HHS Public Access

Author manuscript

J Am Acad Dermatol. Author manuscript; available in PMC 2020 July 26.

Published in final edited form as:

J Am Acad Dermatol. 2011 May ; 64(5): 903–908. doi:10.1016/j.jaad.2010.04.039.

A systematic review of randomized controlled trials for pemphigus vulgaris and pemphigus foliaceus

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Abstract

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

Objective—We sought to evaluate the safety and efficacy of interventions for pemphigus vulgaris and pemphigus foliaceus.

Methods—We undertook a systematic review and meta-analysis according to the methodology of the Cochrane Collaboration. We selected randomized controlled trials including participants with the diagnosis of pemphigus vulgaris or pemphigus foliaceus confirmed with clinical, histopathological, and immunofluorescence criteria. All interventions were considered. Primary outcomes studied were remission and mortality. Secondary outcomes included disease control, relapse, pemphigus severity score, time to disease control, cumulative glucocorticoid dose, serum antibody titers, adverse events, and quality of life.

Results—Eleven studies with a total of 404 participants were identified. Interventions assessed included prednisolone dose regimen, pulsed dexamethasone, azathioprine, cyclophosphamide, cyclosporine, dapsone, mycophenolate, plasma exchange, topical epidermal growth factor, and traditional Chinese medicine. We found some interventions to be superior for certain outcomes, although we were unable to conclude which treatments are superior overall.

Limitations—Many interventions for pemphigus have not been evaluated in controlled trials. All studies were insufficiently powered to establish definitive results.

Conclusions—There is inadequate evidence available at present to ascertain the optimal therapy for pemphigus vulgaris and pemphigus foliaceus. Further randomized controlled trials are required.

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Disclosure: Dr Werth is an author of one of the studies included in this review. Dr Martin, Dr Villaneuva, and Dr Murrell have no conflicts of interest to declare.

Keywords

meta-analysis; pemphigus; systematic review

Pemphigus is rare a group of autoimmune bullous diseases characterized by widespread blistering and erosions of the skin and mucous membranes. It is a chronic and potentially life-threatening condition. There is no international consensus among experts regarding treatment strategy.[1]

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 minimizing adverse effects of treatment. Currently, the primary morbidity and mortality in pemphigus are derived from complications of treatment.[2]

A diverse group of interventions has been reported in pemphigus; however, the optimal therapeutic strategy has not been established. Systemic glucocorticoids are the cornerstone of management in pemphigus; however, the high-dose and prolonged courses of systemic glucocorticoids required for disease control are associated with significant adverse effects. There is considerable variation in the glucocorticoid regimen used.

Steroid-sparing adjuvant medications are widely used in the treatment of pemphigus. A large number of steroid-sparing adjuvant medications have been described, which may be broadly classified into immunosuppressive and anti-inflammatory groups. The rationale for their use is to increase efficacy of treatment, with a theoretical advantage of reducing the cumulative glucocorticoid dose and thereby reducing adverse events. 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.

We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the available evidence regarding efficacy and safety of interventions for pemphigus vulgaris and pemphigus foliaceus.[3]

METHODS

A systematic review and meta-analysis was undertaken following a prespecified protocol[4] according to the methodology of the Cochrane Collaboration.

Search strategy

We searched a number of electronic databases including the Cochrane Skin Group's Specialized Register (October 2008), the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library Issue 4, 2008), MEDLINE (2003–October 2008), PREMEDLINE (OVID) (October 2008), EMBASE (OVID) (2005–October 2008), and LILACS (Latin American and Caribbean Health Science Information database) (1982–October 2008). Ongoing trials were identified from the following online trial registers: The metaRegister of Controlled Trials www.controlledtrials.com, the US 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 Organization International Clinical Trials Registry platform www.who.int/trialssearch, the Ongoing Skin Trials register on www.nottingham.ac.uk/ongoingskin trials, and the International Pemphigus and Pemphigoid Foundation World Wide Web site www.pemphigus.org. In addition we contacted experts in the field, and searched reference lists from included studies and conference proceedings from international research workshops on pemphigus.

Selection criteria

RCTs of any intervention for pemphigus vulgaris and pemphigus foliaceus were included, provided the diagnosis of pemphigus was confirmed with appropriate clinical features, histopathology, and immunofluorescence studies. Because of its distinct etiology, prognosis, and management, paraneoplastic pemphigus was not considered in this review. No language restriction was used and articles in languages other than English were translated before analysis.

Quality assessment

Included studies were assessed for method of randomization, allocation concealment, blinding, follow-up, statistical analysis, and selective reporting.

Data extraction

Raw data were extracted from included studies independently by two reviewers. The primary outcomes considered were remission and mortality. The secondary outcomes analyzed included disease control, relapse, pemphigus severity score, time to disease control, cumulative glucocorticoid dose, serum antibody titers, adverse events, and quality of life. Definitions of outcomes were adopted from an international consensus document.[5]

Screening of abstracts, selection of studies, assessment of methodological quality, and data extraction was performed independently by two authors.

Missing data

Authors were contacted for missing data. For the dichotomous outcomes, remission, control, and relapse, we conducted an intention-to-treat analysis in which participants with missing outcome data were regarded as treatment failures and included in the analysis. For the dichotomous outcomes of death and withdrawal as a result of 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.” For the continuous outcomes cumulative glucocorticoid dose and antibody titer, in the case of missing data an available case analysis was conducted. For the time-to-event outcome “time to control,” where raw data or hazard ratios were not available, data were excluded from the analysis. Where possible, missing statistics not available from authors were imputed. Where insufficient information was available to impute statistics, results were described narratively and were not included in the analysis. Where we were concerned about the possibility of selective reporting of data (eg, only reporting of best responders), authors

were contacted for clarification and if no additional information was available, data were excluded from 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 randomization, allocation concealment, blinding, and loss to follow-up. Statistical heterogeneity was assessed using I,^{2} with I^2 greater than 50% indicating substantial heterogeneity.

Data synthesis

We calculated risk ratio and numbers needed to treat for dichotomous outcomes, mean weighted differences for continuous outcomes, and hazard ratios for time-to-event data. Meta-analysis was performed to calculate a weighted treatment effect across trials using a random effects model. The 95% confidence interval (CI) is reported for all point estimates.

Sensitivity analysis

Sensitivity analyses were undertaken for composite and conditional outcomes and imputed statistics.

RESULTS

Description of studies

A total of 592 abstracts were identified and 37 full-text articles were obtained and evaluated for study inclusion criteria. Eleven RCTs were identified, which evaluated 10 distinct interventions for pemphigus. These included a total of 404 participants (337 pemphigus vulgaris, 27 pemphigus foliaceus, and 40 not specified). Interventions assessed included prednisolone dose regimen,[6] pulsed dexamethasone,[7] azathioprine,[8–10] cyclophosphamide,[9–11] cyclosporine,[11,12] dapsone,[13] mycophenolate,[8,9] plasma exchange,[14] topical epidermal growth factor,[15] and traditional Chinese medicine.[16] Ten studies included participants with newly diagnosed or newly active recurrent disease, and one trial included participants in maintenance phase.

Overall the quality of included studies was poor. Allocation concealment was adequately explained in only 4 of 11 studies[7,10,13,15] and only 3 of 11 studies[7,13,15] were adequately blinded. Duration of follow-up ranged from 9 months to 5 years, although in two studies the duration of follow-up was not reported.[14,16] The sample sizes of included studies were small, ranging from 19 to 120 participants.

Because of the small number of trials and lack of consistent outcome measures, meta-analysis could only be performed for 4 comparisons, and each meta-analysis contained two trials only. Meta-analyses were conducted for cyclophosphamide versus glucocorticoid alone,[9,11] cyclosporine versus glucocorticoid alone,[11,12] azathioprine versus cyclophosphamide,[9,10] and azathioprine versus mycophenolate.[8,9]

Glucocorticoid regimen

Glucocorticoid dose—Initial prednisolone dose comparing 60 to 120 mg per day was evaluated in one study of 22 participants.[6] The effect of prednisolone dose was inconclusive on all reported outcomes including death, disease control, relapse, and withdrawal as a result of adverse events.

Pulsed glucocorticoids—Pulsed oral dexamethasone was evaluated in one study of 20 participants with new-onset disease or disease activity.[7] The effect of pulsed oral dexamethasone was inconclusive on all reported outcomes including remission, death, relapse, and withdrawal because of adverse events. Subjective inspection of the data demonstrated increased adverse events in the pulsed dexamethasone group.

Systemic adjuvant immunomodulatory agents

Azathioprine—Azathioprine was evaluated in 3 studies, including comparisons with prednisolone alone,[9] cyclophosphamide,[9,10] and mycophenolate.[8,9] Azathioprine was less effective than mycophenolate in achieving disease control based on one study with 40 participants (risk ratio 0.72; 95% CI 0.52–0.99).[8] Of note, this calculation incorporates an intention-to-treat analysis; no difference was observed in the per protocol analysis performed by the authors. The effect of azathioprine on disease control compared with cyclophosphamide was inconclusive.[10] Azathioprine appears to have a steroid-sparing effect compared with prednisolone alone, based on one study with 57 participants (mean weighted difference [MWD] −3919 mg; 95% CI −6712 to −1126).[9] Azathioprine appears to have a superior steroid-sparing effect compared with cyclophosphamide based on one study with 51 participants (MWD −564 mg; 95% CI −1049 to −79).[9] Azathioprine appears to have a superior steroid-sparing effect compared with mycophenolate based on two studies with 92 participants (MWD −2076 mg; 95% CI −3543 to −609).[8,9] The clinical relevance of this steroid-sparing effect is not certain. The effect of azathioprine on other outcomes including remission, death, relapse, or withdrawal because of adverse events was inconclusive.

Cyclophosphamide—Cyclophosphamide was evaluated in 3 studies, including comparisons with prednisolone or prednisone alone,[9,11] azathioprine,[9,10] cyclosporine,[11] and mycophenolate.[9] Cyclophosphamide appears to have a steroid-sparing effect compared with prednisolone alone based on one study with 54 participants (MWD −3355 mg; 95% CI −6144 to −566).[9] Cyclophosphamide appears to have a superior steroid-sparing effect compared with mycophenolate based on one study with 54 participants (MWD −1522 mg; 95% CI −2988 to −56).[9] Cyclophosphamide appears to have an inferior steroid-sparing effect compared with azathioprine based on one study with 51 participants (MWD −564 mg; 95% CI −1049 to −79).[9] The clinical relevance of this steroid-sparing effect is not certain. The effect of cyclophosphamide on other outcomes including remission, death, disease control, relapse, and withdrawal because of adverse events was inconclusive.

Cyclosporine—Cyclosporine was evaluated in two studies, including comparisons with prednisone or methylprednisolone alone and cyclophosphamide.[11,12] The effect of cyclosporine was inconclusive for all reported outcomes including remission, death, disease control, relapse, cumulative glucocorticoid dose, and withdrawal because of adverse events.

Dapsone—Dapsone was evaluated in one study of 19 participants compared with placebo.[13] The effect of dapsone on remission and withdrawal because of adverse events was inconclusive.

Mycophenolate—Mycophenolate was evaluated in two studies, including comparisons with prednisolone alone,[9] azathioprine,[8,9] and cyclophosphamide.[9] Mycophenolate appears more effective than azathioprine in inducing disease control based on one study with 40 participants (risk ratio 0.72; 95% CI 0.52–0.99).[8] Of note, this calculation incorporates an intention-to-treat analysis; no difference was observed in the per protocol analysis performed by the authors. However, mycophenolate had an inferior steroid-sparing effect compared with azathioprine based on two studies with 92 participants (MWD −2076 mg; 95% CI −3543 to −609).[8,9] Mycophenolate had an inferior steroid-sparing effect compared with cyclophosphamide based on one study with 54 participants (MWD −1522 mg; 95% CI −2988 to −56).[9] The effect of mycophenolate on other outcomes including remission, death, and withdrawal from adverse events was inconclusive.

Plasma exchange

Plasma exchange was evaluated in one study of 40 participants.[14] The effect of plasma exchange was inconclusive on all reported outcomes including death, disease control, antibody titer, and withdrawal because of adverse events.

Traditional Chinese medicine

Traditional Chinese medicine was evaluated in one study of 40 participants.[16] The effect of traditional Chinese medicine on antibody titer was inconclusive.

Topical agents

Topical epidermal growth factor—Topical epidermal growth factor, an endogenous peptide that is proposed to play a role in keratinocyte migration, was evaluated in one study as an adjunctive agent compared with placebo.[15] Topical epidermal growth factor appears to hasten lesion healing by a median of 6 days, based on one study with 20 participants (hazard ratio 2.35; 95% CI 1.62–3.41).[15]

DISCUSSION

Overall, the RCT evidence regarding interventions for pemphigus is inconclusive and incomplete. There are many therapeutic interventions in use that have not been evaluated in well-designed RCTs. Of the trials that have been conducted, sample sizes were small and insufficient to yield definitive results.

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 measurement of outcome open to bias. Sample sizes of included studies were too small to establish statistically significant differences in the primary end points. Duration of follow-up was variable, limiting the capacity to conduct long-term risk-benefit analyses.

Systemic glucocorticoids have a central role in the management of pemphigus vulgaris and pemphigus foliaceus, although the optimal dosage regimen is not known. Results from a study comparing 0.5 to 1 mg starting dose of prednisolone were inconclusive.[6] Adjuvant pulsed glucocorticoids did not appear beneficial in a small study in participants with new-onset disease and were associated with increased adverse events.[7] The role of pulsed glucocorticoids in recalcitrant disease has not been assessed.

There appears to be a steroid-sparing effect for azathioprine and cyclophosphamide compared with prednisolone alone.[9] These results need to be interpreted with caution, as cumulative steroid dosage is a surrogate outcome and the translation of milligrams of glucocorticoid saved to clinical adverse events avoided is difficult to quantify. No benefit was demonstrated in any clinical outcome in these studies. Moreover, these results were based on studies with small sample sizes and statistical methods to account for multiple comparisons were not used. However, the results indicate a need for further studies of adjuvant agents including adequate follow-up duration for meaningful risk-benefit analyses.

Mycophenolate appeared more effective in inducing disease control than azathioprine, based on an intention-to-treat analysis, although no difference was observed in the per protocol analysis performed by the authors.[8] These results need to be interpreted in conjunction with the finding that azathioprine appeared to have a superior steroid-sparing effect compared with mycophenolate.[8,9] No difference was observed in any outcome for other adjuvant immunomodulatory agent, and the optimal adjuvant immunomodulatory agent remains unclear.

Topical epidermal growth factor appeared to have a beneficial effect on time required for lesions to heal.[15] The role of this intervention requires further evaluation; in particular, although no intervention-related adverse events were noted in this study, the long-term safety is not known.

For the majority of studies, no difference was observed in death or withdrawal as a result of adverse events. However, the interventions studied have differing adverse event profiles, and these small studies are not sufficient to address safety comparisons of these drugs. The high mortality demonstrated in the study on plasma exchange is not in keeping with the general mortality for this intervention.[14] It is not clear whether these results were disease or protocol related. Careful consideration of potential benefits and potential adverse events in context of the individual's comorbidities is required.

Antibody titer is a surrogate measure that has been reported to correlate with disease activity in pemphigus.[17] The effect of pulsed dexamethasone, plasma exchange, and Chinese herbal medicine on antibody titer was inconclusive.[7,16] The usefulness of this outcome measure in monitoring treatment remains unclear.

There is little known regarding disease prognosis, and response to treatment can vary between individuals. The majority of RCTs in pemphigus included participants with new diagnoses, and although there was a spectrum of disease severity in included studies, there is insufficient information to guide treatment according to disease severity. There are no RCTs of participants with recalcitrant disease, and evidence from these studies may not be

applicable to this population. Studies used complex dose regimens to escalate and taper therapy, so results may not be applicable to other regimens of the same intervention.

This meta-analysis was limited by inconsistencies in outcome reporting in included studies. The majority of studies did not report the outcomes pre-specified in our protocol, which were based on an international consensus document. This limited our capacity to pool data. Uniformity of outcome reporting between trials is essential to facilitate comparison of interventions.

The optimal therapeutic strategy for pemphigus vulgaris and pemphigus foliaceus remains unclear. There is a need for further, well-conducted RCTs assessing the optimal glucocorticoid regimen, comparing immunomodulatory adjuvant agents, and assessing the management of recalcitrant disease. Now that there are outcome measures that have been agreed upon by international consensus[5] and severity scores developed for extent of disease,[18,19] these measures should allow comparison of future clinical trials and allow meta-analysis. Multicenter international cooperation and collaboration is likely to be the only framework that will allow sufficient recruitment for determination of efficacy and safety of interventions for this important disease.

Ms Martin was awarded the Schering-Plough Award from the Australasian College of Dermatologists for this project. Dr Anna Liza Agero assisted in screening of abstracts, trial selection, and data extraction. Mrs Janet Segall acted as the consumer representative for the Cochrane review.

Acknowledgments

Funding sources: None.

Abbreviations used

CI	confidence interval
MWD	mean weighted difference
RCT	randomized controlled trial

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CAPSULE SUMMARY

- Eleven randomized controlled trials examining 10 distinct interventions for pemphigus vulgaris and pemphigus foliaceus were identified.
- All studies were limited by small sample sizes and lack of uniform outcome measures, so that meta-analysis was not possible.
- No difference was observed between a starting dose of 60 mg versus 120 mg of prednisolone per day for any outcome.
- Adjuvant high-dose pulsed glucocorticoids did not appear beneficial in one small study in participants with new-onset disease and were associated with increased adverse events.
- Mycophenolate appeared more effective in achieving disease control than azathioprine.
- There was evidence of a steroid-sparing benefit for azathioprine and cyclophosphamide compared with glucocorticoids alone.
- Topical epidermal growth factor appeared to decrease time required for lesions to heal.
- The evidence regarding interventions for pemphigus is inconclusive and incomplete. Further randomized controlled trials using uniform outcome measures are required.