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Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita (Review)

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[Intervention Review]

Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita

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ABSTRACT

Background

Mucous membrane pemphigoid and epidermolysis bullosa acquisita are rare acquired autoimmune blistering diseases of the skin. Both can result in scarring of mucous membranes which may lead to blindness and life threatening respiratory complications.

Objectives

To assess the effects of treatments for mucous membrane pemphigoid and epidermolysis bullosa acquisita.

Search methods

We searched the Cochrane Skin Group Specialised Register (7th April 2005), the Cochrane Controlled Trials Register (*The Cochrane Library* Issue 1, 2005), MEDLINE / PubMed (from 1966 to April 2005), EMBASE (from 1980 to April 2005), www.controlled-trials.com (7th April 2005) and www.clinicaltrials.gov (7th April 2005) and reference lists of articles.

Selection criteria

Randomised controlled trials of any treatments for mucous membrane pemphigoid or epidermolysis bullosa acquisita involving participants of any age with a diagnosis of either disease confirmed by immunofluorescence.

Data collection and analysis

The data was independently extracted by three authors and subsequently checked for discrepancies. Two authors evaluated the studies in terms of the inclusion criteria.

Main results

Two small randomised controlled trials of mucous membrane pemphigoid, both conducted in participants with severe eye involvement were identified.

In the first trial, involving 24 participants, cyclophosphamide 2 mg/kg/day in combination with prednisone starting at 1 mg/kg/day and tapering was superior to prednisone alone (1 mg/kg/day) after 6 months of treatment. All 12 participants responded well to

cyclophosphamide plus prednisone versus a good response in only 5 of 12 participants treated with prednisone (relative risk 2.40, 95% confidence interval 1.23 to 4.69).

In the second trial, involving 40 participants, all 20 participants treated with cyclophosphamide (2 mg/kg/day) responded well after three months of treatment, but only 14 of 20 participants responded to treatment with dapsone (2 mg/kg/day) (relative risk 1.43, 95% confidence interval 1.07 to 1.90). All non-responders had severe inflammatory activity. It was not explicitly stated whether these participants received prednisone in addition to dapsone or cyclophosphamide initially. Hair loss and suppression of the red and white blood cells were common adverse events in the cyclophosphamide groups.

No randomised controlled trials of treatments for epidermolysis bullosa acquisita were identified.

Authors' conclusions

There is limited evidence that mucous membrane pemphigoid involving the eyes responds best to treatment with cyclophosphamide combined with corticosteroids. However, mucous membrane pemphigoid with mild to modest inflammatory activity responds to dapsone in most participants and may therefore be best treated with dapsone due to its lower side effect profile compared to cyclophosphamide. Treatment with mycophenolate mofetil combined with topical steroids seems worth considering in a future randomised controlled trial for mucous membrane pemphigoid.

PLAIN LANGUAGE SUMMARY

Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita (rare autoimmune blistering diseases of the skin, eyes and mouth)

Mucous membrane pemphigoid and epidermolysis bullosa acquisita are rare autoimmune blistering diseases of the skin and mucous membranes (eyes and mouth). They can result in scarring, which may lead to disabling and life threatening complications. Treatments include corticosteroids, mycophenolate mofetil and cyclophosphamide to suppress the immune system, and less toxic drugs such as antibiotics. These diseases often progress despite treatment. There is some evidence that mucous membrane pemphigoid involving the eyes may respond better to treatment with cyclophosphamide combined with corticosteroids, compared to treatment with corticosteroids alone. Cyclophosphamide is, however, associated with potentially severe adverse effects. Dapsone may help moderate disease. More research is needed to identify the most effective treatment options.There is not enough reliable evidence about treatments for the rare blistering diseases, mucous membrane pemphigoid and epidermolysis bullosa acquisita.

BACKGROUND

Description of the condition

Definition and Epidemiology

Mucous membrane pemphigoid (MMP) and epidermolysis bullosa acquisita (EBA) are acquired autoimmune bullous disorders of the skin and mucous membranes (Gammon 1988; Briggaman 1990; Fine 1990; Kirtschig 1998; Wojnarowska 1998). Blisters, erosions, and later scar formation are characteristic features in both diseases and may lead to major disability (e.g. blindness) and life-threatening situations (e.g. respiratory obstruction). They are diseases of the elderly, but can also affect younger people and children (Edwards 1998). For this review, MMP will replace the name "cicatricial pemphigoid", as suggested by Chan 2002. The incidence of MMP and EBA in Western Europe is calculated to be about 1 and 0.2 new cases per 1,000,000 inhabitants per year respectively (Bernard 1995; Zillikens 1995).

Pathogenesis and Diagnosis

Blister formation is thought to result from an antigen-antibody interaction, where IgG autoantibodies circulating in the bloodstream bind to cell adhesion complexes in the basement membrane zone of the skin (Liu 1993; Borradori 1995; Lazarova 1996). In MMP and EBA, direct immunofluorescence (IF) demonstrates

deposits of IgG and complement at the dermo-epidermal junction. Circulating autoantibodies may be detected using indirect IF. Immunofluorescence conducted on skin incubated in 1Molar sodium chloride helps to distinguish certain autoimmune bullous diseases such as EBA and a rare sub-group of MMP (in which fluorescence is at the floor of the blister) from bullous pemphigoid (BP) (in which fluorescence is usually at the roof) thus giving a more accurate diagnosis (Gammon 1984).

Clinical Course

Both MMP and EBA are highly variable and often take a protracted course in contrast to BP, which usually remits within five years (Briggaman 1990; Wojnarowska 1998). Some people with localized disease (for example, only oral involvement in MMP) remain stable for years in the absence of aggressive therapy. Other people may develop rapidly progressive ocular (eye) involvement despite treatment with immunosuppressants. There are several different staging systems describing the changes seen in the eyes in inflammatory diseases. A system based on conjunctival changes, which are relevant in MMP and EBA, is described as follows (Foster 1986a; Foster 1986b):

- stage I - chronic conjunctivitis with subepithelial fibrosis;
- stage II - inferior fornix foreshortening;
- stage III - symblepharon;
- stage IV - end stage with ankyloblepharon, severe sicca syndrome, and ocular surface keratinization.

Description of the intervention

The standard treatment for progressive disease (MMP and EBA) is the administration of systemic corticosteroids at a dose of 1 to 2 mg prednisolone equivalent per 1 kg of body weight, often combined with cyclophosphamide, azathioprine, or methotrexate. It is not known if any of these different immunosuppressive agents is particularly effective in suppressing the two diseases. 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. Alternative treatment regimens involve antibiotics (tetracyclines, erythromycin), nicotinamide and immunoglobulins and these medications are usually better tolerated (Reiche 1998; Dragan 1999; Harman 1999; Foster 1999). Initial reports are promising, but it is not known whether recent alternative treatment regimens are equally or even more effective than traditional medication in people with progressive disease

Why it is important to do this review

Evidence for the most effective immunosuppressive treatment option and other treatment options with less severe adverse effects is needed. A review is therefore required to determine:

1. the most effective drugs or interventions, with the least adverse effects;
2. whether combination therapy (for example, azathioprine plus steroids) offers any advantages over single therapy (for example, oral steroids alone);
3. whether antibiotics such as tetracyclines, erythromycin, dapsone, and sulphonamides useful;
4. whether systemic treatment is more effective than topical treatment in people with MMP or EBA.

OBJECTIVES

To assess the effects of treatments for mucous membrane pemphigoid (MMP) and epidermolysis (EBA).

METHODS

Criteria for considering studies for this review

Types of studies

1. RCTs of interventions for MMP and EBA. Conclusions are based primarily on the findings of these RCTs.
2. Uncontrolled and controlled, but not randomized, therapeutic studies of MMP involving 5 or more participants and reports of EBA involving 2 or more participants identified from MEDLINE or EMBASE between their inception to February 2002 and studies of MMP or EBA involving 10 or more participants identified from MEDLINE or EMBASE between March 2002 and April 2005. These are listed as excluded studies, and their characteristics and results are reported briefly in the additional tables (Table 1; Table 2; Table 3).

Types of participants

Anyone who received treatment after a diagnosis of MMP or EBA, confirmed by immunofluorescence studies.

Types of interventions

Any therapeutic intervention used to treat MMP and EBA.

Types of outcome measures

Primary outcomes

Rate of regression or of healing of the skin and mucosal lesions; in ocular disease, reduction of inflammation and no progression of conjunctival scarring are appropriate measures.

Secondary outcomes

Duration of remission after stopping treatment.
Complications of the primary disease (MMP and EBA) such as scarring leading to severe complications (e.g. blindness, airway obstruction).
Adverse effects of treatment: infection, organ failure, allergic/toxic reactions etc.
Overall mortality.

Search methods for identification of studies

Electronic searches

We searched:
(a) The Cochrane Skin Group Specialised Register (7th April 2005) Appendix 1
(b) The Cochrane Controlled Trials Register (CENTRAL) (*The Cochrane Library Issue* 1, 2005) Appendix 2
(c) MEDLINE / PubMed (from 1966 to April 2005) Appendix 3
(d) EMBASE (from 1980 to April 2005) Appendix 4
(e) www.controlled-trials.com (7th April 2005) and (f) www.clinicaltrials.gov (7th April 2005) Appendix 5

Searching other resources

References from published studies

We searched the reference lists from identified studies.

Unpublished literature

We contacted the trial author (C.S. Foster) who had conducted RCTs in the field to identify unpublished trials.

Conference proceedings

Conference proceedings were not searched.

Adverse effects

A specific search for side effects studies was not carried out.

Other

The search was restricted to articles that had abstracts in English, French or German.

Data collection and analysis

Selection of studies

The primary objective was to identify and summarise data from RCTs, however, as MMP and EBA are rare diseases some evidence from non-randomised studies was also considered. These are listed in the 'Characteristics of excluded studies' table. Two authors (GK and NK) screened abstracts of potentially relevant studies.

Data extraction and management

Three authors (GK, NK, and DM) independently conducted data extraction and subsequently checked for discrepancies; any disagreements were resolved by discussion.
Details of eligible studies were extracted using a data extraction form that was developed based on the outcome measures. Studies that have been published in duplicate were included only once.

Assessment of risk of bias in included studies

Assessment of methodological quality

The identified studies were individually critically appraised to assess methodological quality. For randomised trials, the key criteria were: method of randomisation, allocation concealment, blinded outcome assessment and inclusion of all randomised participants in the analysis.
Specific aspects were assessed for each study:
(a) the method of randomisation;
(b) the method of allocation to treatment groups;
(c) whether complete follow-up was achieved;
(d) the proportion of participants who did not complete the study and whether their outcomes were described and included in the analysis;
(e) whether the investigators blinded to the treatment allocation;
(f) whether the treatment and control groups comparable at entry;
(g) whether the groups treated were identically other than the named interventions.

Measures of treatment effect

For dichotomous outcomes, results are presented as risk ratios (RR) with 95% confidence intervals (CI). For the primary outcome measure, the proportion of participants with improvement greater than minimal is considered as treatment success. Data that has

been recorded for three months is considered to reflect short term benefit and is analysed separately from data that was recorded for over a period of six months. The data at six months is considered as the primary endpoint (short term benefit).

Data synthesis

We initially planned to divide the data analysis into two groups:
(a) Trials where the diagnosis of MMP or EBA was confirmed by direct/indirect IF using intact skin;
(b) Trials where split skin was used for indirect IF- this procedure helps, although not completely, to separate EBA and a subgroup of MMP from BP participants;
however, this was unnecessary as no participant had indirect IF performed on split skin.
The results from the studies were to be pooled using meta-analysis based on random effects (DerSimonian and Laird model) and heterogeneity was to be assessed using I-squared (I^2), however, pooling of data was not performed due to a lack of studies. Therefore, individual results are presented for each study.

RESULTS

Description of studies

Results of the search

We found 580 references in MEDLINE for MMP and EBA; 406 references for MMP and EBA in EMBASE . No RCTs were identified through searching the abstracts. Complete papers were sought and read for the references that had no abstracts in MEDLINE or EMBASE. Two RCTs of treatment for MMP were included in the review (Foster 1986a; Foster 1986b). No RCT for EBA was found.
Searching CENTRAL for controlled trials (CCTs and RCTs) 39 references were identified from MEDLINE and 3 references from EMBASE involving 'pemphigoid' or 'epidermolysis bullosa acquisita'. None of these studies were RCTs that met the inclusion criteria for MMP or EBA.
Eleven reports of uncontrolled studies of treatment for EBA involving two or more participants were found when searching MEDLINE and EMBASE were searched from their inception until February 2002. Two studies involved the same participants. The article by Edwards et al. is a follow up of the data presented by Kirtschig et al. (Edwards 1998).
No studies for EBA involving 10 or more participants were identified when searching MEDLINE and EMBASE between March 2002 and April 2005.
A further 31 reports of mainly uncontrolled studies of treatment for MMP involving 5 or more participants were found when MEDLINE and EMBASE were searched until February 2002. Four of the reports represent follow ups of earlier studies (Rogers 1982; Rogers 1988; Mondino 1990; Tauber 1991).
Searching MEDLINE and EMBASE between March 2002 and April 2005 for MMP studies involving 10 or more participants 5 studies were identified (Gonzalez-Moles 2003; Letko 2004; McCluskey 2004; Ingen-Housz 2005) data of Sami and Letko overlapping.
No studies were identified searching www.controlled-trial.com.
Searching www.clinicaltrials.gov no study was found for pemphigoid, one for EBA (Gordon 1997).

Included studies

Two small RCTs involving participants with MMP affecting the eyes were identified (*see* 'Characteristics of included studies'). Another 30, mainly uncontrolled, studies described the treatment of 5 or more participants with MMP. Eleven similar studies reporting the treatment of 2 or more participants with EBA were identified (see Table 1; Table 2; Table 3).
The first trial (Foster 1986a) included 24 participants with bilateral stage III MMP affecting the eyes. Treatment consisted of either a dextrose placebo plus prednisone, or cyclophosphamide 2 mg/kg/day plus prednisone. The initial prednisone dosage was 1 mg/kg body weight per day. The dosage was then tapered according to the protocol. The prednisone was tapered until completely discontinued in the cyclophosphamide group. In the prednisone only group, a maintenance dose of 0.25 mg/kg every other day was administered, unless drug-induced complications or treatment failures were judged to preclude continued treatment. There was a six month intervention period and after that a six month follow-up period. The effect of the treatment was judged after the six month intervention period.
The second trial (Foster 1986b), conducted by the same investigators, involved 40 participants with active, progressive stage III MMP affecting the conjunctiva. Dapsone 2 mg/kg/d was given to one group, cyclophosphamide 2 mg/kg/d to the other group. The study protocol was identical to that described for the first trial. It was not explicitly stated whether or not these participants received prednisone in addition to dapsone or cyclophosphamide initially. In order to clarify the confusion, the trial author was contacted. He stated: "we typically treated patients with a short course of prednisone while induction with an immunomodulator was being accomplished". There was a six month observation period and the outcome was judged at the end of the six months.

Risk of bias in included studies

The clinical diagnosis of mucous membrane pemphigoid in the two RCTs that compared treatment of progressive MMP affect-

ing the eyes was confirmed by direct immunofluorescence on intact skin (*see* 'Characteristics of included studies'). Both were small, randomised, double-blind studies comparing two active treatments.

The disadvantages in both studies were the small numbers of participants (24 and 40 participants) and the lack of clarity concerning the drug regimen in the follow-up period.

There is some doubt about the concealment of allocation, as the trial author who carried out the randomisation also treated the participants, monitored the drugs and carried out the intervention.

In the first trial the participants received either dextrose placebo plus prednisone or cyclophosphamide plus prednisone. In the second trial, the participants received either dapsone or cyclophosphamide (it is not stated if the tablets are exactly the same).

Otherwise the studies were of good methodological quality because:

1) the method of randomisation was acceptable: A table of random numbers, "incomplete block design", use of sequentially numbered sealed envelopes;

2) disease activity was assessed by a masked observer;

3) there were no drop-outs.

Effects of interventions

Included MMP studies

The two RCTs compared treatment of progressive MMP affecting the eyes (*see* 'Characteristics of included studies'). One included 24 participants with bilateral ocular, stage III MMP (symblepharon formation) in which treatment with cyclophosphamide plus prednisone versus prednisone alone was tested. The second trial included 40 participants with stage III ocular MMP in which treatment with dapsone versus cyclophosphamide was tested. It did not mention if both eyes were affected. The 64 participants in the two trials were part of a study population of 130 participants with MMP involving the eyes, collected between 1975 and 1985 at the Immunology and Uveitis Unit, Harvard Medical School, Boston, USA. All 130 participants had bulbar conjunctival biopsies for histological investigation and direct immunofluorescence. All 64 RCT participants showed linear deposition of immunoglobulins at the basement membrane zone on direct IF.

One gets the impression from the article that all consecutive new participants, who fulfilled the inclusion criteria, were entered in a randomised fashion initially to the first trial, and once this was completed, then to the second trial. However, this is not clearly stated. All participants exhibited stage III conjunctival changes for pemphigoid and were judged, after elimination of potential confounding variables (trichiasis, districhasis, lagophthalmos, etc.) to have active disease. Participants with a history of chronic ocular drug use prior to disease onset were excluded, as were participants with a history of conjunctival scarring secondary to infection, trauma, malignancy, or systemic disease (e.g. Stevens-Johnson syndrome and sarcoidosis). No participants were eliminated from the study once it began, and none had contraindications to immunosuppression. All participants agreed to a follow-up period of one year.

All participants entered into the two trials completed the studies, none were lost to follow up.

Trial 1 showed a superior effect of cyclophosphamide and prednisone in combination compared to prednisone alone in the treatment of bilateral stage III MMP involving the eyes with regard to primary outcome measure (a) and secondary outcome measure (c) (see Analysis 1.1). The clinical evidence of active conjunctival inflammation completely subsided in 12 of 12 participants treated with cyclophosphamide, and the globes appeared white and quiet bilaterally. No evidence of recurrent conjunctival inflammation appeared during prednisone taper and discontinuation, nor did cicatrization of the conjunctiva progress during the six months of the trial (short term benefit) and the six months observation period (long term benefit). The visual acuity was maintained in all participants and improved in eight. In contrast, conjunctival inflammation subsided and the globes appeared white and quiet in only 5 of 12 participants treated with prednisone alone. These five showed no evidence of progressive conjunctival cicatrization for the six month duration of the study period (outcome measure c). When the prednisone was tapered further at the end of the six months, conjunctival inflammation recurred in all five participants. The difference in clinical outcome is statistically significant (Chi-square analysis: $P < 0.005$, relative risk 2.40, 95% confidence interval 1.23 to 4.69; Analysis 1.1) **NB please check, are these figures correct - have I put correct link here?**. It was not clear from the article whether the treatment was stopped after the six month treatment period. In discussing the treatment with the trial author (C.S. Foster) the recommended duration of treatment was found to be at least one year and usually longer.

In trial 2, cyclophosphamide was shown to be superior to dapsone, with regard to outcome measure (a), in the treatment of participants with MMP and severe (4+) inflammation of the eyes (degree of conjunctival inflammation graded 0 to 4+, no further explanation of grading stated). All 20 of the cyclophosphamide therapy participants responded to treatment with an abolition of all clinical evidence of conjunctival inflammation and no evidence of conjunctival scarring throughout the six month observation period. However, only 14 of the 20 dapsone-treated participants responded to treatment (relative risk 1.43, 95% confidence interval 1.07 to 1.90;Analysis 1.1)**NB please check are these figures correct - have I put correct link here?**. Four participants responded incompletely to dapsone, with reduction of inflammation, and 2 participants failed to respond at all within 12 weeks. The six dapsone treatment failures included all four of the participants with 4+ conjunctival inflammation prior to therapy. The two remaining treatment failures had 3+ activity before treatment. All six participants responded well to cyclophosphamide therapy after the three

months treatment with dapsone that had failed to improve their disease. No results were mentioned regarding outcome measure (c).

Adverse Effects

Adverse effects observed in both trials are listed in Analysis 1.2.

None of the participants died during treatment or follow up in either trial (outcome measure e)

Trial 1: None of the participants withdrew from systemic immunosuppression due to adverse effects, and none required hospitalization for intervention for any adverse effect. Ten of 12 participants suffered varying degrees of hair loss, but none needed to wear a wig. The hair loss was reversible when treatment with cyclophosphamide was discontinued. Leukopenia was a routine finding in all participants successfully treated with cyclophosphamide. Foster states: "we have found significant depression in the white blood cell count to be an absolute requirement for achieving the desired therapeutic effect of cyclophosphamide". The leukopenia was reversible, and the cyclophosphamide dose was adjusted to achieve a leukocyte count between 2,500 to 4,000 white cells/microlitre. Macrocytic anaemia, present in 12 of 12 participants, was asymptomatic and of mild to moderate degree. Microcytic haematuria was discovered in routine urinalysis; an alteration in timing of cyclophosphamide administration and increased fluid intake eliminated this potentially serious side effect. Each of the participants in the prednisone group experienced prednisone-induced complications (*see* Analysis 1.2, 'Adverse effects').

Trial 2: Most participants receiving cyclophosphamide showed alopecia, anaemia and leukopenia, the exact numbers are not stated. Microcytic haematuria developed in two participants necessitating a reduction of cyclophosphamide. Evidence of haemolysis was found in 19 of 20 dapsone treated participants; for less common adverse effects see Analysis 1.2, 'Adverse effects'. Foster emphasizes that dapsone is not a benign drug and death may occur as a result of agranulocytosis, aplastic anaemia, or haemolytic anaemia.

Outcome measure (b) is not applicable in either trial, because none of the participants stopped treatment during the described follow-up period.

DISCUSSION

Summary of main results

It is not possible to draw definite conclusions as to the best treatment for MMP or EBA.

Long-term corticosteroid treatment puts participants at risk of serious complications (for example development of hypertension, diabetes mellitus, and osteoporosis) and seems to be less effective than cyclophosphamide in suppressing scarring MMP involving the eyes. Foster believes that systemic immunosuppression with cyclophosphamide poses fewer risks if properly used compared with long-term corticosteroid therapy.

The second trial shows that cyclophosphamide is more effective in suppressing conjunctival inflammation in ocular MMP compared to treatment with dapsone. However, cyclophosphamide usually shows more adverse effects. Most participants will have alopecia, some degree of leukopenia and anaemia. Male sterility and haemorrhagic cystitis may occur and there is a potential for malignancy (DNA damage). With dapsone, some degree of anaemia is common in most participants. There are potentially serious adverse effects in treatment with dapsone, but these are very rare. They include severe haemolytic anaemia, methaemoglobinaemia, agranulocytosis, neuropathy and the dapsone syndrome (rash with fever and eosinophilia). Dapsone syndrome requires the immediate cessation of dapsone as it may progress to exfoliative dermatitis and death. In general, most dermatologists will have used dapsone regularly, but most are probably not familiar with the use of cyclophosphamide (because of the fear of side effects).

According to trial two, most MMP participants with mild to modest inflammatory activity involving the eyes seemed to respond well to dapsone (14 of 16 participants with mild to modest inflammatory activity improved). Therefore, Foster concludes that dapsone is a reasonable first choice medication for participants with MMP without very active and rapidly progressive disease, provided they are not glucose-6-phosphate dehydrogenase (G6PD) deficient (participants who are G6PD deficient will develop severe anaemia when taking dapsone). An increasing dose starting at 25 mg/day, then increasing to 50 mg/day after 4 weeks and then to 100 mg/day after another 4 weeks is recommended, with dosage adjustments based on therapeutic response and drug tolerance. The haemolysis is greatest at four weeks into treatment. A response can be expected within four weeks of treatment (Foster 1986b). In the absence of a placebo group in either study, it is not possible to say how much better any of the tested drugs are than placebo.

Thirty one (36 references; 5 of the 36 references presented follow-up data of previous studies) additional mainly uncontrolled studies of treatment in MMP, involving 5 or more participants were identified (*see* 'Characteristics of excluded studies' table).

Eighteen studies investigated participants with oral and generalized MMP of which 8 comment on sulphur drugs (dapsone, sulfapyridine, sulfamethoxypyridazine); 84 of 131 participants appeared to benefit from this medication.

Of the 18 studies, 3 discuss the use of oral versus topical steroids in oral MMP, the results of which are controversial. One group reports about the use of a gingival tray for the application of 0.05% clobetasol propionate plus 100,000 IU/cc of nystatin in orabase paste (Gonzalez-Moles 2003).

Minocycline treatment is reported in 25 participants with generalized MMP. This medication seems beneficial in oral MMP (orodynia), although little effect is seen in ocular disease.

Mycophenolate mofetil (MMF) treatment (1.5 to 2g daily) was used in a heterogeneous (oral > generalized) group of 14 participants with proven MMP (Ingen-Housz 2005). MMF treatment for MMP may be a promising option for participants with moderate and severe disease; however the authors think that it should not replace cyclophosphamide in severe sight or life threatening MMP. Compared to other immunosuppressive therapies (e.g. cyclophosphamide) adverse effects seem reasonable. RCTs are needed in order to evaluate its true value in the treatment of MMP.

Nineteen articles present participants with mainly ocular MMP. Three of these studies support the effectiveness of sulphur drugs in moderate ocular MMP. One study (Elder 1996) found that sulfapyridine was clinically effective in 50% of participants with moderate or marked inflammation, and had few side effects (Tauber 1991; Fern 1992; Elder 1996). See 'Characteristics of excluded studies' table.

Early studies suggest that ocular MMP shows less progression when participants are immunosuppressed; treatment with cyclophosphamide in addition to oral corticosteroids seems more effective than for example azathioprine (Mondino 1990). Also methotrexate (MTX) is reported to prevent the progression of conjunctival cicatrisation (McCluskey 2004).

Recent trials report topical mitomycin C to be beneficial in severe ocular MMP (Secchi 1996; Donnenfeld 1999).

The use of intravenous immunoglobulins (IVIg) is described in three reports by the same group of investigators (Foster 1999; Letko 2004) the reports by Letko and Sami seem to involve the same participants. In ten participants with ocular MMP resistant to conventional treatment IVIg were used with apparent success (Foster 1999). A non-randomised comparison between conventional immunosuppressive and IVIg therapies investigated eight participants in each group (Letko 2004). All patients received (various) immunosuppressive treatment as an initial treatment before treatment with IVIg was started. The authors recommend a RCT to confirm the results and determine the optimal protocol.

Treatment with topical tacrolimus, topical cyclosporine, tetracycline and nicotinamide, colchicine, thalidomide, leflunomide, plasmapheresis, autologous serum application to ocular epithelial defects and "biologicals" like TNF alpha receptor (etanercept), anti-CD25 (daclizumab), anti-CD20 (rituximab) has been described in single cases.

We identified 11 articles on uncontrolled studies for the treatment of EBA involving two or more participants, detailing results in 20 adults and 11 children (*see* 'Characteristics of excluded studies' table). The adult participants were treated with various medications including systemic corticosteroids, immunosuppressants, dapsone, colchicine and intravenous immunoglobulins; it is not possible to draw any conclusions regarding the superiority of any of these treatments. Most children were treated with systemic corticosteroids and/or dapsone. No reliable evidence-based recommendation can be given for the treatment of EBA at present.

A number of agents have been suggested (see 'Characteristics of excluded studies' table), but this evidence is from a very small case-series and is not reliable in the absence of a suitable control group. Collectively, the uncontrolled studies of EBA suggest that children seem to respond to treatment with a combination of systemic corticosteroids and dapsone. However, 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 (Briggaman 1990; Edwards 1998).

No final results could be obtained regarding the one prospective uncontrolled trial for EBA (Gordon 1997)

AUTHORS' CONCLUSIONS

Implications for practice

Based on these two identified RCTs:

1. In MMP involving the eyes, cyclophosphamide in combination with short term corticosteroids may be more effective in suppressing inflammation of the conjunctiva and progression of scarring than long-term corticosteroids or dapsone; however, both cyclophosphamide and corticosteroids may have severe adverse effects in the long term.

2. In MMP with mild to modest inflammation involving the eyes, dapsone may be an effective first choice treatment in most patients, because the adverse effect profile of dapsone is more tolerable for most patients compared to cyclophosphamide and long term corticosteroids. Serious adverse effects in dapsone are very rare; they are only reported in single case reports.

No reliable evidence-based recommendation can be given for the treatment of EBA.

Implications for research

More research is urgently required. As MMP and EBA are rare diseases, international multicentre RCTs involving larger numbers of participants may be necessary to assess the best treatment for these diseases. Also, collaborating to improve the collection of case data would be worthwhile in order to overcome the many deficiencies of case series due to the possibility of selection bias; comprehensive case detection alleviates this.

Treatments with anti-inflammatory antibiotics such as tetracycline, minocycline, and newer medications like anti-TNF alpha antibodies might be as effective as dapsone and have the benefit of fewer adverse effects, and are worthy of further investigation. For example a RCT for the treatment of bullous pemphigoid suggests some merit in the use of tetracycline and nicotinamide (Fivenson 1994).

Treatment with Mycophenolate mofetil (MMF) combined with topical steroids seems worth considering in a future RCT.

RCT suggestion: Mycophenolate mofetil plus topical corticosteroids versus dapsone plus topical corticosteroids (or versus cyclophosphamide plus topical steroids) in moderate and severe MMP.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Foster 1986a

Methods	Randomized; table of random numbers, "incomplete block design", were placed in sequentially numbered sealed envelopes. double blind: a masked observer graded the disease activity; patients received either dextrose placebo + prednisone or cyclophosphamide + prednisone
Participants	24 patients with bilateral stage III ocular MMP (symblepharon formation) a: 12; b: 12 Evaluable: a: 12; b: 12
Interventions	a: cyclophosphamide (2 mg/kg/day) plus prednisone (1 mg/kg/day) b: prednisone (1 mg/kg/day) (six months treatment)
Outcomes	Criteria for successful treatment: (1) abolition of all clinical signs of conjunctival inflammation, (2) absence of evidence indicating progression of subepithelial fibrosis/conjunctival cicatrization
Notes	No drop outs, all patients completed the follow-up period

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Foster 1986b

Methods	Randomized, table of random numbers, "incomplete block design", were placed in sequentially numbered sealed envelopes. double blind (same design as trial 1)
Participants	40 patients with stage III ocular MMP (symblepharon formation) a: 20; b: 20 Evaluable: a: 20; b:20
Interventions	a: dapsone (2 mg/kg/day) b: cyclophosphamide (2 mg/kg/day) the use of prednisone is not clearly stated; additional information via trial author: all patients usually receive prednisone in the beginning of the treatment (six months treatment)
Outcomes	Same criteria as above

Foster 1986b (*Continued*)

Notes	No drop outs, all patients completed the follow-up period	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	A - Adequate

Add definitions of any other abbreviations used.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arpey 1991	Uncontrolled study
Axt 1995	Uncontrolled study
Bialasiewicz 1994	Uncontrolled study
Callot-Mellot 1997	Uncontrolled study
Carbone 1998	Uncontrolled study
Carrozzo 1997	Uncontrolled study
Cunningham 1996	Uncontrolled study
Donnenfeld 1999	Not randomised
Edwards 1998	Uncontrolled study
Elder 1995	Uncontrolled study
Elder 1996	Uncontrolled study
Fern 1992	Uncontrolled study
Foster 1982	Not randomised, prospective, controlled
Foster 1999	Uncontrolled study
Francis 1990	Uncontrolled study

(*Continued*)

Gillies 1996	Not randomised
Gonzalez-Moles 2003	A descriptive pre-test/post-test clinical study without control group
Gordon 1997	Uncontrolled study
Gupta 1990	Uncontrolled study
Hanson 1988	Uncontrolled study
Harman 1999	Uncontrolled study
Ingen-Housz 2005	Retrospective case series
Lamey 1992	Uncontrolled study
Letko 2004	Non randomised comparison between intravenous immunoglobulin and conventional immunosuppressive therapy
Luke 1999	Uncontrolled study
Matthews 1989	Uncontrolled study
McCluskey 2004	Retrospective, non comparative, interventional case series
McFadden 1989	Uncontrolled study
Megahed 1994	Uncontrolled study
Mondino 1990	Uncontrolled study
Nayar 1993	Uncontrolled study
Poskitt 1995	Uncontrolled study
Rappersberger 1988	Uncontrolled study
Reiche 1998	Uncontrolled study
Rogers 1982	Uncontrolled study
Rogers 1988	Uncontrolled study
Secchi 1996	Uncontrolled study
Tauber 1991	Uncontrolled study

(*Continued*)

Thornhill 2000	Uncontrolled study
Vincent 1993	Uncontrolled study
Wright 1979	Uncontrolled study

DATA AND ANALYSES

Comparison 1. cyclophosphamide v other treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 clinical improvement, short term (at 3 or 6 months)	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 cyclophosphamide+prednisone v prednisone alone for 6 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 cyclophosphamide v dapsone for 3 months	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 adverse effects	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 alopecia: cyclophos+pred versus pred	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 alopecia (severe): cyclophos+pred versus pred	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 anaemia: cyclophos+pred versus pred	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 haematuria: cyclophos+pred versus pred	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 haematuria: cyclophos versus dapsone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 hypertension: cyclophos+pred versus pred	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 hypertension: cyclophos versus dapsone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 diabetes: cyclophos+pred versus pred	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.9 diabetes: cyclophos versus dapsone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.10 osteoporosis: cyclophos+pred versus pred	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.11 osteoporosis: cyclophos versus dapsone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.12 peptic ulcer: cyclophos+pred versus pred	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.13 peptic ulcer: cyclophos versus dapsone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.14 abdominal: cyclophos+pred verus pred	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.15 abdominal: cyclophos versus dapsone	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.16 myopathy: cyclophos+pred versus pred	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

2.17 myopathy: cyclophos versus dapsone	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.18 psychosis: cyclophos+pred versus pred	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.19 psychosis: cyclophos versus dapsone	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.20 nausea: cyclophos+pred versus pred	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.21 nausea: cyclophos versus dapsone	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.22 hepatitis: cyclophos+pred versus pred	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.23 hepatitis: cyclophos versus dapsone	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.24 neuropathy: cyclophos+pred versus pred	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.25 neuropathy: cyclophos versus dapsone	1	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 cyclophosphamide v other treatments, Outcome 1 clinical improvement, short term (at 3 or 6 months).

Review: Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita

Comparison: 1 cyclophosphamide v other treatments

Outcome: 1 clinical improvement, short term (at 3 or 6 months)

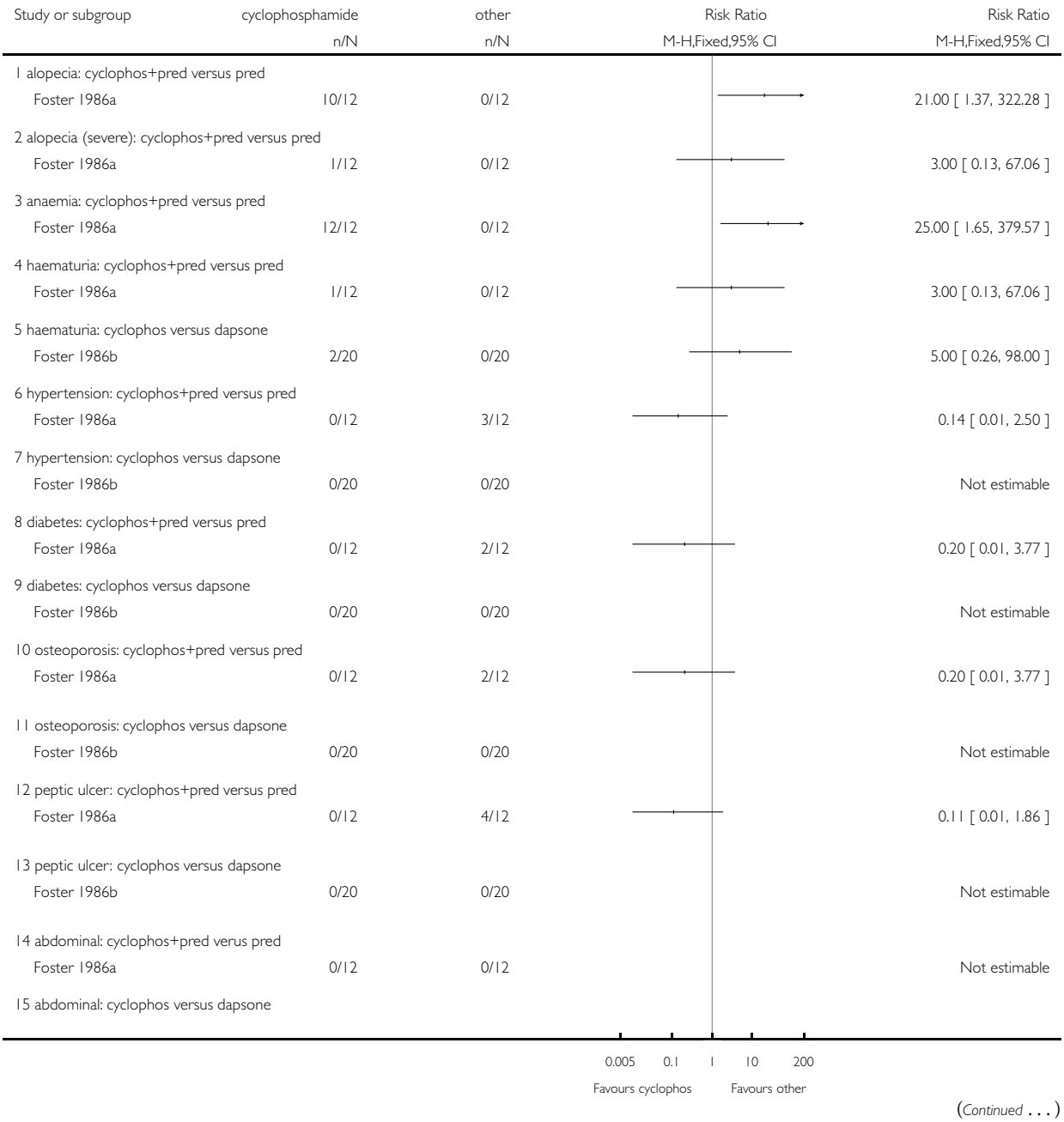
Study or subgroup	cyclophos. n/N	other treatment n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 cyclophosphamide+prednisone v prednisone alone for 6 months				
Foster 1986a	12/12	5/12		2.27 [1.19, 4.33]
2 cyclophosphamide v dapsone for 3 months				
Foster 1986b	20/20	14/20		1.41 [1.05, 1.90]

Analysis 1.2. Comparison 1 cyclophosphamide v other treatments, Outcome 2 adverse effects.

Review: Interventions for mucous membrane pemphigoid and epidermolysis bullosa acquisita

Comparison: 1 cyclophosphamide v other treatments

Outcome: 2 adverse effects



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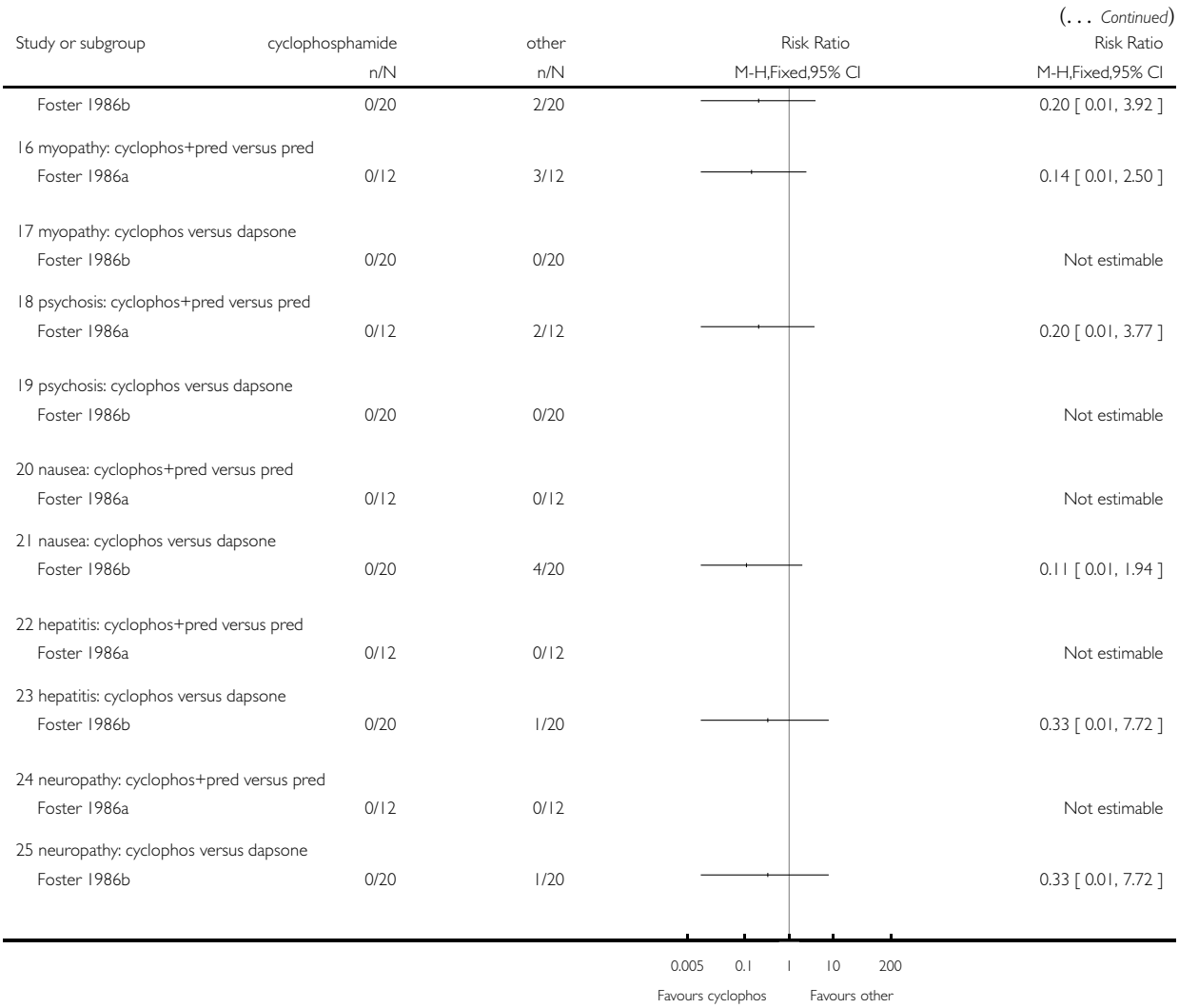

ADDITIONAL TABLES

Table 1. Childhood EBA: Nonrandomised studies

Study	N of participants	Treatments	Results	Conclusions
Arpey 1991	three	Systemic v topical: 40 mg prednisolone/day + 50 mg dapsone (n = 1); topical steroids (n = 2)	improvement with prednisolone+dapsone; no response or spontaneous remission with topical steroids	

Table 1. Childhood EBA: Nonrandomised studies (*Continued*)

Callot-Mellot 1997	three	1. 8 mg/kg/day prednisolone + 2 mg/kg/day dapsone+oral and systemic antimicrobials; 1 mg/kg/day prednisone + 1 mg/kg/day dapsone	remission after two years with prednisolone+dapsone+antimicrol resolution of blisters after two days with prednisone+dapsone (wrong diagnosis?)	dapsone and prednisone may be beneficial
Edwards 1998	five			dapsone may be beneficial

Table 2. EBA: Nonrandomised studies

Study	N of participants	Treatments	Results	Conclusions	Notes
Cunningham 1996	14	colchicine with or without other treatments (n = 4); remaining 10 participants could not tolerate colchicine (diarrhoea) or failed to improve or had contraindications (inflammatory bowel disease)	0.5 to 1 mg/day colchicine+initially prednisone = improvement after 2 weeks (n = 1); 0.6 to 1.2 mg/day colchicine, subsequently additional dapsone = improvement (n = 1); 0.5 to 2 mg/day colchicine + 1 mg/kg/day prednisone, sulfapyridine, azathioprine = improvement after 4 months (n = 1); 0.5 to 1.5 mg/day colchicine = improvement after 2 months, but recurrence after 4 years (n = 1)		
Gordon 1997	three	1 to 1.5 mg/kg 8-methoxypsoralen prior to leukapheresis (6 to 7 cycles)	two participants improved, one did not	some benefit with 8-methoxypsoralen and leukapheresis	interim results for study of ten participants
Gupta 1990	two	6 mg/kg/day cyclosporine (for 30 weeks?)	improvement after two to four weeks	systemic cylosporine of some benefit	

Table 2. EBA: Nonrandomised studies (*Continued*)

Harman 1999	two	0.4 g/kg i.v. immunoglobulins for 5 days	slow improvement after 17 courses (n = 1); rapid response after 6 courses (n = 1)	some benefit of i.v. immunoglobulins	
Luke 1999	4+	60 mg/day prednisolone + 200 mg/day dapsone; 2. 5 to 4 mg/kg/day cyclosporine + 101 to 20 mg/day prednisone	prednisolone+dapsone - good response (n = 1); cyclosporine+prednisone - little benefit (n = 1); no detailed information (n = 2); topical steroids and surgery, daclizumab (a humanized monoclonal antibody directed against the interleukin 2 receptor) were of no benefit (n not specified)		
Megahed 1994	two	2 mg/day colchicine	improvement after two weeks	some benefit with colchicine	
Rappersberger 1988	three	100 mg/day dapsone (n = 1); 200 mg/day dapsone + 200 mg/day methylprednisolone (n = 1) ; 16 mg/day methylprednisone+topical steroids+antibiotics	dapsone - improvement (n = 1); dapsone+methylprednisol - slow improvement (n = 1); methylpredisone+topical steroids+antibiotics - improvement (n = 1)		

Table 3. MMP: Nonrandomised studies

Study	N of participants	Treatments	Results	Conclusions	Notes
Axt 1995	six generalised MMP	500 mg/day i.v. cyclophosphamide + 100 mg/day i.v. dexamethasone pulse		no major effect of cyclophosphamide and dexamethasone pulse therapy in ocular disease	

Table 3. MMP: Nonrandomised studies (*Continued*)

Bialasiewicz 1994	nine ocular MMP (all with symblepharon?)	125 to 150 mg/day azathioprione+nasal mucosal graft	At 15 months follow-up, pain relief in all, recurrence of symblepharon in 2/9?		
Carbone 1998	six oral MMP	50 to 100 mg/day prednisone for 38.5 days on average	2/6 complete remission; 4/6 partial remission	some participants benefited from systemic corticosteroids	
Carrozzo 1997	eight oral MMP	topical clobetasol propionate	4/8 complete remission after 5.7 months on average	some participants benefited from topical corticosteroids	
Donnenfeld 1999	nine ocular MMP	subconjunctival mitomycin C in one eye (second eye served as control) - one dose of 0.1 mg	At 12 to 40 months follow-up, 8/9 treated eyes showed no progression, one required additional cyclophosphamide; 5/9 untreated eyes showed progression	some participants benefited from mitomycin C	
Elder 1995	10 ocular MMP (19 eyes)	1. 5 mg cyclophosphamide (8.7 months treatment and follow-up one average) + 60 mg/day prednisolone (6 months) ; 6 participants had failed to respond to sulfa drugs	Inflammation resolved in 15/18 eyes after 2.4 months, 2/18 eyes perforated, 4/18 eyes showed progression of scarring	participants with severe ocular disease benefit from cyclophosphamide and systemic corticosteroids	
Elder 1996	20 ocular MMP	1000 mg/day sulphapyridine; 8 participants had additional topical treatment	10/20 (22/39 eyes) responded after 2 months at the latest		
Fern 1992	five ocular MMP	100 to 150 mg/day dapsone		dapsone beneficial in acute inflammatory disease, but not in scarring MMP	
Foster 1982	26 ocular MMP	cyclophosphamide 1 to 2 mg/kg/day + pred-	cyclophosphamide: 14/14 beneficial (adverse effects:		

Table 3. MMP: Nonrandomised studies (*Continued*)

		nisone (n = 18); 80 (?) to 20 mg/day (n = 2); control (non-systemic treatment) n = 6	leukopenia, alopecia, anaemia, haemorrhagic cystitis); 3/18 withdrew because of gastrointestinal upset; prednisone - 2/2 progression of disease; controls - 6/6 progression of disease		
Foster 1999	ten ocular MMP	2 to 3 g immunoglobulins/kg/cycle (19 cycles in 18 months)	response seen between a minimum of 4 and a maximum of 12 cycles; inflammation improved in 10/10; all 10 still receiving at time article was written	i.v. immunoglobulins beneficial	
Francis 1990	eight ocular MMP	50 mg/day prednisolone + 1.5 to 2 mg/kg/day cyclophosphamide (n = 2); 5 to 15 mg/week methotrexate (n = 6)	7/8 showed improvement (not specified what sort and which regimen)		
Gillies 1996	five ocular MMP, symblepharon (ten eyes)	interferon alpha 2-b injection into one conjunctiva (worst eye), second eye served as control	3/5 treated eyes improved, 2/5 were unchanged; the 5 untreated eyes showed no progression		
Gonzalez-Moles 2003	22 oral MMP [and 11 oral lichen planus]	0.05% clobetasol propionate plus 100,000 IU/cc of nystatin in orabase paste in gingival trays (applied for 5 mins 3 times daily, the reduced to alternate days with complete or excellent response, then gradual further reduction to 1 5 min application on alternate days depending on clinical response)	all 22 showed a complete pain response after 8 weeks of treatment and this was maintained for the 48 week follow-up; other results were not reported separately for MMP and oral lichen planus. No adverse effects were observed	This method of topical steroid application in the mouth may be a treatment worth considering in a future RCT	

Table 3. MMP: Nonrandomised studies (*Continued*)

Hanson 1988	142 generalized MMP	125 to 150 mg/day dapsone first choice treatment (second choice corticosteroids, azathioprine, cyclophosphamide)	beneficial in most participants, no further details of treatment given (focuses on aerodigestive tract manifestations of MMP)		
Ingen-Housz 2005	14	1.5 to 2 mg MMF daily (depending on body weight): 7 participants with severe MMP received MMF after i.v. bolus treatment with cyclophosphamide; 3 participants with severe MMP who experienced a recurrence after cessation of cyclophosphamide treatment; 4 participants with moderate MMP who received MMP as their primary intervention; (all or most of the participants may have received additional treatment with dapsone (max. 2 mg/kg/day) while being treated with MMF)	MMF after cyclophosphamide bolus - MMP controlled (n = 3), some benefit (n = 2), no effect (n = 2); recurrence after ceasing cyclophosphamide - 2 participants went into remission on MMF, disease progression in 1; MMF as primary intervention - 3 participants went into remission, progression was seen in 1 (and cyclophosphamide was started); overall MMF helped control disease in 10/14, no stabilising effect seen in 4 participants: Adverse effects - MMF was well tolerated in 13/14 participants, 1 had pancytopaenia and gastrointestinal effects		direct IF and immuno-electron microscopy proven MMP
Lamey 1992	50 oral MMP	topical corticosteroids versus systemic treatment	topical fluocinonide (n = 19) - 3 improved, 16 asymptomatic; topical fluocinonide+other topicals (n = 11) - 3 improved, 8 asymptomatic; prednisolone+topicals (n = 14) - 5 improved,		

Table 3. MMP: Nonrandomised studies (*Continued*)

			8 asymptomatic (1 unchanged); azathioprine+prednisolone (n =3) - 0 improved, 3 asymptomatic; dapsone+topicals (n = 2) - 1 improved, 1 asymptomatic; cyclophosphamide+prednisolone (n = 1) - asymptomatic		
Letko 2004	16 ocular MMP (all stage 2)	intravenous immunoglobulin (IVIg) versus conventional immunopressive therapies: IVIg - started at 2 g/kg initially at 2 to 4 week intervals, then prior systemic conventional therapy discontinued and when clinical improvement was observed, the interval between infusion cycles was increased until a 16 week interval was reached; conventional immunosuppressive therapy included dapsone, methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide, prednisone)	8/8 participants in the IVIg group had not progressed from stage 2 ocular MMP after a mean treatment period of 24 months; 4/8 participants in the conventional immunosuppression group had progressed from stage 2 to stage 3, and 4 were stable at stage 2 after a mean treatment period of 45 months: Adverse effects - 4 IVIg participants had drug-related headaches or nausea, which resolved when the rate of infusions was decreased; all participants in the conventional immunosuppression group show multiple drug related effects (anaemia, fatigue, leukopenia, osteoporosis, infection)	Authors recommend a RCT to confirm the results and determine the optimal protocol	diagnosis of MMP confirmed by IF; selection to IVIg treatment dependent on financial support from insurance company; all participants received immunopressive treatment before IVIg
Matthews 1989	seven oral MMP (five completed)	75 mg dapsone for 3 months	3/5 some improvement, 2/5 no ben-	some participants benefited from dap-	

Table 3. MMP: Nonrandomised studies (*Continued*)

			efit; 2/7 withdrew from trial because of adverse effects (headache, nausea)	sone	
McCluskey 2004	17 (12 ocular MMP, 5 drug induced ocular MMP	oral methotrexate at a starting dose of 5 to 15 mg; 3 participants were pretreated with dapsone; ocular surface inflammation, mechanical trichiasis and blepharitis were treated aggressively with topical antibiotics, systemic doxycycline, topical steroids (n = 7), ocular lubrications and epilation; methotrexate dose was then adjusted according to clinical response and presence of adverse effects (5 to 25 mg a week); 5 mg folic acid was given on alternate days to reduce the risk of adverse effects	Mean methotrexate treatment of 15 months prevented progression of conjunctival cicatrisation in 12/17 (26 out of 34 eyes); 11/34 eyes had improved visual acuity, 18 maintained their pretreatment visual acuity; 5 eyes deteriorated		IF confirmed diagnosis (n=4)
McFadden 1989	15 oral and generalised MMP	500 to 1500 mg sulphamethoxypyridazine (SMXP)	MMP controlled (n = 1); effective in 10/15; controlled with dapsone and SMXP (n = 1); no response to combination (n = 13); adverse effect - allergic alveolitis (n = 1) - can be life threatening	some benefit from sulfa drugs	
Mondino 1990	139 ocular MMP	5 treatment modalities - control (n = 35); 1.5 mg/kg/day cyclophosphamide + 20 mg/day	controls: progression in 40% of stage 1, 62% stage 2, 73% stage 3; cyclophos+pred:	non-treated controls seem to have more progression	stage 0: no conjunctival shrinkage; stage 1: up to 25 % shrinkage of conjunctival

Table 3. MMP: Nonrandomised studies (*Continued*)

		prednisone (n = 17) ; 1.5 mg/kg/day cyclophosphamide (n = 13); 1.5 mg/kg/day azathioprine (n = 10); 60 to 80 mg/day prednisone (n = 11); combined treatments (n = 51)	17% stage 1, 21% stage 2, 25% stage 3; cyclophos: 25% stage 1, 10% stage 2, 75% stage 3; azathioprine: 33% stage 1, 56% stage 2, 50% stage 3; prednisone: 0% stage 1, 14% stage 2, 53% stage 3; combination: 14% stage 1, 24% stage 2, 53% stage 3		fornices; stage 2: 25 % to 50 % conjunctival shrinkage; stage 3: about 75 % conjunctival shrinkage; stage 4: obliteration of conjunctival fornices with keratinization of ocular surface
Nayar 1993	48 generalised MMP	40 to 60 mg/day prednisolone (n = 15); 50 to 150 mg/day dapsone (n = 14); 100 to 150 mg azathioprine (n = 9); 50 to100 mg/day minocycline (n = 10)	prednisolone: beneficial in 5/15, no good effect for oral lesions; dapsone: beneficial in 7/14, oral and ocular lesions also improved; azathioprine: some benefit for cutaneous lesions in 6/9; minocycline: beneficial for oral lesions in 2/10, no effect in ocular inflammation		in all groups additional topical or low dose oral corticosteroids may have been used
Poskitt 1995	seven generalised MMP	50 to 100 mg/day minocycline	symptomatic improvement in 6/7 after 2 to 3 months treatment (average treatment duration 10 months)	in particular, those with orodynia benefited	all were started on minocycline because of failing to respond to previous treatment or due to adverse effects with previous treatment; some may have had additional systemic corticosteroid therapy
Reiche 1998	eight oral and generalised MMP	50 to 100 mg/day minocycline + 2.5 to 3 g/day nicotinamide	5/8 participants improved (treatment effect judged at 9 months)	some benefit from oral tetracyclines and nicotinamide	

Table 3. MMP: Nonrandomised studies (*Continued*)

Rogers 1982	24 oral and ocular MMP	75 to 200 mg/day dapsone	complete control (n = 11) or partial control of inflammation within 2 to 12 weeks (n = 19 total for complete and partial?); dapsone stopped in 8/24, because of disease remission (n = 2), no effect of dapsone, adverse effects (anaemia, rash) (n = 4)	some benefit from dapsone	15/24 had other treatment prior to dapsone
Rogers 1988	77 oral, ocular, generalised MMP	150 mg/day dapsone or 1500 to 3000 mg/day sulfapyridine (for a minimum of 12 weeks)	localised oral disease (n = 16) - 0 grade 0 [no improvement], 1 grade 1 [improvement but active disease], 3 grade 2 [major reduction of disease activity], 12 grade 3 [minimal to nil activity]; generalised MMP (no ocular) (n = 31) - 10? grade 0, 0 grade 1, 1 grade 2, 20 grade 3; ocular (n = 30) - 5? grade 0, 0 grade 1, 1 grade 2, 24 grade 3: follow-ip ranged from 1 to 12 years, with a mean of 4. 3 years for localised oral MMp and 5. 3 years for combined MMP and ocular MMP	some benefit from sulfa drugs	follow-up of Rogers 1982
Secchi 1996	four ocular MMP	0.4 mg/ml topical mitomycin C (intraoperative after synechiolysis)	beneficial in 4/4, no recurrence after a follow-up of 12 to 19 months	benefit from topical mitomycin C	participants had no active disease for at least six months before surgery (all eyes were free of inflammatory signs)

Table 3. MMP: Nonrandomised studies (*Continued*)

Thornhill 2000	25 oral MMP	1 g sulphamethoxypyridazine	beneficial 16/25, 6/25 still on treatment, 3/25 withdrawn due to side effects	benefit from SMXP in most patients	
Tauber 1991	117 ocular MMP	dapsone versus cyclophosphamide versus azathioprine: initially 2 mg/kg/day dapsone (additional prednisone in 8) (n = 69); initially 2 mg/kg/day cyclophosphamide (additional prednisone in 23?) (n = 25); initially 2 mg/kg/day azathioprine (additional prednisone in 2?) (n = 23)	By the end of follow-up (3 to 135 months, average 35 months), 81% had dapsone, 34% cyclophosphamide, 49% azathioprine; no significant differences were observed comparing progression rates		
Vincent 1993	19 oral MMP	oral versus topical steroids; topical triamcinolone 0.1 % to 0.5 % aqueous rinse (n = 11) ; 40 mg/day prednisolone for 5 days, 20 mg/day for 10 days (n = 4); topical and oral corticosteroids (n = 2); treatment not stated (n = 2)	triamcinolone - 10/11 required subsequent systemic steroid burst for disease control; prednisolone - results not stated; topical and oral corticosteroids - results not stated		
Wright 1979	22 ocular MMP	topical versus systemic treatment: very potent topical steroids (n = 19) "some of these" with acute ulceration were treated with 60 to 120 mg/day prednisone; 100 mg/day azathioprine+topical steroids (n = 3)	no detailed results given		

APPENDICES

Appendix 1. *Search terms used to locate specific studies in the Cochrane Skin Group Specialised Register*

(cicatricial and pemphigoid) or (mucous and membrane and pemphigoid) or (epidermol and bullosa and acquisita)

Appendix 2. *Search terms used to locate specific studies (CCTs and RCTs) on the Cochrane Library (CENTRAL)*

(cicatricial and pemphigoid)
(mucous next membrane next pemphigoid)
(epidermol next bullosa next acquisita)
(#1 or #2 or #3)
(bullous next pemphigoid)
PEMPHIGOID BULLOUS
(gestationis near pemphigoid)
(#5 or #6 or #7)
(#4 and (not #8))

Appendix 3. *Search strategies to locate specific trials (CCTs and RCTs) in MEDLINE / PubMed (OVID)*

Search lines 1-29, as given in the Cochrane Reviewers' Handbook (Alderson 2004) 5b2.

30. Pemphigoid, Benign Mucous Membrane/
31. cicatricial pemphigoid.mp.
32. ocular pemphigoid.mp.
33. Epidermolysis Bullosa Acquisita/
34. 30 or 31 or 32 or 33
35. 29 and 34

Search strategy to locate any intervention in Mucous membrane pemphigoid and Epidermolysis bullosa acquisita in PubMed

#1
"Epidermolysis Bullosa Acquisita"[MeSH] OR "Pemphigoid, Benign Mucous Membrane"[MeSH] OR Epidermolysis Bullosa Acquisita[tw] OR Acquired Epidermolysis Bullosa[tw] OR Mucous Membrane Pemphigoid[tw] OR Cicatricial Pemphigoid[tw] OR epidermolysis bullosa acquisita[tw]
#2
therapy OR treatment OR medication OR predniso* OR corticosteroid* OR steroid* OR immunosupp* OR azathioprin* OR cyclophosphamid* OR methotrexat* OR chlorambucil* OR cyclosporin* OR antibiotic* OR dapson* OR sulpha* OR sulfa* OR sulfala* OR erythromycin* OR tetracyclin* OR minocin* OR minocyclin* OR nicotinamid* OR plasmaph* OR plasmaexchange* OR surgery OR surgical or immunoglob* OR mycophenolate OR mofetil or tacrolimus or adalimumab or alefacept or efalizumab or etanercept or infliximab or rituximab or anti-CD20 OR anti-TNF alpha OR anti-CD11a

Appendix 4. *Search strategy to locate specific trials (CCTs and RCTs) in EMBASE*

1. random$.mp.
2. factorial$.mp.
3. crossover$.mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name]
7. assign$.mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. Cicatricial Pemphigoid/
15. ocular pemphigoid.mp.
16. mucous membrane pemphigoid.mp.
17. Epidermolysis Bullosa Acquisita/
18. 14 or 15 or 16 or 17
19. 13 and 18

Appendix 5. Search terms for www.controlled-trials.com (7th April 2005) and www.clinicaltrials.gov (7th April 2005)

pemphgoid
epidermolysis bullosa

WHAT'S NEW

Last assessed as up-to-date: 24 January 2006.

Date	Event	Description
7 October 2015	Amended	Author information (affiliation) updated (Gudula Kirtschig)

HISTORY

Protocol first published: Issue 1, 2003

Review first published: Issue 1, 2003

Date	Event	Description
31 March 2015	Amended	Fenella and Dedee's affiliations have been slightly amended.
14 May 2014	Review declared as stable	The conclusion is so certain that the addition of new information will not change it, and there is unlikely to be any more research done on this topic. There were no ongoing studies or studies awaiting classification listed in the last published review, and a search of MEDLINE and Embase in 2014 found no recent results
17 June 2008	Amended	Converted to new review format.
24 January 2006	New citation required and conclusions have changed	Substantive amendment
31 March 2005	New search has been performed	New studies sought but none found
16 June 2003	New search has been performed	Minor update

CONTRIBUTIONS OF AUTHORS

1. GK conceived the idea of the review, contributed to the writing of the protocol, extraction of data, analysis of the results, and the writing of the systematic review.

2. NPK contributed to the writing of the protocol, extraction of data, analysis of the results, and the writing of the systematic review.

3. DFM contributed to the writing of the protocol, extraction of data, analysis of the results, and the writing of the systematic review.

4. FW contributed to the writing of the protocol and analysis of the results.

DECLARATIONS OF INTEREST

Fenella Wojnarowska was invited to speak at a conference on Treatment of Autoimmune Bullous Diseases organised by Bayer, who manufacture IVIgs. Her expenses and an honorarium were paid by Bayer.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Nuffield Trust Fellowship Scheme, UK.

NOTES

The conclusion is so certain that the addition of new information will not change it, and there is unlikely to be any more research done on this topic. There were no ongoing studies or studies awaiting classification listed in the last published review, and a search of MEDLINE and Embase in 2014 found no recent results.

INDEX TERMS

Medical Subject Headings (MeSH)

Cyclophosphamide [therapeutic use]; Epidermolysis Bullosa Acquisita [*drug therapy]; Glucocorticoids [*therapeutic use]; Immunosuppressive Agents [*therapeutic use]; Pemphigoid, Benign Mucous Membrane [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans