A Comparison of Oral Methylprednisolone Plus Azathioprine or Mycophenolate Mofetil for the Treatment of Bullous Pemphigoid FREE

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ABSTRACT

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Objective To investigate the safety and efficacy of oral methylprednisolone combined with azathioprine sodium or mycophenolate mofetil for the treatment of bullous pemphigoid.

Design A prospective, multicenter, randomized, nonblinded clinical trial to compare 2 parallel groups of patients with bullous pemphigoid undergoing different treatments.

Setting Thirteen departments of dermatology in Germany.

Patients Patients with bullous pemphigoid (n = 73) as evidenced by clinical lesions suggestive of bullous pemphigoid, signs of subepidermal blistering on histologic analysis of skin biopsy specimens, linear deposition of IgG and C3 along the dermoepidermal junction, and deposition of autoantibodies at the blister roof in split-skin analysis.

Interventions Treatment with oral methylprednisolone plus azathioprine (azathioprine group) or oral methylprednisolone plus mycophenolate mofetil (mycophenolate mofetil group).

Main Outcome Measures The cumulative total methylprednisolone doses and rates of remission. Secondary outcome measures were safety profiles and duration of remission.

Results In 38 of 38 patients in the azathioprine group (100%), complete remission was achieved after a mean ± SD of 23.8 ± 18.9 days vs 42.0 ± 55.3 days for 35 of 35 patients in the mycophenolate mofetil group (100%). In the azathioprine group, the median ± SD total cumulative methylprednisolone dose used was 4967.0 ± 12 190.7 mg vs 5754.0 ± 9692.8 mg in the mycophenolate mofetil group. Nine of 38 patients in the azathioprine group (24%) experienced grade 3 or 4 adverse effects vs 6 of 35 patients in the mycophenolate mofetil group (17%). Azathioprine therapy induced significantly elevated liver function test results compared with mycophenolate mofetil ($P < .001$). Importantly, patients in the azathioprine group showed significantly higher toxicity grades for aspartate aminotransferase ($P = .03$), alanine aminotransferase ($P = .03$), and γ-glutamyltransferase ($P = .01$) than did those in the mycophenolate mofetil group.

Conclusions Mycophenolate mofetil or azathioprine demonstrate similar efficacy during treatment of bullous pemphigoid, and similar cumulative corticosteroid doses were given in both treatment arms to

control disease. However, mycophenolate mofetil showed a significantly lower liver toxicity profile than azathioprine therapy.

Trial Registration clinicaltrials.gov Identifier: _NCT00431119_

Although in general rare, bullous pemphigoid (BP) represents the most common cutaneous subepidermal bullous autoimmune disorder.[1-3] The disease typically presents in elderly patients with a generalized bullous eruption and, more rarely, mucous membrane involvement.[4,5] Bullous pemphigoid is potentially associated with substantial morbidity. The cutaneous autoantigens are BP antigens 1 and 2 (BP 180 and BP 230), which are expressed in hemidesmosomal plaques as well as anchoring filaments.[6-8] Accordingly, autoantibodies directed against the 2 proteins can be detected by both direct and indirect immunofluorescence. Bullous pemphigoid treatment is based more on clinical experience than on controlled studies. Systemic corticosteroids represent the best-validated and therefore standard therapeutic regimen. Oral prednisone doses range from 0.3 to 1.25 mg/kg of body weight per day, which usually controls disease within 1 to 2 weeks.[9-11] The dose is then progressively tapered. However, the use of systemic corticosteroids in elderly patients is associated with considerable adverse effects.[12-14] Occasionally, corticosteroid pulse therapy is used for the rapid control of BP.

Several uncontrolled and 1 controlled investigation suggested the use of concomitant immunosuppressant drugs to achieve a corticosteroid-sparing effect.[15-17] Combination therapy may be also useful to successfully treat widespread and/or chronic and/or severe forms of BP via induction of more potent immunosuppression. The most frequently used agent is azathioprine at doses ranging from 0.5 to 2.5 mg/kg of body weight. Other case series have reported the successful use of cyclophosphamide, methotrexate, cyclosporine A, and combination tetracycline/minocycline along with nicotinamide and, more recently, mycophenolate mofetil for the treatment of disease.[18-24] Among the immunosuppressants, mycophenolate mofetil has shown great promise for the treatment of cutaneous bullous autoimmune disorders. Since complications related to the use of oral corticosteroids may contribute substantially to the prognosis of patients with BP, we conducted a randomized trial comparing oral corticosteroids in combination with either azathioprine sodium or mycophenolate mofetil. The aim of this investigation was to assess the efficacy and adverse event profiles of both immunosuppressant agents in a combination therapy regime with corticosteroids for the treatment of BP. We also assessed the cumulative doses of corticosteroids used in each combination.

METHODS
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PATIENTS

Thirteen dermatologic centers in Germany participated in this prospective, randomized investigation. The study protocol was approved by the ethics committee of the University of Münster, Münster, Germany, and written informed consent was obtained from each patient. Consecutive patients with BP were eligible for entry if the following criteria were met: clinical lesions suggestive of BP, subepidermal blistering on histologic analysis of skin biopsy specimens, linear deposition of IgG and C3 along the dermoepidermal junction, and deposition of autoantibodies at the blister roof on split-skin analysis. Exclusion criteria were treatment with oral or topical corticosteroids and other immunosuppressive drugs during the previous 4 weeks.

STUDY DESIGN

This multicenter, randomized, nonblinded clinical trial compared 2 parallel groups of patients with BP treated with oral methylprednisolone in combination with either azathioprine (azathioprine group) or mycophenolate mofetil (mycophenolate mofetil group). Since _complete healing_ (also called _complete remission_), defined as a complete reepithelization of all lesions, was a primary outcome measure, blinding was not considered necessary. The second primary outcome measure was the cumulative oral corticosteroid dose used until complete healing was achieved; this outcome allowed us to compare the corticosteroid-sparing effects of the 2 alternative immunosuppressants. Secondary outcome measures were duration of remission and safety profiles of the 2 treatments.

Randomization was stratified according to the clinical center and performed centrally with the use of random numbers of three for each stratum. Patients were randomly assigned, regardless of disease severity, to receive either 0.5 mg/kg of methylprednisolone (Urbason; Aventis Pharma, Frankfurt, Germany) with 2 mg/kg of azathioprine sodium (Imurek; GlaxoSmithKline, Munich, Germany) once daily or 0.5 mg/kg of methylprednisolone once daily with 1000 mg of mycophenolate mofetil (CellCept; Hoffmann-La Roche AG, Grenzach-Wyhlen, Germany) twice daily (2 g/d). The initial dose was maintained until blister formation ceased, crusts and erosions disappeared, and reepithelialization of lesions started. The corticosteroid dose was then sequentially reduced by 10 mg every 2 weeks until a dose of 20 mg/d was reached followed by a reduction in 5-mg steps every 2 weeks until 10 mg/d. Afterwards, corticosteroid reduction was performed in 2.5-mg steps every 2 weeks until a dose of 0 was reached.

After discontinuation of corticosteroid treatment, azathioprine or mycophenolate mofetil administration was maintained at the initial dose as monotherapy for an additional 4 weeks. Then the azathioprine sodium dose was reduced by 0.5 mg/kg every 4 weeks to a dose of 100 mg/d. Thereafter, azathioprine therapy was tapered in 25-mg steps every 4 weeks until discontinuation of treatment. Mycophenolate mofetil treatment was reduced in 500-mg steps every 4 weeks to 1000 mg/d. From then on, the mycophenolate mofetil dose was decreased in 250-mg steps every 4 weeks until discontinuation of treatment.

If new blisters developed 7 days or more after the initiation of therapy, this was considered *disease progression*, and the methylprednisolone dose was increased weekly by 0.5 mg/kg every 7 days until blister development ceased.

Relapse was defined as the formation of new blister formation during dose reduction of either methylprednisolone or immunosuppressant. If a relapse was noticed at a dose of methylprednisolone higher than 40 mg/d, the previous corticosteroid dose that achieved disease control was given. If a relapse was noticed at a dose lower than 40 mg/d of methylprednisolone, including during the phase of immunosuppressant monotherapy or its reduction, the corticosteroid dose was increased to 40 mg/d, and the initial immunosuppressant dose was given.

BASELINE AND FOLLOW-UP EVALUATION

At baseline, each patient underwent a physical examination followed by a complete blood cell count, liver function tests, blood pressure evaluation, hemoccult test, and urinanalysis. Additionally, they underwent abdominal ultrasonography, chest radiography, electrocardiography, quantitative computed tomography for determination of bone density, and ophthalmologic evaluation to measure inner eye pressure and to determine cataract status. The extent and location of blisters and erosions were documented by a physician not otherwise involved in the study. At each follow-up visit (on days 7, 14, 30, 60, 90, 120, 150, 180, 270, 360, 540, and 720), the patient underwent physical examination, blood cell count, liver function tests, blood pressure evaluation, and stool and urine analysis. The extent and locations of their blisters and erosions were noted, as was the cumulative amount of methylprednisolone they had taken. The date of any relapse was noted. Any adverse effects of treatment were assessed, and their severity was graded 1 for mild effects, 2 for moderate effects, 3 for severe effects, or 4 for life-threatening effects, according to the standard criteria of the World Health Organization.

STATISTICAL ANALYSIS

Cumulative corticosteroid doses as the primary end point of the study were compared using the Wilcoxon rank sum test for independent observations. All other analyses presented are of a descriptive or hypothesis-generating nature. Dichotomous and ordered categorical data were analyzed with the Fisher exact and a corresponding exact permutation version of the Mantel-Haenszel test, respectively. Event-related data such as time to achieve complete healing or time to recurrence were estimated according to the Kaplan-Meier method and eventually compared using the log-rank test. All event or censoring times were calculated from the point of randomization. All reported *P* values are 2-sided.
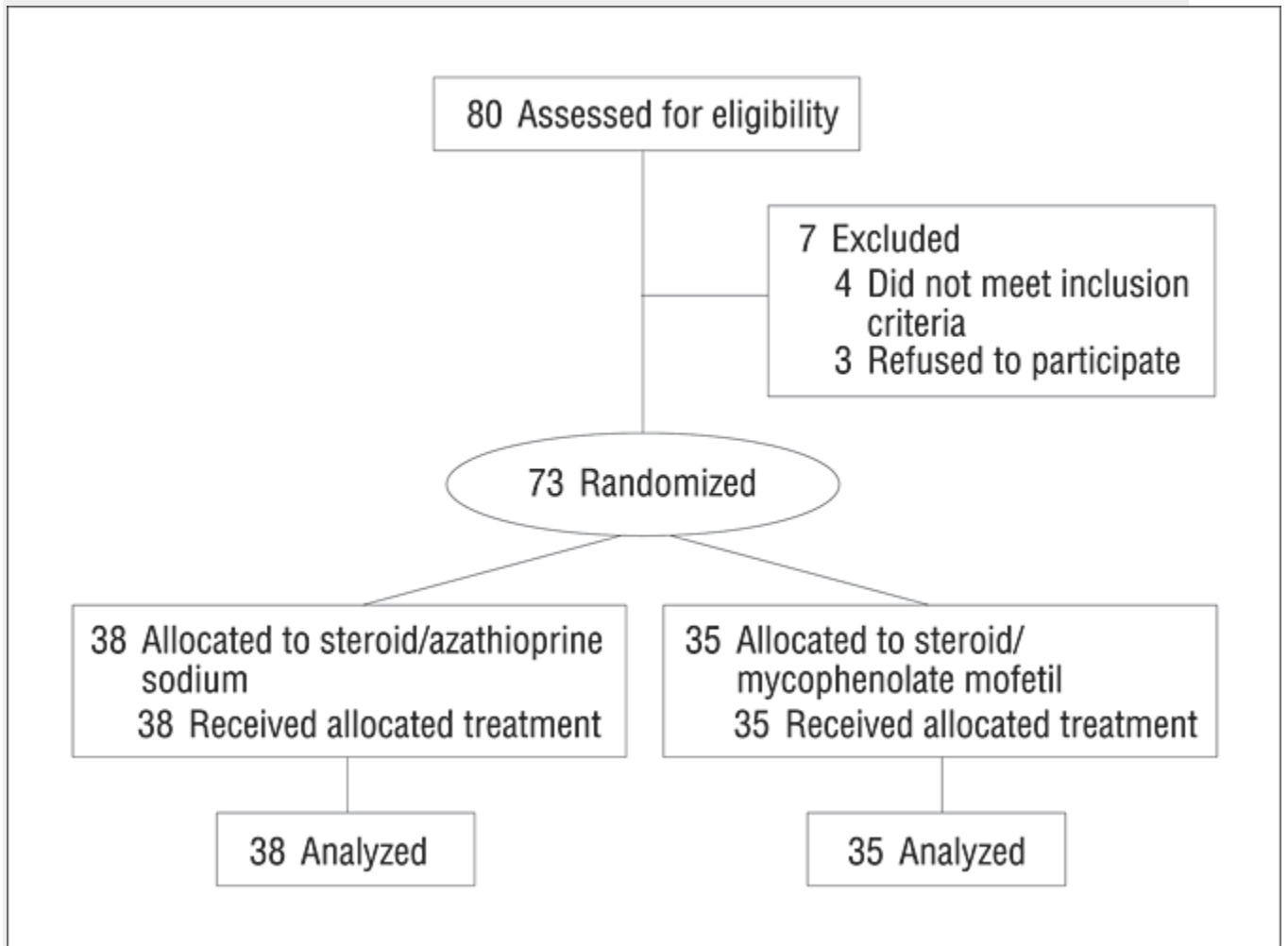
RESULTS

PATIENTS

Between October 1997 and October 2000, 80 patients with BP were assessed for eligibility (Table 1). Three patients declined written consent and were excluded. Other reasons for exclusion were use of other medication effective against BP (1 patient), diagnosis of another skin disorder (1 patient), and severe cardiac insufficiency (2 patients). The remaining 73 patients were randomly assigned to either the azathioprine group (n = 38) or the mycophenolate mofetil group (n = 35) (Figure 1). After randomization all 73 patients were analyzed. Sixty-nine patients (95%) represented newly diagnosed BP cases, and 4 patients (5%) had been previously treated for their disease. The mean duration of follow-up among the patients with BP was 303 days for the azathioprine group and 303 days for the mycophenolate mofetil group.

Figure 1.

Trial enrollment and analysis flowchart.

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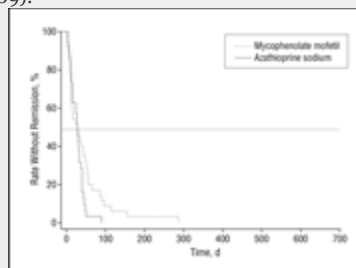
Table 1. Baseline Characteristics of the Study Patients[a]

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DISEASE CONTROL AND RELAPSE

In all 38 patients with BP who were assigned to the azathioprine group and in all 35 patients with BP who were assigned to the mycophenolate mofetil group, disease progression was inhibited by around day 6. In 35 (92%) of the 38 azathioprine patients, complete healing of the lesions and remission was achieved (Figure 2). For the 3 patients with incomplete healing (8%), 2 died from conditions unrelated to the study medication, and so the treatments were prematurely discontinued; the third patient was lost to follow-up. Complete healing of the lesions and disease remission was noted in all 35 of the mycophenolate mofetil patients (100%). Complete healing was achieved after a median ± SD duration of 23.8 ± 18.9 days of treatment in the azathioprine group. In the mycophenolate mofetil group, complete healing was noted after 42.0 ± 55.3 days (P = .09). The disease-free interval from the time when complete remission was achieved until recurrence of lesions was 164.5 ± 135.8 days for the azathioprine group and 126.0 + 89.6 days for the mycophenolate mofetil group. The Kaplan-Meier graph in Figure 3 shows the rate without relapse in patients with BP over time, indicating that both adjuvant therapies in the 2 treatment arms control disease equally well.
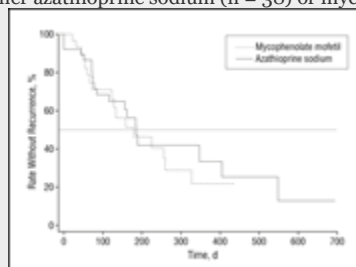
Figure 2.

Rate and duration until clinical remission. Patients with bullous pemphigoid were randomized to receive treatment with either azathioprine sodium (n = 38) or mycophenolate mofetil (n = 35) as adjuvants in combination with oral methylprednisolone. The Kaplan-Meier graph shows the rate without remission over time (P = .09).

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Figure 3.

Disease-free interval. The Kaplan-Meier graph shows the rate without recurrence of disease since once remission was achieved in patients with bullous pemphigoid patients treated with either azathioprine sodium (n = 38) or mycophenolate mofetil (n = 35) as adjuvants (P = .72).
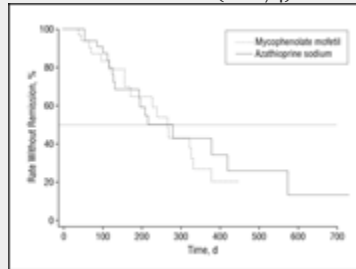
The data in Figure 4 depict the duration until relapse of disease was documented from the time of randomization. The 2 curves show a very similar course and are, therefore, not significantly different. In addition, the duration until relapse was differentiated in relation to the time between diagnosis of BP and beginning of treatment. The results represented in Figure 5 show that the duration between diagnosis and initiation of therapy (≤7 or >7 days) did not significantly influence the time until a relapse of disease was noted. These findings indicate that BP can be successfully controlled with both treatment regimens.
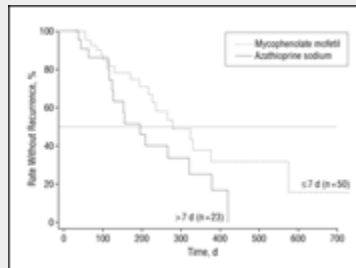
Figure 4.

Duration until relapse. The Kaplan-Meier graph shows the time since randomization until patients with bullous pemphigoid developed a recurrence of disease during the reduction phase of treatment medication ($P = .74$).

Figure 5.

Effects of length of time between diagnosis and initiation of treatment on the recurrence of disease. The Kaplan-Meier graph shows the rate without recurrence of bullous pemphigoid over time in patients treated for more than 7 days or for 7 days or less after the diagnosis of bullous pemphigoid ($P = .07$).

CUMULATIVE CORTICOSTEROID DOSES USED

One of the aims of this investigation was to determine if the corticosteroid-sparing effect of either of the 2 immunosuppressants would be superior. Therefore, the cumulative corticosteroid dose was calculated for each patient with BP from the beginning of treatment to the end of the documentation period (>720 days). The data in Table 2 indicate that patients with BP who were randomized to the azathioprine group received a median ± SD 4967.0 ± 12 190.7 mg of methylprednisolone. In the patient group that was randomized to receive mycophenolate mofetil, 5754.0 ± 9692.8 mg of methylprednisolone was given. In general, these numbers are very similar and possibly reflect a comparable immunosuppressive potential of the 2 drugs.

Table 2. Total Cumulative Corticosteroid Doses Used to Control Bullous Pemphigoid

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Adjuvant Treatment	Patients, No. (%)	Corticosteroid Dose, mg	
		Median (SD)	Range
Azathioprine sodium	38 (52)	4967.0 (12 190.7)	1263-73 231
Mycophenolate mofetil	35 (48)	5754.0 (9692.8)	980-40 715
Combined groups	73 (100)	5131.0 (11 064.3)	980-73 231

The results in Table 3 furthermore demonstrate that each of the 56 patients with BP (77%) received less than 10 000 mg of methylprednisolone as a cumulative dose during the course of treatment. Ten of the patients received between 10 001 and 20 000 mg (14%). The distribution of the patients with BP to the different corticosteroid dose groups (Table 3) was similar for azathioprine or mycophenolate mofetil as adjuvant treatment. In summary, similar cumulative corticosteroid doses were taken during therapy in the 2 treatment arms.

Table 3. Groups of Cumulative Corticosteroid Doses

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Corticosteroid Dose, mg	Azathioprine Sodium (n=38)	Mycophenolate Mofetil (n=35)	Total (n=73)
	Patients, No. (%)		
1-10 000	28 (74)	28 (80)	56 (77)
10 001-20 000	7 (18)	3 (9)	10 (14)
20 001-30 000	2 (5)	1 (3)	3 (4)
30 001-40 000	0	2 (6)	2 (3)
40 001-50 000	0	1 (3)	1 (1)
50 001-60 001	0	0	0
>75 000	1 (3)	0	1 (1)

COMPLIANCE WITH TREATMENT AND ADVERSE EVENTS

The treatments were prematurely discontinued in 2 patients from the azathioprine group who died due to conditions unrelated to the study medications. Another patient from the azathioprine group was lost to follow-up.

Overall, 24 severe (grade 3) or life-threatening (grade 4) adverse effects were reported in 15 patients (Table 4). Grade 3 or 4 adverse effects were documented in 9 of the 38 patients randomized to the azathioprine group (24%) compared with 6 of the 35 patients from the mycophenolate mofetil group (17%). Adverse effects typically associated with the immunosuppressants used in this investigation, including nausea (azathioprine vs mycophenolate mofetil, $P = .60$), vomiting ($P = .64$), and infections ($P = .67$), did not differ significantly between treatment arms.

Table 4. Incidence of Grades 3 and 4 Adverse Events After the Initiation of Treatment

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Symptom	Adverse Event Grade, No. % — 3	4	Total Patients, No.
Azathioprine Sodium Group			
Hypokalemia	0	0	37
Hyperglycemia	1 (3)	0	37
Infection	0	1 (3)	38
Abnormal liver function	4 (11)	2 (5)	37
Myalgia and/or arthralgia	1 (3)	0	37
Dizziness	2 (5)	0	37
Mycophenolate Mofetil Group			
Hypokalemia	1 (3)	0	35
Hyperglycemia	5 (15)	0	34
Infection	4 (11)	0	35
Abnormal liver function	0	1 (3)	35
Myalgia and/or arthralgia	1 (3)	1 (3)	35
Dizziness	0	0	35

However, patients with BP randomized to the azathioprine group showed significant elevated liver function test results compared with patients in the mycophenolate mofetil group ($P < .001$). To investigate the liver function, serum concentrations of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltransferase (GGT) were determined and classified according to toxicity grades. Patients with BP in the azathioprine group showed significantly higher serum concentrations of ALT than patients in the mycophenolate mofetil group ($P = .03$). This was not true of AST and GGT ($P = .06$ and $P = .15$, respectively). Importantly, patients with BP in the azathioprine group showed significantly higher toxicity grades for AST ($P = .03$), ALT ($P = .03$), and GGT ($P = .01$) than patients in the mycophenolate mofetil group (Table 5). Together, these results suggest that the efficacy between both

treatment arms was similar. However, the mycophenolate mofetil treatment involved a significantly lower liver toxicity profile than did azathioprine.

Table 5. Liver Function Test Findings During Treatment

Table 5. Liver Function Test Findings During Treatment

Toxicity Grade	Patients With BP, No. (%)	
	Azathioprine Sodium (n = 36)	Mycophenolate Mofetil (n = 34)
Aspartate Aminotransferase		
0	25 (69)	31 (91)
1	4 (11)	2 (6)
2	5 (14)	0
3	1 (3)	1 (3)
4	1 (3)	0
Alanine Aminotransferase		
0	18 (50)	25 (74)
1	11 (31)	8 (24)
2	3 (8)	0
3	4 (11)	1 (3)
4	0	0
γ-Glutamyltransferase		
0	14 (39)	20 (59)
1	5 (14)	8 (24)
2	6 (17)	3 (8)
3	6 (17)	2 (6)
4	5 (14)	1 (3)

Abbreviation: BP, bullous pemphigoid.

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COMMENT
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In this randomized study, each treatment arm had similar therapeutic benefit. Because no corticosteroid monotherapy arm was included in the study, the level of corticosteroid-sparing effects of each adjuvant agent cannot be determined. Azathioprine induced more liver toxicity than mycophenolate mofetil, suggesting a therapeutic benefit for patients receiving mycophenolate mofetil. Since only 1 dose regimen of immunosuppressants was used, we cannot determine if different drug doses would have had another clinical outcome. Another difference between the 2 arms is the daily cost of treatments. For a 75-kg patient, the cost was €2.58 for azathioprine (2 mg/kg per day) and €14.32 for mycophenolate mofetil (1 g twice daily), azathioprine being 5.5 times less expensive than mycophenolate mofetil.

For several decades, systemic corticosteroids were considered the standard treatment for BP.[9-11,19] They may be responsible for the increased mortality rate, especially in elderly patients. Indeed, in a large study using 1 mg/kg of prednisone, a 1-year mortality rate of 41% was observed, regardless of the extent of disease. This finding suggests that the treatment rather than the extent of the disease determined the poor prognosis.[10] Therefore, the development of corticosteroid-sparing treatment regimens is of particular practical relevance. In a randomized investigation topical application of clobetasol propionate, a very potent corticosteroid agent, resulted in successful control of even extensive BP without inducing increased mortality.[10] Based on these findings, some proposed that topical corticosteroid treatment should be considered standard treatment for patients with even extensive BP. However, topical application of 40 g/d of clobetasol propionate over large body surface areas for long time periods leads to significant skin atrophy, especially in elderly patients. Since the epidermal barrier in BP and in the skin of elderly patients is impaired, topical clobetasol propionate may penetrate the skin at significant concentrations and induce systemic corticosteroid effects.[25-28] In our experience, the disease in a number of patients with BP is difficult to control with topical treatment (S.B., G.B., and T.A.L., unpublished data 2007).

Some physicians prefer to use immunosuppressive drugs as second-line therapy when corticosteroids alone fail to control disease or when the use of corticosteroids is contraindicated. Thus, the use of an immunosuppressant drug follows a period of corticosteroid monotherapy. Since some immunosuppressant agents need several weeks to induce therapeutically relevant immunosuppression, we prefer to treat BP initially with an oral combination of corticosteroids plus immunosuppressant drug. The most frequent adjuvant agent is azathioprine,[15-17,19] which has been used successfully for nearly 4 decades, in a range between 1.5 and 3.0 mg/kg. Our findings concur with the reported efficacy of combination azathioprine/corticosteroid treatment in patients with BP.

In the present study, 1 patient had a severe herpes zoster infection, which required antiviral therapy; 2 patients developed dizziness; and 1 had muscle pain.

Recently, mycophenolate mofetil was shown to be effective and well tolerated.[18,21] Our study supports the effectiveness in that all of our patients with BP treated with mycophenolate mofetil–methylprednisolone combination experienced remission. The time needed to achieve complete remission in 100% of the patients was about 90 days in the azathioprine group compared with about 280 days in the mycophenolate mofetil group (Figure 2). Perhaps interference with 3 enzymatic pathways by azathioprine compared with the suppression of a single pathway by mycophenolate mofetil might reflect the earlier remission after onset of azathioprine treatment.

The adverse effect profile of mycophenolate mofetil was similar to that of azathioprine except for liver toxicity. If elevation of liver function test results occurred, immunosuppressant medication dose was reduced or discontinued. Since in our investigation azathioprine dose was not adjusted to thiopurine methyltransferase (TPMT) activity, we cannot completely rule out that patients experiencing adverse events had lower TPMT activity. However, lower TPMT levels usually result in increased myelotoxicity affecting blood cell counts rather than impaired liver function findings.[29,30] On the other hand, patients with high TPMT activity might have been undertreated. One patient from the mycophenolate mofetil treatment group had muscle pain requiring no treatment; 3 patients had upper respiratory tract infections treated with antibiotics; and 1 developed a recurrent herpes simplex infection, which required oral prophylactic antiviral treatment. Because patients with BP are usually elderly, they usually present with significant comorbidity.

In our investigation, we used methylprednisolone at a lower dose than was used in other reported trials.[9] Methylprednisolone is therapeutically superior to prednisolone in reducing pruritic pemphigoid lesions, and there was no increased mortality observed in either treatment arm (data not shown). Therefore, we recommend the use of an adjuvant immunosuppressive agent at the beginning of the treatment. Adjuvant azathioprine and mycophenolate mofetil are equally effective to induce clinical remission in BP. However, mycophenolate mofetil showed less liver toxicity. In contrast to azathioprine, mycophenolate mofetil is nonmutagenic and has significant antitumoral effect in solid organ transplant recipients receiving long-term mycophenolate mofetil therapy.[31-34] The antitumor effect may be relevant for patients with BP requiring longer-term immunosuppressive treatment.

ARTICLE INFORMATION

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