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.5,6 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...
studies were individually critically appraised to assess methodological quality. The criteria were randomization, method of randomization, allocation concealment, blinded outcome assessment, and inclusion of all randomized patients in the analysis.

The MEDLINE search found 298 references for MMP and 130 references for EBA; EMBASE identified 200 references for MMP and 108 for EBA. No RCTs were identified through searching the abstracts. The CCTR contained 16 references involving pemphigoid, but none of these studies were RCTs that met our inclusion criteria for MMP. No references were found when searching for EBA. Only 2 RCTs of treatment for MMP were identified by reading through single articles (abstracts of the 2 RCTs were not available in MEDLINE, EMBASE, or the Cochrane Library). The author (C. S. Foster) who conducted the 2 trials in MMP was contacted; no more randomized trials could be identified. No RCTs could be found for the treatment of EBA.

DATA EXTRACTION

Data from eligible RCTs were extracted and summarized using a data extraction sheet based on the outcome measures. Three reviewers (G.K., N.K., and D.M.) extracted data independently and subsequently checked for discrepancies. The data were then loaded onto Review Manager software (RevMan 4.0; Cochrane Collaboration, Oxford, England). Outcome measures included the following:

- Rate of regression or of healing of the skin and mucosal lesions
- Duration of remissions after stopping treatment
- Complications of the primary disease (MMP and EBA), such as scarring leading to blindness or airway obstruction
- Adverse effects of treatment, such as systemic infection, organ failure, allergic and/or toxic reactions
- Mortality as a result of primary disease or as a result of treatment

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 in-
cluded 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 ($\chi^2$ 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. Foster11 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.57-19,22,23,29 Of the 14 studies, 3 discuss the use of oral vs topical steroids in oral MMP, the results of which are controversial.20,26 Minocycline treatment is reported in 25 patients with generalized MMP.7,20,26 This medication seems beneficial in oral MMP (orodynia), although little effect is seen in ocular disease. Sixteen articles present patients with mainly ocular disease.

### 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><strong>Trial 1</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Prednisone (1 mg/kg per day [initial dose], tapered to 0.25 mg/kg alternate days during 3 mo, then 3-mo maintenance dose) vs Dapsone (2 mg/kg per day)</td>
<td>6 mo (prescription of dapsone continued?)</td>
<td>12 of 12 patients responded (8 wk)</td>
</tr>
<tr>
<td>20</td>
<td>Prednisone (1 mg/kg per day [initial dose], tapered to 0.25 mg/kg alternate days during 3 mo, then 3-mo maintenance dose) vs Cyclophosphamide (2 mg/kg per day and prednisone [1 mg/kg [initial dose], tapered until completely discontinued)</td>
<td>6 mo (prescription of cyclophosphamide continued?)</td>
<td>14 of 20 patients responded; incomplete cessation of inflammation after 6 mo; 7 of 20 patients responded to cyclophosphamide</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

### Table 2

<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>12</td>
<td>Cyclophosphamide (2 mg/kg per day and prednisone [1 mg/kg [initial dose], tapered until completely discontinued) vs Dapsone (2 mg/kg per day)</td>
<td>6 mo (prescription of dapsone continued?)</td>
<td>14 of 20 patients responded, incomplete response in 4 of 20 patients; good response to cyclophosphamide in 6 of 20 patients</td>
</tr>
</tbody>
</table>

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Elder et al. found sulfapyridine to be superior to dapsone. Early studies suggest that ocular MMP shows less progression when patients are immunosuppressed; treatment with cyclophosphamide in addition to oral corticosteroids seems to be more effective than, for example, azathiaprine.

Recent trials report topical mitomycin to be beneficial in severe ocular MMP (14 patients) and Donnenfeld et al describe no progression in 8 of 9 treated eyes vs remission. If this is due to treatment or represents a spontaneous remission within a few years, and it is not possible to judge the effectiveness of sulfa drugs in moderate ocular MMP, corticosteroids seem to be more effective than, for example, dapsone. Early studies suggest that ocular MMP shows less progression when patients are immunosuppressed; treatment with cyclophosphamide in addition to oral corticosteroids seems to be more effective than, for example, azathiaprine.

Intravenous immunoglobulins have been successfully used in one study of 10 patients with ocular MMP resistant to conventional treatment. Most children were treated with systemic corticosteroids and/or dapsone. In children, EBA seems 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.

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 studies 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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Corresponding author: Gudula Kirtschig, MD, Vrije Universiteit, Academisch Ziekenhuis, Department of Dermatology, Postbus 7057, 1007 MB Amsterdam, the Netherlands (e-mail: G.Kirtschig@vumc.nl).

REFERENCES


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>
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</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>19</td>
</tr>
<tr>
<td>Hematuria</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>
</tr>
<tr>
<td>Abdominal pain</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myopathy</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
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<tr>
<td>Hepatitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</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.