A Systematic Review of Treatments for Bullous Pemphigoid

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Objective: To assess the effectiveness of treatments for bullous pemphigoid.

Methods: The Cochrane Library search strategy was used to identify randomized controlled trials from MEDLINE and EMBASE, from their inception to September 30, 2001. All randomized controlled trials on interventions for bullous pemphigoid, confirmed by immunofluorescence studies, were included.

Results: We found 6 randomized controlled trials with a total of 293 patients. Two trials, one comparing prednisolone, 0.75 mg/kg per day, with prednisolone, 1.25 mg/kg per day, and the other comparing methylprednisolone with prednisolone, did not find any significant difference in effectiveness. The higher dose of prednisolone, however, was associated with more severe adverse effects. Combination treatments of prednisone with azathioprine in one trial and of prednisolone with plasma exchange in another were useful in halving the corticosteroid dose required (mean±SD, 0.52±0.28 mg/kg in the plasma exchange–treated group vs 0.97±0.33 mg/kg in the prednisolone only–treated group). However, a fifth trial, including all 3 treatment groups (prednisolone alone, prednisolone and azathioprine, and prednisolone and plasma exchange), failed to confirm the benefit of combination treatment over prednisolone alone. A trial of 20 patients, comparing prednisone with tetracycline and niacinamide, found no statistically significant difference in response between the 2 groups, but the prednisone-treated group had more serious adverse effects.

Conclusions: There is inadequate evidence for a recommendation of a specific treatment for bullous pemphigoid, and there is a need for larger randomized controlled trials with adequate power. Starting doses of prednisolone greater than 0.75 mg/kg per day do not seem to give additional benefit, and it seems that lower doses may be adequate for disease control. The effectiveness of the addition of plasma exchange or azathioprine to corticosteroids has not been established. Combination treatment with tetracycline and niacinamide seems useful, although this needs further validation.

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BULLOUS PEMPHIGOID is the most common autoimmune blistering disease in the West. It is usually a disease of elderly persons, but it can also affect younger adults and children. The incidence is the same in both sexes. The characteristic clinical picture is the development of tense blisters, which may arise on inflamed or normal-appearing skin. Immunofluorescence (IF) is the most reliable investigation for making the diagnosis: direct IF demonstrates deposits of the autoantibodies at the dermoepidermal junction, and indirect IF demonstrates circulating autoantibodies directed against basement membrane proteins that are localized to the epidermal side of the salt-split skin. The natural history of treated and untreated bullous pemphigoid shows a long-term course within which relapses and exacerbations may occur. However, in most patients, the disease is in remission within 5 years.1,3,4

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Treatments include corticosteroids, antibiotics, and immunosuppressants. Some of these interventions have the potential for severe adverse effects, such as increased susceptibility to serious infections and organ damage, and some are expensive to use. There is also variation in the long-term toxic effect of systemic agents, ranging from mild (antibiotics) to severe (corticosteroids or immunosuppressants). There is wide variation in practice among clinicians as to which drugs or interventions are used and in what order or combinations. This review aimed to establish the following: (1) the most ef-
MATERIALS AND METHODS

The Cochrane Library extended search strategy was used to identify randomized controlled trials (RCTs) from MEDLINE and EMBASE, from their inception to January 30, 2000, and again to September 30, 2001. The Cochrane Controlled Trials Register and hand-searched trials awaiting incorporation into the Cochrane Controlled Trials Register were also examined.

Abstracts of potentially relevant studies were screened, and full articles were obtained if necessary. Articles that were possibleRCTs were assessed for eligibility using the inclusion criteria outlined in the protocol. Each study was individually and critically appraised using a checklist to assess methodological quality (such as concealment allocation, blinded outcome assessment, and inclusion of all randomized patients in the analysis). The bibliographies from identified studies were also searched.

All RCTs of therapeutic interventions that included patients with bullous pemphigoid confirmed by IF studies and all age groups were included.

Data were extracted from all included studies using a predefined data extraction form for the following outcome measures: (1) rate of regression or healing of the skin lesions when first treated and how soon new blisters stopped appearing; (2) effect on the quality of life (ie, relief of soreness or pruritus); (3) duration of remission after stopping treatment; (4) complications of the primary disease (bullous pemphigoid) (eg, a localized skin infection); (5) systemic infection, which may be a result of either the primary disease or the treatment; (6) adverse effects of treatment (eg, organ failure or allergic reactions); and (7) mortality as a result of the primary disease or treatment.

effective drugs or interventions with the least adverse effects; (2) whether combination therapy (eg, azathioprine plus corticosteroids) offers any advantages over single drugs (eg, oral corticosteroids alone); and (3) whether antimicrobials, such as tetracyclines, erythromycin, dapsone, or sulfonamides, are useful.

RESULTS

We identified 72 abstracts from MEDLINE, 27 from EMBASE, and 5 from the Cochrane Controlled Trials Register (Table 1); of these, only 6 were RCTs, with a total of 293 patients. These RCTs were all small trials; none used indirect IF on salt-split skin to make the diagnosis or had a placebo group, and oral corticosteroids were considered standard treatment. The first 2 outcome measures in our protocol were only addressed by one trial each, and none of the trials addressed the third (Table 2). The adverse effects of medication were recorded in varying detail in the different trials (Table 3).

Two trials, one by Dreno and coworkers6 comparing 2 formulations (methylprednisolone with prednisolone) and a second by Morel and Guillaume7 comparing different doses of prednisolone (0.75 vs 1.25 mg/kg per day), did not find any statistical difference in the groups compared for effectiveness. There were more adverse effects associated with the higher dose of prednisolone (Tables 2 and 3).

Burton et al,8 who compared prednisone with prednisone and azathioprine, found a 45% reduction in the amount of prednisone taken by the azathioprine-treated group during a 3-year period.9 The definition of disease control was not stated, and not much clinical data were available. This trial excluded patients with contraindications to oral corticosteroids or azathioprine and those “unlikely to attend follow-up.” Another problem with this trial was that patients were “started on oral prednisone 30-80 mg/day, to suppress new blisters” and then only “did the consultant decide whether to include the patient in the trial.” They compared prednisolone with prednisolone and plasma exchange, and found that disease control was achieved with less than half the total prednisolone dose in the plasma exchange–treated group. They used low-dose prednisolone (0.3 mg/kg) initially, but control was achieved with a mean±SD daily prednisolone dose of 0.52±0.28 mg/kg in the plasma exchange–treated group vs 0.97±0.33 mg/kg in the prednisolone only–treated group. They found a similar adverse effect profile in both groups, and the disease was controlled within weeks (mean±SD, 41±14 vs 32.5±2.0 days for the prednisolone only–treated group vs the plasma exchange–treated group). This trial excluded patients older than 80 years and was not blinded.

However, a fifth trial by Guillaume and coworkers10 included all 3 treatment groups (prednisolone alone, prednisolone and azathioprine, and prednisolone and plasma exchange). It failed to confirm the benefit of combination treatments over prednisolone alone. The adverse effects were not given in detail for each group (except for those listed in Table 3), but the researchers stated that “most of the adverse events could be attributed to corticosteroids.”

The sixth trial,11 comparing prednisone with tetracycline and niacinamide, suggested that there was no statistically significant difference in response to treatment between the 2 groups, but that the prednisone-treated group had more serious adverse effects. Unfortunately, this trial included few patients, two thirds of whom were in the tetracycline-treated group (14 of the 20 patients). The randomization in this study was unclear, and there was a high dropout rate (2 patients in the tetracycline-treated group at 2 months, and 12 patients from both

*Table 1. Retrieved Trials of Treatment of Bullous Pemphigoid by Database*

<table>
<thead>
<tr>
<th>Source, y</th>
<th>MEDLINE</th>
<th>EMBASE</th>
<th>Cochrane Controlled Trials Register</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dreno et al,6 1993</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morel and Guillaume,7 1984</td>
<td>X</td>
<td></td>
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<tr>
<td>Burton et al,8 1978</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Roujeau et al,9 1984</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>Guillaume et al,10 1993</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Fivenson et al,11 1994</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>

*X indicates that this was a randomized controlled trial.*
groups by the end of the study). At 10 months, there were only 3 patients left in the corticosteroid-treated group (2 of whom had multiple recurrences) and only 5 left in the tetracycline-treated group (all of whom remained disease free during medication tapering). The prednisone-treated group was associated with more severe adverse effects (including a death due to sepsis) and disease recurrence.

Table 3 includes the adverse effects in each trial. There are more adverse effects associated with corticosteroids, and these seem to increase with higher doses. Only a 70-kg Patient, mg/d

<table>
<thead>
<tr>
<th>Source, y</th>
<th>Methods</th>
<th>Equivalent Prednisone or Prednisolone Dose for a 70-kg Patient, mg/d</th>
<th>Follow-up</th>
<th>Major Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dreno et al, 1993</td>
<td>Randomized double-blind trial of prednisolone, 1.16 mg/kg (n = 29), vs methylprednisolone, 1.17 mg/kg (n = 28); problem: “scale” for measuring symptoms and signs</td>
<td>81 vs 82</td>
<td>10 d</td>
<td>Disease control defined as a reduction of blisters, redness, and itching by ≥50%; there was no significant difference in the number of blisters and erythema, but there was a significant (P = .04) reduction in pruritus in the methylprednisolone-treated group</td>
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<tr>
<td>Morel and Guillaume, 1984</td>
<td>Randomized, not blinded, trial of prednisolone, 0.75 mg/kg (n = 26), vs prednisolone, 1.25 mg/kg (n = 24); there were 2 dropouts in each group (no reasons given), and they were not included in the analysis; erythromycin was used for infection, but its anti-inflammatory effect was not evaluated</td>
<td>52.5 vs 87.5</td>
<td>51 d</td>
<td>Disease control defined as no new blisters on days 21-51; there was no significant difference in effectiveness (58% vs 64% clearing of skin lesions on day 21 and 33% vs 55% on day 51), but there were more adverse effects with the higher dose</td>
</tr>
<tr>
<td>Burton et al, 1978</td>
<td>After 1 wk of prednisone therapy to suppress lesions, “consultant decided” whether to include patients in the trial; randomized, not blinded, trial of prednisone, 30-80 mg (n = 13), vs azathioprine, 2.5 mg/kg, and prednisone, 30-80 mg (n = 12); it is not clear how the prednisone dose was decided or how the numbers of patients taking lower and higher doses in each group were determined</td>
<td>30-80</td>
<td>3 y</td>
<td>Disease control not defined; there were no clinical data; lower total-dose corticosteroids, 6732 vs 3688 mg during a 3-year period (45% reduction), were given to the azathioprine-treated group</td>
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<tr>
<td>Roujeau et al, 1984</td>
<td>Randomized, not blinded, trial of prednisolone, 0.3 mg/kg (n = 17), vs plasma exchange plus prednisolone, 0.3 mg/kg (n = 24); those older than 80 y were excluded; 2 patients from each group were withdrawn from the study (reasons not given) and were not included in the analysis</td>
<td>21</td>
<td>6 mo</td>
<td>Disease control defined as the complete disappearance of blisters, itching, and erythema (mean ± SD, 41 ± 14 vs 32.5 ± 2.6 d in the prednisolone only–treated group vs the plasma exchange–treated group); control of the disease was achieved with a lower total dose of corticosteroids in the plasma exchange–treated group (1240 ± 728 mg [0.52 ± 0.28 mg/kg] vs the prednisolone only–treated group [2770 ± 1600 mg [0.97 ± 0.33 mg/kg]])</td>
</tr>
<tr>
<td>Guillaume et al, 1993</td>
<td>Randomized, not blinded, trial of prednisolone, 1 mg/kg per day (n = 32), vs azathioprine plus prednisolone, 1 mg/kg per day (n = 36), vs plasma exchange plus prednisolone, 1 mg/kg per day (n = 32); there were 2 dropouts, 1 each from the prednisolone only– and the plasma exchange–treated groups, and they were not included in the analysis</td>
<td>70</td>
<td>6 mo</td>
<td>Disease control defined as no new blisters for 4 wk; similar effectiveness was found in all 3 groups at 28 d (71%, 80%, and 71%, respectively) and at 6 mo (42%, 39%, and 29%, respectively); severe complications were more often noted in the azathioprine-treated group</td>
</tr>
<tr>
<td>Fivenson et al, 1994</td>
<td>Randomized (method not stated), not blinded, trial of prednisolone, 40-80 mg (n = 6), vs niacinamide, 1.5 g/d, in 3 divided doses, plus tetracycline, 2 g/d, in 4 divided doses (n = 14); there were 2 dropouts within the initial 8 wk, and only 3 patients remained in the prednisone-treated group (2 had relapses) and 5 in the tetracycline-treated group (who remained disease free) at the end of the study at 10 mo</td>
<td>40-80 (exact dose not specified, only range given)</td>
<td>2 and 10 mo</td>
<td>Disease control defined as complete (100%) clearing after an 8-wk prescription, partial clearing (~50%), and no response (~25% reduction in blisters and itching); at 8 wk, there were 1 complete and 5 partial responders in the prednisone-treated group vs 5 complete and 5 partial responders and 1 disease progression in the tetracycline-treated group</td>
</tr>
</tbody>
</table>

*Methylprednisolone, 4 mg, is equivalent to prednisone or prednisolone, 5 mg.**
is probably irrelevant for this adverse effect because of a follow-up period of only 10 days. The second, the Roujeau et al\textsuperscript{8} trial, had a follow-up comparable to that of other trials but used significantly lower starting doses of prednisolone (0.3 mg/kg per day). Azathioprine was mostly associated with a reduction in the white blood cell count (2 of 12 patients in the Burton et al\textsuperscript{8} trial and 4 of 36 patients in the Guillaume et al\textsuperscript{9,10} trial). It was not possible to pool the data in a meta-analysis because the studies were heterogeneous.

### Comment

Four of the studies\textsuperscript{6,7,9,10} in this review are French, and 3\textsuperscript{7,9,10} are from a multicentric group in France. Morel was a coauthor in 2 studies\textsuperscript{7,9}; Guillaume in 3\textsuperscript{7,9,10}, and Crickx, Labelle, and Guillot in the same 2.\textsuperscript{9,10} Roujeau was the lead author in one study\textsuperscript{9} and the senior author in another.\textsuperscript{10} The 2 studies from the same group did not overlap in time (1980-1982\textsuperscript{8} and 1984-1989\textsuperscript{10}) and used different dosing regimens of prednisolone. It is unclear if the same patients participated in both studies, as the later study only excluded those who had received oral immunosuppressants in the previous month. The definition of disease control changed, and higher doses of prednisolone were used in the later study\textsuperscript{10}, plasma exchange was a comparison treatment in the 2 studies.\textsuperscript{9,10} with the addition of azothiaprine in the later study.

The studies in this review used oral prednisolone or prednisone in the control group (no comparison with placebo) and are all small trials. Prednisone is converted to the biologically active form, prednisolone, in the liver by the action of 11-\(\beta\)-hydroxydehydrogenase enzyme. Thus, liver disease could impair this conversion. In healthy patients, however, the time to peak levels and half-lives of prednisone and prednisolone are different, as can be seen when looking at the definition of disease control and the interventions used (Table 2).
The short follow-up periods in some of the studies (eg, 10 days in one) make judgment of the significance of the results difficult, especially in view of the long-term nature of this disease. The aim of the Morel and Guillaumé study was to compare the starting dose of prednisolone, so perhaps the follow-up of only 51 days may be more reasonable. The study with the longest follow-up (3 years) had little clinical data.

Probably the most interesting feature of the Roujeau et al study was the lower dose of prednisolone used in both treatment groups. Strict measures of disease control were used (complete disappearance of blisters, pruritus, and erythema), and in both groups, the disease was controlled within weeks (mean±SD, 41±14 vs 32.5±2.0 days for the prednisolone only–treated group vs the plasma exchange–treated group); however, higher doses were needed to achieve disease control. There were no deaths during the study, but this may be partly because of the exclusion of patients older than 80 years. This study found that the plasma exchange–treated group required much less prednisolone than the prednisolone only–treated group. This benefit was, however, not confirmed by the Guillaumé et al study. This latter study also failed to confirm the benefit of the addition of azathioprine to prednisolone.

The Fivenson et al study11 had a flawed method of randomization, a high dropout rate, and small numbers, but does suggest merit in the use of tetracycline and niacinamide. However, further study is needed to confirm these findings.

Because it is unlikely that future studies on interventions for bullous pemphigoid including a placebo group would ever obtain ethics committee approval, a comparison of low-dose prednisolone with tetracyclines and niacinamide (or potent topical corticosteroids for mild and/or localized disease) may prove a worthy alternative. Uncontrolled studies12-19 have suggested the successful use of topical corticosteroids as a first-line treatment for localized and mild disease, and a recent abstract of an RCT20 seems to confirm this view. The use of potent topical corticosteroids is favored because they have minimal adverse effects and a limited number of contraindications.

The results of this review show a need for larger RCTs (with adequate power) of treatments for bullous pemphigoid. The numbers needed can probably only be achieved in multicenter trials. The available evidence is inadequate for a confident recommendation of optimal treatment. However, it seems that a less aggressive approach with lower doses of corticosteroids might be adequate and associated with less morbidity and mortality. The value of the addition of azathioprine and plasma exchange to oral corticosteroids remains doubtful.

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