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Randomized Controlled Trials Needed for Bullous Pemphigoid Interventions

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Abstract

Background—Bullous pemphigoid (BP) is the most common autoimmune blistering disease in the West. Oral steroids are the standard treatment. This is an update of the review published in 2005.

Objectives—To assess treatments for bullous pemphigoid.

Search Strategy—In August 2010 we updated our searches of the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (Clinical Trials), MEDLINE, EMBASE, and the Ongoing Trials registers.

Selection Criteria—Randomized controlled trials of treatments for participants with immunofluorescence-confirmed bullous pemphigoid.

Data Collection And Analysis—At least two authors evaluated the studies for the inclusion criteria, and extracted data independently.

Main Results—We included 10 randomized controlled trials (with a total of 1049 participants) of moderate to high risk of bias. All studies involved different comparisons, none had a placebo group. In 1 trial plasma exchange plus prednisone gave significantly better disease control at 1 month (0.3 mg/kg: RR 18.78, 95% CI 1.20 to 293.70) than prednisone alone (1.0 mg/kg:RR1.79, 95% CI 1.11 to 2.90), while another trial showed no difference in disease control at 6months. No differences in disease control were seen for different doses or formulations of prednisolone (one trial each), for azathioprine plus prednisone compared with prednisone alone (one trial), for prednisolone plus azathioprine compared with prednisolone plus plasma exchange (one trial), for prednisolone plus mycophenolate mofetil or plus azathioprine (one trial), for tetracycline plus nicotinamide compared with prednisolone (one trial). Chinese traditional medicine plus

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prednisone was not effective in one trial. There were no significant differences in healing in a comparison of a standard regimen of topical steroids (clobetasol) with a milder regimen (RR 1.00, 95% 0.97 to 1.03) in one trial. In another trial, clobetasol showed significantly more disease control than oral prednisolone in people with extensive and moderate disease (RR 1.09, 95% CI 1.02 to 1.17), with significantly reduced mortality and adverse events (RR 1.06, 95% CI 1.00 to 1.12).

Authors' Conclusions—Very potent topical steroids are effective and safe treatments for BP, but their use in extensive disease may be limited by side-effects and practical factors. Milder regimens (using lower doses of steroids) are safe and effective in moderate BP. Starting doses of prednisolone greater than 0.75 mg/kg/day do not give additional benefit, lower doses may be adequate to control disease and reduce the incidence and severity of adverse reactions. The effectiveness of adding plasma exchange, azathioprine or mycophenolate mofetil to corticosteroids, and combination treatment with tetracycline and nicotinamide needs further investigation.

Comment

Bullous pemphigoid (BP) is an acquired common autoimmune blistering disease seen predominantly in elderly people, where disease-specific autoantibodies (BPAg1 and BPAg2) are directed against components of the basement membrane zone of the skin. Typically, there are generalized tense blisters, sometimes overlying urticarial or eczematous skin lesions. Pruritus is frequently intense, and lesions may affect mucosal surfaces. Bullous pemphigoid may resolve with treatment but frequently has relapses and exacerbations. The mortality rate is high, despite treatment, secondary to debilitation or adverse effects of treatment, which is why finding an effective, safe treatment is important. There are several available treatments such as oral and topical corticosteroids; immunosuppressive agents such as mycophenolate mofetil, azathioprine, and cyclosporine; and antiinflammatory agents such as dapsone. All regimens are based more on clinical experience than on controlled studies.

In their article, Kirtschig et al review 10 randomized controlled trials comprising 1049 patients, focusing on healing of the skin lesions as the primary outcome; quality of life, duration of remissions, complications, systemic infections and adverse effects of treatment were the secondary outcomes. Each of the trials had a potential source of bias, and the follow-up periods were varied and short (10–51 days) (Table). Also, the trials did not share the same quality of design.

Two of the studies involved different systemic steroid regimens, which are still considered first-line agents.[1,2] The authors found no difference in the effectiveness between prednisolone at doses of 0.75 mg/kg/d and 1.25 mg/kg/d, and thus concluded that a higher dose of steroid did not improve healing rates but did increase mortality (3 deaths of 22 participants in the higher-dose group compared with 2 of 24 in the lower-dose group; relative risk, 1.64).[1] The use of methylprednisolone vs prednisolone did not result in any significant differences in overall improvement, but the follow-up was only 10 days, which did not allow any conclusions to be reached.[2]

Two studies analyzed the benefit of adding immunosuppressive agents to systemic steroid therapy.[3,10] Beissert et al[10] compared oral methylprednisolone plus azathioprine vs oral methylprednisolone plus mycophenolate mofetil. Both regimens were equally effective, although azathioprine was better because this group achieved remission faster and used less total cumulative methylprednisolone, but it also had more serious adverse effects. There was no corticosteroid monotherapy arm, and thus the level of corticosteroid-sparing effects of each agent could not be determined.

Burton et al[3] compared the addition of azathioprine to a prednisone regimen and found that it reduced the total maintenance dose of prednisone by 45% without increasing serious adverse effects or mortality. The follow-up time was 3 years, but the total prednisone dose, not milligrams per kilogram, was recorded.

Two studies analyzed the addition of plasma exchange to baseline treatment.[4,5] Roujeau et al[5] compared prednisolone with and without plasma exchange. They found that the addition of plasma exchange reduced the amount of steroid required and made remission possible (disease control was achieved in 13 of 22 participants compared with none in the prednisolone-only group). In this study the prednisolone dose range varied substantially from patient to patient.

This beneficial effect of adding plasma exchange was not replicated in a later study,[4] where no differences in remission or death rates were found in patients treated with prednisolone alone, prednisolone combined with azathioprine, or prednisolone combined with 4 large-volume plasma exchanges. The azathioprine group did have more serious adverse events (15 patients of 36, including 6 deaths).

Regarding topical steroids, Joly et al[7] compared clobetasol propionate vs prednisone. Patients with moderate disease had similar disease control rates; 1-year survival rates; and adverse effects rates; but patients with extensive disease had better disease control with clobetasol than with prednisone (99% compared with 91% at 3 weeks, not statistically significant); higher 1-year survival rates; and fewer adverse effects. Although this study was not blinded and thus could be biased, we can infer that mild to moderate disease can be controlled with topical steroids, and even in severe disease the addition of topical steroids might reduce, or even eliminate, the need for systemic treatment, consequently reducing adverse effects and mortality of the disease.

A more recent study by the same group compared 2 different regimens of topical steroids depending on severity of disease and body weight.[8] The standard regimen was 40 g/d, and the mild regimen was 10 to 30 g/d. All patients had similar disease control (156 of 159 cases were controlled with the mild regimen, and 150 of 153 with the standard regimen) and similar relapse rates in a period of 21 days, but the median cumulative dose of steroid cream used was 70% lower in the mild-regimen group. Mortality appears to be decreased in patients with moderate disease treated with the mild regimen.

Two studies using treatments other than steroids and immunosuppressants were reviewed.[6,9] The comparison of prednisone vs tetracycline and nicotinamide found similar complete and partial response rates, but the patients available for follow-up showed longer disease-free

periods in the tetracycline group.[6] These results are promising, but this study was not properly randomized; it included few patients; had a high dropout rate; and not many patients were observed.

Liu et al[9] compared prednisone with and without a traditional Chinese medicine, the jingui shenqi pill. There were no differences between groups in disease control or mortality.

It is not easy to determine an optimal treatment from this meta-analysis because the studies were very heterogeneous in their design. The search for an effective, safe therapy is complicated because the patients with BP included in these studies were elderly and had multiple comorbidities, making the attribution of adverse effects and mortality rates to the treatments more challenging.

It is not clear that adding azathioprine, mycophenolate mofetil, or plasma exchange to systemic steroid regimens helps to control disease or reduce steroid dose. In addition, it has been previously demonstrated that some available prednisolone salts are not bioequivalent, and their efficacy might be less than prednisone, making comparison between studies difficult.[11,12]

There are several important lessons from this meta-analysis that are applicable to clinical practice:

- Topical steroids are an effective treatment for BP: they reduce the need for systemic treatment and have less serious adverse effects. When possible, they should be the first-line treatment in moderate or localized BP. However, compliance with topical treatment is hard for patients who are not in nursing homes or do not receive adequate home care.
- Prednisone or prednisolone doses greater than 0.75 mg/kg/d may not be beneficial and may increase adverse effects and mortality associated with treatment.
- Adding another immunosuppressive agent in severe cases of BP may be beneficial but might increase adverse reactions, especially altered liver function with azathioprine.
- The efficacy of tetracycline and nicotinamide needs further study, but it is a safe, relatively benign treatment that appears to be beneficial in disease control and in achieving longer remission periods.

There are many other treatments that need to be compared and tried in randomized trials, including topical tacrolimus, dapsone, anti-CD20 monoclonal antibody (rituximab), doxycycline, leflunomide, anti-IgE monoclonal antibody (Omalizumab), immunoadsorption/immunoapheresis, and intravenous immunoglobulin. These might provide promising new therapies with less adverse effects, including death.

Finally, a severity measure and disease end points were recently derived by an international consensus group, working with the International Pemphigus and Pemphigoid Foundation (IPPF), and should be used for design and interpretation of trials as well as for clinical evaluation of patients with BP.[13]

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Table

Randomized Controlled Trials for Bullous Pemphigoid

Source	Intervention	Sample Size	Outcomes	Follow-up	Mortality	Adverse Effects
Morel and Guillaume,[1] 1984	Prednisolone, 0.75 mg/kg vs 1.25 mg/kg	26 vs 24 patients	No difference between doses at 21 and 51 d	51 d	3 Deaths in the higher dose vs 2 deaths in the lower dose group	Not reported
Dreno et al,[2] 1993	Methylprednisolone vs prednisolone	28 vs 29 patients	Overall improvement in number of blisters and pruritus in both groups	10 d	No deaths	Not reported
Burton et al,[3] 1978	Prednisone + azathioprine vs prednisone	12 vs 13 patients	No difference in disease control, but azathioprine reduced total dose of prednisone by 45%	3 y	Overall mortality of 28% (7 of 25); no differences between groups	Reduction in the white blood cell count in 2 of 12 participants in the azathioprine group
Guillaume et al,[4] 1993	Prednisolone + plasma exchange vs prednisolone + azathioprine vs prednisolone	31 vs 36 vs 31 patients	45% Reduction in the amount of prednisone required for disease control in the azathioprine group (statistically significant). No favorable effect of adding plasma exchange was seen	6 mo	3 of 31 vs 6 of 36 vs 5 of 31 deaths	Complications more often in the azathioprine group (not statistically significant), specifically reduction in the white blood cell counts
Roujeau et al,[5] 1984	Prednisolone + plasma exchange vs prednisolone	22 vs 15 patients	Addition of plasma exchange reduced amount of prednisolone required for disease control (statistically significant)	1 mo	No Deaths during the treatment period	Adverse effects related to steroids and the plasma exchange procedure
Fivenson et al,[6] 1994	Prednisolone vs tetracycline + nicotinamide	6 vs 12 patients	All 5 patients in tetracycline group available for follow-up remained disease free; the 3 remaining participants in steroid group had multiple flares	8 wk	1 Death due to sepsis in the prednisone group	Fewer adverse effects in the nicotinamide/ tetracycline group, most of them mild
Joly et al,[7] 2002	Clobetasol propionate vs prednisone, 0.5 mg/kg and 1 mg/kg	Moderate disease: 77 clobetasol propionate vs 76 prednisone; extensive disease: 93 clobetasol propionate vs 95 prednisone	100% Disease control in both groups, but patients with extensive disease had better control with clobetasol	3 wk	Survival rate of 76% vs 58% in the topical steroids vs oral steroid group	More adverse events in oral steroids group (statistically significant) in the group with extensive disease
Joly et al,[8] 2009	Two different regimens of clobetasol propionate: mild dose (10–30 g/d depending of severity of disease and weight) vs standard dose (40 g/d)	69 received 10–20 g/d; 90 received 20–30 g/d; 153 received 40 g/d	Patients with moderate disease: control at 21 d in 68 of 69 using mild regimen; 63 of 65 using standard regimen. Of those with extensive	21 d	No difference between the groups; adjusted analysis showed 2-fold	Adverse effects related to steroid use, more frequent in the standard regimen group

Source	Intervention	Sample Size	Outcomes	Follow-up	Mortality	Adverse Effects
			disease, control in 88 of 90 using mild regimen and 87 of 88 using standard regimen. 70% reduction in the cumulative doses of cream used in mild regimen		decrease in risk of death in mild regimen	
Liu et al,[9] 2006	Jingui shenqi pill, 1 + prednisone, 0.5 to 1 mg/kg vs prednisone, 0.5 to 1 mg/kg	30 patients	Overall effectiveness in 93.33% of combined therapy group vs 73.33% of prednisone group	4 wk	No deaths	Not reported
Beissert et al,[10] 2007	Methylprednisolone + azathioprine vs methylprednisolone + mycophenolate mofetil	38 vs 35 patients	The azathioprine group achieved remission faster and used less total cumulative methylprednisolone, although equal effectiveness	303 d	2 Deaths in azathioprine group, not treatment related	24% vs 17% More adverse effects in the azathioprine group vs mycophenolate mofetil