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Interventions for pemphigus vulgaris and pemphigus foliaceus (Review)

Martin LK, Agero AL, Werth V, Villanueva E, Segall J, Murrell DF

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[Intervention Review]

Interventions for pemphigus vulgaris and pemphigus foliaceus

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ABSTRACT

Background

A range of interventions have been described for treatment of pemphigus, however the optimal therapeutic strategy has not been established.

Objectives

To assess the efficacy and safety of all interventions used in the management of pemphigus vulgaris and pemphigus foliaceus.

Search methods

We searched the Cochrane Skin Group Specialised Register (October 2008), The Cochrane Central Register of Controlled Trials (*The Cochrane Library* Issue 4, 2008), MEDLINE (2003 to October 2008), EMBASE (2005 to October 2008), LILACS (1981 to October 2008), Ongoing Trials Registers, reference lists of articles, conference proceedings from international pemphigus meetings and contacted experts in the field.

Selection criteria

Randomised controlled trials of any intervention in pemphigus vulgaris or pemphigus foliaceus.

Data collection and analysis

Two authors independently assessed quality and extracted data from studies. All investigators were contacted for further information. Adverse events were identified from included studies.

Main results

Eleven studies with a total of 404 participants (337 pemphigus vulgaris, 27 pemphigus foliaceus and 40 not specified) were identified. The quality of included studies was not high, the majority of studies did not report allocation concealment, and power was limited by very small sample sizes. Interventions assessed included prednisolone dose regimen, pulsed dexamethasone, azathioprine, cyclophosphamide, cyclosporine, dapsone, mycophenolate, plasma exchange, topical epidermal growth factor and traditional Chinese medicine. Ten studies included participants with newly diagnosed or newly active recurrent disease, and one trial included participants in maintenance phase.

There was sufficient data for 4 meta-analyses, each pooling results of two studies only. For the majority of interventions, results were inconclusive. We found some interventions to be superior for certain outcomes, although we were unable to conclude which treatments are superior overall. Mycophenolate was more effective in achieving disease control than azathioprine (1 study; n=40; RR 0.72; 95% CI 0.52 to 0.99, NNT 3.7). There was evidence of a steroid-sparing benefit of azathioprine (1 study; n=57; MWD -3919 mg prednisolone; 95% CI -6712 to -1126) and cyclophosphamide (1 study; n=54; MWD -3355 mg prednisolone; 95% CI -6144 to -566) compared to glucocorticoids alone. Topical epidermal growth factor decreased time to control (1 study; n=20; HR 2.35; 95% CI 1.62 to 3.41).

Authors' conclusions

There is inadequate information available at present to ascertain the optimal therapy for pemphigus vulgaris or pemphigus foliaceus. Further research is required, especially to assess the optimal glucocorticoid dose, the role of adjuvant immunosuppressive medications, and long-term adverse events to improve harm:benefit analyses.

PLAIN LANGUAGE SUMMARY

Interventions for pemphigus vulgaris and pemphigus foliaceus

This review of clinical trials aimed to find out which is the most effective and safest treatment option for pemphigus vulgaris and pemphigus foliaceus.

Pemphigus vulgaris and pemphigus foliaceus are rare diseases characterised by fragile blisters and sores on the skin and mucosa. They are auto-immune diseases which are caused by the body making an antibody against the person's own skin. These diseases are chronic and are not currently curable. Pemphigus vulgaris and foliaceus are managed with drugs which suppress the immune system. The aim of treatment is to suppress blister formation. Systemic glucocorticoids are the cornerstone of management in pemphigus, however adjuvant immunosuppressive and anti-inflammatory agents are commonly used. There are many treatments available, however it is not known which is the most effective or safest treatment option, or which is the best combination.

This review included data from 11 clinical trials involving 404 participants. The studies had very small numbers of participants, so can provide only limited information. Ten different active treatments were studied, including prednisolone, pulsed oral dexamethasone, azathioprine, cyclophosphamide, cyclosporine, dapsone, mycophenolate, plasma exchange, topical epidermal growth factor and traditional Chinese medicine.

This review found insufficient information to conclude which is the most effective and safest treatment plan. We found that mycophenolate mofetil appears to be more effective than azathioprine in controlling disease, although no difference was seen in remission. We found that taking azathioprine and cyclophosphamide decreased the amount of glucocorticoids required. Topical epidermal growth factor decreased time required for lesions to heal by 6 days (median). We found no difference in withdrawal due to adverse events in any study, although differing adverse event profiles were observed for each intervention. We were not able to conclude which treatments are superior overall.

Multiple treatments are available for pemphigus vulgaris and pemphigus foliaceus and there is a variation in dosage plan and combination of drugs used, which makes choice of treatment schedule complex. In addition, response to treatment can vary between individuals. Treatments need to be chosen after careful consideration of the potential benefits and side effects, in the context of the individual's other medical conditions. This review found insufficient information to conclude which is the most effective and safest treatment regimen. Further studies are required to determine the optimal treatment regimen, especially to assess the optimal glucocorticoid dose, the role of adjuvant immunosuppressive medications, and long-term adverse events to improve harm:benefit analyses.

BACKGROUND

Description of the condition

Pemphigus is a group of rare autoimmune blistering diseases characterised by widespread blistering and erosions of the skin and

mucous membranes. It is a chronic and potentially life threatening condition.

Epidemiology

Pemphigus is rare and the incidence has been estimated between 1 to 16 new cases per million people per year (Pisanti 1974; Chams-Davatchi 2005). The disease most commonly starts in adulthood, and the distribution is equal in men and women. Pemphigus occurs in all races, however, it appears to be associated with certain HLA class II alleles, which are inherited molecules involved in the immune response (Tron 2005). There is a form of endemic pemphigus foliaceus (fogo selvagem, or "wild fire" in Portuguese) in Brazil (Quinteiro Ribeiro 05).

Cause

Pemphigus is an acquired auto-immune blistering disease, in which the immune system becomes dysregulated and produces antibodies against normal skin components. The mechanisms leading to immune dysregulation and auto-immunity are complex and incompletely understood, and are beyond the scope of this review. In pemphigus, the body makes auto-antibodies (IgG) against desmogleins, which are adhesion proteins in the skin. They form part of desmosomes which act to bind together the cells in the epidermis, the outermost layer of the skin. Auto-antibodies against both desmoglein 1 and desmoglein 3 may occur; desmoglein 1 is located in the upper epidermis and is found only in the skin, desmoglein 3 is found in the lower epidermis, and is found both in the skin and in mucous membranes. Antigen-specific T cell responses are also involved in the pathogenesis of pemphigus (Hertl 2006).

Deposition of these antibodies is thought to cause separation of epidermal cells (keratinocytes) leading to the formation of fragile blisters and superficial erosions.

Classification

Pemphigus is divided into three main subtypes:
pemphigus vulgaris (PV),
pemphigus foliaceus (PF),
paraneoplastic pemphigus (PNP).

Pemphigus vulgaris is the most common type of pemphigus and accounts for approximately 70% of cases. It is characterised by the presence of IgG against desmoglein 3, although antibodies against desmoglein 1 are also commonly present (Salato 2005). The classification of PV also includes the rare variant pemphigus vegetans.

Pemphigus foliaceus accounts for approximately 20% of cases. It is caused by IgG to desmoglein 1 only. Rare subtypes of PF include pemphigus erythematosus and pemphigus herpetiformis (Burns 2004).

There is some overlap between PV and PF: features may co-exist in the same person, or evolve from one form to the other (Sami 2001). The auto-antibody profile has been reported to correlate with clinical phenotype (Ding 1997; Amagai 1999; Jamora 2003).

Paraneoplastic pemphigus is the rarest type of pemphigus and is associated with the worst prognosis. It is a distinct variant of pemphigus associated with internal malignancy. Management is focused on treatment of the underlying malignancy (Anhalt 1990). Due to its distinct aetiology, prognosis and management, paraneoplastic pemphigus will not be considered in this review.

Clinical features

Pemphigus is characterised by blistering of the skin and/or mucous membranes. As blister formation occurs within the epidermis, fragile blisters are easily ruptured and rapidly evolve into superficial erosions.

In pemphigus vulgaris, both mucous membranes and skin are involved. The majority of cases present with non-healing oral erosions; cutaneous involvement usually follows after a delay of several months.

Pemphigus foliaceus, in contrast, does not affect mucous membranes, and presents with cutaneous blistering and erosions. Blister formation is more superficial than in PV, so erosions are more prominent than blisters.

Impact

PV and PF are chronic and potentially life-threatening conditions. Chronic blistering can result in pain, dehydration, secondary infection and in rare instances, death. Mucosal involvement may cause pain, difficulty swallowing, weight loss, nose bleeds and hoarseness. Side-effects from treatment are common. Pemphigus may have a significant impact on quality of life and the psychological impact of diagnosis of a serious incurable disease may be profound. Knowledge of prognostic factors is limited, but PF has been reported to have a more benign prognosis than PV (Goon 2001). Involvement limited to the mucosa in PV is associated with a better prognosis than mucosal and cutaneous involvement (Mourellou 1995).

Diagnosis

Diagnosis of pemphigus requires a combination of clinical features, histopathology and immunofluorescence studies. Histopathology involves taking a skin biopsy for examination under a microscope. Light microscopy of lesional biopsies shows intraepidermal acantholysis (loss of cohesion between epidermal cells) and vesicle (blister) formation. In PV vesicle formation is suprabasal (lower epidermis) and in PF vesicle formation is subcorneal (upper epidermis) (Burns 2004).

Due to the difficulty in differentiating PV and PF from other bullous diseases, confirmation of the diagnosis with immunofluorescence studies is required. Direct immunofluorescence looks for auto-antibodies in the skin, and indirect immunofluorescence looks for auto-antibodies in the blood. Direct immunofluorescence of perilesional skin shows intercellular epidermal deposition of IgG with or without C3 in both PV and PF. Indirect immunofluorescence on monkey oesophageal cells shows antibodies to keratinocyte cell surface antigen in PV. Enzyme-Linked Immuno Sorbent Assay (ELISA) and immuno-blotting techniques are additional diagnostic tests which allow identification of auto-antibodies to specific epidermal proteins. Antibody titre has been reported to correlate with disease activity in some, but not all people (Fitzpatrick 1980; Cheng 2002).

Description of the intervention

Management

The aim of management in pemphigus is to induce and maintain remission. This entails suppression of blister formation, healing of erosions and ultimately withdrawal of treatment. Ideally effective disease control is established while minimising any adverse effects of treatment. A diverse group of interventions have been reported in pemphigus.

Systemic glucocorticoids are the cornerstone of management in pemphigus. Introduction of glucocorticoids in the 1950's was accompanied by a reduction in mortality from 75% to 30% (Bystryn 1984). However, the high-dose and prolonged courses of systemic glucocorticoids required for disease control are associated with significant adverse effects (Rosenberg 1976). There is considerable variation in the glucocorticoid regimen used. Continuous administration is most common, however it has been argued that adjuvant high dose pulsed therapy may achieve more rapid disease control while reducing the cumulative glucocorticoid dose (Werth 1996; Toth 2002).

Steroid-sparing adjuvant medications are widely used in the treatment of pemphigus. A large number of steroid-sparing adjuvants have been described, and these have been broadly classified into immunosuppressive and anti-inflammatory groups (Bystryn 1996). The rationale for their use is to increase efficacy of treatment, as well as a theoretical advantage of reducing the cumulative glucocorticoid dose and thereby reducing adverse events. These agents are slow-acting, so their role is in maintenance therapy rather than in inducing remission (Harman 2003). Despite their widespread use, it is not known if steroid-sparing agents are beneficial, and they are associated with significant adverse effects themselves. It is not known which is the preferable steroid-sparing agent.

A diverse number of other interventions have been tested for pemphigus. Biological therapies targeting specific molecules in the inflammatory cascade have been applied to pemphigus (Arin 2005) and it is plausible that these therapies may be effective, although clinical experience is limited. Topical and intralesional glucocorticoid usage have been used in mild disease or as an adjunct. Use of intravenous immunoglobulin and plasmapheresis have been reported in refractory cases (Jolles 2001; Engineer 2000; Turner 2000). Certain drugs and foods have been found to be acantholytic in vitro, and it has been suggested that cessation of these may be therapeutic (Ruocco 2001).

Why it is important to do this review

Pemphigus is a serious disease which can be difficult to treat, and there is no consensus among experts regarding treatment (Mimouni 2003). There are many unresolved questions regarding management of pemphigus (Martin 2008). Despite advances in management, the mortality rate is currently estimated at 5 to 10%, and the major morbidity and mortality in pemphigus is due to complications of treatment (Bystryn 1996). Systemic glucocorticoids are the mainstay of treatment, however the optimal regimen has not been established. Steroid-sparing adjuvant medications are widely used, however it is not known if they are beneficial, nor which agent is preferable. The role of other systemic therapies and topical agents is not known.

OBJECTIVES

To assess the efficacy and safety of interventions used in the management of pemphigus vulgaris and pemphigus foliaceus.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

Anyone with pemphigus vulgaris or pemphigus foliaceus confirmed by appropriate clinical features, histopathology and immunofluorescence studies.

Types of interventions

We included any therapeutic intervention used to manage pemphigus vulgaris or pemphigus foliaceus including:

(1) Systemic glucocorticoids

(2) Systemic non-steroidal immunomodulatory therapies

- Immunosuppressive therapies: azathioprine, chlorambucil, cyclophosphamide, cyclosporine, methotrexate, mycophenolate mofetil
- Anti-inflammatory therapies: dapsone, doxycycline, hydroxychloroquine, gold, minocycline, nicotinamide, tetracycline
- Biological therapies: rituximab, etanercept, infliximab
- Intravenous immunoglobulin
- Plasmapheresis
- Protein A immunoadsorption

(3) Topical therapies

- Topical glucocorticoids
- Intralesional glucocorticoids
- Topical immunosuppressive therapies
- Topical nicotine
- Other topical therapies

(4) Cessation of putative causative agents

- e.g. certain medications or foods

(5) Diverse therapies

- Pyridostigmine
- Herbal therapies

The comparators included no treatment, placebo or usual care (e.g. systemic glucocorticoid with or without azathioprine) or another listed therapy. We included trials which compared different doses of the same therapy or different routes of administration (e.g. intravenous versus oral systemic glucocorticoids).

Types of outcome measures

We were primarily interested in measures of disease control. Definitions employed were developed by an international consensus committee, the PV Definitions Committee during 2005 -2007 (Murrell 2008).

Primary outcomes

(i) The proportion of participants achieving remission

Remission is defined as the absence of lesions or the presence of transient new lesions that heal within one week, while the person is receiving minimal therapy. Minimal therapy is defined as less than 10 mg/day of prednisone (or the equivalent) and/or adjuvant therapy for at least two months ('Partial remission on minimal therapy' in the consensus document Murrell 2008).

(ii) Deaths

Secondary outcomes

(iii) The proportion of participants achieving disease control

Disease control is defined as the time at which new lesions cease to form and established lesions begin to heal.

(iv) The proportion of participants suffering relapse

Relapse is defined as the appearance of more than three new lesions a month that do not heal spontaneously within one week, or by the extension of established lesions in a person who has achieved disease control.

(v) Change in pemphigus severity score

(vi)Time to disease control (defined above)

(vii) Cumulative glucocorticoid dose

Cumulative glucocorticoid dose is a surrogate measure of glucocorticoid-induced adverse events. Interventions which result in a lower cumulative glucocorticoid dose are called 'steroid-sparing'.

(viii) Reduction of serum antibody titres

(ix) Adverse events

(x) Change in quality of life score

Search methods for identification of studies

Electronic searches

We searched the Cochrane Skin Group's Specialised Register on 15th October 2008 using the term 'pemphigus' and the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 4, 2008) using the following strategy:
#1(pemphigus)

#2MeSH descriptor Pemphigus explode all trees
#3(#1 OR #2)

We searched MEDLINE (OVID) (2003 to 15th October 2008) using the search strategy displayed in Appendix 1.
We searched PREMEDLINE (OVID) (19th October 2008) using the search strategy displayed in Appendix 1.
We searched EMBASE (OVID) (2005 to 15th October 2008) using the search strategy displayed in Appendix 2.
The UK Cochrane Centre has an ongoing project to systematically search MEDLINE and EMBASE for reports of trials which are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE to 2003 and in EMBASE to 2005. That is why the Cochrane Skin Group has undertaken further searching for this review to cover the years that have not been searched by the UKCC.

We searched LILACS (Latin American and Caribbean Health Science Information database) (1982 to 15th October 2008) using the strategy in Appendix 3.

Ongoing Trials Registers

Ongoing trials were identified from the following registers (October 2008) using the search term 'pemphigus' -

- The metaRegister of Controlled Trials www.controlled-trials.com
- The U.S. National Institutes of Health ongoing trials register www.clinicaltrials.gov
- The Australian and New Zealand Clinical Trials Registry www.anzctr.org.au
- The World Health Organisation International Clinical Trials Registry platform www.who.int/trialsearch
- The Ongoing Skin Trials register on www.nottingham.ac.uk/ongoingskintrials
- The International Pemphigus and Pemphigoid Foundation website www.pemphigus.org

Searching other resources

References Lists

The bibliographies of included RCTs were checked for possible reference to RCTs.

Correspondence

Unpublished trials and grey literature were obtained via correspondence with the trial authors and experts in the field (Hopewell 2007). The following trial authors were contacted: Razzaque Ahmed, Masa Amagai, Grant Anhalt, Luca Borradori, Jean-Claude Bystryn, Marco Carrozzo, Cheyda Chams-Davatchi, Luis Diaz, Giuseppe Cianchini, Farzam Gorouhi, Sergei Grando, Karen Harman, Takashi Hashimoto, Michael Hertl, Nicolas Hunzelmann, Pascal Joly, Marcel Jonkman, Amrinder Kanwar, Michael Meurer, Daniel Mimouni, Mokni Mourad, Alex Ortega, J Pasricha, Christiane Pfeiffer, Ana Maria Quinteiro Ribeiro, K Ratnam and Detlef Zillikens.

Conference proceedings

We checked conference proceedings from international research workshops on pemphigus for controlled trials and the trial authors contacted for information.
We searched the following conference proceedings -
The International Pemphigus Foundation and the American Autoimmune Related disease Association International Meeting: Pemphigus as a model of organ-specific humoral autoimmune diseases; 2001 April 20 21; Bethseda, USA. (Journal of Investigative Dermatology. 2002 p734-40).
The International Pemphigus Foundation and the American Autoimmune Related disease Association International Scientific Meeting, PEMPHIGUS 2005: Progress and Future Directions; 2005 June 15 16; Bethesda USA. (Journal of Investigative Dermatology. 2005 vol 125(5) 1085-92).
Advances in Pemphigus and Pemphigoid. Satellite Symposium to the 36th Annual Meeting of the European Society of Dermatological Research (ESDR); September 6 7; Paris. (Journal of Investigative Dermatology. 2006 vol 126 p2348-54).
Post-International Investigative Dermatology Meeting 2008; International meeting on autoimmune bullous diseases. May 17 19; Otsu Japan.

Adverse events

We did not conduct a separate search for adverse events and considered only those described in the included studies.

Language Restrictions

We did not impose any language restrictions when searching for publications and translations were sought where necessary.

Data collection and analysis

Selection of studies

Two authors (LM and AA or DM) screened and identified potentially-relevant titles and abstracts from the searches. Both authors independently assessed the full text of all relevant studies to determine whether such studies met pre-defined selection criteria. We resolved any differences through discussion with a third author

(DM or EV). All excluded studies included a stated reason for exclusion.

Data extraction and management

Two authors (LM and AA) independently extracted data using pre-designed data extraction forms. We resolved any differences through discussion with a third author (DM). Where possible, the review team attempted to contact trial authors in the event of missing information.

Assessment of risk of bias in included studies

Two authors (LM and AA) independently assessed the quality of included studies, and we resolved any differences through discussion with a third author (DM). Quality assessment included an evaluation of the following components for each study meeting the selection criteria:
(a) the method of generation of the randomisation sequence;
(b) the method of allocation concealment - it was be considered 'adequate' if the assignment could not be foreseen. This was coded in the 'Risk of bias' table as A - adequate, B - unclear, C - inadequate, D - not used;
(c) who was blinded / not blinded (participants, clinicians, outcome assessors);
(d) how many participants were lost to follow up in each arm;
(e) whether participants were analysed in the groups to which they were originally randomised (intention to treat).
In addition, we assessed the following:
(f) baseline assessment of the participants for age, sex, duration and severity of disease;
(g) aims, interventions (including drug doses and duration of treatment) and outcome measures clearly defined;
(h) use and appropriateness of statistical analyses.
We recorded the information in the table 'Characteristics of included studies' and described the quality of each study based on a summary of these components. We excluded non-randomised controlled studies from the analyses, but these were commented on in the discussion.

Measures of treatment effect

We summarised information from included trials in tables and narrative form. We expressed results as risk ratio (RR) with 95% confidence intervals (CI) for dichotomous outcomes, and difference in means (MWD) with 95% CI for continuous outcomes. We presented 'Number needed to treat' (NNT) for dichotomous outcomes which reached statistical significance. For time to event outcomes, we expressed results as hazard ratio (HR) with 95% confidence intervals.

We inspected adverse events reported in included studies. We only included withdrawal due to adverse events in the analysis and discussed other adverse events in the results section.

We assessed short-term benefit with the outcome 'disease control' and long-term benefit with the outcome 'remission'.

Unit of analysis issues

Internally controlled trials were not pooled with studies of other designs. In studies in which multiple relapses per participant were reported, only one relapse per participant was included in the analysis. Where there were multiple intervention groups within a trial, pair-wise comparisons were made of similar active interventions versus another active intervention. Care was taken to ensure than the same group of participants was not included twice within a meta-analysis. Where there were multiple observations on each participant, such as for the outcome antibody titre, only the baseline and longest follow-up data from each trial were analysed. Non-independent hazard ratios were calculated by specifying the variance estimators allowing for intra class correlations.

Dealing with missing data

Authors were contacted for missing data. Several authors provided helpful clarifications regarding methodology and outcome definitions (Beissert 2006; Chams-Davatchi 2007; Chrysomallis 1994; Ioannides 2000; Mentink 2006), however we were not able to obtain any further raw data for use in meta-analysis.

Dichotomous data

For the dichotomous outcomes, remission, control and relapse, we conducted an intention-to-treat analysis. Participants with missing outcome data were regarded as treatment failures and included in the analysis. For the dichotomous outcomes of death and withdrawal due to adverse events, an available case analysis was conducted. The conditional outcome 'relapse after remission' was redefined as a composite outcome 'relapse after remission or unable to achieve remission'.

Continuous data

For the continuous outcomes cumulative glucocorticoid dose and antibody titre, in the case of missing data an available case analysis was conducted.

Time-to-event data

For the time-to-event outcome 'time to control', where raw data or hazard ratios were not available, data was excluded from the analysis. In the paper by Tabrizi, we assumed that participant 3 was administratively censored (Tabrizi 2007).

Missing statistics

Where possible, missing statistics not available from authors were imputed. The standard deviation for change in antibody titre in the paper by Luo was imputed assuming a correlation coefficient r of 0.5 (Luo 2003). Where insufficient information was available to impute statistics, results were described narratively and were not included in the analysis.

Assessment of heterogeneity

Clinical heterogeneity was assessed by inspecting study participants and regimens of interventions, including dose, route and tapering schedule. Methodological heterogeneity was assessed by inspecting key methodological aspects of trials including method of randomisation, allocation concealment, blinding and loss to follow-up. Statistical heterogeneity was assessed using I^2, with I^2 >50% indicating substantial heterogeneity.

Assessment of reporting biases

Due to the large number of interventions and small number of studies, publication bias was not formally assessed. The predominantly negative or inconclusive results of included studies argues against publication bias.
Where we were concerned about the possibility of selective reporting of data (e.g. only reporting of best responders), authors were contacted for clarification and if no additional information was available, data was excluded from the analysis.

Data synthesis

Meta-analysis was performed to calculate a weighted treatment effect across trials using a random effects model. Meta-analyses were only conducted for studies with a similar intervention which reported outcomes prespecified in the protocol for this review (Martin 2006). Interventions were pooled if the same pharmaceutical agent was administered, irrespective of dose or administration route.
Where it was not possible to perform a meta-analysis, for example where reported outcomes were dissimilar to outcomes prespecified in the protocol for this review (Martin 2006), data was summarised for each trial narratively in the results section. Studies with differing definitions of 'remission' were summarised in narrative form, as these definitions were too heterogeneous for a meta-analysis. For 'disease control', outcomes were considered sufficiently similar to our pre-specified definition, and data was included in the analysis; the definition used in the study was specified in the 'Characteristics of included studies' table.

Subgroup analysis and investigation of heterogeneity

We initially planned to conduct subgroup analyses for pemphigus vulgaris and pemphigus foliaceus, however this was not worthwhile due to the wide variety of interventions and small sample sizes.

Sensitivity analysis

Sensitivity analyses were undertaken to test the effect of decisions made in the review methodology. Sensitivity analyses were undertaken for:
- outcome relapse: composite outcome ' relapse after remission or unable to achieve remission' compared to an available case analysis of the conditional outcome 'relapse after discontinuing therapy'.
- missing statistics: with varying assumptions for the correlation coefficient r.

Other

Where there was uncertainty, trial authors were contacted for clarification. A consumer was involved in the review team to help improve the relevance and readability of the final review for other consumers.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; Characteristics of ongoing studies.

Results of the search

In total 577 citations were identified from electronic searches. Nine studies were identified from online trial registries and three studies were identified via correspondence with authors. Two studies were identified from hand searching of conference proceedings and one study was identified from hand searching of reference lists. Full text copies of papers were obtained for 37 papers. Authors were contacted for further information in all included studies.

Included studies

Eleven randomised controlled trials which met the inclusion criteria were identified, with a total of 404 participants (337 pemphigus vulgaris, 27 pemphigus foliaceus, 40 not specified) (Beissert 2006; Chams-Davatchi 2007; Chrysomallis 1994; Guillaume 1988; Ioannides 2000; Luo 2003; Mentink 2006; Ratnam 1990; Rose 2005; Tabrizi 2007; Werth 2008). Full details are described in the 'Characteristics of included studies' tables.

Design

All included studies were randomised controlled trials. Three trials were placebo controlled, although the placebo arm contained an active treatment. (Mentink 2006; Tabrizi 2007; Werth 2008) Eight studies compared one or more active intervention. One study was a left-right comparison trial of a topical agent (Tabrizi 2007), and the remaining 10 examined systemic interventions. Duration of follow-up was generally adequate, ranging from nine months to five years, although in two studies the duration of follow-up was unclear (Guillaume 1988; Luo 2003).

Sample sizes

The sample sizes of included studies were small, ranging from 19 to 120 participants. The small sample sizes are understandable, given the rarity of pemphigus which makes recruitment for large studies difficult, however small sample sizes decrease the power of studies.

Only four papers described sample size calculations (Guillaume 1988; Mentink 2006; Tabrizi 2007; Werth 2008). Only one study performed sample size calculations including provision for participant withdrawal, fulfilled recruitment targets and demonstrated a difference in outcome in keeping with estimates. (Tabrizi 2007). One study fulfilled recruitment targets, however did not demonstrate a difference in outcome in keeping with estimates (Guillaume 1988) Two studies did not fulfil recruitment targets or demonstrate a difference in outcomes (Mentink 2006; Werth 2008).

Setting

Studies were conducted in a number of countries located in Europe, North America, Asia, and the Middle-East. All studies were conducted by Dermatology Departments. Five were multi-centre studies (Beissert 2006; Guillaume 1988; Mentink 2006; Rose 2005; Werth 2008) and six were conducted at single institutions (Chams-Davatchi 2007; Chrysomallis 1994; Ioannides 2000; Luo 2003; Ratnam 1990; Tabrizi 2007).

Participants

All studies included adult participants of both sexes. Five studies included only pemphigus vulgaris (Chams-Davatchi 2007; Chrysomallis 1994; Mentink 2006; Tabrizi 2007; Werth 2008), and five studies included both pemphigus vulgaris and pemphigus foliaceus (Beissert 2006; Guillaume 1988; Ioannides 2000; Ratnam 1990; Rose 2005). In one paper, the subtype of pemphigus was not specified (Luo 2003). The study by Chrysomallis was restricted to participants with involvement of the oral cavity only (Chrysomallis 1994). The majority of studies included only participants with newly diagnosed disease (Chams-Davatchi 2007; Chrysomallis 1994; Guillaume 1988; Ioannides 2000; Luo 2003; Ratnam 1990; Rose 2005). The remainder included a combination of new onset and recurrent disease. One study included participants with chronic disease in the maintenance phase (Werth 2008). No trials included participants with disease recalcitrant to systemic therapies. Baseline disease severity ranged from mild to severe disease. Baseline disease severity was not described in three studies (Chrysomallis 1994; Rose 2005; Tabrizi 2007).

Interventions

The eleven included studies examined the following diverse interventions:

(1) Glucocorticoid regimen

- Two doses of oral prednisolone (starting dose of 1mg/kg versus 0.5mg/kg) (Ratnam 1990)
- Pulsed oral dexamethasone (Mentink 2006)

(2) Adjuvant immunomodulatory agent versus glucocorticoid alone

- Azathioprine plus prednisolone versus prednisolone alone (Chams-Davatchi 2007)
- Cyclosporine plus glucocorticoid versus glucocorticoid alone (prednisone in Chrysomallis 1994 and methylprednisolone in Ioannides 2000)
- Cyclophosphamide plus glucocorticoid versus glucocorticoid alone (prednisolone in Chams-Davatchi 2007 and prednisone in Chrysomallis 1994)
- Dapsone plus prednisone plus immunosuppressant versus placebo plus prednisone plus immunosuppressant (azathioprine, mycophenolate or methotrexate) (Werth 2008)
- Mycophenolate plus prednisolone versus prednisolone alone (Chams-Davatchi 2007)
- Plasma-exchange plus prednisolone versus prednisolone alone (Guillaume 1988)
- Traditional Chinese Medicine plus glucocorticoid versus glucocorticoid alone (type of glucocorticoids not specified) (Luo 2003)

(3) Adjuvant immunomodulatory agent vs adjuvant immunomodulatory agent

- Azathioprine versus cyclophosphamide (Chams-Davatchi 2007; Rose 2005)
- Azathioprine versus mycophenolate (Beissert 2006; Chams-Davatchi 2007)
- Cyclophosphamide versus cyclosporine (Chrysomallis 1994)
- Cyclophosphamide versus mycophenolate (Chams-Davatchi 2007)

(4) Topical interventions

- Epidermal growth factor (Tabrizi 2007)

All systemic interventions involved complex regimens with differing initial doses and regimens for escalation and tapering of therapy according to disease response. Dose regimens are described in detail in the 'Characteristics of included studies' table. Several regimens involved complete discontinuation of all systemic medication, while others maintained long-term low-dose therapy. The ingredients in the traditional Chinese medicine were not specified, and we were unsuccessful in contacting authors for further clarification (Luo 2003).

Outcomes

A large variety of outcomes were reported in included studies.

Only three studies reported remission in participants receiving minimal therapy (<10 mg prednisone equivalent per day) (Chams-Davatchi 2007; Chrysomallis 1994; Werth 2008), the primary outcome measure specified in the protocol for this review (Martin 2006). Two studies reported remission in participants receiving less than 15 mg prednisone equivalent per day (Ioannides 2000; Ratnam 1990). Three studies reported remission in participants receiving no systemic glucocorticoids (Ioannides 2000; Mentink 2006; Rose 2005).

Mortality was reported in all but one study (Luo 2003).

The proportion of participants achieving disease control was reported in eight studies (Beissert 2006; Chams-Davatchi 2007; Chrysomallis 1994; Guillaume 1988; Ioannides 2000; Ratnam 1990; Rose 2005). The definition of control varied in each study, and individual definitions are described in the 'Characteristics of included studies' table.

Five studies reported the proportion of participants suffering relapse. In four studies, relapse was reported in participants on continuing systemic therapy (Chrysomallis 1994; Ioannides 2000; Ratnam 1990; Rose 2005) and in one study, relapse was only reported in participants who had discontinued systemic therapy (Mentink 2006). The definition of relapse varied in each study, and individual definitions are described in the 'Characteristics of included studies' table.

Time to disease control was reported in nine studies (Beissert 2006; Chams-Davatchi 2007; Chrysomallis 1994; Guillaume 1988; Ioannides 2000; Luo 2003; Ratnam 1990; Rose 2005; Tabrizi 2007), although only one study utilised appropriate statistics for time-to event data (Tabrizi 2007).

Cumulative glucocorticoid dose was reported in six studies. Cumulative glucocorticoid dose was reported until 12 months in 2 studies (Chams-Davatchi 2007; Mentink 2006), and to 24 months in one study (Beissert 2006). In one study, cumulative glucocorticoid dose was only reported for successfully treated participants (Guillaume 1988).

Antibody titres were reported in three studies, however the time course and method of measurement differed between studies. Change in antibody titre was variously reported over 4 weeks (Guillaume 1988), 12 months (Mentink 2006), and before and after treatment with no time-frame specified (Luo 2003). One paper reported antibody titres only for those responding to treatment, and only the best response was reported (Rose 2005). Serum antibody titres were measured with ELISA (Mentink 2006), indirect immunofluorescence (Guillaume 1988; Rose 2005), and assay not specified (Luo 2003).

Changes in pemphigus severity score and quality of life were not reported in any studies.

Adverse events were not reported in one study (Luo 2003). Only withdrawal due to adverse events was entered into the meta-analysis.

Excluded studies

Twenty-six papers were excluded, mostly because they were non-randomised or the diagnosis of pemphigus was not confirmed with immunofluorescence studies. One randomised controlled trial on adjuvant gold was excluded as it did not report any of the outcomes of interest (Auad 1986). Further information on excluded studies can be found in the 'Characteristics of excluded studies' table. Non-randomised controlled trials were commented on in the discussion.

Ongoing studies

Nine ongoing studies were identified. Eight studies were identified from ongoing trial registers and one study was identified from correspondence with authors. Further information on ongoing studies can be found in the 'Characteristics of ongoing studies' table.

Studies awaiting assessment

We identified three studies which have been completed, but are awaiting publication (Hashimoto; Immunoadsorption; Werth 2005). All authors were contacted, but no unpublished data was available for inclusion in the meta-analysis. An additional potentially relevant title was identified from searches, but has not yet been assessed (Meyer 2008). Further information of ongoing studies can be found in the 'Characteristics of studies awaiting classification' table.

Risk of bias in included studies

Allocation

Allocation concealment was adequate in only 4/11 studies, and unclear in 7/11 studies.

Blinding

Only 3/11 studies were blinded (Mentink 2006; Tabrizi 2007; Werth 2008). In the study by Mentink, blinding of investigators may have been compromised due to noticeable adverse events of high dose pulsed glucocorticoids (Mentink 2006). Lack of blinding of outcome assessors in the majority of studies may have biased results, especially given that most outcomes were arbitrary clinical classifications.

Incomplete outcome data

Follow-up and exclusions

Participant losses ranged between 0 and 25%, with an average of 10% of participants lost or withdrawn. Reasons for participant loss were described in most studies.

Selective reporting

There was some evidence of selective reporting of outcomes in trials. The paper by Mentink did not include the pulsed dexamethasone doses in the cumulative glucocorticoid dose, and this data was excluded from analysis (Mentink 2006). The paper by Guillaume only reported cumulative glucocorticoid dose for 'controlled patients' and was excluded from the analysis (Guillaume 1988). The paper by Rose only reported antibody titre for those responding to treatment, and only best response was given, and was excluded from the analysis (Rose 2005). The study by Ioannides reports a follow-up period of five years, however outcomes are only reported at 12 months.

Other potential sources of bias

Baseline characteristics

Baseline participant characteristics were not specified for each group in two studies (Beissert 2006; Chrysomallis 1994). In other studies baseline characteristics appeared to be similar for each group, although sample sizes were small.

Aims

The aims of the studies were generally well defined. However in some studies the methodology was not appropriate for the stated aims. In particular, two studies which aimed to demonstrate the steroid-sparing role of adjuvant medications, used identical glucocorticoid regimens in both arms (Chrysomallis 1994; Ioannides 2000).

Interventions

The dose and duration of treatment were explained in detail in most studies. In many studies, the interventions consisted of complex regimens for escalation and tapering of doses, and it is conceivable that efficacy was attributable in part to the particular regimen used.

Outcomes

The outcomes of studies were not always well defined and many studies used multiple endpoints. In most cases arbitrary clinical endpoints were designated, and definitions of endpoints varied between studies. In some studies, the categorisation of outcomes was complicated and difficult to understand (Rose 2005).

Statistical analysis

Statistical analysis was generally adequate, however only one trial used appropriate statistical techniques for time to event data (Tabrizi 2007).

Effects of interventions

This review identified 11 randomised controlled trials which evaluated 10 distinct interventions for pemphigus. Meta-analysis was only performed for four comparisons, and each meta-analysis contained two trials only. Meta-analyses were conducted for cyclophosphamide vs glucocorticoid alone (Chams-Davatchi 2007; Chrysomallis 1994), cyclosporine vs glucocorticoid alone (Chrysomallis 1994; Ioannides 2000), azathioprine vs cyclophosphamide (Chams-Davatchi 2007; Rose 2005), and azathioprine vs mycophenolate (Chams-Davatchi 2007; Beissert 2006). There was no evidence of statistical heterogeneity, and each meta-analysis showed I^2 of 0.

(1) Primary outcomes

(i) The proportion of participants achieving remission

Studies which reported remission on minimal therapy (less than 10 mg prednisone equivalent per day as defined in the protocol for this review) (Martin 2006) were included in the analysis. Studies reporting differing definitions of remission were not included in the analysis, but are discussed narratively. Two studies defined remission as less than 15 mg prednisone equivalent per day (Ioannides 2000; Ratnam 1990). Three studies defined remission as cessation of all systemic treatment (Ioannides 2000; Mentink 2006; Rose 2005). The effects of all interventions which reported remission were inconclusive.

Glucocorticoid regimen

The effect of differing glucocorticoid regimens on remission were inconclusive. No difference was observed in remission between 1mg/kg compared to 0.5mg/kg prednisolone (remission defined as less than 15mg per day) (all participants achived outcome; 1 study; n=22) (Ratnam 1990). No difference was observed in remission between pulsed oral dexamethasone compared to placebo (remission defined as cessation of systemic treatment) (8/11 participants on pulsed dexamethasone, compared to 9/9 in the control group discontinued treatment) (Mentink 2006).

Adjuvant immunomodulatory agent versus glucocorticoid alone

The effects of adjuvants compared to glucocorticoids alone on remission were inconclusive. No difference in remission was observed for azathioprine compared to prednisolone (RR 1.04; 95% CI 0.80 to 1.36; 1 study; n=60; Analysis 3.1) (Chams-Davatchi 2007). No difference in remission was observed for cyclophosphamide compared to prednisolone / prednisone (RR 0.96; 95% CI 0.71 to 1.28; 2 studies; n=80; Analysis 4.1) (Chams-Davatchi 2007; Chrysomallis 1994). No difference in remission was observed for cyclosporine compared to prednisone (all participants achieved outcome; 1 study; n=18; Analysis 5.1) (Chrysomallis 1994). No difference in remission was observed for dapsone compared to placebo (RR 1.85; 95% CI 0.61 to 5.63; 1 study; n=19; Analysis 6.1) (Werth 2008). No difference in remission was observed for mycophenolate compared to prednisolone (RR 0.91; 95% CI 0.67 to 1.24; 1 study; n=60; Analysis 7.1) (Chams-Davatchi 2007).

No difference was observed between cyclosporine compared to prednisone for remission defined as less than 15mg prednisone per day (12/16 participants on cyclosporine compared to 12/17 on methylprednisolone alone) (Ioannides 2000). No difference was observed between cyclosporine compared to methylprednisolone for remission defined as cessation of systemic treatment (4/17 participants on cyclosporine compared to 5/17 on methylprednisolone discontinued treatment) (Ioannides 2000).

Adjuvant immunomodulatory agent versus adjuvant immunomodulatory agent

Studies which compared the effect on remission of differing immunomodulatory adjuvant agents were inconclusive. No difference in remission was observed for azathioprine compared to cyclophosphamide (RR 1.09; 95% CI 0.82 to 1.44; 1 study; n=60; Analysis 9.1) (Chams-Davatchi 2007). No difference in remission was observed for azathioprine compared to mycophenolate (RR 1.14; 95% CI 0.85 to 1.53; 1 study; n=60; Analysis 10.1) (Chams-Davatchi 2007). No difference in remission was observed for cyclophosphamide compared to cyclosporine (all participants achieved outcome; 1 study; n=18; Analysis 11.1) (Chrysomallis 1994). No difference in remission was observed for cyclophosphamide compared to mycophenolate (RR 1.05; 95% CI 0.76 to 1.44; 1 study; n=60; Analysis 12.1) (Chams-Davatchi 2007).

No difference in remission was observed between azathioprine/methylprednisolone compared to dexamethasone/cyclophosphamide (remission defined as cessation of systemic treatment) (3/11 participants on methylprednisolone / azathioprine, compared to 3/11 on dexamethasone / cyclophosphamide discontinued treatment) (Rose 2005).

Topical interventions

Remission was not reported for any topical interventions.

(ii) Deaths

The effect of all interventions on mortality was inconclusive. In the study on plasma exchange, there were 4/22 deaths in the plasma exchange group compared to 0/18 deaths in the control group , although the difference was not statistically significant (RR 7.43; 95%CI 0.43 to 129.55; 1 study; n=40; Analysis 8.1) (Guillaume 1988). The control treatment included a combination of prednisolone with or without intravenous methylprednisolone and cyclophoshamide. Deaths occurred due to infection and thromboembolism. There were no deaths in any other study. Mortality was not reported by Luo 2003.

(2) Secondary outcomes

(iii) The proportion of participants achieving disease control

No studies used the definition of disease control defined in the protocol for this review (Martin 2006), however outcomes were considered sufficiently similar for inclusion in the analysis. The exact definition was specified in the comparison table and the Characteristics of included studies. Only mycophenolate demonstrated a significant effect on disease control. The effects of other interventions which reported disease control were inconclusive.

Glucocorticoid regimen

No difference in disease control was observed for 1mg/kg compared to 0.5mg/kg starting dose prednisolone (all participants achieved outcome; n=22 Analysis 1.1) (Ratnam 1990).

Adjuvant immunomodulatory agent versus glucocorticoid alone

No difference in disease control was observed for cyclophosphamide compared to prednisone (all participants achieved outcome; 1 study; n=20; Analysis 4.2) (Chrysomallis 1994). No difference

in disease control was observed for cyclosporine compared to prednisone / methylprednisolone (RR 1.06; 95% CI 0.86 to 1.32; 2 studies; n=51; Analysis 5.2) (Chrysomallis 1994, Ioannides 2000). No difference in disease control was observed for plasma exchange compared to control (RR 1.12; CI 0.70 to 1.78; 1 study; n=40; Analysis 8.2) (Guillaume 1988).

Adjuvant immunomodulatory agent versus adjuvant immunomodulatory agent

Mycophenolate was more effective in achieving disease control than azathioprine (RR 0.72; 95% CI 0.52 to 0.99, NNT 3.7; 1 study; n=40; Analysis 10.2) (Beissert 2006). However no difference was observed in the per protocol analysis performed by the authors. No difference in disease control was observed for azathioprine compared to cyclophosphamide (RR 1.8; 95% CI 0.89 to 3.64; 1 study; n=22; Analysis 9.2) (Rose 2005). No difference in disease control was observed for cyclophosphamide compared to cyclosporine (all participants achieved outcome; 1 study; n=18; Analysis 11.2) (Chrysomallis 1994).

Topical interventions

Disease control was not reported for any topical interventions.

(iv) The proportion of participants suffering relapse

All studies used different definitions of relapse, which were all more severe than the definition described in the protocol for this review (Martin 2006). Data on relapse was considered sufficiently similar for inclusion in the analysis, and individual definitions are specified in the 'Characteristics of included studies' table. In studies in which multiple relapses per participant were reported, only one relapse per participant was included in the analysis. Where the conditional outcome, relapse after remission or discontinuation of therapy was reported, a composite outcome of relapse after remission or unable to achieve remission was used. The effects of all interventions which reported relapse were inconclusive.

Glucocorticoid regimen

No difference in relapse was observed for 1mg/kg compared to 0.5mg/kg starting dose prednisolone (RR 0.70; 95% CI 0.43 to 1.14; 1 study; n=22; Analysis 1.2) (Ratnam 1990). No difference in relapse was observed for pulsed dexamethasone compared to placebo (RR 1.9; 95% 0.68 to 5.33; 1 study; n=20; Analysis 2.1) (Mentink 2006).

Adjuvant immunomodulatory agent versus glucocorticoid alone

No difference in relapse was observed for cyclophosphamide compared to prednisone (RR 0.50; 95% CI 0.05 to 4.67; 1 study; n=20; Analysis 4.3) (Chrysomallis 1994). No difference in relapse was observed for cyclosporine compared to prednisone / methylprednisolone (RR 0.92; 95% CI 0.23 to 3.65; 2 studies; n=51; Analysis 5.3) (Chrysomallis 1994; Ioannides 2000).

Adjuvant immunomodulatory agent versus adjuvant immunomodulatory agent

No difference in relapse was observed for azathioprine compared to cyclophosphamide (RR 1.00; 95% CI 0.53 to 1.88; 1 study; n=22; Analysis 9.3) (Rose 2005). No difference in relapse was observed for cyclophosphamide compared to cyclosporine (RR 0.40; 95% CI 0.04 to 3.66; 1 study; n=18; Analysis 11.3) (Chrysomallis 1994).

Topical interventions

Relapse was not reported for any topical interventions.

(v) Change in pemphigus severity score

No trials reported this outcome.

(vi)Time to disease control (defined above)

Topical epidermal growth factor significantly decreased time to control compared to control (1 study; n=20; HR 2.35; 95% CI 1.62 to 3.41 Analysis 13.1) (Tabrizi 2007).

The majority of studies reported only mean time to disease control, which is an inappropriate measure for time-to-event data (Beissert 2006; Chams-Davatchi 2007; Chrysomallis 1994; Guillaume 1988; Ioannides 2000; Ratnam 1990). Authors were contacted for individual raw participant data, however this was not forthcoming.

(vii) Cumulative glucocorticoid dose

Cumulative glucocorticoid dose is a surrogate measure for glucocorticoid-induced adverse events. The clinical translation of milligrams of glucocorticoids 'saved' to adverse events is not known. A steroid-sparing effect was demonstrated for azathioprine and cyclophosphamide compared to glucocorticoids alone. The effects of other interventions which reported cumulative glucocorticoid dose were inconclusive.

Glucocorticoid regimen

The study by Mentink on pulsed oral dexamethasone did not include the pulsed dexamethasone dose in the cumulative glucocorticoid dose, so this data was not included in the analysis (Mentink 2006).

Adjuvant immunomodulatory agent versus glucocorticoid alone

Azathioprine decreased the cumulative glucocorticoid dose compared to prednisolone alone (MWD -3919 mg; 95% CI -6712 to -1126; 1 study; n=57; Analysis 3.2) (Chams-Davatchi 2007). Cyclophosphamide decreased the cumulative glucocorticoid dose compared to prednisolone alone (MWD -3355 mg; 95% CI -6144 to -566; 1 study; n=54; Analysis 4.4) (Chams-Davatchi 2007).
The effect of the following interventions on cumulative glucocorticoid dose was inconclusive. No difference in cumulative glucocorticoid dose was observed for cyclosporine compared to control (MWD -51.00 mg; 95% CI -183.38 mg to 81.38 mg; 1 study; n= 33; Analysis 5.4) (Ioannides 2000). No difference in cumulative glucocorticoid dose was observed for mycophenolate compared to control (MWD -1833.00 mg; 95% CI -4949.85 to 1283.85; 1 study; n=60; Analysis 7.2) (Chams-Davatchi 2007)
In the study by Luo, the cumulative glucocorticoid dose was reported as superior in the traditional Chinese medicine group to the control, however raw data was not reported and the time point was not specified (Luo 2003). The study by Guillaume on plasma-exchange, only reported cumulative glucocorticoid dose for participants responding to treatment, and was not included in the analysis (Guillaume 1988).

Adjuvant immunomodulatory agent versus adjuvant immunomodulatory agent

One study evaluated the steroid-sparing effect of three adjuvant immunosuppressants. Azathioprine decreased the cumulative glucocorticoid dose compared to cyclophosphamide (MWD -564 mg; 95% CI -1049 to -79; 1 study; n=51; Analysis 9.4) (Chams-Davatchi 2007). Azathioprine decreased the cumulative glucocorticoid dose compared to mycophenolate (MWD -2076 mg; 95% CI -3543 to -609; 2 studies; n=92; Analysis 10.3) (Beissert 2006; Chams-Davatchi 2007). Cyclophosphamide decreased the cumulative glucocorticoid dose compared to mycophenolate (MWD -1522 mg; 95% CI -2988 to -56; 1 study; n=54; Analysis 12.2) (Chams-Davatchi 2007). However the majority of these results come from a single study comparing multiple interventions, and analysis of variance performed by (Chams-Davatchi 2007) did not demonstrate a significant difference between azathioprine and cyclophosphamide or cyclosphamide and mycophenolate.

Topical interventions

Relapse was not reported for any topical interventions.

(viii) Reduction of serum antibody titre

Where there were multiple observations for serum antibody titre on each participant, only the baseline and longest follow-up data from each study was analysed. The effect of all interventions which reported serum antibody titre was inconclusive.

Glucocorticoid regimen

The data on serum antibody titres in the study on pulsed dexamethasone was not included in the analysis as standard deviation values were not available. In this study, for desmoglein-1 antibody there was a mean decrease from baseline to 12 months of 31 (n = 7) in the dexamethasone group and 27 (n = 5) for placebo (measured with ELISA). For desmoglein-3 antibody there was a mean decrease of 69 (n = 7) in the dexamethasone group compared to a mean decrease of 46 (n = 5) for placebo. There was missing data for eight participants (Mentink 2006).

Adjuvant immunomodulatory agent versus glucocorticoid alone

No difference in serum antibody titre was observed for plasma exchange compared to control from baseline to end of protocol (measured by indirect immunofluorescence) (MWD 44.38; 95% CI -222.43 to 311.19; 1 study; n=33; Analysis 8.3) (Guillaume 1988). No difference in serum antibody titre was observed for traditional Chinese medicine compared to glucocorticoids alone (assay not specified, time of measurement not reported) (MWD 0.75; 95% CI -1.12:1 to 2.62:1; 1 study; n=40; Analysis 14.1) (Luo 2003).

Adjuvant immunomodulatory agent versus adjuvant immunomodulatory agent

The data on serum antibody titres comparing dexamethasone / cyclophosphamide and methylprednisolone / azathioprine was not analysed, as antibody titres were only reported for those responding to treatment and only the best response was given (Rose 2005).

Topical interventions

Serum antibody titre was not reported for any topical interventions.

(ix) Adverse events

Withdrawal due to adverse events was the only adverse event included in the analysis. Other adverse events are discussed in the narrative. No difference was observed in withdrawal due to adverse events for any intervention. However subjective inspection of adverse events demonstrated differing adverse event profiles for interventions. Withdrawal due to adverse events may not correspond with long-term safety profiles.

Glucocorticoid regimen

No difference in withdrawal due to adverse events was observed for 1mg/kg compared to 0.5mg/kg starting dose prednisolone (no events reported; 1 study; n=22; Analysis 1.3) (Ratnam 1990). The incidence of other adverse events was similar in both groups.
No difference in withdrawal due to adverse events was observed for dexamethasone pulse compared to placebo (RR 2.45; 95% CI 0.30 to 19.74; 1 study; n=20; Analysis 2.2) (Mentink 2006). Withdrawals occurred due to infection, myalgia, hyperglycaemia and cognitive disturbance in the pulsed dexamethasone group, and carcinoma of the lung in the placebo group. There was an increased total number of adverse events in the pulsed dexamethasone group (30 vs 14) and an increase in the absolute number of participants experiencing adverse events (10 vs 5). There was a significant difference in the incidence of weight gain (8/11 pulsed dexamethasone compared to 1/9 placebo).

Adjuvant immunomodulatory agent versus glucocorticoid alone

One study compared adjuvant azathioprine, cyclophosphamide, mycophenolate and prednisolone alone (Chams-Davatchi 2007). There was one withdrawal from the prednisolone group due to a gastrointestinal bleed. No difference in withdrawal due to adverse events was observed for azathioprine compared to prednisolone (RR 2.00; 95% CI 0.19 to 20.90; 1 study; n=60; Analysis 3.3). There were two withdrawals from the azathioprine group due to abnormal liver function tests (Chams-Davatchi 2007).
No difference in withdrawal due to adverse events was observed for cyclophosphamide compared to prednisolone / prednisone (RR 0.33; 95% CI 0.01 to 7.87; 2 studies; n=80; Analysis 4.5) (Chams-Davatchi 2007; Chrysomallis 1994). There were no withdrawals from the cyclophosphamide group in either study. No difference in withdrawal due to adverse events was observed for mycophenolate compared to prednisolone (RR 1.00; 95% CI 0.07 to 15.26; 1 study; n=60; Analysis 7.3) (Chams-Davatchi 2007).The incidence of other adverse events was similar in all groups. The most frequent adverse events were infection, hyperlipidaemia and hyperglycaemia.
No difference in withdrawal due to adverse events was observed for cyclosporine compared to prednisone /methylprednisolone (no events reported; 2 studies; n=51; Analysis 5.5) (Chrysomallis 1994; Ioannides 2000). Hypertrichosis and renal function abnormalities were reported in association with cyclosporine in both studies.
No difference in withdrawal due to adverse events was observed for dapsone compared to placebo (RR 0.37; 95% CI 0.05 to 2.95; 1 study; n=19; Analysis 6.2) (Werth 2008). Three participants in the placebo group withdrew due to a flare in disease activity, and one participant in the dapsone group withdrew due to pneumonia. Adverse events reported in the dapsone group included dyspnoea (shortness of breath) secondary to methaemoglobinaemia (oxidised haemoglobin with reduced oxygen-carrying capacity), paresthesia (pins and needles), and cutaneous exanthem (widespread rash) associated with abnormal liver function tests.
No difference in withdrawal due to adverse events was observed for plasma-exchange compared to control (RR 7.20; 95% CI 0.42 to 124.08; 1 study; n=34; Analysis 8.4) (Guillaume 1988). The withdrawal due to adverse events in this study was due to death and is described above. The incidence of adverse events was similar in both groups.
Adverse events were not reported for traditional Chinese medicine (Luo 2003).

Adjuvant immunomodulatory agent versus adjuvant immunomodulatory agent

No difference in withdrawal due to adverse events was observed for azathioprine compared to cyclophosphamide (RR 3.91; 95% CI 0.45 to 33.66; 2 studies; n=82; Analysis 9.5) (Chams-Davatchi 2007; Rose 2005). There was one withdrawal from the azathioprine group due to generalised herpes simplex infection, gastrointestinal bleed and leucopaenia (Rose 2005). Inspection of data showed increased cushingoid features in the methylprednisolone / azathioprine group compared to the dexamethasone / cyclophosphamide (8/11 vs 2/11), although this may be related to differing glucocorticoid regimens. The incidence of other adverse events was similar in both groups. The study by Chams-Davatchi is discussed above.
No difference in withdrawal due to adverse events was observed for azathioprine compared to mycophenolate (RR 3.01; 95% CI 0.48 to 18.97; 2 studies; n=99; Analysis 10.4) (Beissert 2006; Chams-Davatchi 2007). There were 2 withdrawals due to adverse events in the azathioprine group, although the cause was not reported (Beissert 2006). The incidence of other adverse events was similar in both groups. The incidence of grade 3 (severe) or grade 4 (life-threatening) adverse events was similar in both groups (6/18 in azathioprine and 4/21 in mycophenolate. The study by Chams-Davatchi is discussed above.
No difference in withdrawal due to adverse events was observed for cyclophosphamide compared to cyclosporine (no events reported; 1 study; n=18; Analysis 11.4) (Chrysomallis 1994). No difference in withdrawal due to adverse events was observed for cyclophosphamide compared to mycophenolate (RR 0.33; 95% CI 0.01 to 7.87; 1 study; n=60; Analysis 12.3) (Chams-Davatchi 2007). These studies are discussed above.

Topical interventions

There was one withdrawal due to adverse events in the internally controlled left-right comparison study on topical epidermal growth factor, due to flare in disease activity and generalised herpes simplex infection (Tabrizi 2007).

(x) Change in quality of life scores

No trials reported this outcome.

DISCUSSION

Summary of main results

This review identified 11 randomised-controlled trials, including 10 distinct interventions for pemphigus. All studies were insufficiently powered to establish definitive results. There are no interventions for which there is sufficient evidence to provide clear guidelines for practice.

A) Forms of care that appear promising, but require further evaluation

Azathioprine

Azathioprine was evaluated in three studies, including comparisons with glucocorticoids alone (prednisolone) (Chams-Davatchi 2007), cyclophosphamide (Chams-Davatchi 2007; Rose 2005) and mycophenolate (Beissert 2006; Chams-Davatchi 2007).

Azathioprine was less effective than mycophenolate in achieving disease control based on one study with 40 participants (Beissert 2006). The effect of azathioprine on disease control compared to cyclophosphamide was inconclusive (Rose 2005).

Azathioprine appears to have a steroid-sparing effect compared to prednisolone alone, based on one study with 57 participants (Chams-Davatchi 2007). Azathioprine appears to have a superior steroid-sparing effect compared to cyclophosphamide based on one study with 51 participants (Chams-Davatchi 2007). Azathioprine appears to have a superior steroid-sparing effect compared to mycophenolate based on 2 studies with 92 participants (Beissert 2006; Chams-Davatchi 2007). The clinical relevance of this steroid-sparing effect is not certain.

The effect of azathioprine on other outcomes including remission, death, relapse, or withdrawal due to adverse events was inconclusive. The effect of azathioprine on severity score, time to disease control, antibody titre and quality of life was not assessed.

Cyclophosphamide

Cyclophosphamide was evaluated in three studies, including comparisons with glucocorticoids alone (prednisolone and prednisone) (Chams-Davatchi 2007; Chrysomallis 1994), azathioprine (Chams-Davatchi 2007; Rose 2005), cyclosporine (Chrysomallis 1994) and mycophenolate Chams-Davatchi 2007).

Cyclophosphamide appears to have a steroid-sparing effect compared to prednisolone alone based on one study with 54 participants (Chams-Davatchi 2007). Cyclophosphamide appears to have a superior steroid-sparing effect compared to mycophenolate based on one study with 54 participants (Chams-Davatchi 2007). Cyclophosphamide appears to have an inferior steroid-sparing effect compared to azathioprine (Chams-Davatchi 2007). The clinical relevance of this steroid-sparing effect is not certain.

The effect of cyclophosphamide on other outcomes including remission, death, disease control, relapse, withdrawal due to adverse events was inconclusive. The effect of cyclophosphamide on severity score, time to disease control, antibody titre and quality of life was not assessed.

Mycophenolate

Mycophenolate was evaluated in two studies, including comparisons with prednisolone alone (Chams-Davatchi 2007), azathioprine (Beissert 2006; Chams-Davatchi 2007), and cyclophosphamide (Chams-Davatchi 2007).

Mycophenolate appears more effective than azathioprine in inducing disease control based on one study with 40 participants (Beissert 2006). However mycophenolate had an inferior steroid-sparing effect compared to azathioprine based on one study with 51 participants (Chams-Davatchi 2007). Mycophenolate had an inferior steroid-sparing effect compared to cyclophosphamide based on one study with 54 participants (Chams-Davatchi 2007).

The effect of mycophenolate on other outcomes including remission, death, withdrawal from adverse events was inconclusive. The effect of mycophenolate on relapse, severity score, time to disease control, antibody titre and quality of life was not assessed.

Topical epidermal growth factor

Topical epidermal growth factor was evaluated in one study compared with control (Tabrizi 2007).

Topical epidermal growth factor appears to hasten lesion healing by a median of 6 days, based on one study with 20 participants (Tabrizi 2007). The long-term safety of this intervention is not known.

The effect of topical epidermal growth factor on remission, disease control, relapse, severity score, cumulative glucocorticoid dose, antibody titre and quality of life was not assessed.

B) Forms of care that have not been shown to have the effects expected

from them, but which require further attention

Glucocorticoid dose

Initial prednisolone dose comparing 1mg/kg to 0.5mg/kg per day was evaluated in one study of 22 participants (Ratnam 1990). The effect of prednisolone dose was inconclusive on all reported outcomes including death, disease control, relapse and withdrawal due to adverse events. The effect of prednisolone dose on remission, severity score, time to disease control, cumulative glucocorticoid dose, antibody titre and quality of life was not assessed.

Pulsed glucocorticoids

Pulsed oral dexamethasone was evaluated in one study of 20 participants with new onset disease or disease activity (Mentink 2006). The effect of pulsed oral dexamethasone was inconclusive on all reported outcomes including remission (defined as cessation of systemic treatment), death, relapse and withdrawal due to adverse events. Subjective inspection of the data demonstrated increased adverse events in the pulsed dexamethasone group. The effect of pulsed oral dexamethasone on disease control, severity score, time to disease control, cumulative glucocorticoid dose, antibody titre and quality of life was not assessed.

Cyclosporine

Cyclosporine was evaluated in two studies, including comparisons with glucocorticoids alone (prednisone Chrysomallis 1994; methylprednisolone Ioannides 2000)and cyclophosphamide (Chrysomallis 1994). The effect of cyclosporine was inconclusive for all reported outcomes including remission, death, disease control, relapse, cumulative glucocorticoid dose and withdrawal due to adverse events. The effect of cyclosporine on severity score, time to disease control, antibody titre and quality of life was not assessed.

Dapsone

Dapsone was evaluated in one study of 19 participants compared to placebo (Werth 2008). The effect of dapsone on remission and withdrawal due to adverse events was inconclusive.The effect of dapsone on disease control, relapse, severity score, time to disease control, cumulative glucocorticoid dose, antibody titre and quality of life was not assessed.

Plasma exchange

Plasma exchange was evaluated in one study of 40 participants (Guillaume 1988). The effect of plasma exchange was inconclusive on all reported outcomes including death, disease control, antibody titre and withdrawal due to adverse events. The effect of plasma exchange on remission, relapse, severity score, time to disease control, cumulative glucocorticoid dose and quality of life was not assessed.

Traditional Chinese medicine

Traditional Chinese medicine was evaluated in one study of 40 participants (Luo 2003)). The effect of traditional Chinese medicine on antibody titre was inconclusive. No other outcomes specified in the protocol of this review (Martin 2006) were reported.

Overall completeness and applicability of evidence

Overall, the evidence regarding interventions for pemphigus is inconclusive and incomplete. There are many therapeutic interventions in use which have not been evaluated in well-designed controlled trials. These include a number of systemic immunomodulatory agents, including biological agents which have recently been developed. Oral glucocorticoids have a central role in management, however there are no randomised controlled trials evaluating glucocorticoids, and the use of glucocorticoids is established from case series (Bystryn 1984). Of the trials which have been conducted, sample sizes were small and insufficient to yield definitive results. There are a large number of potential interventions in pemphigus for which the efficacy has not been adequately studied. There is little known regarding disease prognosis, and response to treatment can vary between individuals. The majority of randomized controlled trials in pemphigus included newly diagnosed participants, and while there was a spectrum of disease severity in included studies, there is insufficient information to guide treatment according to disease severity. There are no trials of participants with recalcitrant disease, and evidence from these studies may not be applicable to this population. For example, no benefit was demonstrated for pulsed oral dexamethasone in newly diagnosed participants, however the role of pulsed glucocorticoids in recalcitrant disease has not been assessed. Studies used complex dose regimens to escalate and taper therapy, so results may not be applicable to other regimens of the same intervention.

Potential modalities to reduce the risk of adverse events were not evalualated in the included studies, including assessment of thiopurinemethyltransferase (TPMT) activity to assess the risk of myelosuppression with azathioprine. Use of adjuvant medications to reduce adverse events, such as bisphosphonates for prevention of glucocorticoid-induced osteoporosis varied between studies. This review did not examine the cost of interventions.

Quality of the evidence

In general the quality of evidence in included studies was poor. Allocation concealment, the most important determinant of study quality, was unclear in the majority of studies. Very few studies were blinded, making assessment of outcome open to bias.

Sample sizes of included studies were too small to establish statistically significant differences in the primary endpoints. Sample size calculations were not performed for the majority of studies, and

other studies did not meet recruitment targets. Although small sample sizes are understandable given the rarity of the disease, the consequence is that trials were inadequately powered to establish definitive results.

Reporting of outcomes varied between studies. A number of studies had poor reporting of important outcomes, including clinical response and adverse events. Duration of follow-up was variable, limiting the capacity to conduct long-term risk-benefit analyses. In particular, duration of follow-up was inadequate to assess long-term adverse events such as fracture from glucocorticoid-induced osteoporosis or secondary malignancy with cytotoxic agents.

Potential biases in the review process

This review was intentionally broad in including all interventions for pemphigus vulgaris and pemphigus foliaceus and a large number of outcomes. We aimed to collate and evaluate the available body of evidence. Although we were unable to establish the optimal treatment strategy, we were able to delineate areas for further research, and in the future it may be possible to refine the clinical questions assessed in this systematic review.

This review included only randomized controlled trials and excluded studies of other designs. We excluded one randomized controlled trial (Auad 1986) due to insufficient reporting of outcomes. Although it would be preferable to include available information from this study, outcomes of interest were not reported, presumably related to the pre-consort date of publication. Data from ongoing trials was not available for inclusion in this review.

In this review we combined data together for people with pemphigus vulgaris and pemphigus foliaceus, although it is not known whether these two diseases have the same response to treatment. We initially intended to perform subgroup analyses for pemphigus vulgaris and pemphigus foliaceus, however this was not performed, as there were insufficient participant numbers to make this worthwhile.

We analysed data from studies with differing routes and doses of an intervention and differing assays for antibody titre. The impact of this could be assessed in sensitivity analyses, however there were too few trials assessing the same intervention to make this worthwhile. There was considerable variation among included studies in outcomes reported and definitions of treatment endpoints. We analysed data from studies with differing definitions of disease control and relapse. We excluded definitions of remission which differed from that specified in the protocol for this review (Martin 2006). Sensitivity analyses were conducted to look at the impact of a composite endpoint for conditional remission compared to an available case analysis; these showed no substantial difference in results.

This review incorporated a broad range of outcomes, including surrogate outcomes and biomarkers, the clinical value of which is not known. Cumulative glucocorticoid dose is a surrogate for glucocorticoid-induced adverse effects, although the translation of milligrams of glucocorticoid saved to clinical adverse events avoided is difficult to quantify. Similarly, the clinical relevance of change in serum antibody titre is not known.

There was missing data for several studies in this review which we were not able to obtain from authors. Where possible we conducted an intention-to-treat analysis, although in some cases there was only sufficient information to conduct an available case analysis. Sensitivity analyses were conducted to look at the impact of differing values of the correlation coefficient r for the imputed standard deviation difference for antibody titre (Luo 2003), which showed no substantial difference in results.

Where studies included comparisons of multiple interventions (Chams-Davatchi 2007; Chrysomallis 1994), pair-wise comparisons were undertaken as specified in the protocol for this review (Martin 2006). Statistical methods to compensate for multiple comparisons were not used.

This review only analysed withdrawal due to adverse events. We observed no difference in withdrawal due to adverse events for any intervention. However there were differences in adverse event profiles between interventions. Withdrawal due to adverse events does not reflect long-term safety of an intervention.

Agreements and disagreements with other studies or reviews

No other systematic reviews have been conducted on interventions for pemphigus, however guidelines for the management of pemphigus vulgaris have been published which incorporate recommendations from all levels of evidence (Harman 2003).The guidelines conclude that there is 'fair evidence' to support use of adjuvant azathioprine, mycophenolate and cyclophosphamide, and 'poor evidence' on pulsed glucocorticoids, dapsone, cyclosporine, plasmapheresis, and topical therapies.

The findings of included studies were in agreement with results of 3 non-randomised controlled trials. A retrospective non-randomised controlled series on initial glucocorticoid dose compared initial doses of 1mg/kg/day or 2mg/dg/day prednisone in 28 participants, with groups assigned according to disease severity (Fernandes 2001). This study reported no difference in clinical response, and higher incidence of adverse events in the 2mg/kg/day group, particularly infection and death. A non-randomised controlled trial on pulsed glucocorticoids comparing oral prednisone or pulsed intravenous betamethasone in twenty participants with pemphigus vulgaris observed no difference in time to resolution of disease (Femiano 2002). A non-randomised controlled trial of pulsed cyclophosphamide and methylprednisolone versus oral prednisolone and azathioprine in 123 participants with pemphigus vulgaris showed no difference in clinical response, remission or adverse events (Shahidi-Dadras 2007).

This review found insufficient evidence to determine the role of adjuvant immunosuppressive agents in pemphigus. While adjuvant immunosuppressants are widely used to minimize glucocor-

ticoid-related adverse effects in other fields of medicine, such as rheumatology and transplantation medicine, their use in pemphigus is controversial and opinions vary among experts. This review demonstrated a steroid-sparing effect for azathioprine and cyclophosphamide compared to prednisolone alone, however no difference was seen in clinical endpoints.

The mortality rate observed in the plasma-exchange study is higher than the complication rate reported in studies of plasma-exchange for other indications (Reimann 1990). The participants included in this study had a severe baseline disease, and it is not possible to know whether the high mortality observed was due to the disease or to treatment. (Guillaume 1988).

AUTHORS' CONCLUSIONS

Implications for practice

The optimal therapeutic strategy for pemphigus vulgaris and pemphigus foliaceus is not known. Multiple potential therapeutic modalities are available and multiple regimens are in use, making choice of treatment schedule complex. Few randomised controlled trials have been conducted, and those performed were limited by small sample sizes.

Systemic glucocorticoids have a central role in the management of pemphigus vulgaris and pemphigus foliaceus, although the optimal dose regimen is not known. Adjuvant pulsed glucocorticoids did not appear beneficial in a small study in participants with new onset disease, although their role in recalicitrant disease has not been assessed.

The role of immunomodulatory adjuvants has not been established. There is evidence of a steroid-sparing role for azathioprine and cyclophosphamide, although there was no benefit observed in clinical endpoints. The optimal adjuvant has not been established. Mycophenolate showed superior disease control compared to azathioprine, although azathioprine and cyclophosphamide showed superior steroid-sparing capacity compared to mycophenolate. The effects of cyclosporine, dapsone, plasma-exchange and traditional Chinese medicine is unclear.

Topical epidermal growth factor appears to decrease time required for healing of erosions, however the long-term safety of this intervention is not known.

No difference was observed in death or withdrawal due to adverse events, although interventions have differing adverse event profiles and these small studies are not sufficient to address safety comparisons of these drugs. Careful consideration of potential benefits and potential adverse events in context of the individual's comorbidities is required.

Implications for research

There is a lack of evidence on interventions for pemphigus. There is a need for large randomized controlled trials to address the following questions:

Interventions

- What is the optimal glucocorticoid dose regimen?
- Are adjuvant immunosuppressive agents beneficial?
- Which is the optimal adjuvant?
- Is intravenous immunoglobulin beneficial?
- Are biological agents beneficial?
- For how long should therapy be continued?

Populations

- What is the optimal first-line treatment in newly diagnosed disease?
- What is the optimal treatment in recalcitrant disease?

Disease course

- Do interventions modify the course of the disease ('disease-modifying'), or function by suppressing disease activity?

Outcomes

- There is a need for use of uniform outcomes in trials, and in particular uniform definitions of disease control, remission and relapse. There is a need for the use of patient-based measures, such as quality of life assessment. There is a need for assessment of long-term adverse effects in studies, to improve harm:benefit analyses. There is a need for studies which assess the clinical value of surrogate endpoints (cumulative glucocorticoid dose) and biomarkers (antibody titre).

Due to the rarity of pemphigus and the difficulty of recruiting sufficient participants for trials, there is a need for multicentre co-operation and collaboration.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Beissert 2006

Methods	Non-blind multi-centre randomised controlled trial Country: Germany Method of randomisation: random numbers of 3 for each strata Allocation concealment: Not specified (NS) 'randomisation performed centrally' Blinding: No Intention to treat analysis: No Participant losses: one withdrew consent, one lost, two withdrew due to adverse events, one withdrawn due to noncompliance Follow-up: two years
Participants	40 participants (33 pemphigus vulgaris and 7 pemphigus foliaceus) Gender: 16 male, 23 female Inclusion criteria: diagnosis confirmed on clinical, histological, immunofluorescence and immunoblotting criteria Exclusion criteria: treatment with oral or topical glucocorticoids and other immunosuppressive drugs during the previous 4 weeks Disease duration: newly diagnosed and chronic disease, mean duration of disease 129 days (SD 325) Baseline severity: Body surface area involvement 0% 1/37, <5% 16/37, <10% 11/37, <20% 2/37, >/20% 7/37 Previous management: nil in preceding four weeks
Interventions	Oral methylprednisolone + azathioprine versus oral methylprednisolone + mycophenolate mofetil Initial dose: methylprednisolone 2 mg/kg/day, azathioprine 2 mg/kg/day, mycophenolate mofetil 2g/day Regimen: methylprednisolone increased by 1 mg/kg every 7 days until blister development stopped and erosions healed. Methylprednisolone then tapered to 40 mg/day, then reduced by 20 mg every 2 weeks until 20m/day, then 5 mg every 2 weeks until 10 mg/day until then 2.5 mg every 2 weeks until stopped. Adjuvant maintained for 12 weeks after cessation glucocorticoids, then tapered and discontinued
Outcomes	Primary - Complete healing of lesions (defined as 'complete re-epithelization of all previous lesions'), cumulative glucocorticoid dose until end of study Secondary - duration of remission, adverse events Other reported - time to inhibition of disease progression and to complete healing
Notes	Complicated regimen.

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Chams-Davatchi 2007

Methods	Non-blind single-centre randomised controlled trial Country: Iran Method of randomisation: NS Allocation concealment: NS Blinding: No Intention to treat analysis: Yes Participant losses: 10 lost, 4 withdrew due to adverse events, 1 withdrawn due to noncompliance, 15 withdrawn due to treatment failure Follow-up: one year
Participants	120 participants with pemphigus vulgaris Gender: 40 Male, 71 female Inclusion criteria: diagnosis confirmed on clinical, histological and immunofluorescence criteria; new cases not previously treated with prednisolone or immunosuppressive drugs; no contraindications for cytotoxic drugs; no pregnancy or lactation Disease duration: newly diagnosed and chronic disease, mean duration of disease 3.8-10.0 months Baseline severity: number of skin lesions <20 33/120, 20-49 20/120, 50-100 23/120, >100 6/120 Previous management: nil
Interventions	Prednisolone alone versus prednisolone plus azathioprine, mycophenolate mofetil or IV pulsed cyclophosphamide Prednisolone: initial dose 2 mg/kg/day with maximum 120 mg/day until no new blisters and old lesions dried, then reduced to 2/3 of initial value, then tapered by 5 mg every 3 days until 30 mg/day, then by 1.25 mg/day weekly for 2 months, then by 1.25 mg 2 weekly until 7.5 mg/day Azathioprine: 2.5 mg/kg/day for 2 months, then 50 mg/day Mycophenolate mofetil: 2g/day Cyclophosphamide: 1000 mg IV monthly for 6 months, then 1000 mg 2 monthly for 6 months
Outcomes	Primary: cumulative glucocorticoid dose, number of recurrences, complete response, treatment failures, time to glucocorticoid tapering, adverse events
Notes	Definitions Partial response: when new lesions stopped appearing and preexisting erosions formed a crust Complete response: lesion-free state, while the participant was receiving a minimum dose of glucocorticoid Failure: three minor recurrences or one major recurrence Minor recurrence: appearance of less than 20 lesions on less than 3 sectors of the body Major recurrence: more than 20 lesions on 3 or more sectors of the body

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Chrysomallis 1994

Methods	Non-blind single-centre randomised controlled trial Country: Greece Method of randomisation: NS 'randomly divided' Allocation concealment: NS Blinding: Participant yes, Investigator no Intention to treat analysis: NS Participant losses: Nil Follow-up: five years
Participants	28 participants with oral pemphigus vulgaris Gender: 13 male, 15 female Inclusion criteria: diagnosis confirmed on clinical, histological, and immunofluorescence criteria; no other skin or systemic disease; no drug intake in the 3 months before diagnosis Disease duration: newly diagnosed Baseline severity: NS, oral involvement only Previous management: nil in preceding three months
Interventions	Oral prednisone alone versus prednisone + cyclophosphamide 100 mg/d versus prednisone + cyclosporine 5 mg/kg/d Initial dose: prednisone 40 mg/day, cyclophosphamide 100 mg/day, cyclosporine 5 mg/kg Regimen: doses maintained until 50% of old lesions healed and no new lesions developed. Prednisone tapered to 10 mg/day over 2 to 4 weeks and at maintained at 10 mg for one month. Cyclophosphamide or cyclosporine then tapered and discontinued over one month and prednisolone subsequently gradually reduced/withdrawn
Outcomes	Time until 50% of old lesions healed and no new lesions developed, number of relapses, adverse events
Notes	Definitions Relapse: appearance of more than five new lesions within a period of three days

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Guillaume 1988

Methods	Non-blind multi-centre randomised controlled trial Country: France Method of randomisation: computer generated permuted blocks of six stratified by disease subtype Allocation concealment: NS Blinding: No Intention to treat analysis: No Partcipant losses: five protocol violations or non-communication data, one inclusion criteria not met Follow-up: unclear

Guillaume 1988 (*Continued*)

Participants	40 participants (33 pemphigus vulgaris and 7 pemphigus foliaceus) Gender: male 15, female 19 Inclusion criteria: diagnosis confirmed on clinical, histological, and immunofluorescence criteria; less than 80 years of age; no previous treatment of disease with systemic glucocorticoids or immunosuppressive agents; adequate peripheral veins allowing plasma exchange Exclusion criteria: poorly controlled heart failure; severe coronary or hepatic failure Disease duration: newly diagnosed Baseline severity: body surface area involvement <5% 21/34, 5-30% 10/34, >30% 3/34; total number of bullae control mean=55 (range 1-500) plasma exchange 61 (1-295) ; number of new bullae per day control 51 (0-450), plasma exchange 19 (0-100) Previous management: nil
Interventions	Oral prednisolone alone versus oral prednisolone + 10 large-volume plasma exchanges over four weeks Initial doses: prednisolone 0.5 mg/kg/day, plasma exchange 55 ml/kg exchanged by filtration or centrifugation. Replaced with 4% albumin plus 10g gamma-globulin Regimen: prednisolone increased weekly according to response to 1 mg/kg/day then 1.5 mg/kg/day then 2 mg/day IM methylprednisolone then cyclophosphamide added. Continued for one month until healing, then tapered by 10% every 10 days Concomitant medication: iron, antacids, subcutaneous heparin
Outcomes	Number disease controlled at four weeks, cumulative glucocorticoid dose at one month after healing of lesions, adverse events, death, duration of treatment, antibody titres (indirect immunofluorescence)
Notes	Complicated criteria for 'effective treatment' which changes weekly Definitions Control: 'Treatment was considered effective after the first week if no new blisters occurred and if the total length of erosions was not above the initial one; after the second week if, in addition, Nikolsky's sign was not present; after the third week a lowering of the total length of erosions below 80% of the initial length was required; after four weeks this length had to be below 60% of the initial one.'

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Ioannides 2000

Methods	Non-blind single-centre randomised controlled trial Country: Greece Method of randomisation: Computer generated in permuted blocks of four Allocation concealment: NS Blinding: Participant yes, Investigator no Intention to treat analysis: NS Participant losses: Nil Follow-up: five years
Participants	33 participants (29 pemphigus vulgaris and 4 pemphigus foliaceus) Gender: 14 male, 19 female Inclusion criteria: diagnosis confirmed on clinical, histological, and immunofluorescence criteria; newly diagnosed disease; no previous systemic therapy with glucocorticoids or immunosuppressive agents Disease duration: newly diagnosed Baseline severity: mean severity score (based on body surface area involvement and frequency of new lesions) placebo 4.7/8 and cyclosporine 5.2/8 Previous management: nil
Interventions	Oral methylprednisolone alone versus oral methylprednisolone + cyclosporine 5 mg/kg Initial doses: methylprednisolone 1 mg/kg/day prednisone equivalent, cyclosporine 5 mg/kg/day Regimen: methylprednisolone increased by 50% every 5 to 10 days until disease activity controlled (no more than 2 lesions during the previous 3 days) and maintained until 80%-90% lesions cleared. Methylprednisolone decreased by 50% every 2 weeks until 50% of maximum dose, then cyclosporine decreased to 3 mg/kg. Methylprednisolone then taped to 10 mg prednisone equivalent and maintained for 1 month. Methylprednisolone and cyclosporine then discontinued over one month. If unresponsive to 240 mg prednisone equivalent, pulsed glucocorticoids or plasmapheresis added
Outcomes	Time to heal 80% lesions, to partial and to complete remission; number partial and complete remissions; number relapses; cumulative glucocorticoid dose to achieve disease control, to partial and to complete remission; adverse events
Notes	Complicated regimen Definitions Control : appearance of no more than two new lesions during the previous three days Partial remission: absence of lesions in participant requiring treatment with prednisone equivalents 15 mg/d or less, with or without cyclosporine. Complete remission: absence of lesions in participants requiring no systemic therapy for pemphigus Relapse: appearance of greater than two lesions during the previous three days

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Luo 2003

Methods	Single-centre randomised controlled trial Country: China Method of randomisation: permuted blocks Allocation concealment: NS Blinding: NS Intention to treat analysis: No Participant losses: Nil Follow-up: NS
Participants	40 participants Gender: 24 male, 16 female Inclusion criteria: diagnosis confirmed on clinical, histological, and immunofluorescence criteria Disease duration: 2.25 months (SD 2.78) group 1; 2.28 months (SD 2.90) group 2 Baseline severity: body surface area involvement 25% +/- 21.% group 1, 31+/- 21% group 2 Previous management: NS
Interventions	glucocorticoids alone versus glucocorticoids plus traditional Chinese medicine (Tianpaochuang #1)
Outcomes	Cumulative glucocorticoid dose, antibody titres, time to lesion control, serum cytokine assays (IL-10, IFN-g, sIL-2R)
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Mentink 2006

Methods	Blinded multi-centre placebo-controlled randomised trial Country: Netherlands, Italy, Serbia, Hungary, Spain, Belgium Method of randomisation: computer generated code in permuted blocks of eight Allocation concealment: sealed box sent express mail after inclusion in study Blinding: participant yes, clinician yes, outcome assessor yes, statistician unsure Intention to treat analysis: NS Participant losses: four withdrawn adverse events, one lost follow-up: one year
Participants	20 participants with pemphigus vulgaris- new onset PV or new disease activity after being in remission Gender: 13 male, 7 female Inclusion criteria: 18 years or older; new pemphigus vulgaris or new disease activity; diagnosis confirmed on clinical, histological, and immunofluorescence criteria Exclusion criteria: treatment with glucocorticoids within the past 2 months, treatment with adjuvant therapy other than azathioprine; contraindications for the use of high-dose glucocorticoids or azathioprine; concomitant disease treated with glucocorticoids; no ability to attend follow-up Disease duration: newly diagnosed or chronic with new disease activity Baseline severity: mean number of skin lesions dexamethasone 28 and placebo 26

Mentink 2006 (*Continued*)

	Previous management: no systemic glucocorticoids in preceding two months
Interventions	Oral prednisolone + azathioprine + pulsed oral dexamethasone versus versus oral prednisolone + azathioprine + placebo pulses Initial dose: prednisolone 80 mg/day, azathioprine 3 mg/kg/day or 1.5 mg/kg/day if TPMT low, pulsed oral dexamethasone 300 mg over 3 consecutive days per month Regimen: oral prednisolone increased to 240 mg/day over 2 weeks according to disease activity. Prednisolone tapered and withdrawn over 19 weeks according to pre-determined schedule. Monthly dexamethasone or placebo pulses continued until oral prednisolone withdrawn Concomitant medication: ranitidine, etidronate, calcium or vitamin D
Outcomes	Number of participants in remission, time to remission, duration of remission, relapse, cumulative glucocorticoid dose until 12 months, antibody titres, adverse events
Notes	Definitions Disease activity :1) skin had more than one new pemphigus lesion per week and presence of a positive direct Nikolsky sign or 2) old or new lesions on the mucous membrane scored as severe by the physician and pain experienced by the participant that was rated at least 5 on a scale of 0 to 10.' Remission: the day prednisolone tapered to 0 mg Relapse: new disease activity requiring additional prednisolone administration

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Ratnam 1990

Methods	Non-blind single-centre randomised controlled trial Country: Singapore Method of randomisation: NS Allocation concealment: NS Blinding: No Intention to treat analysis: NS Participant losses: Nil Follow-up: Five years
Participants	22 participants (19 pemphigus vulgaris, 3 pemphigus foliaceus) Gender: 6 male; 16 female Inclusion criteria: diagnosis confirmed on clinical, histological, and immunofluorescence criteria; new cases; no medication prior; severe disease with more than 50% body surface involved Disease duration: newly diagnosed; range 1 to 73 weeks Baseline severity: >50% body surface area involvement Previous management: nil

Ratnam 1990 (*Continued*)

Interventions	Oral prednisolone 45 to 60 mg/day versus oral prednisolone 120 to 150 mg/day Regimen: Initial dose continued until no new blisters developed during one week period and existing lesions dried up, then tapered. When prednisolone tapered to 20 mg/day, either methotrexate or cyclophosphamide added. Prednisolone then tapered by 2.5 mg per month
Outcomes	Time to disease control, number relapses, adverse events
Notes	Definitions Control: no new blisters in one week and old lesions dried up Relapse: more than five fresh blisters per day

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Rose 2005

Methods	Non-blind multi-centre randomised controlled trial Country: Germany Method of randomisation: NS 'previously established list' Allocation concealment: Central telephone Blinding: No Intention to treat analysis: NS Participant losses: one withdrawn due to adverse event Follow-up: 24 months
Participants	22 participants (pemphigus vulgaris 16 and pemphigus foliaceus 6) Gender: 6 male, 16 female Inclusion criteria: diagnosis confirmed on clinical, histological, and immunofluorescence criteria; newly diagnosed; no previous long-term systemic treatment Exclusion criteria: paraneoplastic pemphigus, age <18 years, pregnancy and lactation; congenital or acquired immunodeficiency; malignancy; serious infectious disease; diabetes mellitus; glaucoma resistant to treatment Duration disease: newly diagnosed (median 3-4months) Baseline severity: NS Previous management: 3 participants had previously received short-term systemic glucocorticoids which were stopped 4 weeks before commencement of the trial
Interventions	Pulsed IV dexamethasone + pulsed IV cyclophosphamide plus daily oral cyclophosphamide versus oral methylprednisolone + oral azathioprine Regimen: dexamethasone 100 mg + cyclophosphamide 500 mg over 3 consecutive days every 2 to 3 weeks, plus cyclophosphamide 50 mg/day. Interval between pulses lengthened according to response. Cyclophosphamide pulses stopped when no relapses after six week interval and dexamethasone pulses continued every 12 weeks then stopped. Oral cyclophosphamide discontinued after six months Methylprednisolone 2 mg/mg/day plus azathioprine 2 to 2.5 mg/kg/day until cessation of new blister formation. Methylprednisolone decreased by 50% then tapered and withdrawn. Azathioprine tapered

Rose 2005 (*Continued*)

	four weeks after methylprednisolone withdrawn Concomitant medication: cholecalciferol, calcium, ranitidine, nystatin for all participants. Uromitexan and subcutaneous heparin for the dexamethasone-cyclophosphamide group
Outcomes	Proportion of participants in remission (categorised as complete remission a, complete remission b, partial remission) or progression at 24 months, adverse events, antibody titres, time to remission
Notes	Complicated regimen and tapering schedule. Complicated definitions of outcomes Definitions Complete remission a: clearing of all lesions and cessation of new blister formation after discontinuation of treatment Complete remission b: clearing of all lesions and cessation of new blister formation under continuing therapy Partial remission: clearing of more than 50% of lesions and/or occurrence of <5blisters/month Progression: minimal clearing of lesions (<50%) or worsening of disease) Relapse: not defined NB: partial remission, complete remission a and complete remission b included in 'disease control'

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Tabrizi 2007

Methods	Double-blind single-centre within participant left-right randomised controlled trial Country: Iran Method of randomisation: computer generated list given to head nurse Allocation concealment: creams packaged by pharmaceutical company in identical tubes labelled 'A' and 'B' Blinding: participant yes, clinician yes, outcome assessor yes, statistician unsure Intention to treat analysis: yes Participant losses: one withdrawn due to adverse event Follow-up: 9 to 15 months
Participants	20 participants with mucocutaneous pemphigus vulgaris Gender: 13 male, 7 female Inclusion criteria: diagnosis confirmed on clinical, histological, and immunofluorescence criteria; symmetrical skin lesions of approximately the same size (difference no more than 15%), 2mm or less in depth, which bled easily and with mild to moderate inflammation, which appeared within 1 day of each other, and had failed to respond to systemic treatment and rinsing with normal saline over a 2 week period Exclusion criteria: pregnancy; lactation; drug reaction to study drug; infection; history of skin cancer Disease duration: 12 newly diagnosed and 8 recurrent disease Baseline severity: NS Previous management: NS

Tabrizi 2007 (*Continued*)

Interventions	Topical 10ug/g epidermal growth factor (EGF) in 0.1% silver sulfadiazine cream versus 0.1% silver sulfadiazine (SSD) cream alone Regimen: applied daily until complete healing of lesions Concomitant medication: prednisolone alone or in combination with azathioprine, mycophenolate or cyclophosphamide
Outcomes	Median time to heal skin lesions, adverse events
Notes	Definitions Complete healing: completely resolved crust and non-ulcerated skin, which could be inflamed, replacing the lesion

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Werth 2008

Methods	Blinded multi-centre randomised placebo-controlled trial with cross-over phase for treatment failures Country: United States Method of randomisation: computer generated code in permuted blocks of four Allocation concealment: study medication packaged and labeled with 3-digit medication code Blinding: participant yes, clinician yes, outcome assessor yes, statistican no Intention to treat analysis: yes Participant losses: four (participant withdrawal two, imprisonment one, hospitalisation other causes) follow-up: one year
Participants	19 participants with pemphigus vulgaris Gender: 11 male, 8 female Inclusion criteria: diagnosis confirmed on histological and immunofluorescence criteria; chronic disease in maintenance phase, controlled with glucocorticoids and /or stable doses (for at least 2 months) of cytotoxic agents including azathioprine, mycophenolate mofetil or methotrexate; unable to taper glucocorticoids at least twice prior to inclusion; glucocorticoid dose not tapered more than 10% within last 30 days; glucocorticoid dose at baseline 15-40mg or 20-60mg every other day; 18-80 years Exclusion criteria: able to taper glucocorticoids without recurrence or disease; early severe disease that did not respond to high doses of prednisolone, cytotoxic agents, plasmaphereseis or other modalities; pregnant; breastfeeding; ischaemic heart disease; hb<10g/dL; quantitatively insufficient G6PD; dapsone allergy or contraindications; pulsed glucocorticoids, pulsed cyclophosphamide or plasmapheresis within 2 months Disease duration: 3 to 180 months Baseline severity: participants in maintenance phase controlled with glucocorticoides and/or cytotoxics and two unsuccessful attempts to taper glucocorticoids using one of two standardized tapering methods to less than 15 mg/d Previous management: two unsuccessful tapers of glucocorticoids

Interventions	Dapsone vs placebo in addition to glucocorticoids plus cytotoxics Initial dose: Dapsone 50 mg/day, increased by 25 mg per week until 150 mg/day. Increased to 200 mg/day if no response to 150 mg/day. Prednisone 15 to 20 mg/day or 20 to 60 mg/ every other day Cytotoxics: azathioprine, mycophenolate or methotrexate Regimen: Different tapering regimens used at various centres.
Outcomes	Ability to reduce prednisone dose to predefined amount in predefined time, adverse events
Notes	Definitions Success: 'ability of patients to taper to less than or equal to 7.5 mg/day' of glucocorticoids (prednisone) within one year of reaching maximum dose of study drug Failure: ' inability to taper glucocorticoids by more than 25% within four months'

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

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

Study	Reason for exclusion
Akhtar 1998	Non-randomised controlled trial, Immunoflourescence studies not performed
Auad 1970	Non-randomised controlled trial, Immunoflourescence studies not performed
Auad 1986	Outcomes of interest not reported
Bystryn 2006	Non-controlled trial
Calebotta 1999	Retrospective control
Chaidemenos 2007	Non-controlled trial
Chams-Davatchi C 2007	Non-controlled trial
Cianchini 2007	Non-controlled trial
Czernik 2008	Non-controlled trial
David 1993	Retrospective control (same study as Lapidoth 1994)

(*Continued*)

Faurschou 2008	Case series
Femiano 2002	Non-randomised controlled trial
Fernandes 2001	Non-randomised controlled trial
Goh 2007	Non-controlled trial
Iraji 2006	Non-randomised controlled trial
Iranzo 2007	Retrospective case series
Joly 2007	Non-controlled trial
Lapidoth 1994	Retrospective control (same study as David 1993)
Li 2005	Systematic review
Lozada-Nur 1994	Immunoflourescence studies not performed
Mamelak 2007	Case series
Muhlhoff 2007	Case report
Pasricha 2008	Retrospective case series
Shahidi-Dadras 2007	Non-randomised controlled trial
Tan-Lim 1990	Retrospective control
Toth 1999	Case report (same paper as Jonkman 1999)

Characteristics of studies awaiting assessment *[ordered by study ID]*

Hashimoto

Methods	Blinded multi-centre placebo-controlled randomised trial
Participants	61 participants with pemphigus Inclusion criteria: glucocorticoid resistent pempighus
Interventions	Single cycle of IVIG (400mg/kg/day) versus single cycle of IVIG (200mg/kg/day) versus placebo for five consecutive days
Outcomes	Time to escape, disease activity scores, antibody titres, safety

Hashimoto (*Continued*)

Notes	

Immunoadsorption

Methods	Open label, uncontrolled trial
Participants	8 participants with pemphigus (6 pemphigus vulgaris, 2 pemphigus foliaceus)
Interventions	Combination of Protein A immunoadsorption, rituximab, dexamethasone and azathioprine; plus/minus IVIG
Outcomes	Short and long term remission, side effects, antibody titres, relapse
Notes	

Meyer 2008

Methods	
Participants	
Interventions	
Outcomes	
Notes	No information available at time of publication of this systematic review

Werth 2005

Methods	Multi-centre open-label phase I study
Participants	17 participants with pemphigus vulgaris Inclusion criteria: requiring daily glucocorticoid therapy
Interventions	PI-0824 (desmoglein-3 synthetic peptide) in three different doses Regimen: two IV infusions of PI-0824 separated by 7 days: 0.4mg/kg, 2.0 or 10.0mg/kg
Outcomes	Anti-desmoglein 3 (Dsg3) titre, number of Dsg3 specific CD4 T cells, IgG subsets for Dsg3, adverse events, disease flare
Notes	

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

Azathioprine

Trial name or title	Use of Prednisone with placebo or azathioprine in pemphigus vulgaris
Methods	Blinded placebo-controlled randomised trial
Participants	48 people with new cases of pemphigus vulgaris
Interventions	Azathioprine vs placebo in participants receiving prednisone
Outcomes	Disease activity score, disease control, cumulative glucocorticoid dose, adverse events, antibody titres
Starting date	April 2008
Contact information	Cheyda Chams-Davatchi, Tehran University of Medical Sciences
Notes	

Clobetasol

Trial name or title	Effect of Topical Cortiocosteroids on Epidermal Adhesion Strength in Pemphigus Vulgaris
Methods	
Participants	Pemphigus vulgaris
Interventions	Clobetasol vs placebo
Outcomes	Time to blister formation with suction cup
Starting date	
Contact information	Harbor-UCLA Medical Centre, David Geffen School of Medicine
Notes	

Cyclophosphamide

Trial name or title	Phase II study of high-dose cyclophosphamide in participants with refractory pemphigus
Methods	
Participants	35 people with pemphigus with persistent disease activity despite treatment with mycophenolate or azathioprine
Interventions	IV cyclophosphamide and G-CSF

Cyclophosphamide (*Continued*)

Outcomes	
Starting date	April 1999
Contact information	Grant Anhalt, John Hopkins University
Notes	

Etanercept

Trial name or title	Study of Etanercept (Enbel) in the Treatment of Pemphigus Vulgaris
Methods	Blinded placebo-controlled randomised trial
Participants	12 people with pemphigus vulgaris, with at least 6 active blisters or erosions
Interventions	Etanercept vs placebo
Outcomes	Mean time (in days) to reduce active lesions, including blisters and erosions by 50%, cumulative glucocorticoid dose
Starting date	June 2004
Contact information	Alexandra Kimball, Clinical Unit for Research Trials in Skin, Boston, Massachusetts, USA
Notes	

Infliximab

Trial name or title	Use of Infliximab for the Treatment of Pemphigus Vulgaris
Methods	Blinded placebo-controlled randomised trial
Participants	20 people with pemphigus vulgaris, failure to respond to standard glucocorticoid therapy
Interventions	Infliximab vs placebo
Outcomes	treatment-related adverse events of Grade 3 or higher. Response to treatment at week 18
Starting date	March 2006
Contact information	Russell Hall, Duke University Medical Center, National Institute of Allergy and Infectious Diseases
Notes	

IVIG

Trial name or title	Randomised trial of IVIG with or without cyclophosphamide in Pemphigus
Methods	Open-label, randomised, active control
Participants	24 participants with pemphigus vulgaris or pemphigus foliaceus not responding to standard treatment
Interventions	IVIG alone vs IVIG and cyclophosphamide
Outcomes	Extent and severity of disease, antibody titres, toxicity
Starting date	April 2007
Contact information	Jean-Claude Bystryn, NYU Medical Center
Notes	

KC706

Trial name or title	The use of KC706 for the Treatment of Pemphigus Vulgaris
Methods	Open-Label Uncontrolled
Participants	People with active pemphigus vulgaris taking stable doses of glucocorticoids or immunosuppressives or both
Interventions	KC706
Outcomes	Efficacy, safety
Starting date	November 2007
Contact information	Victoria Werth, University of Pennsylvania
Notes	

Mycophenolate

Trial name or title	A study to assess the effect of Cellcept (mycophenolate mofetil) and reduced corticosteroids in partients with active pemphigus vulgaris
Methods	Multi-centre randomised controlled trial
Participants	64 people with pemphigus vulgaris
Interventions	Mycophenolate mofetil vs placebo
Outcomes	Response (minimal disease activity and low glucocorticoid dose), number of days prednisone <= 10mg/day, time to relapse, time to initial response, adverse events, laboratory paramenters, vital signs

Mycophenolate (*Continued*)

Starting date	May 2004
Contact information	Hoffman-La Roche
Notes	

Stem Cell Support

Trial name or title	Hematopoietic Stem Cell Support in Patients with Autoimmune Bullous Skin Disorders
Methods	Non-Randomized, Open Label, Uncontrolled
Participants	20 people with pemphigus vulgaris or pemphigus foliaceus with refractory disease
Interventions	High dose cyclophosphamide plus anti-thymoctye globulin plus hematopoietic stem cell transplantation
Outcomes	Percent surface area involved, new skin or mucosal blister development, immune suppressive medication requirements, survival
Starting date	October 2002
Contact information	Northwestern University, Feinberg School of Medicine, Chicago, Illinois, USA
Notes	

DATA AND ANALYSES

Comparison 1. 1mg/kg vs 0.5mg/kg oral prednisolone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Disease control (no new blisters in one week and old lesions dried up)	1	22	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Relapse (during maintenance therapy)	1	22	Risk Ratio (M-H, Random, 95% CI)	0.7 [0.43, 1.14]
3 Withdrawal due to Adverse events	1	22	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 2. Pulsed oral dexamethasone vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relapse (after discontinuing and not stopping)	1	20	Risk Ratio (M-H, Random, 95% CI)	1.91 [0.68, 5.33]
2 Withdrawal due to Adverse events	1	20	Risk Ratio (M-H, Random, 95% CI)	2.45 [0.31, 19.74]

Comparison 3. Azathioprine vs glucocorticoid (prednisolone) alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission	1	60	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.80, 1.36]
2 Cumulative glucocorticoid dose	1	57	Mean Difference (IV, Random, 95% CI)	-3919.0 [-6710.00, -1126.00]
3 Withdrawal due to Adverse events	1	60	Risk Ratio (M-H, Random, 95% CI)	2.0 [0.19, 20.90]

Comparison 4. Cyclophosphamide vs glucocorticoid (prednisone / prednisolone) alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission	2	80	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.71, 1.28]
2 Disease control	1	20	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Relapse (during maintenance therapy)	1	20	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.05, 4.67]
4 Cumulative glucocorticoid dose	1	54	Mean Difference (IV, Random, 95% CI)	-3355.0 [-6143.57, -566.43]
5 Withdrawal due to adverse events	2	80	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]

Comparison 5. Cyclosporine vs glucocortoid (prednisone / methylprednisolone) alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission	1	18	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Disease control	2	51	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.86, 1.32]
3 Relapse (during maintenance therapy)	2	51	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.23, 3.65]
4 Cumulative glucocorticoid dose (until treatment discontinued)	1	33	Mean Difference (IV, Random, 95% CI)	-51.0 [-183.38, 81.38]
5 Withdrawal due to Adverse events	2	51	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 6. Dapsone vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission (<7.5mg prednisone) at 12 months	1	19	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.61, 5.63]
2 Withdrawal due to adverse events	1	19	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.05, 2.95]

Comparison 7. Mycophenolate vs glucocortoid (prednisolone) alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission	1	60	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.67, 1.24]
2 Cumulative glucocorticoid dose	1	60	Mean Difference (IV, Random, 95% CI)	-1833.0 [-4949.85, 1283.85]
3 Withdrawal due to Adverse events	1	60	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.07, 15.26]

Comparison 8. Plasma-exchange vs control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	1	40	Risk Ratio (M-H, Random, 95% CI)	7.43 [0.43, 129.55]
2 Disease control (complicated definition involving relative healing time)	1	40	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.70, 1.78]
3 Reduction antibody titre (baseline to end protocol)	1	33	Mean Difference (IV, Random, 95% CI)	44.38 [-222.43, 311.19]
4 Withdrawal due to Adverse events	1	34	Risk Ratio (M-H, Random, 95% CI)	7.2 [0.42, 124.08]

Comparison 9. Azathioprine vs cyclophosphamide

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission	1	60	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.82, 1.44]
2 Disease control (healing of >50% of lesions and/or occurrence of <5 blisters/month)	1	22	Risk Ratio (M-H, Random, 95% CI)	1.8 [0.89, 3.64]
3 Relapse (composite after remission or no remission)	1	22	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.53, 1.88]
4 Cumulative glucocorticoid dose	1	51	Mean Difference (IV, Random, 95% CI)	-564.0 [-1048.54, -79.46]
5 Withdrawal due to Adverse events	2	82	Risk Ratio (M-H, Random, 95% CI)	3.91 [0.45, 33.66]

Comparison 10. Azathioprine vs mycophenolate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission	1	60	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.85, 1.53]
2 Disease control	1	40	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.52, 0.99]
3 Cumulative glucocorticoid dose	2	92	Mean Difference (IV, Random, 95% CI)	-2074.00 [-3543.33, -608.67]
4 Withdrawal due to Adverse events	2	99	Risk Ratio (M-H, Random, 95% CI)	3.01 [0.48, 18.97]

Comparison 11. Cyclophosphamide vs cyclosporine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission (<10mg prednisone equivalent) at 5 years	1	18	Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Disease control	1	18	Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Relapse (during maintenance therapy)	1	18	Risk Ratio (M-H, Random, 95% CI)	0.4 [0.04, 3.66]
4 Withdrawal due to adverse events	1	18	Risk Ratio (M-H, Random, 95% CI)	Not estimable

Comparison 12. Cyclophosphamide vs mycophenolate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission	1	60	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.76, 1.44]
2 Cumulative glucocorticoid dose	1	54	Mean Difference (IV, Random, 95% CI)	-1522.0 [-2987.84, -56.16]
3 Withdrawal due to Adverse events	1	60	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.87]

Comparison 13. Topical epidermal growth factor (EGF) vs placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to control	1		Hazard Ratio (Fixed, 95% CI)	2.35 [1.62, 3.41]

Comparison 14. Traditional Chinese Medicine

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Antibody titre	1	40	Mean Difference (IV, Random, 95% CI)	0.75 [-1.12, 2.62]

Analysis 1.1. Comparison 1 1mg/kg vs 0.5mg/kg oral prednisolone, Outcome 1 Disease control (no new blisters in one week and old lesions dried up).

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 1 1mg/kg vs 0.5mg/kg oral prednisolone

Outcome: 1 Disease control (no new blisters in one week and old lesions dried up)

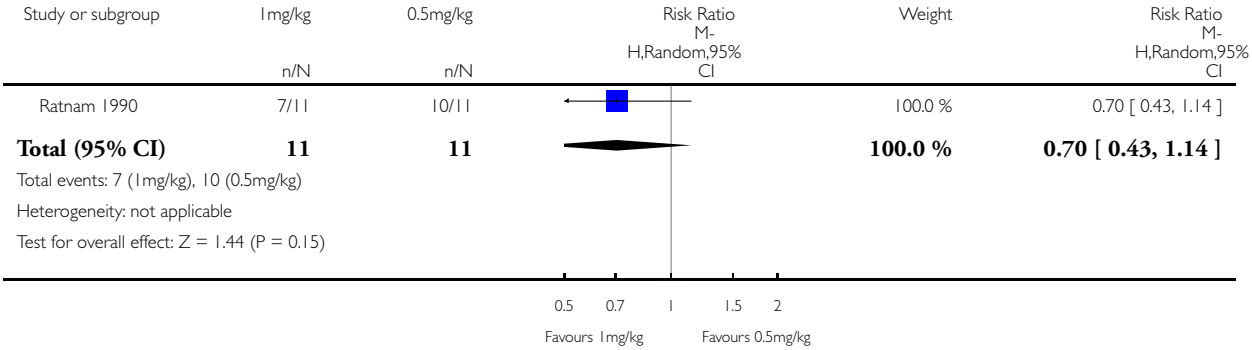
Study or subgroup	1mg/kg n/N	0.5mg/kg n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Ratnam 1990	11/11	11/11			Not estimable
Total (95% CI)	**11**	**11**			**Not estimable**
Total events: 11 (1mg/kg), 11 (0.5mg/kg)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 1.2. Comparison 1 1mg/kg vs 0.5mg/kg oral prednisolone, Outcome 2 Relapse (during maintenance therapy).

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 1 1mg/kg vs 0.5mg/kg oral prednisolone

Outcome: 2 Relapse (during maintenance therapy)

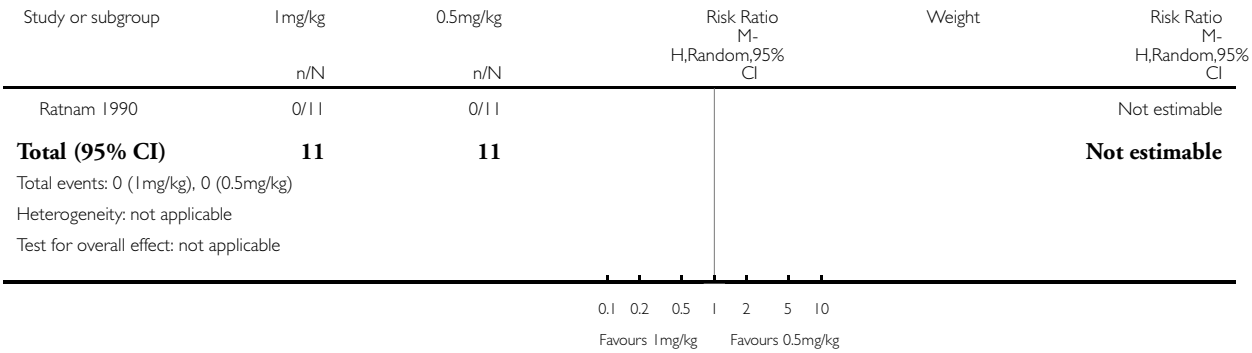


Analysis 1.3. Comparison 1 1mg/kg vs 0.5mg/kg oral prednisolone, Outcome 3 Withdrawal due to Adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 1 1mg/kg vs 0.5mg/kg oral prednisolone

Outcome: 3 Withdrawal due to Adverse events

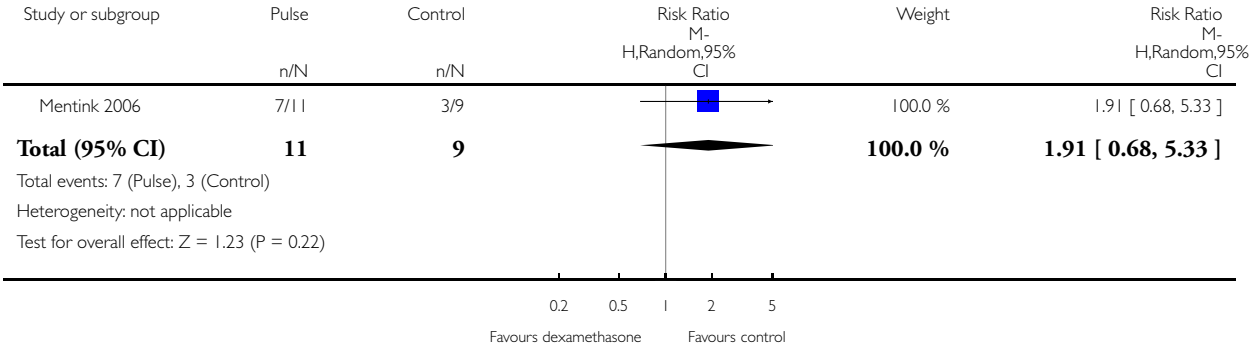


Analysis 2.1. Comparison 2 Pulsed oral dexamethasone vs placebo, Outcome 1 Relapse (after discontinuing and not stopping).

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 2 Pulsed oral dexamethasone vs placebo

Outcome: 1 Relapse (after discontinuing and not stopping)

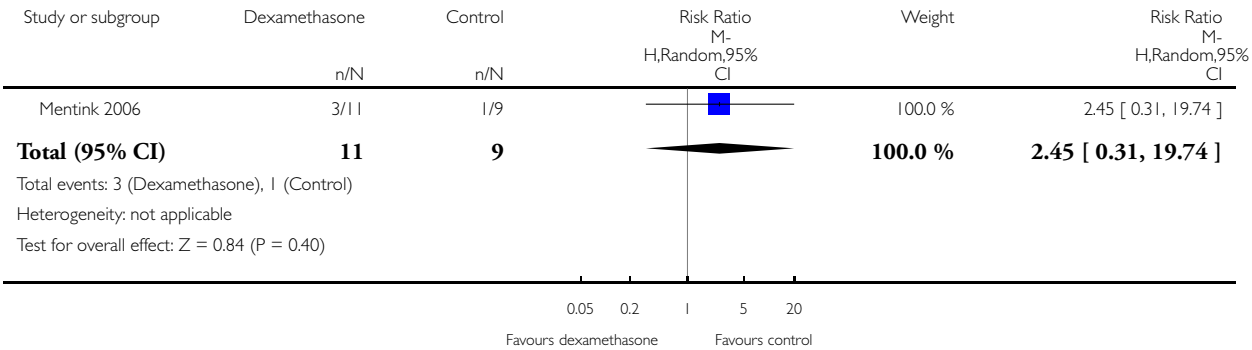


Analysis 2.2. Comparison 2 Pulsed oral dexamethasone vs placebo, Outcome 2 Withdrawal due to Adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 2 Pulsed oral dexamethasone vs placebo

Outcome: 2 Withdrawal due to Adverse events

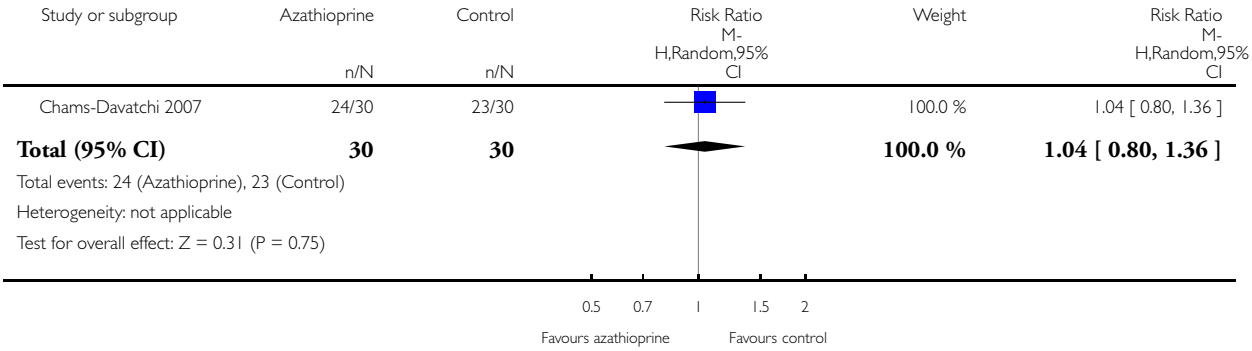


Analysis 3.1. Comparison 3 Azathioprine vs glucocorticoid (prednisolone) alone, Outcome 1 Remission.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 3 Azathioprine vs glucocorticoid (prednisolone) alone

Outcome: 1 Remission

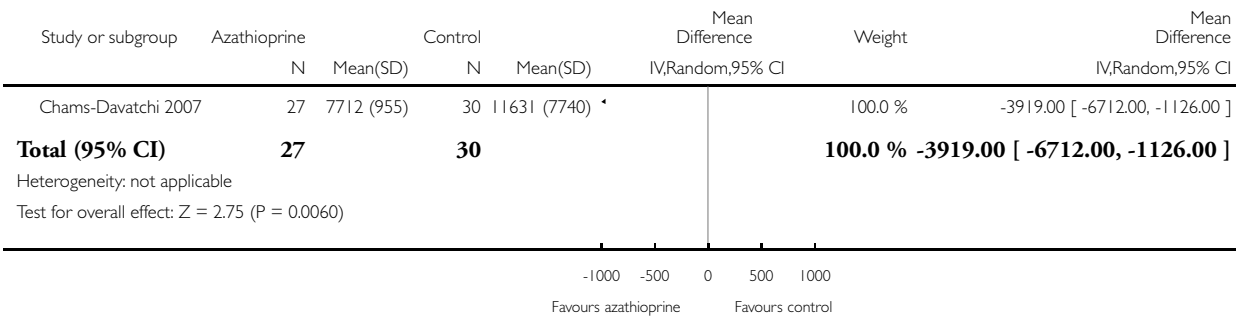


Analysis 3.2. Comparison 3 Azathioprine vs glucocorticoid (prednisolone) alone, Outcome 2 Cumulative glucocorticoid dose.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 3 Azathioprine vs glucocorticoid (prednisolone) alone

Outcome: 2 Cumulative glucocorticoid dose



Analysis 3.3. Comparison 3 Azathioprine vs glucocorticoid (prednisolone) alone, Outcome 3 Withdrawal due to Adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 3 Azathioprine vs glucocorticoid (prednisolone) alone

Outcome: 3 Withdrawal due to Adverse events

Study or subgroup	Azathioprine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chams-Davatchi 2007	2/30	1/30		100.0 %	2.00 [0.19, 20.90]
Total (95% CI)	**30**	**30**		**100.0 %**	**2.00 [0.19, 20.90]**
Total events: 2 (Azathioprine), 1 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.58 (P = 0.56)					

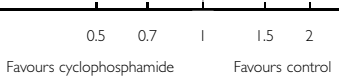
Analysis 4.1. Comparison 4 Cyclophosphamide vs glucocorticoid (prednisone / prednisolone) alone, Outcome 1 Remission.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 4 Cyclophosphamide vs glucocorticoid (prednisone / prednisolone) alone

Outcome: 1 Remission

Study or subgroup	Cyclophosphamide n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chams-Davatchi 2007	22/30	23/30		100.0 %	0.96 [0.71, 1.28]
Chrysomallis 1994	10/10	10/10			Not estimable
Total (95% CI)	**40**	**40**		**100.0 %**	**0.96 [0.71, 1.28]**
Total events: 32 (Cyclophosphamide), 33 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.30 (P = 0.77)					



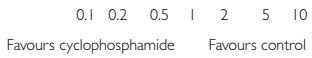
Analysis 4.2. Comparison 4 Cyclophosphamide vs glucocorticoid (prednisone / prednisolone) alone, Outcome 2 Disease control.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 4 Cyclophosphamide vs glucocorticoid (prednisone / prednisolone) alone

Outcome: 2 Disease control

Study or subgroup	Cyclophosphamide n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chrysomallis 1994	10/10	10/10			Not estimable
Total (95% CI)	**10**	**10**			**Not estimable**
Total events: 10 (Cyclophosphamide), 10 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



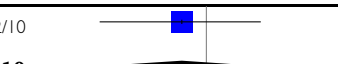
Analysis 4.3. Comparison 4 Cyclophosphamide vs glucocorticoid (prednisone / prednisolone) alone, Outcome 3 Relapse (during maintenance therapy).

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 4 Cyclophosphamide vs glucocorticoid (prednisone / prednisolone) alone

Outcome: 3 Relapse (during maintenance therapy)

Study or subgroup	Cyclophosphamide n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chrysomallis 1994	1/10	2/10		100.0 %	0.50 [0.05, 4.67]
Total (95% CI)	**10**	**10**		**100.0 %**	**0.50 [0.05, 4.67]**
Total events: 1 (Cyclophosphamide), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.61 (P = 0.54)					

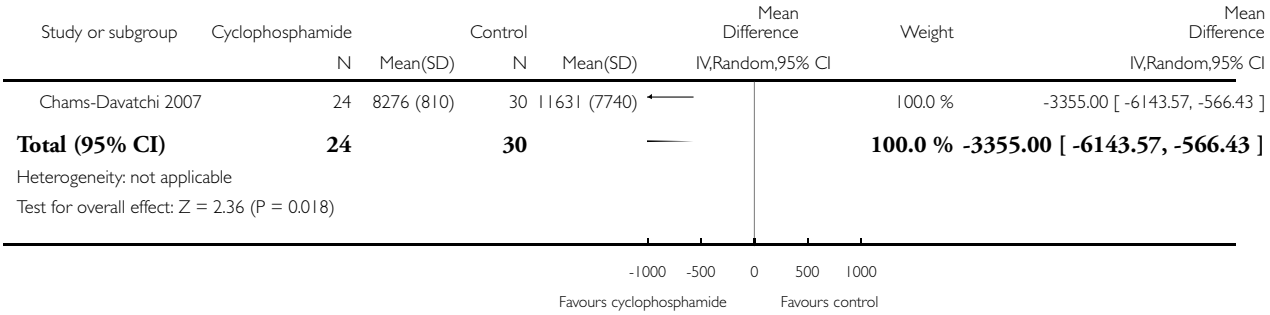


Analysis 4.4. Comparison 4 Cyclophosphamide vs glucocorticoid (prednisone / prednisolone) alone, Outcome 4 Cumulative glucocorticoid dose.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 4 Cyclophosphamide vs glucocorticoid (prednisone / prednisolone) alone

Outcome: 4 Cumulative glucocorticoid dose

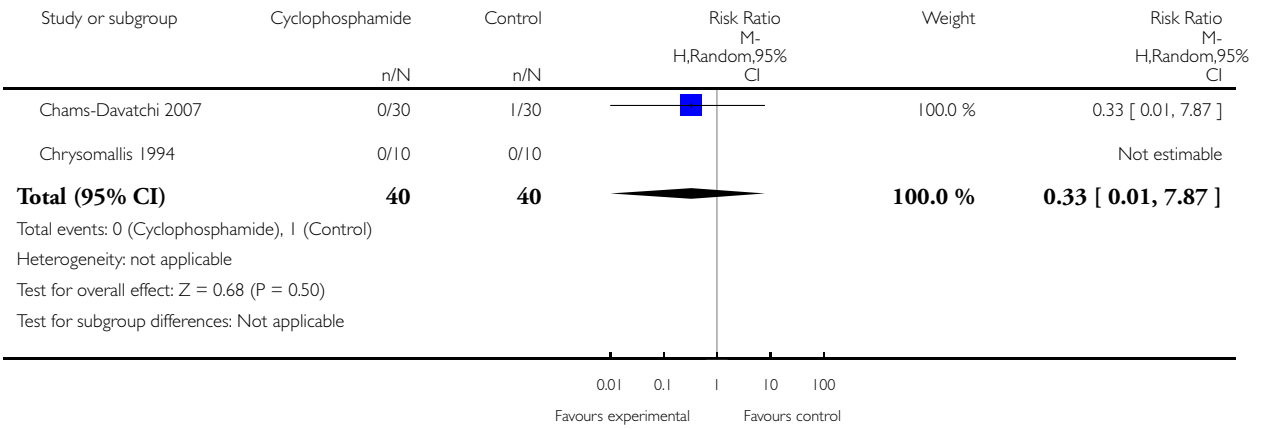


Analysis 4.5. Comparison 4 Cyclophosphamide vs glucocorticoid (prednisone / prednisolone) alone, Outcome 5 Withdrawal due to adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 4 Cyclophosphamide vs glucocorticoid (prednisone / prednisolone) alone

Outcome: 5 Withdrawal due to adverse events



Analysis 5.1. Comparison 5 Cyclosporine vs glucocortoid (prednisone / methylprednisolone) alone, Outcome 1 Remission.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 5 Cyclosporine vs glucocortoid (prednisone / methylprednisolone) alone

Outcome: 1 Remission

Study or subgroup	Cyclosporine n/N	Steroid alone n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chrysomallis 1994	8/8	10/10			Not estimable
Total (95% CI)	**8**	**10**			**Not estimable**
Total events: 8 (Cyclosporine), 10 (Steroid alone)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 5.2. Comparison 5 Cyclosporine vs glucocortoid (prednisone / methylprednisolone) alone, Outcome 2 Disease control.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 5 Cyclosporine vs glucocortoid (prednisone / methylprednisolone) alone

Outcome: 2 Disease control

Study or subgroup	Cyclosporine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chrysomallis 1994	8/8	10/10			Not estimable
Ioannides 2000	15/16	15/17		100.0 %	1.06 [0.86, 1.32]
Total (95% CI)	**24**	**27**		**100.0 %**	**1.06 [0.86, 1.32]**
Total events: 23 (Cyclosporine), 25 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.55 (P = 0.58)					

Analysis 5.3. Comparison 5 Cyclosporine vs glucocortoid (prednisone / methylprednisolone) alone, Outcome 3 Relapse (during maintenance therapy).

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 5 Cyclosporine vs glucocortoid (prednisone / methylprednisolone) alone

Outcome: 3 Relapse (during maintenance therapy)

Study or subgroup	Cyclosporine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chrysomallis 1994	2/8	2/10		64.0 %	1.25 [0.22, 7.02]
Ioannides 2000	1/16	2/17		36.0 %	0.53 [0.05, 5.31]
Total (95% CI)	**24**	**27**		**100.0 %**	**0.92 [0.23, 3.65]**

Total events: 3 (Cyclosporine), 4 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.34$, df = 1 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 0.12 (P = 0.90)

Analysis 5.4. Comparison 5 Cyclosporine vs glucocortoid (prednisone / methylprednisolone) alone, Outcome 4 Cumulative glucocorticoid dose (until treatment discontinued).

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

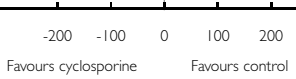
Comparison: 5 Cyclosporine vs glucocortoid (prednisone / methylprednisolone) alone

Outcome: 4 Cumulative glucocorticoid dose (until treatment discontinued)

Study or subgroup	Cyclosporine N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ioannides 2000	16	2657 (189)	17	2708 (199)		100.0 %	-51.00 [-183.38, 81.38]
Total (95% CI)	**16**		**17**			**100.0 %**	**-51.00 [-183.38, 81.38]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.76 (P = 0.45)



Analysis 5.5. Comparison 5 Cyclosporine vs glucocortoid (prednisone / methylprednisolone) alone, Outcome 5 Withdrawal due to Adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 5 Cyclosporine vs glucocortoid (prednisone / methylprednisolone) alone

Outcome: 5 Withdrawal due to Adverse events

Study or subgroup	Cyclosporine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chrysomallis 1994	0/8	0/10			Not estimable
Ioannides 2000	0/16	0/17			Not estimable
Total (95% CI)	**24**	**27**			**Not estimable**
Total events: 0 (Cyclosporine), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

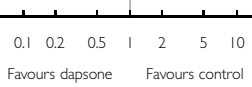
Analysis 6.1. Comparison 6 Dapsone vs placebo, Outcome 1 Remission (<7.5mg prednisone) at 12 months.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 6 Dapsone vs placebo

Outcome: 1 Remission (<7.5mg prednisone) at 12 months

Study or subgroup	Dapsone n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Werth 2008	5/9	3/10		100.0 %	1.85 [0.61, 5.63]
Total (95% CI)	**9**	**10**		**100.0 %**	**1.85 [0.61, 5.63]**
Total events: 5 (Dapsone), 3 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.09 (P = 0.28)					

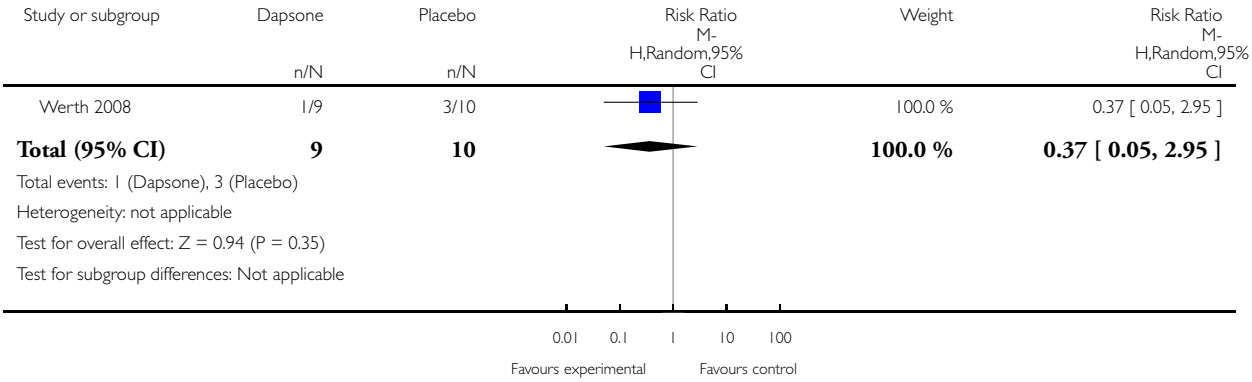


Analysis 6.2. Comparison 6 Dapsone vs placebo, Outcome 2 Withdrawal due to adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 6 Dapsone vs placebo

Outcome: 2 Withdrawal due to adverse events

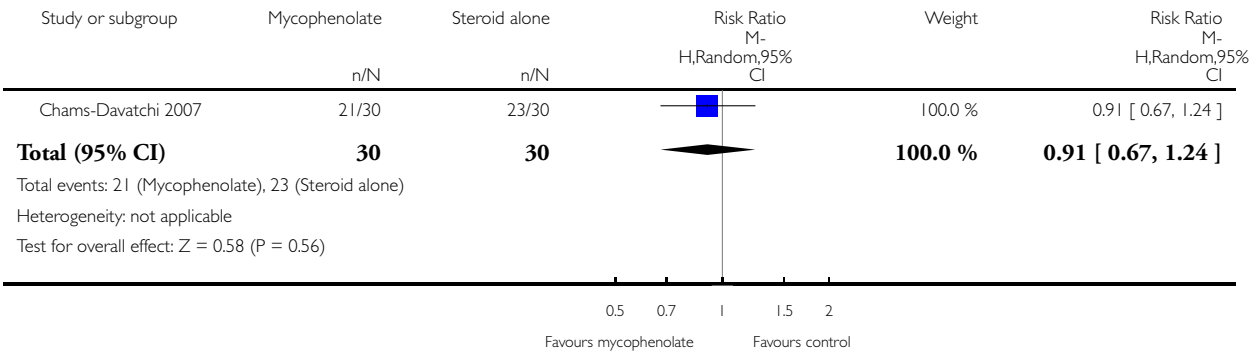


Analysis 7.1. Comparison 7 Mycophenolate vs glucocortoid (prednisolone) alone, Outcome 1 Remission.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 7 Mycophenolate vs glucocortoid (prednisolone) alone

Outcome: 1 Remission

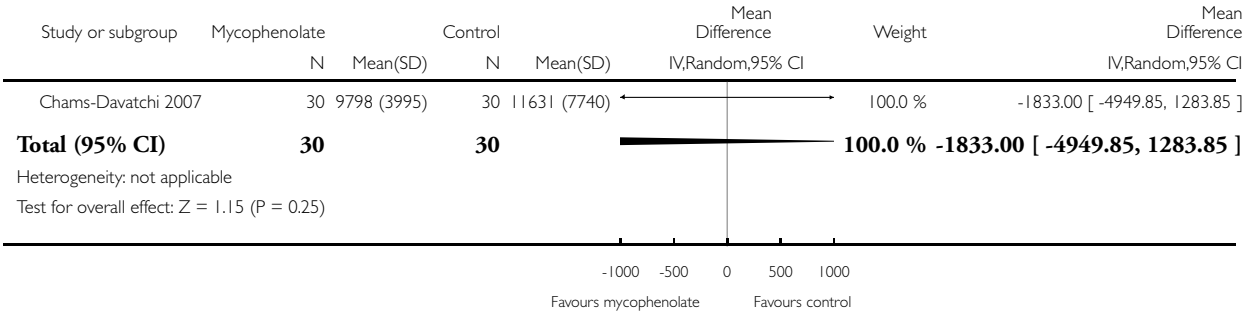


Analysis 7.2. Comparison 7 Mycophenolate vs glucocortoid (prednisolone) alone, Outcome 2 Cumulative glucocorticoid dose.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 7 Mycophenolate vs glucocortoid (prednisolone) alone

Outcome: 2 Cumulative glucocorticoid dose

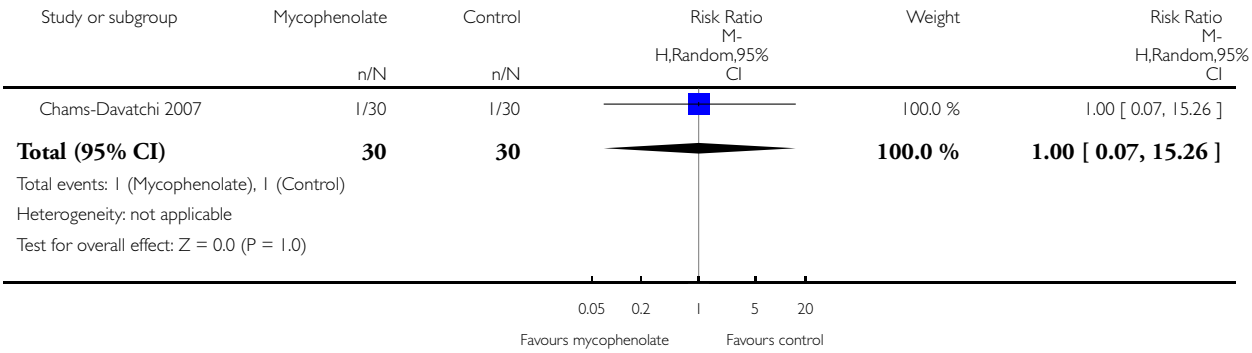


Analysis 7.3. Comparison 7 Mycophenolate vs glucocortoid (prednisolone) alone, Outcome 3 Withdrawal due to Adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 7 Mycophenolate vs glucocortoid (prednisolone) alone

Outcome: 3 Withdrawal due to Adverse events

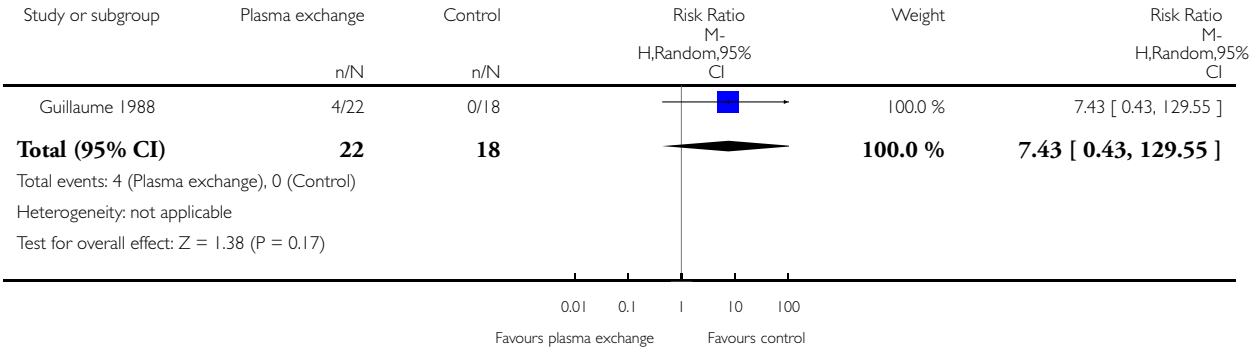


Analysis 8.1. Comparison 8 Plasma-exchange vs control, Outcome 1 Death.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 8 Plasma-exchange vs control

Outcome: 1 Death

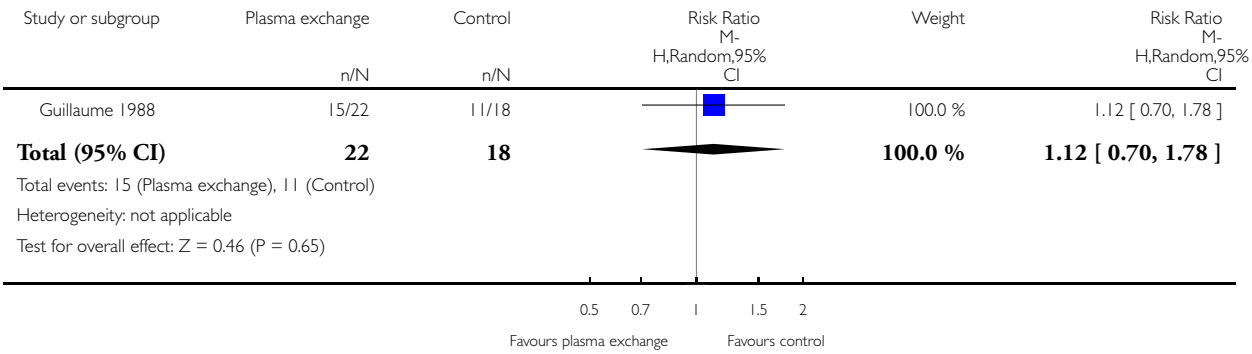


Analysis 8.2. Comparison 8 Plasma-exchange vs control, Outcome 2 Disease control (complicated definition involving relative healing time).

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 8 Plasma-exchange vs control

Outcome: 2 Disease control (complicated definition involving relative healing time)

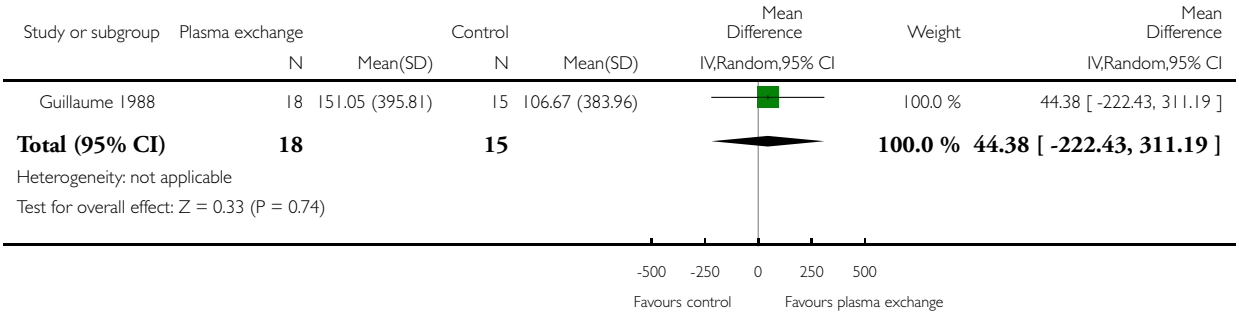


Analysis 8.3. Comparison 8 Plasma-exchange vs control, Outcome 3 Reduction antibody titre (baseline to end protocol).

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 8 Plasma-exchange vs control

Outcome: 3 Reduction antibody titre (baseline to end protocol)

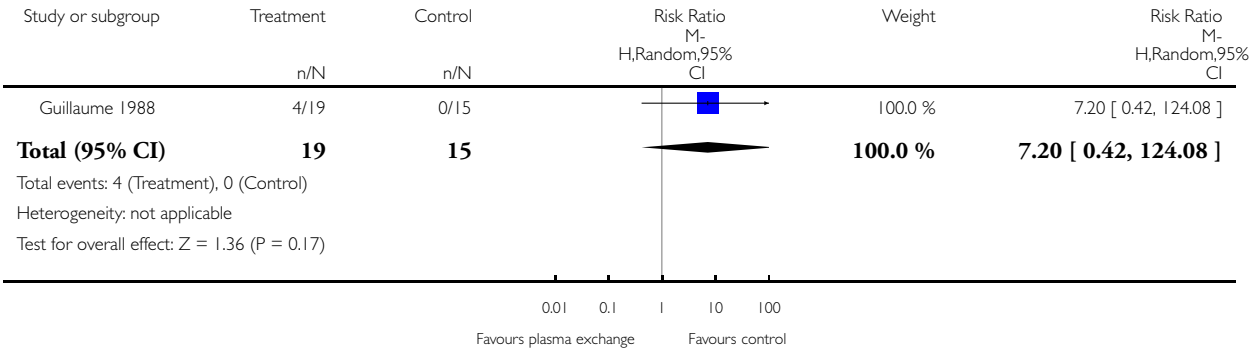


Analysis 8.4. Comparison 8 Plasma-exchange vs control, Outcome 4 Withdrawal due to Adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 8 Plasma-exchange vs control

Outcome: 4 Withdrawal due to Adverse events

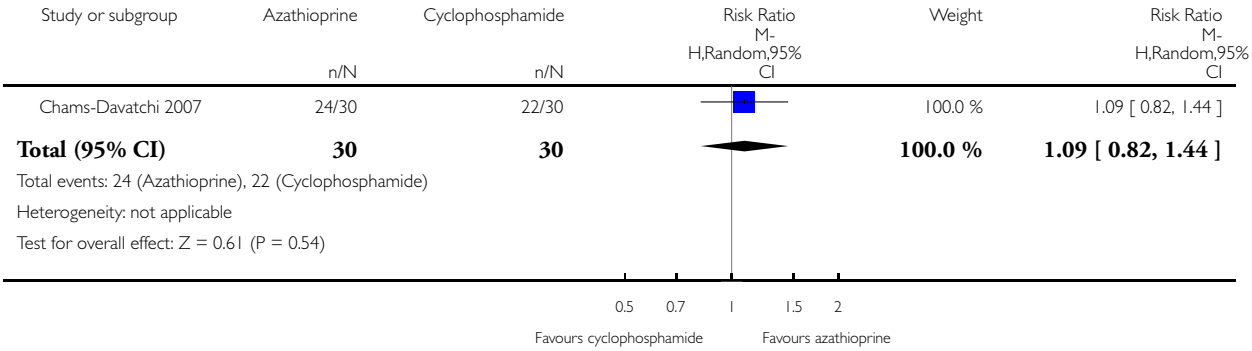


Analysis 9.1. Comparison 9 Azathioprine vs cyclophosphamide, Outcome 1 Remission.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 9 Azathioprine vs cyclophosphamide

Outcome: 1 Remission

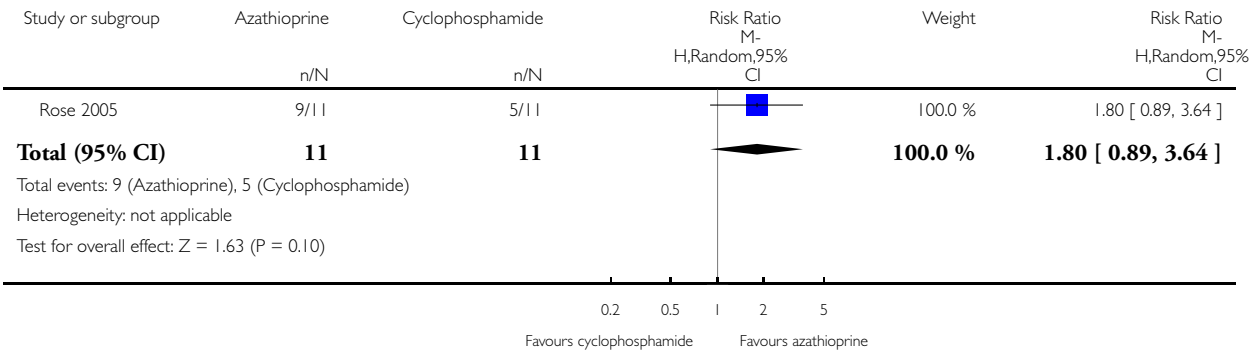


Analysis 9.2. Comparison 9 Azathioprine vs cyclophosphamide, Outcome 2 Disease control (healing of >50% of lesions and/or occurrence of <5 blisters/month).

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 9 Azathioprine vs cyclophosphamide

Outcome: 2 Disease control (healing of >50% of lesions and/or occurrence of <5 blisters/month)

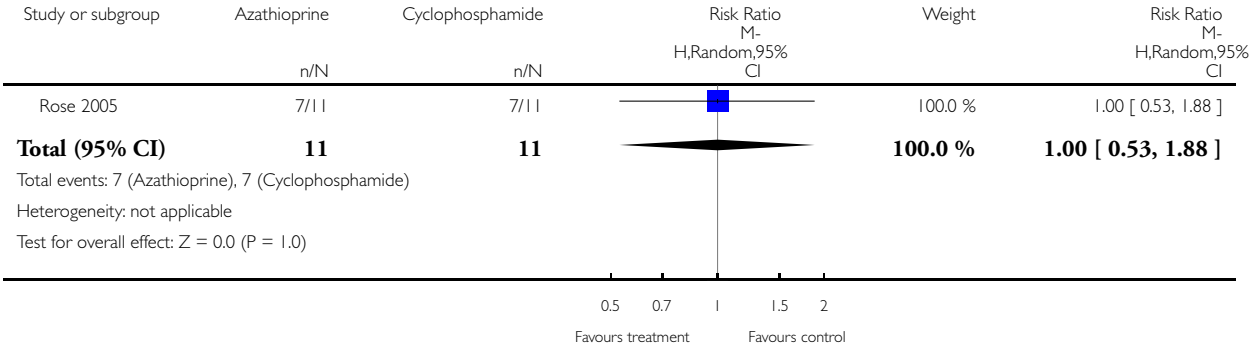


Analysis 9.3. Comparison 9 Azathioprine vs cyclophosphamide, Outcome 3 Relapse (composite after remission or no remission).

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 9 Azathioprine vs cyclophosphamide

Outcome: 3 Relapse (composite after remission or no remission)

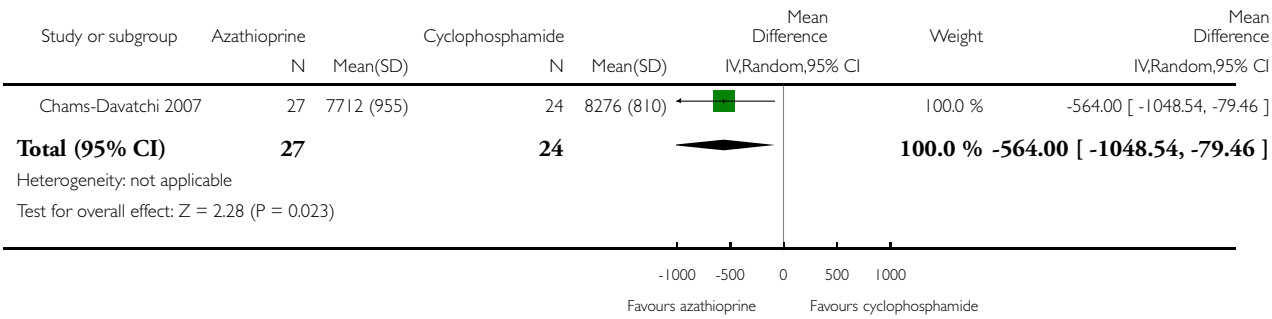


Analysis 9.4. Comparison 9 Azathioprine vs cyclophosphamide, Outcome 4 Cumulative glucocorticoid dose.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 9 Azathioprine vs cyclophosphamide

Outcome: 4 Cumulative glucocorticoid dose

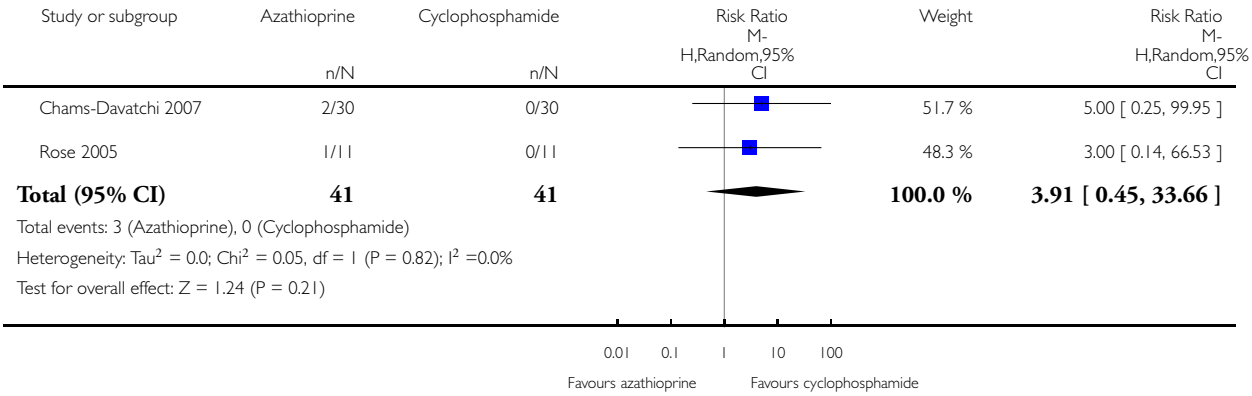


Analysis 9.5. Comparison 9 Azathioprine vs cyclophosphamide, Outcome 5 Withdrawal due to Adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 9 Azathioprine vs cyclophosphamide

Outcome: 5 Withdrawal due to Adverse events

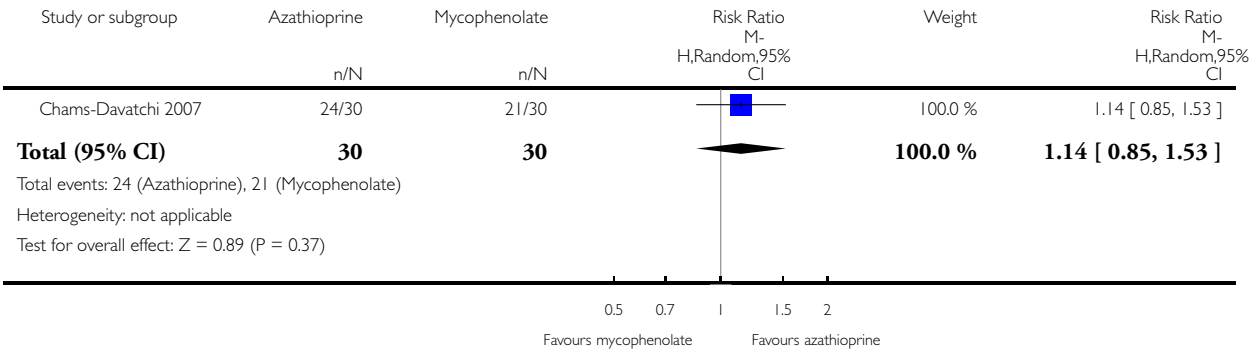


Analysis 10.1. Comparison 10 Azathioprine vs mycophenolate, Outcome 1 Remission.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 10 Azathioprine vs mycophenolate

Outcome: 1 Remission

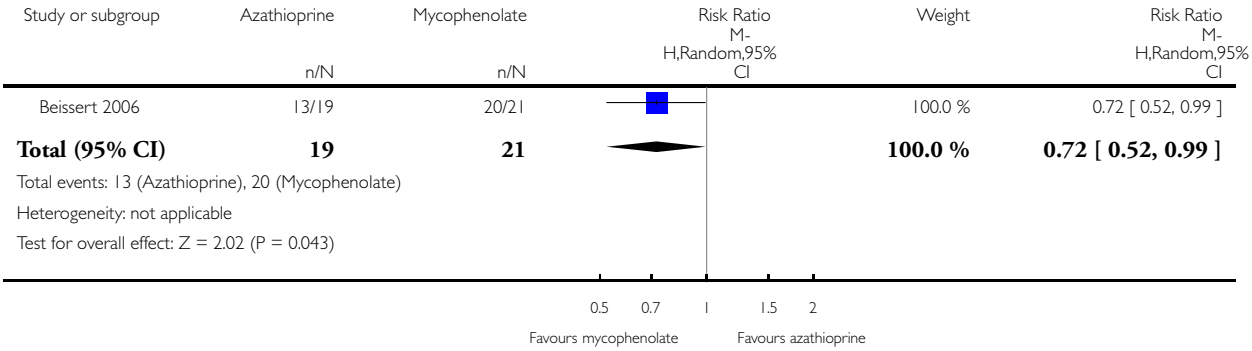


Analysis 10.2. Comparison 10 Azathioprine vs mycophenolate, Outcome 2 Disease control.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 10 Azathioprine vs mycophenolate

Outcome: 2 Disease control

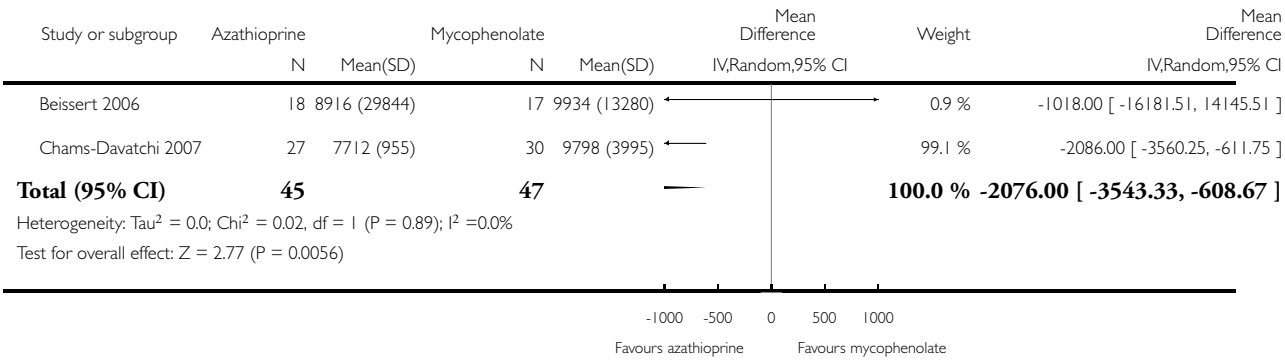


Analysis 10.3. Comparison 10 Azathioprine vs mycophenolate, Outcome 3 Cumulative glucocorticoid dose.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 10 Azathioprine vs mycophenolate

Outcome: 3 Cumulative glucocorticoid dose



Analysis 10.4. Comparison 10 Azathioprine vs mycophenolate, Outcome 4 Withdrawal due to Adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 10 Azathioprine vs mycophenolate

Outcome: 4 Withdrawal due to Adverse events

Study or subgroup	Azathioprine n/N	Mycophenolate n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Beissert 2006	2/18	0/21		38.4 %	5.79 [0.30, 113.26]
Chams-Davatchi 2007	2/30	1/30		61.6 %	2.00 [0.19, 20.90]
Total (95% CI)	**48**	**51**		**100.0 %**	**3.01 [0.48, 18.97]**

Total events: 4 (Azathioprine), 1 (Mycophenolate)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.31$, df = 1 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 1.17 (P = 0.24)

Analysis 11.1. Comparison 11 Cyclophosphamide vs cyclosporine, Outcome 1 Remission (<10mg prednisone equivalent) at 5 years.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 11 Cyclophosphamide vs cyclosporine

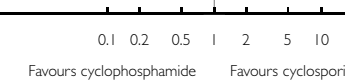
Outcome: 1 Remission (<10mg prednisone equivalent) at 5 years

Study or subgroup	Cyclophosphamide n/N	Cyclosporine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chrysomallis 1994	10/10	8/8			Not estimable
Total (95% CI)	**10**	**8**			**Not estimable**

Total events: 10 (Cyclophosphamide), 8 (Cyclosporine)

Heterogeneity: not applicable

Test for overall effect: not applicable



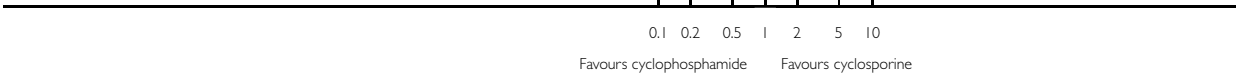
Analysis 11.2. Comparison 11 Cyclophosphamide vs cyclosporine, Outcome 2 Disease control.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 11 Cyclophosphamide vs cyclosporine

Outcome: 2 Disease control

Study or subgroup	Cyclophosphamide n/N	Cyclosporine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chrysomallis 1994	10/10	8/8			Not estimable
Total (95% CI)	**10**	**8**			**Not estimable**
Total events: 10 (Cyclophosphamide), 8 (Cyclosporine)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



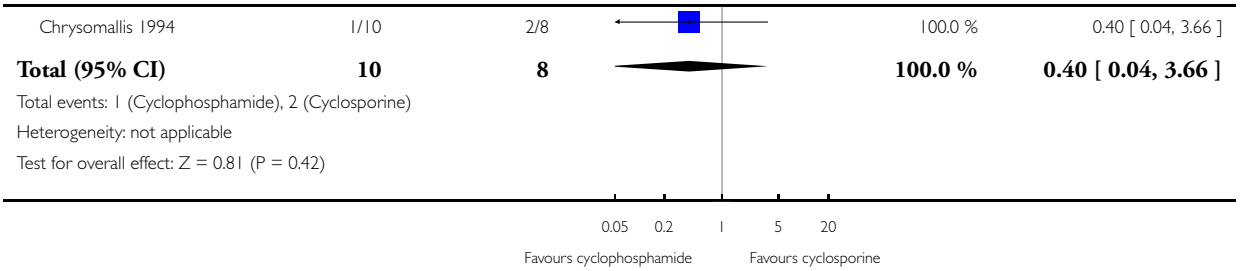
Analysis 11.3. Comparison 11 Cyclophosphamide vs cyclosporine, Outcome 3 Relapse (during maintenance therapy).

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 11 Cyclophosphamide vs cyclosporine

Outcome: 3 Relapse (during maintenance therapy)

Study or subgroup	Cyclophosphamide n/N	Cyclosporine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chrysomallis 1994	1/10	2/8		100.0 %	0.40 [0.04, 3.66]
Total (95% CI)	**10**	**8**		**100.0 %**	**0.40 [0.04, 3.66]**
Total events: 1 (Cyclophosphamide), 2 (Cyclosporine)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.81 (P = 0.42)					



Analysis 11.4. Comparison 11 Cyclophosphamide vs cyclosporine, Outcome 4 Withdrawal due to adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 11 Cyclophosphamide vs cyclosporine

Outcome: 4 Withdrawal due to adverse events

Study or subgroup	Cyclophosphamide n/N	Cyclosporine n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chrysomallis 1994	0/10	0/8			Not estimable
Total (95% CI)	**10**	**8**			**Not estimable**

Total events: 0 (Cyclophosphamide), 0 (Cyclosporine)

Heterogeneity: not applicable

Test for overall effect: not applicable

Test for subgroup differences: Not applicable

Analysis 12.1. Comparison 12 Cyclophosphamide vs mycophenolate, Outcome 1 Remission.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 12 Cyclophosphamide vs mycophenolate

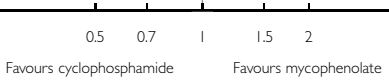
Outcome: 1 Remission

Study or subgroup	Cyclophosphamide n/N	Mycophenolate n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Chams-Davatchi 2007	22/30	21/30		100.0 %	1.05 [0.76, 1.44]
Total (95% CI)	**30**	**30**		**100.0 %**	**1.05 [0.76, 1.44]**

Total events: 22 (Cyclophosphamide), 21 (Mycophenolate)

Heterogeneity: not applicable

Test for overall effect: Z = 0.29 (P = 0.77)

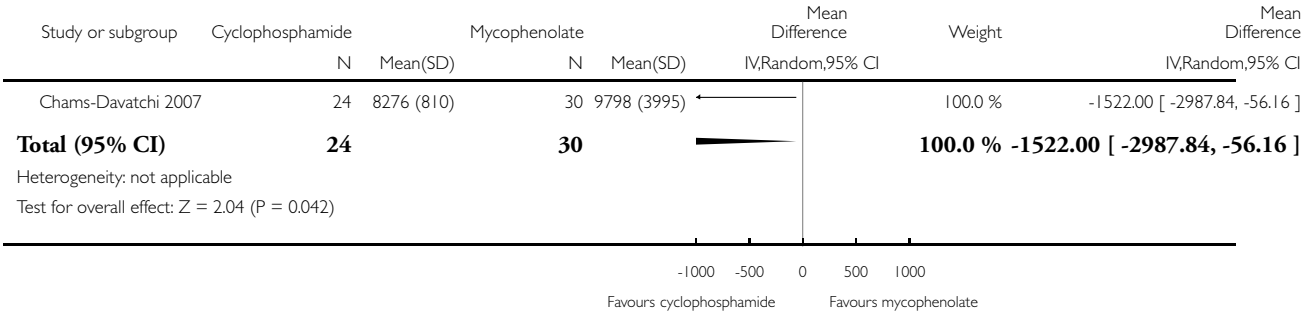


Analysis 12.2. Comparison 12 Cyclophosphamide vs mycophenolate, Outcome 2 Cumulative glucocorticoid dose.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 12 Cyclophosphamide vs mycophenolate

Outcome: 2 Cumulative glucocorticoid dose

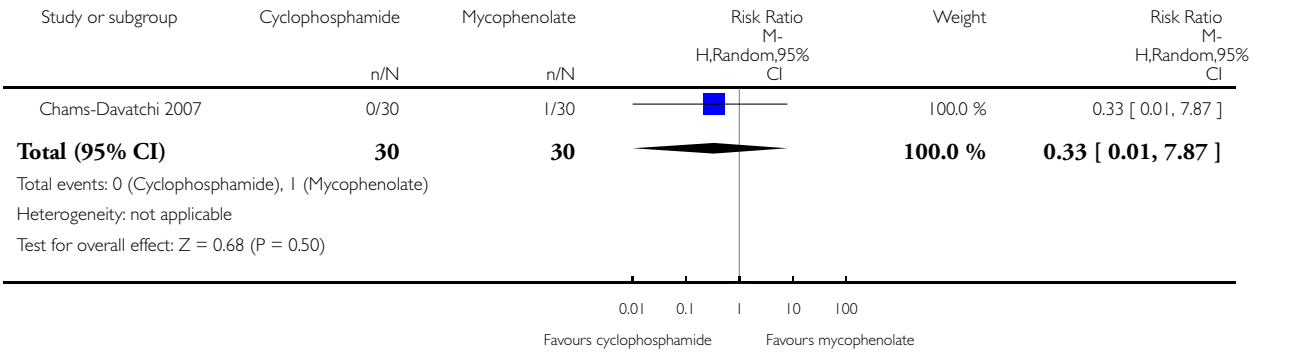


Analysis 12.3. Comparison 12 Cyclophosphamide vs mycophenolate, Outcome 3 Withdrawal due to Adverse events.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 12 Cyclophosphamide vs mycophenolate

Outcome: 3 Withdrawal due to Adverse events



Analysis 13.1. Comparison 13 Topical epidermal growth factor (EGF) vs placebo, Outcome 1 Time to control.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

Comparison: 13 Topical epidermal growth factor (EGF) vs placebo

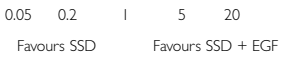
Outcome: 1 Time to control

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Fixed,95% CI	Weight	Hazard Ratio IV,Fixed,95% CI
Tabrizi 2007	0.8541844 (0.1901707)		100.0 %	2.35 [1.62, 3.41]
Total (95% CI)			**100.0 %**	**2.35 [1.62, 3.41]**

Heterogeneity: not applicable

Test for overall effect: Z = 4.49 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 14.1. Comparison 14 Traditional Chinese Medicine, Outcome 1 Antibody titre.

Review: Interventions for pemphigus vulgaris and pemphigus foliaceus

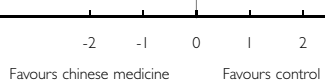
Comparison: 14 Traditional Chinese Medicine

Outcome: 1 Antibody titre

Study or subgroup	Traditional Chinese N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Luo 2003	20	0.87 (2.69)	20	0.12 (3.31)		100.0 %	0.75 [-1.12, 2.62]
Total (95% CI)	**20**		**20**			**100.0 %**	**0.75 [-1.12, 2.62]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.79 (P = 0.43)



APPENDICES

Appendix 1. MEDLINE Search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. humans.sh.
10. 8 and 9
11. exp Pemphigus/ or pemphigus.mp.
12. 11 and 10

Appendix 2. EMBASE Search strategy

1. random$.mp.
2. factorial$.mp.
3. crossover$.mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. assign$.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. exp PEMPHIGUS VULGARIS/ or exp PEMPHIGUS/ or exp PEMPHIGUS FOLIACEUS/ or pemphigus.mp.
15. 13 and 14

Appendix 3. LILACS Search strategy

((Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Pt clinical trial OR Ex E05.318.760.535$ OR (Tw clin$ AND (Tw trial$ OR Tw ensa$ OR Tw estud$ OR Tw experim$ OR Tw investiga$)) OR ((Tw singl$ OR Tw simple$ OR Tw doubl$ OR Tw doble$ OR Tw duplo$ OR Tw trebl$ OR Tw trip$) AND (Tw blind$ OR Tw cego$ OR Tw ciego$ OR Tw mask$ OR Tw mascar$)) OR Mh placebos OR Tw placebo$ OR (Tw random$ OR Tw randon$ OR Tw casual$ OR Tw acaso$ OR Tw azar OR Tw aleator$) OR Mh research design) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) OR (Ct comparative study OR Ex E05.337$ OR Mh follow-up studies OR Mh prospective studies OR Tw control$ OR Tw prospectiv$ OR Tw volunt$ OR Tw volunteer$) AND NOT (Ct animal AND NOT (Ct human and Ct animal))) AND (Pemphigus OR penfigo OR fovo selvagem)

WHAT'S NEW

Last assessed as up-to-date: 14 October 2008.

Date	Event	Description
28 May 2008	Amended	converted to new review format

HISTORY

Protocol first published: Issue 4, 2006

Review first published: Issue 1, 2009

CONTRIBUTIONS OF AUTHORS

Link with editorial base and co-ordinate contributions from co-authors (DM)

Draft protocol (LM, DM, VW, EV, JS)

Run search (LM)

Identify relevant titles and abstracts from searches (LM, AA, DM)

Obtain copies of trials (LM, DM)

Selection of trials (LM, AA, EV, DM)

Extract data from trials (LM, AA, DM)

Enter data into RevMan (LM)

Carry out analysis (LM, DM, VW, EV)

Interpret data (LM, DM, VW, EV)

Draft final review (LM, DM, EV, VW, JS)

DECLARATIONS OF INTEREST

VW was an author of one of the included papers (Werth 2008).

SOURCES OF SUPPORT

Internal sources

- Premier Research and Development, Kogarah, Australia.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The definitions of outcomes remission and relapse were modified in the review, in keeping with published definitions in an international consensus document (Murrell 2008).

The protocol for this review (Martin 2006) specified time points of of 8 weeks and 12 months for assessment of short and long term benefit, however in the review we utilised the outcomes 'disease control' to reflect short term benefit and 'remission' for long term benefit, in keeping with an international consensus document (Murrell 2008).

Additional interventions identified during the review process were added to the list of potential interventions.

We elaborated methodology utilised for data analysis, including dealing with multiple observations, time to event data, missing data, heterogeneity and reporting bias.

We substituted the term 'corticosteroid' with 'glucocorticoid' which is more precise.

Subgroup analyses for pemphigus vulgaris and pemphigus foliaceus planned in the protocol were not performed due to the small number of trials.

INDEX TERMS

Medical Subject Headings (MeSH)

Glucocorticoids [*therapeutic use]; Immunosuppressive Agents [*therapeutic use]; Pemphigus [classification; *drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans