A COMPARISON OF ORAL AND TOPICAL CORTICOSTEROIDS IN PATIENTS WITH BULLOUS PEMPHIGOID

PASCAL JOLY, M.D., PH.D., JEAN-CLAUDE ROUJEAU, M.D., JACQUES BENICHOU, M.D., PH.D., CATHERINE PICARD, M.D., BRIGITTE DRENO, M.D., PH.D., EMMANUEL DELAPORTE, M.D., PH.D., LOÏC VAILLANT, M.D., PH.D., MICHEL D'INCAN, M.D., PH.D., PATRICE PLANTIN, M.D., CHRISTOPHE BEDANE, M.D., PH.D., PAUL YOUNG, M.D., AND PHILIPPE BERNARD, M.D., PH.D., FOR THE BULLOUS DISEASES FRENCH STUDY GROUP*

ABSTRACT

Background Bullous pemphigoid is the most common autoimmune blistering skin disease of the elderly. Because elderly people have low tolerance for standard regimens of oral corticosteroids, we studied whether highly potent topical corticosteroids could decrease mortality while controlling disease.

Methods A total of 341 patients with bullous pemphigoid were enrolled in a randomized, multicenter trial and stratified according to the severity of their disease (moderate or extensive). Patients were randomly assigned to receive either topical clobetasol propionate cream (40 g per day) or oral prednisone (0.5 mg per kilogram of body weight per day for those with moderate disease and 1 mg per kilogram per day for those with extensive disease). The primary end point was overall survival.

Results Among the 188 patients with extensive bullous pemphigoid, topical corticosteroids were superior to oral prednisone (P=0.02). The one-year survival rate was 76 percent in the topical-corticosteroid group and 58 percent in the oral-prednisone group. Disease was controlled at three weeks in 92 of the 93 patients in the topical-corticosteroid group (99 percent) and 86 of the 95 patients in the oral-prednisone group (91 percent, P=0.02). Severe complications occurred in 27 of the 93 patients in the topical-corticosteroid group (29 percent) and in 51 of the 95 patients in the oral-prednisone group (54 percent, P=0.006). Among the 153 patients with moderate bullous pemphigoid, there were no significant differences between the topical-corticosteroid group and the oral-prednisone group in terms of overall survival, the rate of control at three weeks, or the incidence of severe complications.

Conclusions Topical corticosteroid therapy is effective for both moderate and severe bullous pemphigoid and is superior to oral corticosteroid therapy for extensive disease. (N Engl J Med 2002;346:321-7.)

BULLOUS pemphigoid is the most common blistering autoimmune disease of the skin[1,2]; it is manifested by cutaneous blisters without mucosal involvement.[3] Histologic features include subepidermal blisters.[4] Autoantibodies directed against two proteins of the basement-membrane zone, bullous pemphigoid antigens 1 and 2, are detectable by both direct and indirect immunofluorescence.[5-10] Bullous pemphigoid is most common in elderly persons.[11-14] Systemic corticosteroids are considered the standard treatment for bullous pemphigoid.[3,15] A dose of prednisone of 1 mg per kilogram of body weight per day is usually recommended for the treatment of patients with severe disease; a lower dose may be used for patients with moderate disease.[15] Systemic corticosteroids are poorly tolerated by elderly patients, however, and have been suspected of contributing to the high rates of death observed in some series.[11,12,16-18]

Many efforts have been devoted to finding corticosteroid-sparing agents for the treatment of bullous pemphigoid. Uncontrolled studies have suggested the usefulness of immunosuppressive drugs.[19-26] Unfortunately, the single controlled study published to date failed to demonstrate a benefit from the addition of azathioprine to corticosteroid therapy.[27] Topical corticosteroids have been proposed as possible treatments for mild forms of bullous pemphigoid.[28-30] Because complications attributable to oral corticosteroids may contribute to the poor prognosis of patients with bullous pemphigoid, we conducted a randomized trial comparing topical corticosteroid treatment with oral corticosteroid treatment in patients with bullous pemphigoid. The aim of the present study was to assess whether topical corticosteroids could substantially increase the rate of survival among patients with bullous pemphigoid and whether they could effectively control the disease.

METHODS

Study Patients

Twenty dermatologic centers in France participated in this prospective, randomized study. The study was approved by the ethics committee of Seine Maritime, and written informed consent was obtained from each patient.

From the Departments of Dermatology and Biostatistics, INSERM Unite 519, University of Rouen, Rouen (P.J., J.B., P.Y.); and the Departments of Dermatology at the University of Paris XII, Creteil (J.-C.R.); Bichat University, Paris (C.P.); the University of Nantes, Nantes (B.D.); the University of Lille, Lille (E.D.); the University of Tours, Tours (L.V.); the University of Clermont-Ferrand, Clermont-Ferrand (M.D.); the General Hospital of Quimper, Quimper (P.P.); the University of Limoges, Limoges (C.B.); and the University of Reims, Reims (P.B.) — all in France. Address reprint requests to Dr. Joly at the Clinique Dermatologique, Hôpital Charles Nicolle, 1, rue de Germont, 76031 Rouen CEDEX, France, or at pascal.joly@chu-rouen.fr.

*Other participants in the Bullous Diseases French Study Group are listed in the Appendix.

Consecutive patients with newly diagnosed bullous pemphigoid were eligible for entry if the following criteria were met: clinical features suggestive of bullous pemphigoid[14]; subepidermal blister on skin biopsy; and linear deposits of IgG and C3 along the basement-membrane zone. Exclusion criteria were predominant or exclusive mucosal involvement and treatment with oral or topical corticosteroids, dapsone, or immunosuppressive drugs during the previous six months.

Study Design

This randomized, nonblinded study compared two parallel groups of patients treated with topical or oral corticosteroids. Since overall survival was the primary outcome, blinding was not deemed necessary. Randomization was stratified according to the clinical center and the severity of disease, which was determined on the basis of the mean number of new bullae that had appeared daily during the three previous days (moderate disease was defined by $\leq$10 new bullae daily and extensive disease by $>$10). Randomization was performed centrally with the use of random numbers in permuted blocks of four within each stratum. Patients were randomly assigned to receive either topical applications of 0.05 percent clobetasol propionate cream (Dermoval cream, Glaxo SmithKline, Philadelphia), or oral prednisone (Cortancyl, Roussel, Paris). Prednisone was administered once daily at a dose of 0.5 mg per kilogram of body weight per day in patients with moderate disease and a dose of 1 mg per kilogram per day in those with extensive disease. The initial dose was maintained for 15 days after control of the disease had been attained; thereafter, the dose was reduced by 15 percent every 3 weeks. Treatment was stopped after 12 months.

Irrespective of the severity of their disease, patients who were assigned to receive topical corticosteroids received a daily dose of 40 g of clobetasol propionate that was applied twice daily on the entire surface of the body until 15 days after control of the disease had been attained. The doses were then gradually reduced — to 20 g daily for one month, 10 g daily for two months, 10 g every other day for four months, and finally 10 g twice a week for four months. When possible, topical corticosteroids were applied by the patients themselves or by members of their households. A nurse performed this task for patients who were in poor condition generally.

Relapse was defined as the occurrence of at least three new bullae daily for three consecutive days during treatment. In patients who had a relapse during the period when the dose was being reduced, the dose was increased to the previous level that had permitted control of the disease. Other therapy that might affect the activity of bullous pemphigoid was avoided throughout the study period. Investigators stopped treatment if a life-threatening side effect occurred, irrespective of the patient's treatment group.

Base-Line and Follow-up Measurements

At base line, each patient underwent physical examination. The Karnofsky score was assessed. The score is a measure of the patient's general condition and degree of autonomy on a scale ranging from 0 to 100, with higher scores indicating better condition and greater autonomy.[31] The number of new bullae that appeared daily was noted by a nurse who was not otherwise involved in the study. Because of the high mortality reported in recent studies during the first year after the diagnosis of bullous pemphigoid, we planned 12 months of follow-up. At each follow-up visit (on days 7, 14, 21, 30, 90, 180, and 360), the patients underwent physical examination, and the number of new bullae that appeared daily was noted, as was the number of units of clobetasol propionate cream that had been used. The date of any relapse was recorded, as were the date and cause of death in any patient who had died. Any side 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 standard criteria of the World Health Organization.[32]

Statistical Analysis

The primary end point was overall survival during the first year after the onset of bullous pemphigoid. Secondary end points were control of the disease at day 21, defined as the absence of new bullae for three consecutive days; occurrence of severe (grade 3 or 4) side effects (adverse events requiring hospitalization or prolongation of hospitalization or life-threatening events) during the first year; and cumulative hospital days (including the initial hospitalization plus all rehospitalizations).

The study was designed to have 80 percent power to detect a 50 percent reduction in the one-year mortality rate for both moderate and extensive bullous pemphigoid, from 40 to 20 percent, with the two-sided log-rank test and a type I error of 5 percent. To achieve this power, 75 patients were needed in each treatment group. Separate intention-to-treat analyses were performed for patients with moderate and severe bullous pemphigoid. No interim efficacy analysis was either scheduled or performed.

Distributions of overall survival according to treatment group were estimated by the Kaplan–Meier method and compared with the use of the log-rank test. A Cox model was used to adjust the comparisons between treatment groups for base-line characteristics that were suspected a priori to have prognostic significance — namely, older age ($\geq$80 years vs. $<$80 years) and poor general condition as measured by the Karnofsky score ($\leq$40 vs. $>$40).[11] Fisher's exact test was used to compare the treatment groups in terms of the proportions of patients with controlled bullous pemphigoid at day 21, as well as the frequency of severe side effects. Exact binomial probabilities were used to estimate 95 percent confidence intervals for the rates of control of disease. Student's t-test was used to compare the mean durations of hospitalization. For all tests, two-sided P values of less than 0.05 were considered to indicate statistical significance. Continuous variables are expressed as means $\pm$SD.

RESULTS

Patients

Between January 1996 and December 1998, 364 patients were assessed for eligibility. Eight declined to provide informed consent. Previous use of medication effective against bullous pemphigoid (in eight patients), diagnosis of another autoimmune blistering-skin disease (in four patients), spontaneous healing of skin lesions (in two patients), and immediate withdrawal of consent (in one patient) were other reasons for exclusion. Of the 341 remaining patients, 153 had 10 or fewer new bullae daily (moderate disease) and 188 had more than 10 new bullae daily (extensive disease). A total of 77 patients with moderate disease were randomly assigned to receive clobetasol propionate cream and 76 to receive oral prednisone at a dose of 0.5 mg per kilogram per day. A total of 93 patients with extensive disease were randomly assigned to receive clobetasol propionate cream and 95 to receive oral prednisone at a dose of 1 mg per kilogram per day. The base-line characteristics of the patients are shown in Table 1. Among both patients with moderate bullous pemphigoid and patients with extensive bullous pemphigoid, the treatment groups were well balanced in terms of the base-line charac-

teristics. The mean duration of follow-up among surviving patients with severe bullous pemphigoid was 360 days in the oral-prednisone group and 359 days in the topical-corticosteroid group. The corresponding figures among surviving patients with moderate bullous pemphigoid were 361 and 360 days, respectively. One patient with moderate bullous pemphigoid who was randomly assigned to the topical-corticosteroid group decided to stop treatment during the third month of the study.

Overall Survival

A total of 107 patients died during the one-year follow-up; 46 of these had moderate bullous pemphigoid, and 61 had extensive bullous pemphigoid. The causes of death were determined in 71 cases; the main causes were sepsis (in 27 patients, including 20 with pneumonia), cardiovascular disease (in 13 patients), and stroke (in 9 patients).

Among the patients with moderate bullous pemphigoid, 23 patients in the topical-corticosteroid group died (30 percent), and 23 in the oral-prednisone group died (30 percent). The log-rank test did not indicate any difference in overall survival between the two treatment groups ($P=0.95$). The one-year Kaplan–Meier survival rate was 69 percent in both groups (Fig. 1A). Similarly, no difference was evident in the Cox regression model that included age and Karnofsky score ($P=0.69$).

Among the patients with extensive bullous pemphigoid, 22 patients in the topical-corticosteroid group died (24 percent), and 39 patients in the oral-prednisone group died (41 percent). Overall survival was significantly longer with topical corticosteroids than with oral prednisone ($P=0.02$). One-year Kaplan–Meier survival rates were 76 percent and 58 percent, respectively (Fig. 1B). With the use of the Cox regression model, this beneficial effect of clobetasol propionate was confirmed after adjustment for age and Karnofsky score ($P=0.009$).

Disease Control and Relapse

In all 77 patients with moderate bullous pemphigoid who were assigned to the topical-corticosteroid group (100 percent; 95 percent confidence interval, 95 to 100 percent) and 72 of the 76 patients with moderate bullous pemphigoid who were assigned to the oral-prednisone group (95 percent; 95 percent confidence interval, 87 to 99 percent), control of bullous pemphigoid was achieved by day 21 ($P=0.06$). Control was achieved by day 21 in 92 of the 93 patients with extensive bullous pemphigoid in the topical-corticosteroid group (99 percent; 95 percent confidence interval, 94 to 100 percent) and in 86 of

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	MODERATE DISEASE (≤10 NEW BULLAE/DAY)		EXTENSIVE DISEASE (>10 NEW BULLAE/DAY)	
	TOPICAL CLOBETASOL PROPIONATE (N=77)	ORAL PREDNISONE (N=76)	TOPICAL CLOBETASOL PROPIONATE (N=93)	ORAL PREDNISONE (N=95)
Age — yr	82±8	81±10	80±11	81±9
Sex — no.				
Male	29	28	40	32
Female	48	48	53	63
Days since onset of disease	106±205	79±79	66±160	79±213
Karnofsky score	63±25	66±24	65±23	63±24
No. of new bullae daily	3±3	4±3	65±54	65±75
Coexisting conditions — no. (%)				
Cardiovascular disease	46 (60)	55 (72)	67 (72)	61 (64)
Neurologic disorder	26 (34)	22 (29)	25 (27)	32 (34)
Dementia	11 (14)	10 (13)	17 (18)	18 (19)
Diabetes mellitus	3 (4)	8 (11)	7 (8)	11 (12)
Chronic lung condition	3 (4)	3 (4)	7 (8)	6 (6)
Eosinophil count — per mm^3	1054±1005	1021±1474	1851±1664	1940±1737
Presence of circulating antibodies against basement-membrane–zone antigens — no. (%)	50 (65)	51 (67)	61 (66)	66 (69)

*Plus–minus values are means ±SD. Among both patients with moderate bullous pemphigoid and patients with extensive bullous pemphigoid, no significant differences were observed between patients assigned to receive topical applications of clobetasol propionate cream and those assigned to receive oral prednisone.

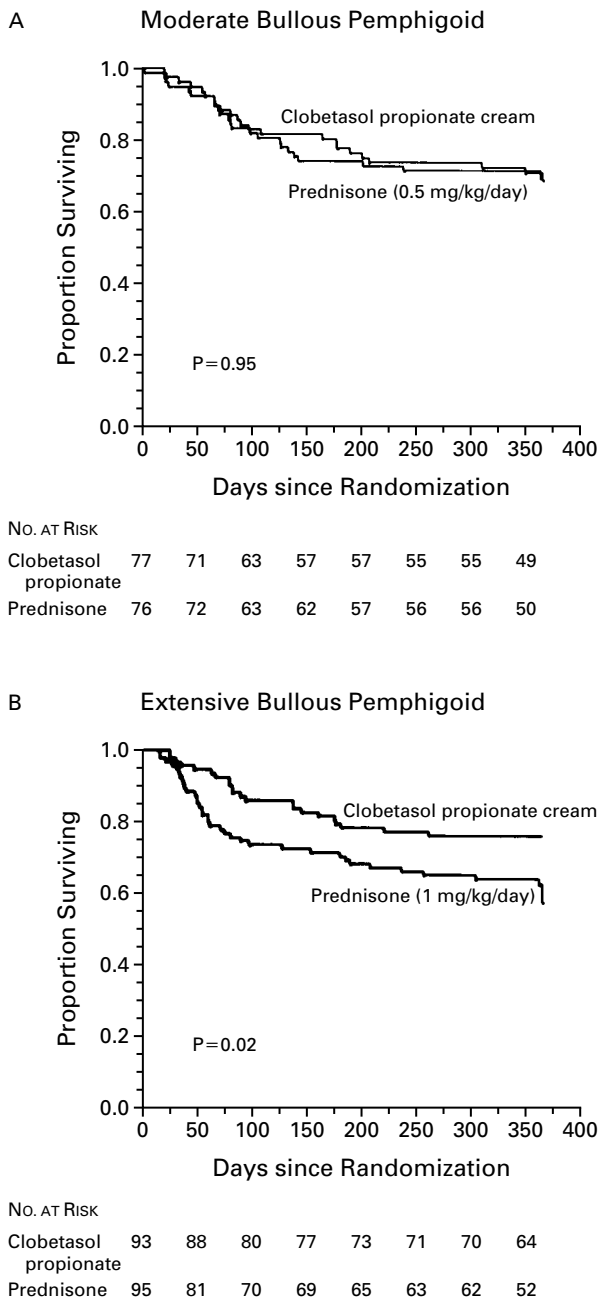

Figure 1. Kaplan–Meier Estimates of the Overall Survival of Patients with Moderate Bullous Pemphigoid (Panel A) or Extensive Bullous Pemphigoid (Panel B), According to Treatment-Group Assignment.

P values were determined by the log-rank test.

the 95 patients with extensive bullous pemphigoid in the oral-prednisone group (91 percent; 95 percent confidence interval, 83 to 96 percent; P=0.02).

A total of 30 of the 76 patients with moderate disease in the oral-prednisone group (39 percent; 95 percent confidence interval, 28 to 50 percent) and 27 of the 77 patients in the topical-corticosteroid group (35 percent; 95 percent confidence interval, 24 to 46 percent) had relapses during follow-up after a mean interval of 149±109 days and 178±118 days, respectively. The corresponding figures among the patients with extensive disease were 44 of the 95 patients in the oral-prednisone group (46 percent; 95 percent confidence interval, 36 to 56 percent) after a mean interval of 210±133 days and 34 of the 93 patients in the topical-corticosteroid group (37 percent; 95 percent confidence interval, 27 to 46 percent) after a mean interval of 187±118 days.

Compliance with Treatment and Adverse Effects

In accordance with the study protocol, the investigators switched three patients with moderate bullous pemphigoid and four with extensive bullous pemphigoid from the oral-prednisone group to the topical-corticosteroid group because of side effects of treatment. The life-threatening side effects in these patients were septicemia (in two patients), severe pneumonia with respiratory distress (in two patients), postoperative sepsis after hip fracture (in one patient), necrotizing cellulitis of the leg (in one patient), and myocardial infarction with acute cardiac failure (in one patient). Two of these seven patients died during the study period. There were no life-threatening side effects in patients assigned to the topical-corticosteroid group. One patient with severe bullous pemphigoid who was initially assigned to the topical-corticosteroid group was later treated with oral prednisone, at a dose of 1 mg per kilogram per day, by a physician who was not aware of the protocol; this patient died of pneumonia 15 days after the treatment was changed.

Overall, 172 severe (grade 3) or life-threatening (grade 4) side effects were reported in 132 patients (Table 2). Severe side effects were reported in 29 of the 76 patients with moderate disease in the oral-prednisone group (38 percent), as compared with 25 of the 77 patients with moderate disease in the topical-corticosteroid group (32 percent, P=0.46). Severe side effects were observed in 51 of the 95 patients with extensive disease in the oral-prednisone group (54 percent), as compared with 27 of the 93 patients with extensive disease in the topical corticosteroid group (29 percent, P=0.006). Among the 10 patients with extensive bullous pemphigoid in whom disease was not controlled by day 21, severe adverse events occurred in 5 of the 9 patients in the

TABLE 2. INCIDENCE OF GRADE 3 OR 4 ADVERSE EVENTS AFTER THE INITIATION OF TREATMENT.*

ADVERSE EVENT	MODERATE DISEASE (≤10 NEW BULLAE/DAY)			EXTENSIVE DISEASE (>10 NEW BULLAE/DAY)		
	TOPICAL CLOBETASOL PROPIONATE (N=77)	ORAL PREDNISONE (N=76)	P VALUE	TOPICAL CLOBETASOL PROPIONATE (N=93)	ORAL PREDNISONE (N=95)	P VALUE
	no. of events (% of all events)			no. of events (% of all events)		
Pneumonia	8 (10)	11 (14)	0.47	6 (6)	11 (12)	0.31
Other severe infection (septicemia, arthritis, cellulitis, or peritonitis)	3 (4)	5 (7)	0.49	2 (2)	11 (12)	0.02
Diabetes mellitus requiring insulin†	2 (3)	7 (9)	0.10	4 (4)	13 (14)	0.04
Myocardial infarction or cardiac failure	7 (9)	6 (8)	1.00	4 (4)	11 (12)	0.10
Psychiatric symptoms (psychosis or delirium)	0	4 (5)	0.06	0	6 (6)	0.03
Stroke	4 (5)	4 (5)	1.00	7 (8)	5 (5)	0.57
Deep venous thrombosis or pulmonary embolism	4 (5)	6 (8)	0.53	5 (5)	4 (4)	0.75
Bone fracture‡	3 (4)	3 (4)	1.00	2 (2)	4 (4)	0.68

*All P values were calculated with the use of Fisher's exact test.

†Diabetes was diagnosed according to the standard criteria of the American Diabetes Association, but only cases of diabetes requiring insulin were included in the analysis of severe (grade 3) or life-threatening (grade 4) adverse events.

‡Data include both clinically apparent fractures and vertebral fractures visible on radiography.

oral-prednisone group, and 3 of the 9 patients in that group died, whereas neither a severe adverse event nor death occurred in the 1 patient in the topical-corticosteroid group.

Duration of Hospitalization

Most patients were initially hospitalized during the acute phase of their disease. Some patients were rehospitalized during the follow-up period because of relapse or side effects. The length of hospital stay according to treatment group is shown in Table 3. The mean cumulative duration of hospitalization was shorter in the topical-corticosteroid group than in the oral-prednisone group: 11±11 days and 17±14 days, respectively, among patients with moderate bullous pemphigoid (P=0.02) and 17±14 days and 25±20 days, respectively, among those with extensive bullous pemphigoid (P=0.002).

DISCUSSION

Systemic corticosteroids have been considered the mainstay of treatment for bullous pemphigoid for 40 years.[3] However, this treatment is responsible for numerous side effects in elderly people and has been suspected of being associated with a mortality rate of up to 40 percent per year among elderly persons with bullous pemphigoid.[11,12,16-18,33,34] The present study confirms the poor prognosis of patients with bullous pemphigoid who are treated with 1 mg of prednisone per kilogram per day, among whom the one-year mortality rate was 41 percent. Among the patients who received topical treatment, there was no difference in overall survival between patients with moderate bullous pemphigoid and those with extensive bullous pemphigoid, suggesting that survival of patients with bullous pemphigoid is more likely to be related to the type of treatment than to the severity of disease.[11,27]

The present study was designed to test the hypothesis that topical corticosteroids could be an effective alternative treatment for patients with bullous pemphigoid and would result in a decrease in the incidence of severe adverse events. Our results clearly demonstrate the efficacy of clobetasol propionate cream. In all patients with moderate bullous pemphigoid and 99 percent of those with extensive bullous pemphigoid, the disease was controlled by day 21 — an improvement over oral-corticosteroid treatment that was significant among those with extensive disease. Moreover, the rates of control of disease in both subgroups of the oral-prednisone group were higher than those usually reported with oral corticosteroids.[27,35] This finding may be related to the high bioavailability of prednisone and seems consistent

TABLE 3. NUMBER OF HOSPITAL STAYS AND DURATION OF HOSPITALIZATION.*

VARIABLE	MODERATE DISEASE (≤10 NEW BULLAE/DAY)			EXTENSIVE DISEASE (>10 NEW BULLAE/DAY)		
	TOPICAL CLOBETASOL PROPIONATE (N=77)	ORAL PREDNISONE (N=76)	P VALUE	TOPICAL CLOBETASOL PROPIONATE (N=93)	ORAL PREDNISONE (N=95)	P VALUE
Cumulative duration of hospitalization (days)	11±11	17±14	0.02	17±14	25±20	0.002
Duration of initial hospitalization (days)	9±10	12±10	0.16	13±8	17±10	0.002
Rehospitalization						
No. of patients	18	20		22	31	
No. of rehospitalizations for rehospitalized patients	1.2±0.4	1.5±0.6		1.4±0.6	1.5±0.7	
Cumulative duration for rehospitalized patients (days)	11±8	21±13		18±12	25±25	
Cumulative duration among all patients (days)	2±6	5±11	0.04	4±10	8±18	0.08

*Plus–minus values are means ±SD. Student's t-test was used to compare the mean durations of hospitalization.

with the greater effectiveness reported for prednisone than for prednisolone in controlling bullous pemphigoid.[35]

The main finding of this study is the significant and substantial improvement in outcome among patients with extensive bullous pemphigoid who were treated with clobetasol propionate cream, as compared with those treated with 1 mg per kilogram per day of oral prednisone. This difference was observed consistently for all the outcomes we studied: overall survival, control of disease, occurrence of severe side effects, and duration of hospitalization.

It is important to consider whether the nonblinded nature of the study may have biased our results. We think such bias is unlikely, for several reasons. First, it is unlikely that overall survival, our primary end point, could be subject to such bias. Moreover, bias concerning secondary end points is unlikely as well, because most were graded semiquantitatively and were not directly dependent on subjective judgment. Indeed, assessment of the control of disease was based on the determination of the number of new bullae that appeared daily by nurses who were not directly involved in the study, and most grade 3 and grade 4 side effects represented well-known side effects of corticosteroids that were characterized biologically (diabetes mellitus), radiologically (stroke, pneumonia, and bone fracture), or bacteriologically (septicemia, arthritis, and peritonitis). Differences in the cumulative duration of hospitalization were due, at least in part, to rehospitalizations initiated by the patients' general practitioners — not by study investigators — because of side effects of the treatments.

Our study demonstrates the superiority of an alternative treatment regimen over oral corticosteroids in the treatment of extensive bullous pemphigoid, in terms of both the control of disease and survival. In patients with extensive bullous pemphigoid, topical corticosteroids led to a 43 percent reduction (95 percent confidence interval, 19 to 69 percent) in the one-year mortality rate. This benefit is further supported by the demonstration of a 50 percent reduction in the mortality rate (95 percent confidence interval, 15 to 71 percent) after adjustment by Cox regression for age and Karnofsky score — two factors strongly suspected to be related to the prognosis in patients with bullous pemphigoid.[11] The chief explanation for the present results is the fact that topical treatment has lower toxicity than 1 mg of prednisone per kilogram per day, as demonstrated by the fact that fewer patients in the topical-corticosteroid group had severe side effects of treatment. This difference was particularly marked in the case of side effects, such as sepsis and diabetes mellitus requiring insulin, that are classically reported with high-dose systemic corticosteroids. Our results suggest that topical corticosteroids should be considered the standard treatment for patients with extensive bullous pemphigoid.

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APPENDIX

The following persons also participated in the Bullous Diseases French Study. *Investigators:* P. Saiag, M.D., Ph.D., Boulogne Billancourt; E. Tancrede-Bohin, M.D., Paris; B. Sassolas, M.D., Brest; C. Lok, M.D., Ph.D.,

Amiens; B. Labeille, M.D., Valence; J.C. Guillaume, M.D., Colmar; F. Loche, M.D., Toulouse; M.S. Doutre, M.D., Ph.D., Bordeaux; I. Gorin, M.D., Paris; O. Chosidow, M.D., Ph.D., Paris; C. Pauwels, M.D., Saint Germain en Laye. *Contributors:* C. Neveu, M.D., Lillebonne; M.F. Hellot, M.Sc., Rouen; I. Noblesse, M.D., Rouen.

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