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International multicentre observational study to assess the efficacy and safety of a 0.5 mg kg⁻¹ per day starting dose of oral corticosteroids to treat bullous pemphigoid

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Summary

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Conflicts of interest

The authors declare they have no conflicts of interest.

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Background European guidelines propose a 0.5 mg kg⁻¹ per day dose of oral prednisone as initial treatment for bullous pemphigoid (BP). We assessed the safety and efficacy of this regimen depending on BP extent and general condition of the patients.

Methods In a prospective international study, we consecutively included all patients diagnosed with BP. Patients received a 0.5 mg kg⁻¹ per day dose of prednisone, which was then gradually tapered 15 days after disease control, with the aim of stopping prednisone or maintaining minimal treatment (0.1 mg kg⁻¹ per day) within 6 months after the start of treatment. The two coprimary endpoints were control of disease activity at day 21 and 1-year overall survival. Disease severity was assessed according to the Bullous Pemphigoid Disease Area Index (BPDAI) score.

Results In total, 198 patients were included between 2015 and 2017. The final analysis comprised 190 patients with a mean age of 80.9 (SD 9.1) years. Control of disease activity was achieved at day 21 in 119 patients [62.6%, 95% confidence interval (CI) 55.3–69.5]; 18 of 24 patients (75%, 95% CI 53.3–90.2), 75 of 110 patients (68.8%, 95% CI 59.2–77.3) and 26 of 56 patients (46.4%, 95% CI 33.0–60.3) had mild, moderate and severe BP, respectively ($P = 0.0218$). A total of 30 patients died during the study. The overall Kaplan–Meier 1-year survival was 82.6% (95% CI 76.3–87.4) corresponding to 90.9%, 83.0% and 80.0% rates in patients with mild, moderate and severe BP, respectively

($P = 0.5$). Thresholds of 49 points for BPDAI score and 70 points for Karnofsky score yielded maximal Youden index values with respect to disease control at day 21 and 1-year survival, respectively.

Conclusions A 0.5 mg kg^{-1} per day dose of prednisone is a valuable therapeutic option in patients with mild or moderate BP whose general condition allows them to be autonomous.

What is already known about this topic?

- Superpotent topical corticosteroids are the gold standard treatment for bullous pemphigoid (BP), whatever the severity.
- High doses of oral corticosteroids are effective but poorly tolerated in patients with BP.
- Medium doses of oral corticosteroids are effective in paucibullous BP, but their efficacy in severe forms has not yet been assessed.

What does this study add?

- Medium doses of oral corticosteroids have poor efficacy in severe BP.
- A baseline Bullous Pemphigoid Disease Area Index score < 50 and a Karnofsky score ≥ 70 are predictors of treatment efficacy and low mortality, respectively.

Bullous pemphigoid (BP) is the most common autoimmune blistering disease.^{1–7} It typically affects older patients in poor general condition, with a high prevalence of neurological and cardiovascular disorders.^{5–12} High doses of oral corticosteroids (CS) (prednisone/prednisolone, 1 mg kg^{-1} per day) are poorly tolerated in these older populations.^{10,11} Superpotent topical CS have been demonstrated to be safer and more effective than a 1 mg kg^{-1} per day dose of oral prednisone in patients with severe BP.^{13,14} However, topical CS therapy is not always practically feasible. Based on these limitations, European Academy of Dermatology and Venereology (EADV) and European Dermatology Forum guidelines have proposed oral prednisone at 0.5 mg kg^{-1} per day as an alternative to topical CS.¹⁵ Indeed, the efficacy and safety of medium doses of oral CS were assessed only in patients with moderate BP but not in those with severe BP in the study by Joly et al. at the time the guidelines were published.¹³ Since then, a 0.5 mg kg^{-1} per day dose of prednisone has been tested vs. a strategy that starts treatment with doxycycline and topical CS.¹⁶ Unfortunately, only 17% of the patients assessed for eligibility were included in that study, which significantly limits its external validity.

We sought to conduct a large international clinical trial to validate the safety and efficacy of a 0.5 mg kg^{-1} per day starting dose of prednisone in BP. By using the BP Disease Area Index (BPDAI) score to measure BP activity, and the Karnofsky score to measure the general condition of the patients, we further determined thresholds in these scoring systems that provided the highest positive predictive values for treatment success and safety, respectively.¹⁷

Patients and methods

Study patients

The inclusion criteria were patients with newly diagnosed BP based on (i) compatible clinical features, i.e. presence of at least three of the four clinical criteria proposed for the diagnosis of BP;¹⁸ (ii) histological features, including the presence of subepidermal blister or other features suggestive of BP, i.e. eosinophilic spongiosis, margination of eosinophils along the dermoepidermal junction;^{19,20} (iii) the presence of linear IgG and/or C3 deposits along the dermoepidermal junction by direct immunofluorescence; (iv) the investigators' decision to treat the patient according to a starting dose of 0.5 mg kg^{-1} per day of prednisone, followed by a tapering of prednisone doses as previously defined¹⁵ and (v) patient's informed consent to be treated and followed for 1 year according to the schedule proposed in the EADV guidelines.

The main exclusion criteria were (i) predominant or exclusive mucosal involvement suggesting a diagnosis of mucous membrane pemphigoid; (ii) pemphigoid gestationis; (iii) localized BP; (iv) associated severe and/or uncontrolled medical conditions that contraindicated the use of prednisone and (v) concomitant use of any other treatment that was potentially effective for BP (oral or topical CS, dapsone, immunosuppressants).

Patients who had been treated for fewer than 14 days prior to the diagnosis of BP with low doses of moderate-to-potent topical CS ($\leq 10 \text{ g per day}$) or with a dose of oral prednisone $\leq 0.3 \text{ mg kg}^{-1}$ per day could be included as these treatments

are frequently used by general practitioners in patients with a pruritic eruption before the diagnosis of BP and because of the demonstrated inefficacy of such low doses of CS.²¹

Study design

This was a prospective international study. The starting prednisone dose of 0.5 mg kg⁻¹ per day was maintained until disease control, which was defined as the first day on which either no new lesions or pruritus were observed, with pre-existing lesions beginning to heal.¹⁵ The initial dose of prednisone was then gradually tapered 15 days after achieving disease control in order to stop CS or maintain minimal CS treatment (0.1 mg kg⁻¹ per day) within 6 months after the start of treatment. Discontinuation of treatment was proposed in patients who had been free of symptoms for at least 3 months on minimal treatment (0.1 mg kg⁻¹ per day).

Patients who did not achieve disease control by day 21 had their prednisone dose increased to either 0.75 mg kg⁻¹ per day or 1 mg kg⁻¹ per day, or were treated with a combination of topical and oral CS, depending on the investigators' decision. If the regimen proposed in the EADV guidelines was considered ineffective or poorly tolerated, the investigators were free to adapt prednisone doses and/or add any other treatment they considered useful at any time; such patients were therefore considered to have a 'failure of the therapeutic strategy' in the statistical analysis.

This study was approved by the ethics committees of all participating centres.

Baseline and follow-up measurements

The Karnofsky score was used to assess patients' general condition and the BPDAI was used for scoring BP severity. We used the cut-off values that we recently identified in the BPDAI score, to differentiate between mild (≤ 19), moderate (≥ 20 and ≤ 56) and severe BP (≥ 57).²² Patients were followed according to the schedule proposed in the EADV guidelines. Side-effects of treatment were assessed, and their severity was graded according to the standard criteria of the World Health Organization.^{23,24} Patients were followed for 1 year after BP diagnosis.

Outcome measures

The two coprimary endpoints were control of disease activity at day 21, and overall survival during the first year after the start of BP treatment. Secondary endpoints were (i) complete remission (CR) off therapy or on minimal therapy (prednisolone/prednisone dose < 0.1 mg kg⁻¹ per day) at the end of the study, defined as the absence of new or established lesions or pruritus for at least 2 months; (ii) success in following the regimen proposed in the EADV guidelines; (iii) occurrence of severe and life-threatening adverse events and (iv) the number of patients who needed to switch from the initial treatment regimen to another regimen.

Statistical analysis

The primary and secondary endpoints were analysed in the whole patient sample and in the subgroups of patients with mild, moderate and severe BP. Proportions of patients achieving control of disease activity at day 21 were compared between the three severity subgroups (mild, moderate, severe) using Pearson's χ^2 -test. In addition, multiple logistic regression was used to compare control of disease activity between severity subgroups while adjusting for age and Karnofsky score. The distribution of the second coprimary endpoint (1-year overall survival) was estimated using the Kaplan–Meier method and comparisons between the three severity subgroups relied on the log-rank test, and were complemented by comparisons based on the Cox model and adjusted for age and Karnofsky score.

For the analysis of dichotomous secondary endpoints, (e.g. CR off therapy/on minimal therapy at the end of the study, success/failure in following the proposed treatment regimen), Pearson's χ^2 -test was used to compare observed proportions with endpoint between the three BP severity subgroups, and the relative risk of observing the endpoint was estimated with corresponding 95% confidence interval (CI). For quantitative variables, Student's *t*-test was used to compare means of two groups. ANOVA and the Kruskal–Wallis test were used to compare means and medians of the three groups, respectively.

A receiver operating characteristic (ROC) curve was estimated, to help determine optimal cut-off values for the prediction of best efficacy and safety using the BPDAI and Karnofsky scores. The area under the ROC curve (AUC) was estimated along with corresponding 95% CIs and the estimated AUC was compared with 0.5 to assess overall diagnostic value. Internal cross-validation of optimal threshold selection based on bootstrap resampling was performed using 500 bootstrap replicates.

Sample size calculation was based on the precision in estimating the overall proportion rate of control of disease activity at day 21. For an expected proportion of disease control of 75%, 200 patients had to be included to obtain a 95% CI of $\pm 6\%$ width around the observed rate of disease control. Statistical analyses were performed using Graph Pad Prism version 5.0 software (San Diego, CA, USA) and SAS version 9.4 software (SAS Institute, Cary, NC, USA).

Results

Patients

Between June 2015 and June 2017, 309 patients with BP were assessed for eligibility. In total, 188 patients were included and initially treated according to the European guidelines starting with a 0.5 mg kg⁻¹ per day dose of prednisone. Overall, 33 centres participated in the study, including five tertiary care centres, 23 secondary care centres and five primary care centres located in Bulgaria, Czech Republic, France, Germany, Greece, Italy, the Netherlands and Poland. Among the 309

patients with BP, 111 patients were not included mainly because of poor general condition and/or associated disorders (Figure 1). The mean Karnofsky score of patients who were not included because of their poor general condition was 41.4 (SD 17.1), corresponding to patients who had a permanent disability and required specialized care and assistance. The main associated disorders that constituted a contraindication to the use of oral CS according to the investigators' decision included severe diabetes mellitus, neurological and psychiatric disorders and cardiovascular disorders (Figure 1). Data from eight patients were not usable (two patients who rapidly withdrew consent, three patients with misdiagnosis and three patients with insufficient data). Thus, the statistical analysis was performed for 190 patients. The mean age and baseline Karnofsky score were 80.9 (SD 9.1) years and 71.0 (SD 19.8) years, respectively. The mean baseline BPDAl score of the whole population was 47.4 (SD 28.6). According to the observed distribution of baseline BPDAl score, 24 patients (12.6%) had mild BP, 110 patients (57.9%) had moderate BP and 56 patients (29.5%) had severe BP, and one patient was not assessed for severity. The 111 patients who were excluded from the study had a lower mean Karnofsky

score ($P < 0.001$) than the 190 patients who were included in the study (Table 1). Most of these patients (82 of 111, 73.9%) were treated with topical clobetasol propionate cream alone.

Efficacy outcomes

Early efficacy outcome: control of disease activity

Control of BP activity was achieved at day 21 in 119 of the 190 patients (62.6%, 95% CI 55.3–69.5), including 18 of 24 patients with mild BP (75.0%, 95% CI 53.3–90.2), 75 of 110 patients with moderate BP (68.8%, 95% CI 59.2–77.3) and 26 of 56 patients with severe BP (46.4%, 95% CI 33.0–60.3) ($P = 0.008$). After adjustment for age and Karnofsky score through logistic regression, BP severity remained associated with control of disease activity at day 21 ($P = 0.0218$). The absolute difference regarding control of disease activity at day 21 between mild and moderate BP (69.9%) vs. severe BP (46.4%) was 23.5 percentage points (95% CI 8.3–38.7, $P = 0.0030$) and the corresponding relative risk was 1.51 (95% CI 1.11–2.04, $P = 0.003$). The mean baseline BPDAl

Figure 1 Flowchart showing distribution of patientsBP, bullous pemphigoid; CS, corticosteroids. *Severe extent of skin lesions, which in the judgement of investigators made treatment with a 0.5 mg kg⁻¹ per day dose of prednisone inappropriate for the patient.

Table 1 Baseline characteristics of patients included and not included in the study

Characteristics	Included patients n = 190	Excluded patients n = 111	
Age, mean (SD)	80.9 (9.1)	80.3 (9.0)	P = 0.61
Sex			
Female	111 (58.4)		
Male	78 (41.1)		
NA	1 (0.5)		
Karnofsky score, mean (SD)	71.0 (19.8)	59.7 (22.0)	P < 0.001
Bullous pemphigoid severity			
Mild	24 (12.6)	14 (12.6)	
Moderate	110 (57.9)	27 (24.3)	
Severe	56 (29.5)	17 (15.3)	
BPDAI, mean (SD)	47.4 (28.6)	40.1 (27.0)	P = 0.05
BPDAI, Bullous Pemphigoid Disease Area Index. NA, Not available. Data are presented as mean (SD) or n (%).			

score of patients with control of disease activity at day 21 was lower than that of patients without control of disease activity [41.1 (SD 23.4) vs. 58.2 (SD 33.5) points; $P = 0.0003$]. Control of disease activity at any time during the study was achieved in 144 of the 190 patients with available data (75.8%, 95% CI 69.1–81.7), including 21 of 24 patients with mild BP (88%, 95% CI 67.6–97.3), 88 of 110 patients with moderate BP (80.0%, 95% CI 72.1–87.7) and 35 of 56 patients with severe BP (63%, 95% CI 48.6–75.1) ($P = 0.0160$).

Late efficacy outcomes: complete remission on minimal therapy and off therapy

Overall, 11 of the 190 patients (5.8%) did not complete the 12-month follow-up. The reasons for dropping out were withdrawal of consent in five cases, and loss to follow-up in six cases, which included four patients who withdrew after having been switched to topical CS for treatment failure, and two patients who were lost to follow-up at month 6, while in CR.

Of the 144 patients for whom control of disease activity was achieved, 43 patients relapsed (29.9%) either before dropping out or up to month 12, including six of 21 patients (29%) with mild BP, 29 of 88 patients (33%) with moderate BP, and eight of 35 patients (23%) with severe BP. The median time to relapse was 68 days [interquartile range (IQR) 14–173] in patients with mild BP, 69 days (IQR 46–173) in patients with moderate BP and 68 days (IQR 53–162) in patients with severe BP.

At the 12-month evaluation, 68 (38.0%) of the 179 patients who completed the study were in CR, including 48 patients on minimal therapy (26.8%) and 20 patients off therapy (11.2%). The proportions of patients with mild, moderate

and severe BP in CR (including both CR off therapy and CR on minimal therapy) were 11 of 20 (55%, 95% CI 31.5–76.9), 42 of 105 (40%, 95% CI 30.9–50.5) and 15 of 54 (28%, 95% CI 16.5–41.6; $P = 0.0786$), respectively. The median time to onset of CR (BPDAI score of 0) was 270 days in each group, whatever the baseline severity.

Safety outcomes

1-year survival

A total of 30 patients died during the study. The Kaplan–Meier 1-year overall survival probability was 82.6% (95% CI 76.3–87.4) and 90.9% (95% CI 68.3–97.6) in patients with mild BP, 83.0% (95% CI 74.4–89.0) in patients with moderate BP and 80.0% (95% CI 66.7–88.4) in patients with severe BP ($P = 0.50$) (Figure 2). After adjustment for age and Karnofsky score, BP severity remained unrelated to overall survival ($P = 0.8654$). The cause of death was recorded in 22 patients. A total of 11 deaths could be related to CS treatment [pulmonary infection ($n = 4$), stroke ($n = 3$), myocardial infarction ($n = 2$), septic shock ($n = 2$)]. Other main causes of death were cancer ($n = 4$), occlusive syndrome ($n = 1$) and 'natural death' according to investigator's opinion ($n = 6$).

Adverse events

A total of 253 adverse events were reported in 98 patients. Overall, 80 severe adverse events (SAEs) (grade III–IV) occurred in 52 patients. Main SAEs were well-known CS-related side-effects, including endocrine side-effects ($n = 24$), infections ($n = 15$) cardiovascular disorders ($n = 13$) and psychiatric disorders ($n = 7$).

Predictors of treatment failure and mortality

Two ROC curves were estimated to help determine cut-off values for the baseline BPDAI score for the achievement of control of disease activity and for the baseline Karnofsky score for being alive at 1 year after the start of treatment. A baseline BPDAI score of 49 or less provided 71.8% sensitivity, 55.9% specificity, and 73.7% and 53.5% of positive and negative predictive values for control of disease activity at day 21, respectively (AUC 0.66, 95% CI 0.57–0.74; $P = 0.0002$). Cross-validation based on bootstrap resampling identified a 49-point threshold of BPDAI as optimal in 21.2% of bootstrap replicates. The median threshold was 49 (IQR 45–51, range 29–83). A baseline Karnofsky score of 80 or more provided 55.0% sensitivity, 79.2% specificity, and 93.5% and 24.4% of positive and negative predictive values for being alive at 1 year after the start of treatment, respectively (AUC 0.71, 95% CI 0.59–0.82; $P = 0.0004$). Cross-validation based on bootstrap resampling identified a 70-point threshold as optimal in 56.6% of bootstrap replicates. The median threshold was 70 (IQR 60–70, range 40–80). Baseline enzyme-linked immunosorbent assay BP180 values were not predictive of

Figure 2 Kaplan–Meier estimates of overall survival according to baseline severity of bullous pemphigoid

control of disease activity at day 21 (AUC 0.52; 95% CI 0.43–0.62; $P = 0.63$).

Treatment modifications during patient follow-up

We then studied how investigators managed the treatment regimen proposed in the EADV guidelines. Overall, the oral CS regimen was modified or stopped in 84 patients (46.9%), including in nine of 20 (45%) patients with mild BP, 45 of 105 (42.9%) patients with moderate BP and 30 of 54 (56%) patients with severe BP. The main reasons for stopping or modifying the oral CS regimen were treatment failure in 65 patients and safety concerns in six patients. Alternative treatments used by investigators were topical CS in 73 patients (88%), conventional immunosuppressants in eight patients, dapsone in one patient, and doxycycline in one patient.

Discussion

The main finding of this study is that a 0.5 mg kg^{-1} per day starting dose of prednisone allowed control of disease activity to be achieved at day 21 in 75.0% of patients with mild BP and 68.8% of patients with moderate BP, but only in 46.4% of patients with severe BP. Disease control at any time during the 1-year follow-up was achieved in a high proportion (> 80%) of patients with mild and moderate BP, but only in 63% of patients with severe BP. In two large randomized controlled trials (RCTs) conducted in France and in the UK,^{13,16} disease control was reported in 98% and 75% of patients with moderate and severe BP treated with a 0.5 mg kg^{-1} per day

starting dose of prednisolone, respectively. This discrepancy was likely related to different inclusion criteria and the fact that achievement of control of disease activity was assessed earlier (week 3) in both the present and our previous study, relative to week 6 in the UK BLISTER trial. In addition, the definition of disease control used in the present study was that of the international consensus statement¹⁷ ‘new lesions cease to form and established lesions begin to heal’, whereas it was ‘3 or less new blisters’ in the BLISTER trial. In the present study, 63% of patients with severe disease achieved disease control, whereas 95–100% of patients with severe disease achieved disease control using 40 g clobetasol cream per day, which is a marked difference in favour of high-dose topical steroids.^{13,25}

The 29.9% rate of relapse that occurred after a mean delay of 123 (SD 113) days in the present study was relatively close to the 39% rate of relapse that occurred after a mean delay of 149 (SD 109) days, previously reported in an RCT in patients with moderate BP treated with a 0.5 mg kg^{-1} per day dose of prednisone.¹³

Overall, 38.0% of patients were in CR at 1 year after starting treatment. However, only a few patients with severe BP (15 of 54, 28%) were in CR at the end of the study, and even fewer (eight of 54, 15%) were in CR off therapy. Accordingly, 55.6% of patients with severe BP had their treatment switched to another regimen, most often topical CS, during follow-up.

We showed that a BPDAI threshold score ≤ 49 points provided a 73.7% positive predictive value for disease control. Interestingly, this threshold calculated from an ROC curve in

the present study was very close to the 57-point threshold corresponding to the 75th percentile on the BPDAl scale that differentiates between moderate and severe BP.²² This difference in efficacy between mild, moderate and severe BP reinforces the usefulness of the BPDAl score in adequately managing the initial treatment of patients with BP.²⁶

The 17.9% 1-year mortality rate observed in the present study was exactly the same as that reported in the BLISTER trial (17%).¹⁶ This rather low death rate in these two studies was likely related to the exclusion of the most fragile patients either by inclusion and exclusion criteria in the BLISTER trial or by investigators' decision in the present study. This is also suggested by the very close mean Karnofsky scores of patients included in the BLISTER trial and the present study (69.7% and 71.0%, respectively); whereas the mean Karnofsky score of patients who were not included in our study was only 59.7%, indicating a much poorer general condition. Accordingly, a higher 30% 1-year mortality rate was reported with the same 0.5 mg kg⁻¹ per day starting dose of prednisone in the French RCT, which included a less selected population of patients with BP whose Karnofsky score was around 60%.¹³ Finally, most SAEs and causes of death were related to well-known CS-related side-effects. Based on the ROC curve analysis, patients with a Karnofsky score higher than 70% (roughly corresponding to patients who were autonomous and able to care for themselves) had a 94% positive chance of still being alive 12 months after the start of treatment. It must be underlined that only 35% of the patients included in the present study had both a baseline BPDAl score lower than 50 and a Karnofsky score higher than 70%, once 30% of the patients with the poorest general condition had been excluded from the study according to the exclusion criteria.

This study has some limitations. Firstly, one might consider that our results may have been biased by the fact that investigators did not include patients in the poorest general condition or those whose BP extent was too severe. Indeed, in addition to the fact that this corresponds to the usual therapeutic decision of clinicians in real-world settings, this indicates that the external validity of our safety and efficacy findings is limited to a population of patients who are in rather good general condition, which likely slightly overestimates the real efficacy and safety of medium doses of prednisone in BP. This is why we determined the population of patients with BP who could most benefit from this treatment using thresholds in the BPDAl and Karnofsky scores. Selection bias is unlikely, as most patients were recruited locally in secondary care centres, with very few tertiary care centres participating in the study. Secondly, 11 patients (6%) were lost to follow-up. However, their mean age, mean Karnofsky score and mean BPDAl score were not different to those of patients who completed the study (data not shown) and it is unlikely that they could have significantly affected the final results and conclusions of this study. Finally, the optimal thresholds that were selected from the ROC curve analysis should be considered with caution. In particular, the 49-point threshold for disease control at day 21 should not be taken at face value in

view of cross-validation analysis showing substantial variability in optimal threshold selection. Rather, any threshold in the range of 45 to 51 could be considered as optimal at this stage. Confirmation using external samples is needed.

Overall, this study demonstrates that the 0.5 mg kg⁻¹ per day starting dose of prednisone proposed in the EADV guidelines seems to be a valuable therapeutic option in patients with mild or moderate BP, in particular in those whose general condition allows them to be autonomous (Karnofsky score $\geq$ 80). Unfortunately, such patients constitute a minority of patients with BP.

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References

- Bernard P, Vaillant L, Labeille B et al. Incidence and distribution of subepidermal autoimmune bullous skin diseases in three French regions. Bullous Diseases French Study Group. *Arch Dermatol* 1995; **131**:48–52.
- Zillikens D, Wever S, Roth A et al. Incidence of autoimmune subepidermal blistering dermatoses in a region of central Germany. *Arch Dermatol* 1995; **131**:957–8.
- Gudi VS, White MI, Cruickshank N et al. Annual incidence and mortality of bullous pemphigoid in the Grampian Region of North-east Scotland. *Br J Dermatol* 2005; **153**:424–7.
- Joly P, Baricault S, Sparsa A et al. Incidence and mortality of bullous pemphigoid in France. *J Invest Dermatol* 2012; **132**:1998–2004.
- Langan SM, Smeeth L, Hubbard R et al. Bullous pemphigoid and pemphigus vulgaris—incidence and mortality in the UK: population based cohort study. *BMJ* 2008; **337**:a180.
- Jung M, Kippes W, Messer G et al. Increased risk of bullous pemphigoid in male and very old patients: a population-based study on incidence. *J Am Acad Dermatol* 1999; **41**:266–8.
- della Torre R, Combescurre C, Cortés B et al. Clinical presentation and diagnostic delay in bullous pemphigoid: a prospective nationwide cohort. *Br J Dermatol* 2012; **167**:1111–7.
- Beissert S, Werfel T, Frieling U et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. *Arch Dermatol* 2007; **143**:1536–42.
- Cordell N, Chosidow O, Hellot M-F et al. Neurological disorders in patients with bullous pemphigoid. *Dermatology* 2007; **215**:187–91.
- Roujeau JC, Lok C, Bastuji-Garin S et al. High risk of death in elderly patients with extensive bullous pemphigoid. *Arch Dermatol* 1998; **134**:465–9.
- Rzany B, Partsch K, Jung M et al. Risk factors for lethal outcome in patients with bullous pemphigoid: low serum albumin level, high dosage of glucocorticosteroids, and old age. *Arch Dermatol* 2002; **138**:903–8.
- Bastuji-Garin S, Sbidian E. How to validate outcome instruments for pemphigus. *J Invest Dermatol* 2009; **129**:2328–30.
- Joly P, Roujeau J-C, Benichou J et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. *N Engl J Med* 2002; **346**:321–7.
- Terra JB, Potte WJB, Jonkman MF. Whole body application of a potent topical corticosteroid for bullous pemphigoid. *J Eur Acad Dermatol Venereol* 2014; **28**:712–8.

- 15 Feliciani C, Joly P, Jonkman MF et al. Management of bullous pemphigoid: the European Dermatology Forum consensus in collaboration with the European Academy of Dermatology and Venereology. *Br J Dermatol* 2015; **172**:867–77.
- 16 Williams HC, Wojnarowska F, Kirtschig G et al. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. *The Lancet* 2017; **389**:1630–8.
- 17 Murrell DF, Daniel BS, Joly P et al. Definitions and outcome measures for bullous pemphigoid: recommendations by an international panel of experts. *J Am Acad Dermatol* 2012; **66**:479–85.
- 18 Vaillant L, Bernard P, Joly P et al. Evaluation of clinical criteria for diagnosis of bullous pemphigoid. French Bullous Study Group. *Arch Dermatol* 1998; **134**:1075–80.
- 19 Joly P, Courville P, Lok C et al. Clinical criteria for the diagnosis of bullous pemphigoid: a reevaluation according to immunoblot analysis of patient sera. *Dermatology* 2004; **208**:16–20.
- 20 Courville P, Kupfer I, Gilbert D et al. [Evaluation of histological criteria for bullous pemphigoid. Correlation with antigens recognized by immunoblotting of anti-epidermal autoantibodies]. *Ann Pathol* 2000; **20**:564–9 (in French).
- 21 Roujeau JC, Guillaume JC, Morel P et al. Plasma exchange in bullous pemphigoid. *Lancet* 1984; **2**:486–8.
- 22 Masmoudi W, Vaillant M, Vassileva S et al. International validation of the Bullous Pemphigoid Disease Area Index severity score and calculation of cut-off values for defining mild, moderate and severe types of bullous pemphigoid. *Br J Dermatol* 2021; **184**:1106–12.
- 23 Tedbirt B, Gillibert A, Andrieu E et al. Mixed individual-aggregate data on all-cause mortality in bullous pemphigoid: a meta-analysis. *JAMA Dermatol* 2021; **157**:421–30.
- 24 National Institutes of Health. Common Terminology Criteria for Adverse Events (CTCAE). Available at: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf (last accessed 14 July 2021).
- 25 Joly P, Roujeau J-C, Benichou J et al. A comparison of two regimens of topical corticosteroids in the treatment of patients with bullous pemphigoid: a multicenter randomized study. *J Invest Dermatol* 2009; **129**:1681–7.
- 26 Joly P, Benichou J, Lok C et al. Prediction of survival for patients with bullous pemphigoid: a prospective study. *Arch Dermatol* 2005; **141**:691–8.