

Assessment of Bullous Pemphigoid Disease Area Index during Treatment: A Prospective Study of 30 Patients

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Key Words

Bullous pemphigoid · Activity score · Bullous Pemphigoid Disease Area Index

Abstract

Background: Recently, a consensus Bullous Pemphigoid Disease Area Index (BPDAI) was proposed to measure therapeutic outcomes in bullous pemphigoid (BP). **Objective:** To compare BPDAI with other clinical parameters of disease activity at baseline and to describe the variations of BPDAI during the initial phase of treatment. **Methods:** Thirty BP patients were included and followed for 1 year. BPDAI was assessed at baseline and on days 30, 90 and 360 by the same investigator. Concomitantly, the number of daily new blisters, the skin surface area of erythematous/eczematous/urticarial plaques and blisters/erosions, total lesion area (TLA), pruritus score and mucosal involvement were recorded. **Results:** At baseline, BPDAI was 46.7 ± 25 (mean $\pm$ SD); it was well correlated with erythematous/eczematous/urticarial skin surface ($r = 0.63$), TLA ($r = 0.83$), number of daily new blisters ($r = 0.7$; $p \leq 0.0002$) and anti-BP180 autoantibodies ($r = 0.49$; $p = 0.006$), but not with anti-BP230 autoantibodies. For the 8 patients with severe BP at baseline, the mean

BPDAI was 76.5, versus 35.9 for moderate BP ($p = 0.0007$). A value of 56 was proposed as a cut-off value for severe BP. BPDAI decreased to 11.9 ± 8.7 , 10.7 ± 12.7 and 2.5 ± 4.1 on days 30, 90 and 360, respectively. **Conclusion:** BPDAI rapidly decreased during the early treatment stage of BP with variations almost totally conditioned by the skin activity component.

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Introduction

Scientific knowledge in the field of clinical research of bullous pemphigoid (BP), the most common autoimmune bullous disease, has significantly increased during the past years [1–10]. But until recently, the assessment of clinical activity in autoimmune bullous diseases was somewhat empirical and no activity score was systematically used. In autoimmune bullous diseases, clinical activity varies with time according both to disease fluctuations and to treatment, raising the necessity to have a standardized scoring system. Such a tool would be useful to measure longitudinal variations in disease activity and to improve direct comparisons between treatment regimens in

randomized controlled trials. In this setting, efforts to evaluate the clinical extent and severity of autoimmune bullous diseases have recently led to the establishment of clinical measurement instruments. Two scoring systems for pemphigus were first introduced and validated: the Autoimmune Bullous Skin Disorder Intensity Score in 2007 [11] and the Pemphigus Disease Area Index, which was developed by an International Pemphigus Committee in 2008 [12–14]. In 2011, an international panel of experts proposed a disease extent score, the Bullous Pemphigoid Disease Area Index (BPD AI) to assist in the development of consistent reporting of outcome in future BP reports and studies [15]. Since then, only one study used the BPD AI in practice, aiming to correlate this score with the titres of circulating autoantibodies in a series of BP patients (anti-BP180, anti-BP230) [16]. This prompted us to perform a prospective study on a series of consecutive BP patients to compare BPD AI with other clinical parameters of disease activity at baseline, including the number of daily new blisters, the total lesion area (TLA) and pruritus, and to describe the variations of BPD AI, especially during the initial phase of treatment (first 3 months).

Methods

Study Patients and Design

A prospective, single-centre pilot study was conducted in the Dermatology Department of the Reims University Hospital (French Referral Center for Autoimmune Bullous Diseases) between January 2011 and January 2012. Consecutive patients with newly diagnosed BP were included in this prospective study using the same inclusion criteria as previously reported [2, 7, 9]. Patients were diagnosed as having BP using the following criteria: clinical features typical of BP with the presence of at least of three of four well-established criteria according to Vaillant et al. [17]; subepidermal blister on skin biopsy, and deposits of IgG and/or C3 in a linear pattern along the epidermal basement membrane zone by direct immunofluorescence. Non-inclusion criteria were administration of a specific BP treatment for more than 2 days, pregnancy and expected survival after BP diagnosis shorter than 3 months. Patients included were followed for 1 year after the diagnosis. Four visits were planned, at baseline and then on days 30, 90 and 360, to record disease activity, including BPD AI and treatment modalities.

Clinical Data Collection

Clinical data recorded at baseline were gender, age, associated medical conditions (neurological disorders: dementia, stroke, Parkinson's disease, multiple sclerosis; malignancy; other diseases) and concomitant treatments. Photographs were taken at baseline in all cases, as well as in patients who relapsed. The following clinical data were recorded at baseline and at follow-up visits: presence of pruritus (scored absent, moderate or severe), number of daily

Table 1. Baseline characteristics of patients

Patients	30
Gender	
Female	18 (60)
Male	12 (40)
Age (mean $\pm$ SD), years	82.5 $\pm$ 10.8
Patients with severe disease	8 (27)
Mucosal involvement	7 (23)
Associated neurological disorders	18 (60)
Dementia	10 (33)
Alzheimer's disease	4 (13)
Stroke	2 (7)
Parkinson's disease	2 (7)
Other	4 (13)
First-line therapy	
Superpotent topical CS alone	18 (60)
Methotrexate + short topical CS course	8 (27)
Other	3 (10)
None	1 (3)
BPD AI score (mean $\pm$ SD)	46.7 $\pm$ 25
Positive BP180 ELISA value	24 (80)
Positive BP230 ELISA value	18 (60)

Data are expressed as n (%) unless otherwise indicated. CS = Corticosteroids.

new blisters (determined over a 3-day period) and their localization on skin or external mucous membranes, and presence and skin surface area of erythematous/eczematous/urticarial plaques. The surface area of skin and/or mucous membrane lesions was recorded and calculated using the 'rule of nine', so as to calculate TLA as a percentage of body surface area (BSA) corresponding to the total of erythematous/eczematous/urticarial plaques and blisters/erosions. Extensive BP was defined as the occurrence of at least 10 daily new blisters [18, 19]. Clinical examination also included Karnofsky score [20], Mini-Mental State Examination [21], body mass index, blood pressure measurement and cardiopulmonary auscultation.

BPD AI was calculated according to the International Pemphigoid Committee recommendations [15]. At each visit, BPD AI and the BPD AI pruritus component were recorded separately. BPD AI has a total maximum score of 372 consisting of 252 points for cutaneous involvement (120 for erosions/blisters, 120 for urticaria/erythema and 12 for damage) and 120 points for mucosal involvement. The BPD AI pruritus component was based on a visual analogue scale, measuring the severity of itch during the past 24 h (0–10), the past week (0–10) and the past month (0–10) with a total score of 30. If the patient was unable to complete a reliable visual analogue scale rating, as a result of dementia, for instance, the degree of pruritus was based on the extent of excoriations alone (total score 30).

Treatment modalities for BP were recorded at each visit, besides the date of relapse (defined as the appearance of 3 or more daily new blisters along with pruritus and/or erythematous/eczematous/urticarial plaques), if a relapse occurred.

Table 2. BPDAl scores and parameters of clinical activity of BP from baseline to day 90

	Day 0	Day 30	Day 90
BPDAl global score (/372)	46.7±25	11.9±8.7	10.7±12.7
Activity, skin involvement (/240)	44.5±36.8	5±8.5	4.9±8.7
Blisters/erosions (/120)	26.7±15.5	4.9±6.8	3.1±6.8
Erythema, urticaria (/120)	17.8±13.9	0.1±0	1.8±0
Activity, mucosal involvement (/120)	0.5±1.1	0.3±0.8	0.04±0.2
Damage (/12)	2±3.3	7±3.1	5.8±3.2
Number of daily new blisters	24.6±34.8	0	0.8±2.4
Erythema/urticaria, % of BSA	12.4±11	0.04±0.2	0.1±0.6
TLA, % of BSA	20.3±13.8	0.9±1.2	1.3±3.7
BPDAl pruritus index (/30)	16.8±5.3	3.2±5.2	2.4±4.6
Data are expressed as mean ± SD.			

On day 360, the occurrence and number of relapses and the BPDAl score were recorded for each surviving patient. Details of drop-out such as date and cause (death, lost to follow-up, serious adverse reaction ...) were also recorded.

Comparison of BPDAl with Clinical or Immunological Parameters at Baseline

At baseline, BPDAl was compared with (1) disease severity based on elementary clinical features, including the number of daily new blisters, the surface area of erythematous/eczematous/urticarial plaques or erosions, and TLA (percentage of BSA) and (2) serum anti-BP180 and anti-BP230 autoantibodies detected using specific commercially available enzyme-linked immunosorbent assays (ELISAs) following the manufacturer's instructions [10, 22]. ELISA values were expressed as units per millimetre of serum (U/ml), and the 9 U/ml cut-off value recommended by the manufacturer was used in both BP180 and BP230 ELISAs. On the basis of previous literature [23, 24], severe BP at baseline was defined as: (1) TLA ≥30%, (2) number of daily new blisters ≥10, and (3) moderate to severe pruritus with a score of ≥15. BP patients who did not fulfil these criteria were classified as having moderate BP.

Statistical Analysis

Quantitative variables were described as mean ± standard deviation (SD) and qualitative data as number and percentage. Comparisons between groups at baseline were performed using Wilcoxon's rank test or Spearman's correlation coefficient, as appropriate: Wilcoxon's rank test to evaluate significant differences to BPDAl mean score between severe or moderate BP or BPDAl and associated dementia; Spearman's correlation coefficient was used to explore the relationship between continuous variables (BPDAl with clinical or immunological parameters). Sensitivity and specificity of BPDAl score for BP classified as severe (see above) were calculated. A receiver operating characteristic (ROC) curve representing sensitivity and (1 – specificity) calculated for each BPDAl score was established to determine the cut-off value of BPDAl with optimal sensitivity and specificity. Survival curve was established by the Kaplan-Meier method. A p value <0.05 was considered statistically significant. All analyses were performed using Microsoft Excel and SAS version 9.3 (SAS Inc., Cary, N.C., USA).

Results

Patient Characteristics at Baseline

A total of 30 patients with newly diagnosed BP were included and followed for 1 year. Clinical characteristics of patients included are shown in tables 1 and 2. Patients were 18 females and 12 males, with a mean age of 82.5 ± 10.8 years (median: 85.4; range: 44.9–97.3). BPDAl mean score among the 30 patients included was 46.7 ± 25 (range: 6–106). The distribution of BPDAl among the 30 BP patients at baseline is illustrated in figure 1. Eighteen patients (60%) had at least one associated neurological disorder, including dementia in 10 patients (33%). No significant association was found between BPDAl at baseline and associated dementia (45.1 ± 24.8 vs. 50.0 ± 26.4; p = 0.97).

Besides, 8 patients (27%) had severe BP at baseline as defined above. BPDAl was significantly higher in patients with severe BP as compared with patients with moderate BP (76.5 ± 19.7 vs. 35.9 ± 16.5; p = 0.0007). An ROC curve was performed to determine a cut-off value for a BP scored as severe. At baseline, a cut-off value of 56 for BPDAl provided a sensitivity of 88% (95% CI = 64.6–100), a specificity of 91% (95% CI = 78.9–100), a positive predictive value of 78% (95% CI = 50.6–100) and a negative predictive value of 95% (95% CI = 86.1–100) for severe BP (fig. 2).

Other parameters of clinical activity of BP are summarized in table 2. At baseline, BPDAl was well correlated with surface area of erythematous/eczematous/urticarial skin (r = 0.63; p = 0.0002), TLA (r = 0.83; p < 0.0001) and the number of daily new blisters (r = 0.7; p < 0.0001). Concomitantly, a positive anti-BP180 ELISA score was found in 24/30 patients (80%) with a mean titre of 79.2 ±

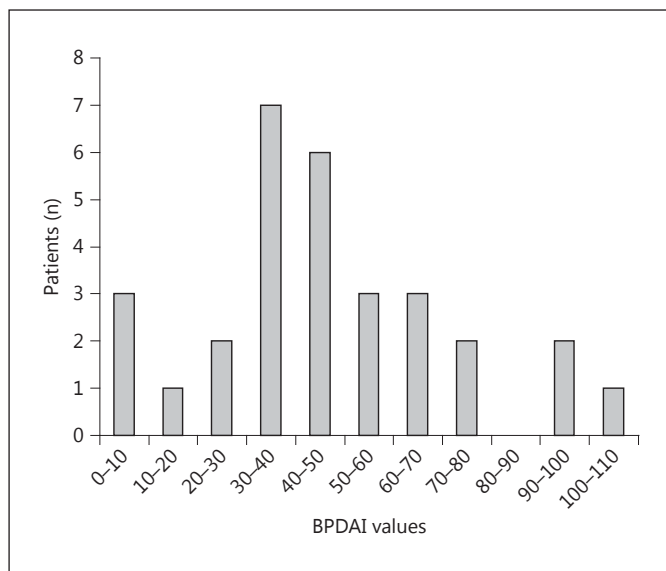


Fig. 1. Distribution of BPDAl of BP patients at baseline. Diagram bars represent the distribution of BPDAl values (total of activity and damage components) of study patients at baseline.

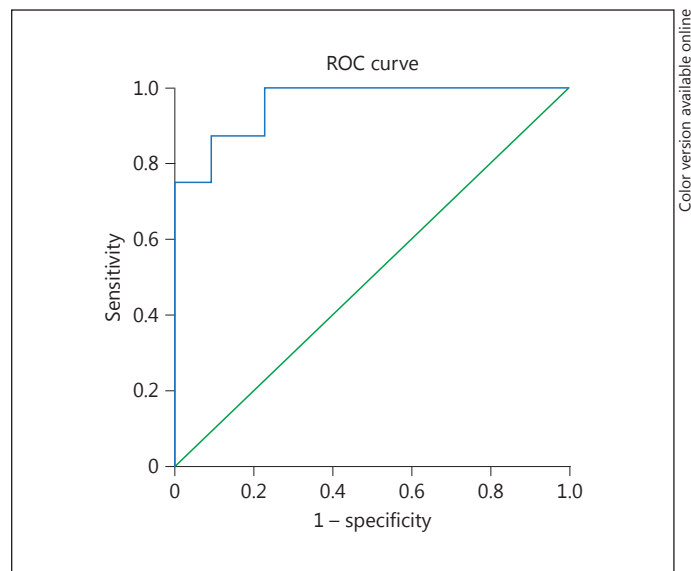


Fig. 2. ROC curve of BPDAl values of 30 BP patients. The optimal cut-off point of BPDAl to separate severe and non-severe disease was 56 with a sensitivity of 88% and a specificity of 91%.

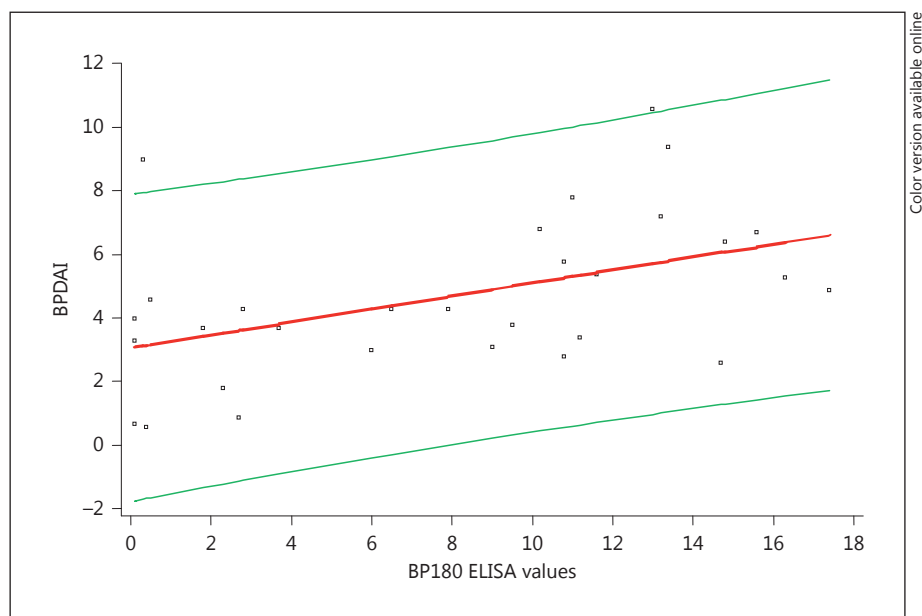


Fig. 3. Correlation curve between BPDAl score and anti-BP180 autoantibody rates at baseline. Association between BPDAl and anti-BP180 values by ELISA was calculated using non-parametric methods (Spearman's correlation coefficient). The correlation coefficient (ρ) was 0.49 ($p = 0.006$).

57.4 U/ml. BPDAl and ELISA BP180 values were well correlated at baseline ($r = 0.49$; $p = 0.006$) (fig. 3). A positive anti-BP230 ELISA score was found in 18/30 patients (60%) with a mean titre of 44.2 ± 55.1 U/ml. BP230 ELISA values were not correlated with BPDAl at baseline ($r = -0.07$, $p = 0.71$).

Clinical Outcome and Relapse

Variations of BPDAl and other elementary parameters of BP clinical activity according to time are shown in table 2. By day 30, 2 patients had died and 1 was lost to follow-up. All remaining patients were in remission on therapy. The mean decreases between baseline and day 30

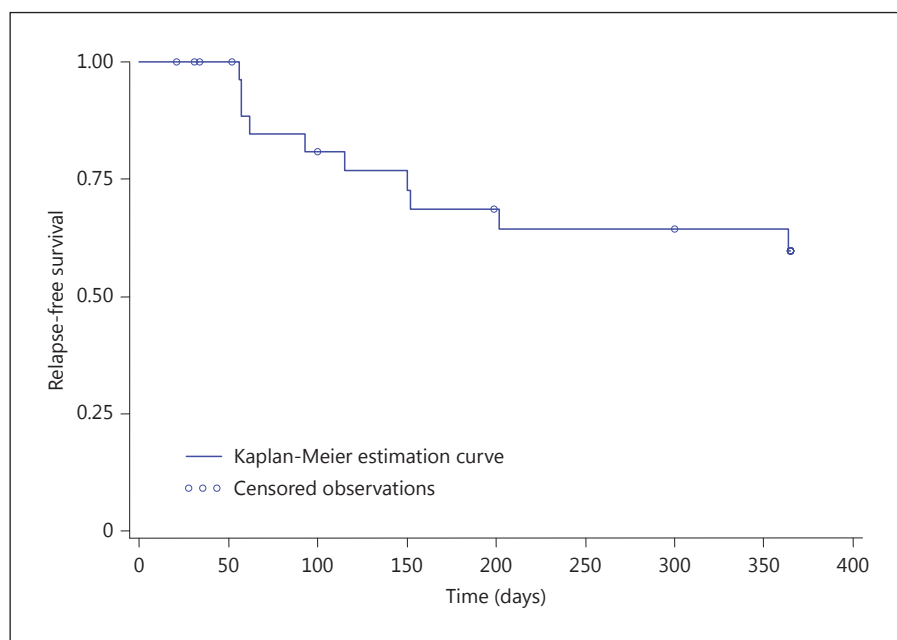


Fig. 4. Relapse-free survival curve of BP patients during the 1-year follow-up. Kaplan-Meier survival curve showing relapse-free survival of 30 BP study patients 1 year after initial diagnosis. On day 360, 60% of patients had not relapsed.

were -75 , -96 and -81% , for BPDAI, TLA, and pruritus index, respectively (table 2).

By day 90, 1 additional patient had died and another 2 were lost to follow-up. Five out of the 24 assessable patients had relapsed. Half of the 6 patients with initially severe BP had relapsed at least once, whereas 16/18 patients with moderate BP (89%) remained in remission without relapse on therapy. The mean decreases between baseline and day 90 were -77 , -94 and -86% for BPDAI, TLA, and pruritus index, respectively. Between days 90 and 360, another 2 patients died and another 2 were lost to follow-up. On day 360, BPDAI mean score was 2.5 ± 4.1 with a mean decrease from baseline of 95%.

Overall, 10 patients relapsed during the 1-year follow-up, among whom 9/10 were on therapy, and 3/10 had severe BP at baseline. Twelve out of 20 patients (60%) followed until day 360 did not relapse (fig. 4).

Discussion

The present study is the first to compare BPDAI, which was recently proposed by an international expert committee, with other elementary parameters of clinical activity more routinely investigated and to try to determine a cut-off value defining severe BP. To date, there is no consensus definition, but a few attempts at defining severe BP, all based on clinical characteristics at baseline

and none of them being validated by adequate prospective studies. BP severity was previously classified according to the extent and number of blisters, with extensive disease defined by a lesion BSA of $>20\%$ and widespread bullae corresponding to 23/35 (65%) study patients [25]. Then, BP was defined as severe according to a single criterion, i.e. lesion BSA $>40\%$, which corresponded to 9/38 (24%) study patients [26]. In a third study, BP disease severity was based on the percentage of BSA involvement and BP was severe when BSA involved was $>30\%$, corresponding to 69/123 (56%) study patients [24]. Finally, BP severity was also determined as the sum of the extent and activity of skin disease and the intensity of pruritus, on a scale ranging from 0 to 8; severe disease had a score ranging from 6 to 8 along with a BSA $>36\%$, the number of new blisters arising on 2 consecutive days >10 and severe pruritus at diagnosis, which corresponded to 20/49 (41%) study patients [23]. In addition, in previous prospective studies from our French group [18, 19], we defined severe BP by a number of daily new blisters >10 , although this observation fits more with a definition of extensive disease. In an attempt to synthesize these previous proposals, we here proposed to define severe BP at baseline by a TLA ≥ 30 , a number of daily new blisters ≥ 10 and moderate to severe pruritus, which corresponded to less than a third of study patients. The choice of a TLA $\geq 30\%$ of BSA was made because of the excessive proportion (65%) of se-

vere BP using a TLA cut-off at 20% [25], and, conversely, the low proportion (24%) of severe BP diagnosed with a TLA cut-off at 40% [26]. Although a consensus definition of severe BP still remains pending, our study provided, for the first time, a cut-off value with high sensitivity and specificity of BPDAl for disease severity of BP at baseline.

In the present study, we showed that BPDAl was correlated with serum anti-BP180 autoantibody titres at baseline. In a previous study, anti-BP180 and anti-BP230 autoantibodies were detected by ELISA at baseline, and then at months 3 and 6, and correlated both with BPDAl score and Autoimmune Bullous Skin Disorder Intensity Score [16]. At baseline, BPDAl mean scores were similar in both studies, and anti-BP180 and anti-BP230 ELISA values were consistent with previous reports [10, 22, 27–29]. Likewise, at baseline, we did not find a correlation between BPDAl and anti-BP230 ELISA values, which is consistent with the results obtained by Patsatsi et al. [16]. Collectively, these results were in accordance with previous studies, which showed that titres of anti-BP180 autoantibodies were correlated with disease activity assessed by the number of daily new blisters, pruritus intensity or disease duration [10, 27, 30, 31]. Conversely, anti-BP230 autoantibodies were correlated neither with outcome nor with severity of BP [10, 23, 27, 28, 30, 31]. Finally, we observed a smaller drop in BPDAl mean score at day 90 in our study compared to Patsatsi et al. [16] (77 vs. 97%). This is likely due to the use of superpotent topical steroids for the treatment of the majority of our patients, instead of systemic prednisolone in the series of Patsatsi et al. [16]. However, superpotent topical corticosteroids alone were clinically effective, as illustrated by the control of the disease of all BP patients at day 30, in accordance with previous studies [18, 19, 29].

Beyond serological parameters, our study is the first to compare BPDAl at baseline with more routinely used, elementary clinical signs of disease activity in a prospective series of BP patients. At baseline, BPDAl was well correlated with other clinical parameters of BP disease activity, including TLA, erythematous/eczematous/urticarial cutaneous surface area and number of daily new blisters. Actually, BPDAl appeared more sharp and accurate, either at baseline or during treatment, than the simple number of daily new blisters. Moreover, this score is more reproducible and reliable than the use of ‘the rule of nine’ to calculate BSA, even for experienced physicians [32–34]. Although the BPDAl score appeared accurate, its maximal value at baseline remained

very far from the theoretical maximum value. This is due to the disproportionate role of the mucosal score in BPDAl, as mucosal involvement is rare and, if present, usually not severe in BP. In addition, the damage score, i.e. post-inflammatory pigmented macules and milia, may persist unchanged several months after clinical remission of BP. Indeed, only 23% of our BP patients at baseline had a mucosal involvement, restricted to oral mucosa in nearly all cases, with a mean score of 0.5 (from a total of 120). Besides, damage was present in all BP patients in clinical remission, which explained why BPDAl was never 0 on day 30 although all patients were controlled. Finally, pruritus being a major symptom of BP, we wanted to determine the role of the pruritus component used apart from BPDAl. We therefore analysed the association between BPDAl added to the pruritus component and the other clinical parameters of BP disease activity. This new score was also well correlated with TLA ($r = 0.89$), erythematous/eczematous/urticarial cutaneous surface area ($r = 0.72$) and the number of daily new blisters ($r = 0.69$, $p < 0.0001$ for each association). In addition, mean early decreases between baseline and day 30 were –96, –74 and –81% in TLA, BPDAl and pruritus index values, respectively (table 2). Consequently, adding the BPDAl pruritus component to the BPDAl global score would be useless.

Of note our study has some limitations. The first limitation is the absence of different investigators to evaluate interindividual reproducibility. Then, a BPDAl threshold value at baseline, which both discriminated patients with severe BP from those with moderate BP and was predictive of relapse, could not be determined because of the limited study population. Other prospective studies including a large number of patients are therefore still necessary to determine and refine a cut-off value of BPDAl at baseline.

In conclusion, BPDAl is a clinical score in which all skin components are involved, whereas the mucosal component only plays a marginal role. It varies less than expected theoretically, since variations with time almost exclusively concerned the skin activity score. The pruritus component, used separately from BPDAl as currently proposed, has an important role. Noteworthy, BPDAl rapidly decreased during the early treatment stage of BP, which is in line with the complete clearing of all patients after 1 month of treatment with superpotent topical corticosteroids in our study. Further advances, including refinement of a cut-off value defining severe BP, rely on a systematic use of BPDAl assessment in future randomized therapeutic trials.

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