Acta Derm Venereol 2015; 95: 307–311

CLINICAL REPORT

A Retrospective Consecutive Case-series Study on the Effect of Systemic Treatment, Length of Admission Time, and Co-morbidities in 98 Bullous Pemphigoid Patients Admitted to a Tertiary Centre

Line KIBSGAARD[1], Bjørn BAY[2], Mette DELEURAN[1] and Christian VESTERGAARD[1]
[1]Department of Dermato-Venereology, Aarhus University Hospital, and [2]School of Public Health, Section for Epidemiology & Institute of Clinical Medicine, Department of Obstetrics and Gynaecology, Aarhus, Denmark

Bullous pemphigoid (BP) is a common blistering disease caused by antibodies directed against hemi-desmosomal proteins BPAG1 and BPAG2. The disease is characterised by intense pruritus and blistering of the skin. The systemic treatment with the highest level of evidence for BP is systemic glucocorticoids. However, since the disease often occurs in the elderly patients, and since the most common co-morbidities are diabetes and neurological diseases, glucocorticoid-sparing drugs are often introduced. We retrospectively identified all BP patients admitted to our tertiary clinic over a 7-year period in order to register demography, treatment and co-morbidities. The most common steroid-sparing drugs were azathioprine (87%) and methotrexate (11%). Less than 2% were treated with dapsone, rituximab and cyclosporin A. As expected, we found a relatively high rate of neurological disorders, diabetes, and malignancies, but surprisingly we also found an increased rate of cardiovascular diseases compared to the Danish population in general. *Key words: bullous pemphigoid; systemic treatment; co-morbidities; demography*.

Accepted Jun 30, 2014; Epub ahead of print Jun 30, 2014

Acta Derm Venereol 2015; 95: 307–311.

Christian Vestergaard, Department of Dermatology, Aarhus University Hospital, P.P. Oerumsgade 11, DK-8000 Aarhus, Denmark. E-mail: chr-vest@post9.tele.dk

Bullous pemphigoid (BP) is the most common autoimmune blistering disease caused by autoantibodies in the skin. The disease typically appears in the elderly (1–3) and is characterised by an intensely pruritic rash dominated by tense blisters arising in normal looking or erythematous skin (4). The incidence of BP has been reported to increase over the last decades and was in 2008 estimated to be 4.3/100,000 person years (5, 6) with a mortality twice that of the general population (6). In addition, a significant association with neurological diseases including previous stroke, Parkinson's disease, and dementia has been demonstrated (1, 3, 7).

The treatment of BP is immunosuppression. The treatment may be systemic or topical depending on the severity of the disease. Looking at specific outcomes (3 weeks control and survival), the best evidence for therapy is topical glucocorticoid (2). However, some patients do not respond sufficiently to topical treatment. As a result, severe cases of BP are commonly treated with systemic agents. The first choice of systemic treatment is oral corticosteroid with recommended doses in the range of 0.5–0.75 mg/kg/day (8). Although higher doses may be more effective, the risk of inexpedient side effects and 1-year mortality has been proven to rise (2, 9, 10). This, added to the risk of interference with existing comorbidities, makes treatment with systemic glucocorticoid a challenge to the clinician. Thus, steroid sparing immunomodulating therapy (IMT) such as methotrexate (MTX), azathioprine, cyclosporin A, and mycophenolate mofetil may be required. The steroid sparing effect among different IMT's have only been addressed in a few randomised controlled trials (RCTs). A comparison of azathioprine and mycophenolate mofetil, as supplemental therapy to oral methylprednisolone, found similar efficacy and cumulative corticosteroid doses between the 2 groups (11). In 1984, plasma exchange was suggested as a substantial saving factor of corticosteroid (12). On the contrary, Guillaume and colleagues (9) found no difference in complete remission and mortality in 98 BP patients randomised to receive either oral prednisolone as monotherapy, in combination with azathioprine, or in combination with plasma exchange. Conclusively they rejected both plasma exchange and azathioprine as routine adjuvants to corticosteroids in the management of BP. In the absence of a steroid monotherapy arm in the first RCT and differing results in the following 2, no consistent conclusions about which IMT to prefer have been made. In a recent review of the literature on the treatment of BP it is concluded that systemic as well as topical glucocorticoids remain the treatments with the highest level of evidence and recommendation (10).

The aim of this study was to retrospectively describe the demography, co-morbidities, treatment, and treatment outcomes in a cohort of all patients with BP admitted to a tertiary centre from 2006–2013, in which the use of steroid-sparing drugs is common practice. Further, we hypothesised that length of admission, rate of remission and relapse, and total treatment duration are related to the initial doses of systemic glucocorticoid.

 doi: 10.2340/00015555-1925
 ISSN 0001-5555

METHODS

Design and patients

In this retrospective consecutive case-series study, medical records of all patients admitted with the diagnoses of BP, at the Department of Dermatology and Venereology at Aarhus University Hospital during a 7-year period, were investigated. Patients were identified using the ICD10 system. Diagnoses of relevance were BP (DL12.0), other pemphigoid (DL12.8), and pemphigoid unspecified (DL12.9). The project was approved by the Danish Data Protection Agency.

Patient characteristics at admission, systemic treatment during admission, and predefined treatment outcomes were recorded in a Filemaker Pro 10 constructed database. Patients were included if characteristic clinical presentations of BP such as pruritus, bullae, or positive indirect Nikolsky's sign were described, and/or if skin biopsies revealed subepidermal bullae and/or clusters of eosinophils, and/or if direct immunofluorescence (IF) showed linear deposits of IgG or complement C3 along the basement membrane zone. In the cases, where the IF turned out negative patients were excluded. Patients with primarily mucosal involvement were re-diagnosed as having mucus membrane pemphigoid (MMP) and excluded. From discriptions in the medical records, primary skin lesions were retrospectively classified as mild disease (localised lesions with minimal skin-affection less than 20%), moderate disease (extensive distribution of skin lesions, more than 20% without signs of infection), or severe disease (protracted disease, treatment resistant prior to hospitalisation (if information available), or extensive distribution of skin lesions with more than 20% skin affection and secondary infection). Skin lesions were defined as bullae or urticarial lesions. One trained assessor performed the classification. Treatment of the patients was based on the guidelines in the department of dermatology in Aarhus. Primary treatments are topical steroids for the entire body (betamethasone-17-valerate or clobetasol propionate for body and extremities and hydrocortisone-17 butyrate for face and skin folds) in combination with systemic glucocorticoids (prednisolone). Prednisolone was usually administered as 37.5 mg/day and updosed until effect (no appearance of new blisters). The department has no guidelines for the drug of choice as steroid sparing drug, which was at the discretion of the treating doctor. Treatment may have been started before confirmation of diagnosis due to the severity of the disease in the patients. After consolidation of the IMTs (2–3 weeks) systemic steroid was tapered with 5 mg/14 days and topical was tapered to every other day for 14 days and then twice weekly for 3–4 weeks.

Outcomes

On the first day of admission, patients were typically initiated on systemic glucocorticoid alternatively pre-hospitalisation dosages were increased. For each patient dosage of systemic glucocorticoid at admission was recorded. During admission, adjuvant immune modulating therapy (IMT) was initiated, typically when BP diagnoses was confirmed by histopathology and/or positive IF. Patients were discharged when appearance of new bullae had been absent for at least 2 days, and primary skin lesions were starting to re-epithelialise. Thus, mean length of primary admission in days was thought to represent the disease course. Approximately 6 weeks after discharge, a planned outpatient consultation was arranged. At this clinical control, patients were registered as in remission if the appearance of new blisters had been absent for at least one week, and if all skin lesions were objectively healed.

As treatment outcomes, total treatment duration expressed the total time in weeks each patient received systemic therapy prescribed from our department. Further, we estimated the median duration of both systemic glucocorticoid and IMTs. If new blisters occurred, or if itchy red plaques appeared at any time during the study period, patients were registered as relapsed. To test our hypothesis, that treatment outcomes are related to initial doses of systemic glucocorticoid, all outcomes were secondarily stratified in low or high initial doses of systemic glucocorticoid at admission.

Subanalyses were performed, to examine if disease severity was associated with initial doses of systemic glucocorticoid. Further, we investigated whether there was an association between disease severity and admission time or between disease severity and total treatment duration.

Statistical analysis

In the descriptive analyses all continuous variables are reported with means and standard deviations (SD) and all categorical variables with percentages. In order to evaluate whether treatment outcomes were dependent on initial doses of systemic glucocorticoid, we dichotomised the initial dose into 2 groups. To compare the treatment outcomes between groups receiving either low (<45 mg/day) or high dose systemic glucocorticoid (>45 mg/day), we used Fisher's exact test for categorical outcome variables, *t*-test for continuous outcome variables following Gaussian distributions, and Wilcoxon Mann-Whitney *U* test for continuous non-Gaussian outcome variables. *p*-values less than 0.05 were considered statistically significant.

RESULTS

Patients

Between January 1, 2006 and February 18, 2013, a total of 117 patients were identified. Eight patients were retrospectively diagnosed as MMP and excluded. A total of 11 patients were excluded on other criteria. Of these, 4 patients were initially misdiagnosed with final diagnoses of epidermolysis bullosa acquisita, scabies, cutaneous vasculitis, and chronic urticaria, respectively. Two patients were exclusively treated in the outpatient clinic, and 5 patients did not fulfil any of the predefined inclusion criteria. Baseline characteristics and prehospitalisation treatments of the remaining 98 patients are presented in Table I.

The age at debut ranged from 50 to 96 years with a mean ± SD age of 78 ± 10 years. There was a significant difference between the sexes in mean ± SD age at debut of women 80 ± 11 compared to men (75 ± 9) ($p=0.023$). Of the 98 patients, 62 were women (63%) and 36 were men (37%) ($p=0.01$). In the most elderly population (>80 years), the gender difference was even more pronounced with a total of 76% being women.

With regard to comorbidity, a total of 69 patients (70%) suffered from cardiovascular diseases (as determined by ICD10 diagnoses: I00 to I99) of which 39 were hypertension. Congestive heart failure, arrhythmias, prior acute myocardial infarcts, dilated cardiomyopathy, and valve diseases amounted the rest. Referring to previous shown associations between BP on one hand and dementia, prior stroke, or Parkinsonism on the other (1, 3, 7), it was notable that the second most frequent comorbidity was neurologic disorders which was present in 36 patients (37%).

Table I. *Baseline characteristics and pre-hospitalisation treatments of patients admitted with bullous pemphigoid (*n*=98) during the study period (Jan 2006–Feb 2013)*

Characteristics	Patients
Gender, %	
Male	37
Female	63
Age at debut, years, mean ± SD	78 ± 10
Severity, %	
Mild	3
Moderate	56
Severe	41
Diagnose methods, %	
Objective	10
+ Histology	10
+ Immunofluorescence	80
Prior treatment, %	
Topical steroids	66
Systemic glucocorticoid as monotherapy	36
+ immunosupressants[a]	10
Comorbidities, %	
Cardiovascular disease[b]	70
Neurologic disorders[c]	37
Lung diseases[d]	18
Diabetes	15
Cancers[e]	14

[a]Azathioprine ($n=9$), methotrexate ($n=1$); [b]Hypertension ($n=39$), cardiac disorders ($n=30$); [c]Stroke ($n=12$), dementia ($n=17$), Parkinsonism ($n=4$), epilepsy ($n=2$), multiple sclerosis ($n=1$); [d]Asthma ($n=2$), chronic obstructive lung disease ($n=16$); [e]Breast cancer, endometrial cancer, head and neck cancer, prostate cancer, rectal cancer, malignancies of the nasal cavity, laryngeal cancer, coecum cancer, vesical cancer.

Treatment outcomes

At admission, 89 out of 98 patients (91%) were initiated or increased in systemic glucocorticoid. Dosages ranged from 10 to 90 mg with a mean ± SD of 44 ± 15 mg. Potential increase in systemic steroid dose was performed over the first days of admission, until an effect was observed (no new bullae), and did not depend on the weight of the patient. Four patients continued systemic glucocorticoid as monotherapy, whereas 85 patients were supplied with adjuvant IMTs. Of the 9 patients not treated with systemic glucocorticoid, one patient was treated with MTX as monotherapy, 2 with azathioprine, and one with cyclosporin A. All treatment strategies were supplied with daily application of topical glucocorticoids, and 5 patients were sufficiently treated with topical glucocorticoids alone.

The choice of steroid sparing IMT was based on individual assessments depending on comorbidities (existing or prior neoplasms or cardiovascular disease), blood tests (haematology, liver and kidney function), age, and history of alcohol abuse. As department standard, choice of IMT was always conferred with the Department of Oncology in cases of patients with prior neoplasms. However, the use was never contraindicated. The vast majority of our cohort (82%) received azathioprine (range 50–200 mg/day), whereas MTX (range 7.5–15 mg/week) was the second most preferred adjuvant drug (11%). A few cases, resistant or intolerant to usual treatment strategies, were treated with alternative drugs such as mycophenolate mofetil ($n=3$), rituximab ($n=1$), and dapson ($n=1$). The distribution of IMTs and outcomes are presented in Table II.

The mean ± SD admission time of the patients were 14 ± 9 days. Subanalyses showed that admission time was significantly shorter in patients receiving low dose predisolone compared to the patients receiving high dose predisolone ($p=0.02$) (Table III). There was no significant difference in the IMT treatment strategies, 6 weeks remission rate, relapse rate, or the total treatment length between the low and high dose predisolone groups. There was no significant association between disease severity and dosage of systemic glucocorticoid at admission ($p=0.20$). Further, we found no significant association between disease severity on one hand and admission time and total treatment duration on the other (results not shown).

DISCUSSION

In this retrospective case series of 98 patients admitted with BP 97% suffered from moderate to severe disease. Ten percent of the patients were diagnosed purely on the classical clinical presentation of the disease. Women accounted for 63% of the cohort and were significantly overrepresented ($p=0.01$) in concordance with other studies on BP in Caucasians (2, 3, 5, 7). On the contrary men seem to dominate in Asians (1, 13). Yet, no unambiguous conclusions have been made on the gender-distribution of patients suffering from BP.

Cardivascular disease was the most dominant co-morbidity (70%) followed by CNS disorders (37%),

Table II. *Treatment, and treatment outcomes in all patients admitted with bullous pemphigoid (*n *= 98) 2006–2013*

Treatment and outcomes	Patients
Length of primary admission, days, mean ± SD	14 ± 9
Dosage of systemic glucocorticoid at admission, mg, mean ± SD[a]	44 ± 15
Duration of systemic glucocorticoid, weeks, median, (25/75 percentile)[a,b]	20 (10/39)
Choice of immune modulating therapy[c], patients, *n*	
Azathioprine	80
Methotrexate	11
Cyclosporine	5
Mycophenolate mofetil	3
Rituximab	1
Dapson	1
Duration of immune modulating treatment, weeks, median, (25/75 percentile)[c]	21 (9/49)
Total treatment duration, weeks, median (25/75 percentile)	29 (11/60)
6 weeks remission, %	74
Relapse[d], %	34

[a]Nine patients did not receive systemic glucocorticoid and did not contribute to this value ($n=89$); [b]From journal review it was not possible to determine duration of systemic glucocorticoid in additional 4 cases ($n=85$); [c]From the original cohort ($n=98$) 12 patients did not receive immune modulating therapy > 1 week ($n=86$); [d]At any time of the study period.

Table III. *Treatment outcomes stratified by dosages of systemic corticosteroid at admission*

Treatment and outcomes	All patients[a]	
	Systemic glucocorticoid (<45 mg/day) (n=46)	Systemic glucocorticoid (>45 mg/day) (n=43)
Dosage of systemic glucocorticoid at admission, mg, mean ± SD	34 ± 8	56 ± 11
Length of primary admission, days, mean ± SD*	12 ± 8	17 ± 9
Duration of systemic glucocorticoid, weeks, median (25/75 percentile)[b]	19 (10/40)	22 (10/35)
Immune modulating therapy, %		
Azathioprine	85	91
Methotrexate	11	12
Cyclosporine	4	5
Mycophenolate mofetil	2	5
Rituximab	0	2
Dapson	0	2
Duration of immune modulating treatment, weeks, median (25/75 percentile)[c]	22 (7/45)	18 (9/59)
Duration of total treatment, weeks, median (25/75 percentile)	34 (16/60)	25 (11/87)
6 weeks remission, %	82	74
Relapse, %[d]	31	42

[a]Of 98 patients, 5 patients were treated with topical steroids alone and 4 patients with azathioprine, methotrexate or cyclosporine as monotherapy. The remaining 89 patients received systemic glucocorticoid. [b]Four missing values on systemic glucocorticoid were excluded (low dose group (n=43), high dose group (n=42)). [c]With reference to Table II, additionally 4 patients received IMT as monotherapy and did not contribute to these values (low dose group (n=41), high dose group (n=41)). [d]At any time of the study period.
*Significant difference (p=0.02).

diabetes (15%), and malignancies (including all types of cancer, Table I) (14%). It is well known that BP is associated with neurologic disorders (1, 3, 7). Also accumulated cases of malignancies and diabetes mellitus in BP patients have previously been shown (14). Cardiovascular disease has not been described as an associated disorder. Although this study did not include a reference group, parallels may be drawn to prevalences in the general population. The prevalence of cardiovascular diseases in Denmark (ICD10 diagnoses: I00 to I99) has been assessed in a report from the Danish National Institute of Public Health from 2011. As expected, the prevalence increased with increasing age in both sexes. The highest prevalence was found among men older than 85 years, where a total of 43% was reported to have a cardiovascular disease (15). Since the prevalence of cardiovascular diseases was considerably higher in the present study, our results indicate that there may be an association between BP and cardiovascular disease. However, the patients included in this study are admitted to a specialised centre, and in limited numbers, which means that this association needs to be studied further.

Of all patients, 91% were treated with systemic glucocorticoids with a median duration of 20 weeks. Of these patients 87% received azathioprine as adjuvant therapy, whereas MTX was second in preference (11.5%). After dichotomising the initial doses of systemic glucocorticoid at admission (at 45 mg/day), we found a significant difference in admission time in favour of the low dose group (p=0.02). This may be caused by the fact that patients treated with high doses of systemic glucocorticoid were initially suffering from more severe disease. However, this association could not be shown in the following sub-analysis. In contrast, rate of remission and relapse, median duration of systemic corticosteroid and IMTs, and total treatment duration were independent of the dichotomized initial doses of systemic glucocorticoids. As this is not a RCT a direct comparison of the effect on BP of the initial dose of glucocorticoid is not possible.

The evidence-based literature, on the steroid-sparing effect of azathioprine in treating patients with BP, consists of 2 RCTs from 1978 and 1993, respectively (9, 16). The largest RCT showed no significant difference in remission-rates after 4 weeks (71 vs. 80.5%) glucocorticoids as monotherapy (n=31) compared to a combination of glucocorticoid and azathioprine (n=36). The authors concluded that azathioprine should not represent a routine adjuvant treatment (9). In contrast, Burton et al. (16) found a significant reduction (p<0.01) in mean annual dose of predisolone in patients treated with azathioprine and predisolone (n=12) compared to predisolone alone (n=13). They concluded that azathioprine should be a standard adjuvant to systemic glucocorticoid in treating patients with BP. Since our study is not a RCT with a placebo group, rather a descriptive study of a given group of patients, no firm conclusions on effect of steroid sparing agents can be made.

In contrast, systemic glucocorticoid as standard treatment of BP has been thoroughly investigated (2, 9, 10, 17). Unfortunately, studies have also proved systemic glucocorticoid as a poor prognostic factor for one-year mortality (2, 9, 10) with infections and heart diseases being the dominant causes of death (18, 19). The incidence of severe side effects to glucocorticoid (septicaemia, diabetes mellitus, psychiatric disorders) have been proven to rise according to the dosage (0.5 mg/kg/day versus 1

mg/kg/day) and administration form (topical versus oral) (2). If, as our results implies, this group of patient have an increased risk of cardiovascular disease, then addition of steroid sparing drugs certainly has its merits.

The strengths of our study are both the long study period, and the validation of all BP diagnoses in terms of a review of each individual medical record. Further, a total of 80 BP patients received an identical combination of systemic glucocorticoid and azathioprine. All data were extracted from one of only 5 specialised centres in Denmark covering a population of approximately 1.6 million people.

As our department consults the most severe cases in our region outcomes might be affected by selection bias. On the contrary, the same specialists assessed all patients, and treatment strategies were conducted referring to the same standard procedures. However, especially the long-term outcomes, such as relapse rate, could be biased by disease severity or patient compliance and must be interpreted with caution. In the vast majority of patients, end of follow-up was caused by a successfully completed treatment. However, in a small number of cases, end of follow-up was due to absence from outpatient controls or death, which might underestimate the size of appertaining outcomes. Additionally it should be remembered that this study is not a randomised prospective study, but a retrospective case-series study.

In conclusion, we found that our patients had an increased rate of cardiovascular disease as compared to the known prevalence of these diseases in the Danish population. However, further studies are needed to confirm this association. As previously shown, our results also suggest an association between BP and neurological diseases, and we found relatively high prevalences of malignancies and diabetes among the BP patients in our population. Many of these comorbidities are potentially worsened by glucocorticoids, and the clinician should consider these comorbidities in patients suffering from BP when prescribing treatment. Combined with the knowledge of infections and heart diseases being dominant contributors to increased one-year mortality after receiving systemic glucocorticoids (18, 19), we believe that steroid sparing strategies are a necessity in these patients. Whether azathioprine or e.g. methotrexate should be the first choice of steroid sparing therapy must be studied with a randomised controlled trial.

The author declare no conflict of interest.

REFERENCES

1. Chen YJ, Wu CY, Lin MW, Chen TJ, Liao KK, Chen YC, et al. Comorbidity profiles among patients with bullous pemphigoid: A nationwide population-based study. Br J Dermatol 2011; 165: 593–599.
2. Joly P, Roujeau JC, Benichou J, Picard C, Dreno B, Delaporte E, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. N Engl J Med 2002; 346: 321–327.
3. Langan SM, Groves RW, West J. The relationship between neurological disease and bullous pemphigoid: A population-based case-control study. J Invest Dermatol 2011; 131: 631–636.
4. Korman NJ. Bullous pemphigoid. The latest in diagnosis, prognosis, and therapy. Arch Dermatol 1998; 134: 1137–1141.
5. Bastuji-Garin S, Joly P, Lemordant P, Sparsa A, Bedane C, Delaporte E, et al. Risk factors for bullous pemphigoid in the elderly: A prospective case-control study. J Invest Dermatol 2011; 131: 637–643.
6. Langan SM, Smeeth L, Hubbard R, Fleming KM, Smith CJ, West J. Bullous pemphigoid and pemphigus vulgaris – incidence and mortality in the UK: population based cohort study. BMJ (Clinical research ed) 2008; 337.
7. Taghipour K, Chi CC, Vincent A, Groves RW, Venning V, Wojnarowska F. The association of bullous pemphigoid with cerebrovascular disease and dementia: A case-control study. Arch Dermatol 2010; 146: 1251–1254.
8. Borradori L BP. bullous pemphigoid, cicatricial pemphigoid, epidermolysis bullosa acquisita. In: Bolognia JL Jorizzo JL, Rapini RP, ed. Dermatology. London: Elsevier Science, 2006: p. 431–445.
9. Guillaume JC, Vaillant L, Bernard P, Picard C, Prost C, Labeille B, et al. Controlled trial of azathioprine and plasma exchange in addition to prednisolone in the treatment of bullous pemphigoid. Arch Dermatol 1993; 129: 49–53.
10. Venning VA, Taghipour K, Mohd Mustapa MF, Highet AS, Kirtschig G. British Association of Dermatologists' guidelines for the management of bullous pemphigoid 2012. Br J Dermatol 2012; 167: 1200–1214.
11. Beissert S, Werfel T, Frieling U, Böhm M, Sticherling M, Stadler R, et al. A comparison of oral methylprednisolone plus azathioprine or mycophenolate mofetil for the treatment of bullous pemphigoid. Arch Dermatol 2007; 143: 1536–1542.
12. Roujeau JC, Guillaume JC, Morel P, Crickx B, Dalle E, Doutre MS, et al. Plasma exchange in bullous pemphigoid. Lancet 1984; 2: 486–488.
13. Yang YW, Chen YH, Xirasagar S, Lin HC. Increased risk of stroke in patients with bullous pemphigoid: A population-based follow-up study. Stroke 2011; 42: 319–323.
14. Li J, Zuo YG, Zheng HY, Qiu-Ning S. Association between bullous pemphigoid and internal diseases. J Dtsch Dermatol Ges 2013; 11: 263–264.
15. Koch MB, Davidsen M, Juel K. [Cardivascular diseases in Denmark. Incidens and development 2000-2009.] SiF, ed. Copenhagen. National Institute of Public Health, 2011 (in Danish).
16. Burton JL, Harman RRM, Peachey RDG, Warin RP. Azathioprine plus prednisone in treatment of pemphigoid. BMJ 1978; 2: 1190–1191.
17. Morel P, Guillaume JC. Treatment of bullous pemphigoid with prednisolone only: 0.75 mg/kg/day. Results of a randomized pluricentric study. Traitment de la pemphigoide bulleuse par la prednisone seule: 0.75 mg/kg/j contre 1.25 mg/kg/j etude randomisee multicentrique. Ann Dermatol Venereol 1984; 111: 925–928.
18. Cortés B, Marazza G, Naldi L, Combescure C, Borradori L. Mortality of bullous pemphigoid in Switzerland: A prospective study. Br J Dermatol 2011; 165: 368–374.
19. Gual A, Mascaró JM, Rojas-Farreras S, Guilabert A, Julià M, Iranzo P. Mortality of bullous pemphigoid in the first year after diagnosis: A retrospective study in a Spanish medical centre. J Eur Acad Dermatol Venereol 2014; 28: 500–506.