tr>
<td>Associated dementia, No. (%)</td>
<td>14 (40)</td>
<td>22 (26)</td>
<td>.07</td>
<td>2.09 (1.0-4.2)</td>
<td>.04</td>
</tr>
<tr>
<td>Positive anti-BP230 ELISA score, day 0, No. (%)</td>
<td>17 (49)</td>
<td>55 (65)</td>
<td>.097</td>
<td>0.62 (0.3-1.2)</td>
<td>.17</td>
</tr>
<tr>
<td>Head and neck involvement, No. (%)</td>
<td>9 (26)</td>
<td>11 (13)</td>
<td>.046</td>
<td>1.71 (0.8-3.8)</td>
<td>.18</td>
</tr>
</tbody>
</table>
| Age, mean (SD), y | 79.6 (11.5) | 81.7 (10.4) | .37 | ... | ...
| Sex, No. F/No. M (ratio) | 25/10 (2.5) | 44/41 (1.1) | .18 | ... | ...
| Associated neurological disorders, No. (%) | 21 (60) | 38 (45) | .09 | ... | ...

Abbreviations: BP, bullous pemphigoid; CS, corticosteroid; ELISA, enzyme-linked immunosorbent assay; HR, hazard ratio.

* Patients with more than 10 new blisters daily.
* Percentage reflects missing data for 1 patient.
* Percentage reflects missing data for 2 patients.
* 3N = 27 U/mL.
ist and could connect these 2 clinical diseases, BP and dementia, that both involve elderly patients.

Up to now, to our knowledge, no prospective study has shown clinical predictive factors for BP relapse. We demonstrated herein that dementia and initial extensive disease are 2 independent factors associated with BP relapse during the first year of treatment, whereas other clinical parameters at disease onset were not, including older age at diagnosis, which is associated with late relapse following cessation of CS treatment.22 During the 1-year follow-up period, 35% of the study patients experienced at least 1 relapse, which is consistent with previous clinical trials.23-24,46 Most relapses occurred within the first year of treatment, and the mean time to relapse was approximately 5 months. The relapse-free survival curve shows that relapses in patients with BP with associated dementia occurred mainly after day 150. Such a delay before relapse could be related to specific mechanisms bound to disease progression or to untimely therapy cessation related to nonadherence or other difficulties in management stemming from the patients’ dementia. In contrast, relapses for patients with initial extensive BP started to occur earlier (from day 30) and then continued to have onset throughout the entire 1-year follow-up period. Thus, our results may have clinical implications for the practical management and follow-up of patients with BP with associated dementia or with extensive disease at diagnosis because both patient groups may require effective and long-duration maintenance treatment. Previous studies suggested that low-dose methotrexate may be useful in BP management for long-term maintenance of a clinical remission obtained by an initial short-term course of superpotent topical Cs.47-49 In this setting, we are currently conducting a randomized clinical trial in France to compare low-dose methotrexate treatment for 1 year with reference treatment by superpotent topical Cs.

Among patients with BP, either extensive disease or dementia enhanced the susceptibility to disease relapse. Although our study has some limitations, diagnostic bias cannot be excluded but seems unlikely because all included patients fulfilled the clinical criteria used in previous studies.23 In the present study, the absence of major selection bias is supported by the fact that the mean age, mean (SD) number of new blisters daily (18 [30]), and 1-year mortality are comparable to those of other recent French studies.9,10,22-24 As well, the rates of positive results of anti-BP180 and anti-BP230 ELISA were 90% and 60%, respectively, also quite similar to those found in previous studies.5,10,16-18,50 In particular, the rate of associated neurological disorders among our patients (47.5%) was consistent with those previously observed (between 36%50 and 50.3%).50 Overall, the present study demonstrates that a pronounced decrease in anti-BP180 autoantibodies and, to a lesser extent, those directed against BP230 confirms the use of superpotent topical Cs alone as a reference first-line treatment for BP. Furthermore, our study suggests that neurological diseases play a major role in BP, not only as a predisposing but also as a prognostic factor.

ARTICLE INFORMATION

Accepted for Publication: May 19, 2013.
Published Online: November 13, 2013.

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Author Contributions: Drs Barbe and Bernard had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Fichet, Barbe, Joly, Bedane, Vabres, Truchetet, Aubin, Michel, Jegou, Grange, Bernard.

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Critical revision of the manuscript for important intellectual content: Barbe, Joly, Bedane, Vabres, Truchetet, Aubin, Michel, Jegou, Grange, Antonicelli, Bernard.

Statistical analysis: Barbe.

Obtained funding: Bernard.

Administrative, technical, or material support: Barbe, Bedane, Bernard.

Study supervision: Antonicelli, Bernard.

Conflict of Interest Disclosures: None reported.

Funding/Support: This study was supported by research grants from the French Department of Health’s Projet Hospitalier de Recherche Clinique (PHRC) Interrégional 2009.

Role of the Sponsor: The French Department of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Michael Maizieres, Clinical Research Unit, Reims University Hospital, provided technical assistance during the study, and Amélie Couraud and Céline Dionisius, Clinical Research Unit, Reims University Hospital, provided data management. None were specifically compensated for their contribution. Drs Bernard and Antonicelli contributed equally to this work.

Correction: This article was corrected on December 11, 2013, for an error in the Introduction.

REFERENCES


Bullous Pemphigoid Relapse During Treatment Year 1

Original Investigation Research

and dementia: a case-control study.


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