Interventions for Mucous Membrane Pemphigoid/
Cicatricial Pemphigoid and
Epidermolysis Bullosa Acquisita

A Systematic Literature Review

Gudula Kirtschig, MD; Dédée Murrell, FAAD; Fenella Wojnarowska, DM; Nonhlanhla Khumalo

Objective: To identify and critically evaluate evidence from randomized controlled trials for the efficacy of treatments for mucous membrane pemphigoid (MMP)/cicatricial pemphigoid (CP) and epidermolysis bullosa acquisita (EBA).

Search Strategy: Review of MEDLINE from 1966 through March 2000, EMBASE from 1980 through March 2000, and the Cochrane Controlled Trials Register (February 28, 2001) to identify randomized controlled trials for the efficacy of treatments in MMP/CP and EBA.

Selection Criteria: All randomized controlled trials of therapeutic interventions that included patients with MMP/CP or EBA confirmed by immunofluorescence study findings. All age groups were included.

Results: We found 2 small randomized controlled trials of MMP/CP, both conducted in patients with severe eye involvement. We were not able to identify a randomized controlled trial of therapeutic interventions in EBA.

Conclusions: There is evidence from 2 small trials that severe ocular CP responds best to treatment with cyclophosphamide, and mild to moderate disease seems effectively suppressed by treatment with dapsone. No treatment recommendations can be made for EBA because to our knowledge no randomized controlled trials are published. Even though systemic corticosteroids are regarded as the gold standard in the treatment of MMP/CP and EBA, there is poor evidence from the literature that they are the best treatment for these diseases.

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Mucous membrane pemphigoid (MMP) and epidermolysis bullosa acquisita (EBA) are acquired autoimmune bullous disorders of the skin.1-3 In the present study, we have followed the suggestion by Chan et al4 that MMP should replace the name cicatricial pemphigoid.

In MMP and EBA, direct immunofluorescence demonstrates deposits of IgG and C3 at the dermoepidermal junction, and on indirect immunofluorescence, circulating autoantibodies may be detected.1-3 The incidence of MMP and EBA in western Europe is calculated to be about 1 and 0.2 new cases per 1000000 inhabitants per year, respectively.3,6 Scar formation is a characteristic feature in both and may lead to major disability (eg, blindness) and life-threatening situations (eg, respiratory obstruction).

Both MMP and EBA are highly variable and often take a protracted course in contrast to bullous pemphigoid (BP), which usually remits within 5 years.1-3 Some patients with localized disease (eg, oral involvement [only in MMP]) remain stable for years in the absence of aggressive...
therapy. Some other patients may develop rapidly progressive ocular involvement despite treatment with immunosuppressants. The standard treatment for progressive disease is the administration of systemic corticosteroids at a dose of 1 to 2 mg of prednisolone equivalent per 1 kg of body weight, which is often combined with cyclophosphamide, azathioprine, or methotrexate; dapsone seems to be an alternative treatment in milder disease. These drugs, however, are accompanied by potentially life-threatening complications and may still not lead to the desired therapeutic effect. It is therefore reasonable to search for other treatment options with less severe adverse effects. Newer treatment regimens involve antibiotics, nicotinamide, and immunoglobulins, and these medications are usually better tolerated. Initial reports are promising, but it is not known whether recent alternative treatment regimens are equally or even more effective in patients with progressive disease than traditional medication. A review of the evidence is therefore needed to determine the following:

- Which are the most effective drugs or interventions with the least adverse effects?
- Does combination therapy (eg, azathioprine plus steroids) offer any advantages over single drugs (eg, oral steroids alone)?
- Are antibiotics such as tetracyclines, erythromycin, dapsone, and sulfonamides useful?
- Is systemic treatment better than topical treatment (topical cyclosporine or interferon) in patients with MMP or EBA?

RESULTS AND COMMENT

Ten reports of treatment for EBA involving 2 or more patients and 31 reports of treatment for MMP involving 5 or more patients were found. Some of the reports represent follow-ups of earlier studies. Two RCTs (trials 1 and 2) on the treatment of MMP were identified; no RCT for EBA was found.

The 2 RCTs compared treatments of progressive MMP affecting the eyes (Table 1). Both were small, randomized double-blind, non-placebo-controlled studies (grade C according to the criteria set out by Sackett). One
Table 1. Summary of Randomized Controlled Trials in the Treatment of Ocular Cicatricial Pemphigoid

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Intervention (6 mo)</th>
<th>Follow-up*</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Cyclophosphamide (2 mg/kg per day) and prednisone (1 mg/kg [initial dose], tapered until completely discontinued) vs Prednisone (1 mg/kg per day [initial dose], tapered to 0.25 mg/kg alternate days during 3 mo, then 3-mo maintenance dose)</td>
<td>6 mo (prescription of cyclophosphamide continued?) vs 6 mo (prescription of prednisone continued?)</td>
<td>12 of 12 patients responded (8 wk) vs 5 of 12 patients responded (6 wk); incomplete cessation of inflammation after 3 mo in 7 of 12 patients; 7 of 12 patients responded to cyclophosphamide</td>
</tr>
<tr>
<td>20</td>
<td>Dapsone (2 mg/kg per day) vs Cyclophosphamide (2 mg/kg per day)</td>
<td>6 mo? (prescription of dapsone continued?) vs 6 mo? (prescription of cyclophosphamide continued?)</td>
<td>14 of 20 patients responded, incomplete response in 4 of 20 patients, no response in 2 of 20 patients; good response to cyclophosphamide in 6 of 8 patients</td>
</tr>
</tbody>
</table>

*Question mark indicates that it was not clear if the treatment was continued after the trial period in the article by Foster.11

Included 24 patients with bilateral ocular stage III MMP (symblepharon formation); treatment with cyclophosphamide plus prednisone vs prednisone alone was tested. The second trial included 40 patients with stage III ocular MMP, but it did not mention if both eyes were affected; treatment with dapsone vs cyclophosphamide was tested. The 64 patients in the 2 trials were part of a study population of 130 patients with MMP involving the eyes collected between 1975 and 1985 at the Immunology and Uveitis Unit, Harvard Medical School, Boston, Mass. All 130 patients had bulbar conjunctival biopsies for histological investigation and direct immunofluorescence. All 64 RCT patients showed linear deposition of immunoglobulins at the basement membrane zone on direct immunofluorescence. All patients entered into the 2 trials completed the studies; none were lost to follow-up.

Trial 1 demonstrates a superior effect of cyclophosphamide and prednisone in combination compared with prednisone alone in the treatment of bilateral stage III MMP involving the eyes. The difference is statistically significant (χ² analysis, P<.005). It was not clear from the article whether the treatment was stopped after the 6-month treatment period. In discussing the treatment with C. S. Foster (the author of the 2 RCTs), we found out that the recommended duration of treatment is at least 1 year and usually longer.

In trial 2, cyclophosphamide is shown to be superior to dapsone in the treatment of patients with MMP and severe (4+) inflammation of the eyes. The 6 dapsone treatment failures included all 4 of the patients with 4+ conjunctival inflammation prior to therapy. The 2 remaining treatment failures had 3+ activity before treatment. All 6 patients responded well to cyclophosphamide therapy after 3 months of treatment with dapsone had failed to improve their disease. Foster concludes that dapsone is a reasonable first-choice medication for patients with MMP without very active and rapidly progressive disease, provided they are not glucose-6-phosphate dehydrogenase deficient. Foster recommends a dose starting at 25 mg twice daily for 1 week, increasing to 50 mg twice daily, with dosage adjustments based on therapeutic response and drug tolerance. A response can be expected within 4 weeks of treatment.

Adverse effects observed in both trials are listed in Table 2. None of the patients died during treatment or follow-up in either trial.

In trial 1, none of the patients withdrew from systemic immunosuppression because of adverse effects, and none required hospitalization for intervention of any adverse effect. The hair loss was reversible when treatment with cyclophosphamide was discontinued. Leukopenia was a routine finding in all patients successfully treated with cyclophosphamide. The leukopenia was reversible, and the cyclophosphamide dose was adjusted to achieve a leukocyte count between 2500/µL and 4000/µL. Macrocytic anemia was asymptomatic and of mild to moderate degree. Microcytic hematuria was discovered in routine urinalysis; an alteration in timing of cyclophosphamide administration and increased fluid intake eliminated this potentially serious adverse effect. Foster believes that systemic immunosuppression poses fewer risks if properly used compared with long-term corticosteroid therapy.

In trial 2, microcytic hematuria developed in 2 patients, necessitating a reduction of cyclophosphamide. Foster emphasizes that dapsone is not a benign drug, and death may occur as a result of agranulocytosis, aplastic anemia, or hemolytic anemia.

We found 30 additional studies of treatment in MMP involving 5 or more patients. Fourteen studies investigated patients with oral and generalized MMP,7,17-19,21-30 7 of which comment on sulfa drugs (dapsone, sulfapyridine, and sulfamethoxypyridazine); 68 of 106 patients benefited from this medication.5,17-19,22,23,29 Of the 14 studies, 3 discuss the use of oral vs topical steroids in oral MMP, the results of which are controversial.26-28 Minoxidil treatment is reported in 25 patients with generalized MMP.7,20,30 This medication seems beneficial in oral MMP (orodynia), although little effect is seen in ocular disease. Sixteen articles present patients with mainly ocu-
lar MMP. Three of these articles support the effectiveness of sulfa drugs in moderate ocular MMP. Elder et al. found sulfapyridine to be superior to dap- et al. describe no progression in 8 of 9 treated eyes vs if this is due to treatment or represents a spontaneous remit within a few years, and it is not possible to judge the effectiveness of sulfa drugs in moderate ocular MMP.; Donnenfeld et al. describe no progression in 8 of 9 treated eyes vs if this is due to treatment or represents a spontaneous remit within a few years, and it is not possible to judge the effectiveness of sulfa drugs in moderate ocular MMP. 

Recent trials report topical mitomycin to be beneficial in severe ocular MMP (14 patients); Donnenfeld et al. describe no progression in 8 of 9 treated eyes vs progression in 5 of 9 untreated eyes (internal control). Intravenous immunoglobulins have been successfully used in one study of 10 patients with ocular MMP resistant to conventional treatment. 

We identified 11 articles on treatment in EBA involving 2 or more patients, detailing results in 20 adults and 11 children. The adult patients were treated with various medications including systemic corticosteroids, immunosuppressants, dapsone, colchicine, and intravenous immunoglobulins; it is not possible to draw any conclusion regarding the superiority of any of these treatments. Most children were treated with systemic corticosteroids and/or dapsone. In children, EBA seems to remit within a few years, and it is not possible to judge if this is due to treatment or represents a spontaneous remission.

**CONCLUSIONS**

It is not possible to draw definite conclusions for the treatment of MMP or EBA. Long-term corticosteroid treatment puts patients at risk of serious complications and seems to be less effective than cyclophosphamide in suppressing scarring MMP involving the eyes. Mild to moderate MMP involving the eyes seems to respond well to dapsone in most patients; however, dapsone has potentially serious adverse effects as well.

No evidence-based recommendation can be given for the treatment of EBA. However, uncontrolled stud-
ies suggest that children seem to respond to treatment with a combination of systemic corticosteroids and dapsone. International multicenter RCTs involving larger numbers of patients are required to assess the best treatment for MMP and EBA. Perhaps newer treatments with anti-inflammatory antibiotics such as tetracycline and minocycline are as effective as dapsone and have the benefit of fewer adverse effects.

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**Table 2. Adverse Effects Observed in Ocular Cicatricial Pemphigoid During 1-Year Treatment and Follow-up**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Prednisone (n = 12)</th>
<th>Cyclophosphamide (n = 12)</th>
<th>Cyclophosphamide (n = 20)</th>
<th>Dapsone (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>10</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Severe leukopenia</td>
<td>0</td>
<td>1</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>12</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Hematruia</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Abdominal pain</td>
<td>0</td>
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<td>Myopathy</td>
<td>3</td>
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<td>Psychosis</td>
<td>2</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
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</tr>
<tr>
<td>Hepatitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Data are number of patients. Plus sign indicates that the complication occurred, but it was not stated in how many patients in the article by Foster.


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