Interventions for mucous membrane pemphigoid/cicatricial pemphigoid and epidermolysis bullosa acquisita: a systematic literature review

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Authors' objectives
To identify and critically evaluate evidence from randomised controlled trials (RCTs) for the efficacy of treatment for mucous membrane pemphigoid (MMP; also known as cicatricial pemphigoid) and epidermolysis bullosa acquisita (EBA).

Searching
MEDLINE (from 1966 to March 2000), EMBASE (from 1980 to March 2000), and the Cochrane Controlled Trials Register (February, 2001) were searched. The full search terms were reported in the paper. The bibliographies of the identified studies were examined, and experts in the field were contacted for unpublished trials.

Study selection
Study designs of evaluations included in the review
Studies involving at least two patients with EBA and at least five patients with MMP were eligible for inclusion.

Specific interventions included in the review
Studies including any medical intervention used for the treatment of MMP and EBA were eligible. The following treatments were included: cyclophosphamide (2 mg/kg per day) and prednisone (initial dose of 1 mg/kg tapered to discontinuation) versus prednisone (initial dose of 1 mg/kg per day for 6 months, tapered to 0.25 mg/kg alternate days during 3 months, then 3-month maintenance dose); dapsone (2 mg/kg per day) versus cyclophosphamide (2 mg/kg per day) for 6 months; sulfa drugs (dapsone, sulfapyridine, and sulfamethoxypyridazine); oral and topical steroids; [A:antibiotics] (minocycline, mitomycin); intravenous immunoglobulins; systemic corticosteroids; colchicines.

Participants included in the review
MMP or EBA. Studies that included male and female patients (all ages) with a diagnosis of MMP or EBA, as confirmed by immunofluorescence findings, were eligible for inclusion.

Outcomes assessed in the review
The authors do not report specific inclusion criteria for the outcome measures. The outcomes of interest included the following: the rate of regression or of healing of the skin and mucosal lesions; the duration of remissions after stopping treatment; complications of the primary disease (MMP and EBA); adverse effects of treatment; and mortality.

How were decisions on the relevance of primary studies made?
Abstracts of potentially relevant studies were screened by two reviewers.

Assessment of study quality
The methodological quality of the studies was assessed using the following criteria: randomisation, method of randomisation, allocation concealment, blinded outcome assessment, and the inclusion of all randomised patients in the analysis. The authors report a method for the assessment of validity, but do not report the number of reviewers who carried out the assessment.

Data extraction
The data were extracted and summarised using a data extraction sheet based on the outcome measures. Three reviewers extracted the data independently and subsequently checked for any discrepancies. The data from RCTs were extracted under the headings of the number of patients, intervention, follow-up, and outcome.
Methods of synthesis
How were the studies combined?
A narrative synthesis was undertaken.

How were differences between studies investigated?
The results of the studies were grouped according to study design.

Results of the review
Two RCTs (n=64) on the treatment of MMP were identified; no RCTs were identified on the treatment of EBA. The authors identified 30 additional studies of MMP involving at least 5 patients and 11 articles on treatment for EBA involving at least 2 patients.

The combination of cyclophosphamide and prednisone had a superior effect, compared with prednisone alone, in the treatment of bilateral stage III MMP involving the eyes (p<0.005). Cyclophosphamide was shown to be superior to dapsone in the treatment of patients with MMP and severe (4+) inflammation of the eyes. The adverse effects observed in the 2 RCTs included alopecia, severe leukopenia, anaemia, haematuria, hypertension, diabetes mellitus, osteoporosis, peptic ulcer disease, abdominal pain, myopathy, psychosis, nausea, hepatitis and neuropathy.

In 30 additional studies of treatment in MMP, 14 studies investigated patients with oral and generalised MMP. Seven commented that patients benefited from sulfa drugs and 3 discussed the use of oral versus topical steroids; minocycline treatment seemed beneficial in oral MMP, but little effect was seen in ocular disease. Sixteen articles presented patients with ocular MMP. Three articles supported the effectiveness of sulfa drugs in moderate ocular MMP, and another article reported the benefit of topical mitomycin in severe ocular MMP.

Eleven articles addressed treatment for EBA. It was not possible to draw any conclusions regarding the superiority of any of the treatments investigated.

Authors' conclusions
It was 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.

CRD commentary
The methodological quality of this review was fair. The authors reported a clear review question and reported adequate inclusion criteria (except with regard to the outcomes). The search was comprehensive, and is unlikely that any publications were missed as attempts were made to locate unpublished material. The authors also reported the process of, and the number of reviewers who carried out the study selection and data extraction. The assessment of methodological quality was also appropriate. The details of the included RCTs were adequately presented in tables but, although details of the additional studies could be found in the text, they were not well described. Due to the nature of the identified studies, pooling was not appropriate and was not undertaken by the authors. The authors' conclusions follow from the data presented.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors state that international, multicentre RCTs involving larger numbers of patients are required to assess the best treatment for MMP and EBA.

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