Original Article

Evidence-based treatments for pemphigus vulgaris, pemphigus foliaceus, and bullous pemphigoid: A systematic review

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ABSTRACT

Background: Pemphigus, bullous pemphigoid, and epidermolysis bullosa acquisita are autoimmune diseases of skin associated with considerable morbidity and sometimes mortality. There is no cure for these diseases. **Aims:** To summarize evidence-based treatments for these diseases by performing a systematic review. **Methods:** The research protocol included the following steps: identification of databases to be searched, defining search strategy, searching the databases for references, first-stage screening of the abstracts, second-stage screening of full texts of articles identified after the first-stage screening, data extraction from the identified articles after second-stage screening, quality appraisal of the studies using the Delphi list, and summarizing the findings. **Results:** No randomized controlled trials of interventions in pemphigus vegetans, pemphigus erythematosus, and epidermolysis bullosa acquisita could be found. After the second-stage screening, 12 randomized controlled trials were analyzed, which included patients with pemphigus vulgaris or pemphigus vulgaris and pemphigus foliaceus, and 7 which included patients with bullous pemphigoid. **Conclusions:** Number of high-quality randomized controlled trials conducted on pemphigus and bullous pemphigoid is small. Oral corticosteroid along with a steroid-sparing agent appears to be the most effective treatment for pemphigus. Azathioprine may be most effective as a steroid-sparing agent. Topical corticosteroid therapy (as studied) is effective for bullous pemphigoid and appears to be superior to oral corticosteroid for extensive disease. Some suggestions about future research are made.

Key words: Bullous pemphigoid, evidence-based treatment, interventions, pemphigus, review, systematic review, treatment

INTRODUCTION

Pemphigus is a group of autoimmune diseases of skin and mucous membranes, which is characterized by autoantibodies directed against antigens desmogleins 1 and/or 3 in the epidermis. This results in acantholysis in epidermis and clinically in the formation of flaccid blisters. There are mainly two types of pemphigus, pemphigus vulgaris (and its variant pemphigus vegetans), and pemphigus foliaceus (and its variant pemphigus erythematosus). The diseases are associated with considerable morbidity and sometimes mortality. Use of systemic glucocorticoids and other immunosuppressive drugs has changed the outlook in a large proportion of patients, but presently there is no cure of pemphigus.

Bullous pemphigoid is an autoimmune disease of skin usually occurring in the elderly. It is characterized by autoantibodies against the 180-kd (BP 180) and/or 230-kd (BP 230) molecules present in basal keratinocyte

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hemidesmosomes in the dermoepidermal junction. This results in split at the dermoepidermal junction and clinically in the formation of tense blisters. Pemphigoid is associated with considerable morbidity and sometimes mortality. Corticosteroids, topical or systemic, and sometimes other immunosuppressive agents help many patients, but presently there is no cure.

Epidermolysis bullosa acquisita (EBA) is a rare autoimmune disease characterized by skin fragility and subepidermal blisters due to the formation of autoantibodies against type VII collagen within the anchoring fibrils at the dermoepidermal junctions. EBA is associated with considerable morbidity.

In the present review, an attempt will be made to answer the question: what are the evidence-based (randomized controlled trials-based) treatments for pemphigus, bullous pemphigoid, and epidermolysis bullosa acquisita?

METHODS

Pemphigus

The research protocol included the following steps: identification of databases to be searched, defining search strategy, searching the databases for references, first-stage screening of the abstracts, second-stage screening of full texts of articles identified after the first-stage screening, data extraction from the identified articles after second-stage screening, quality appraisal of the studies, and summarizing the findings.

Databases searched

Following two databases were searched:

1. PubMed [http://PubMed.gov (http://www.ncbi.nlm.nih.gov/pubmed/)].
2. Cochrane Central Register of Controlled Trials (Clinical Trials) (http://onlinelibrary.wiley.com/o/cochrane/cochrane_clcentral_articles_fs.html).

Search strategy

1. PubMed: This was searched for the phrases "pemphigus vulgaris," "pemphigus foliaceus," "pemphigus vegetans," and "pemphigus erythematosus" separately by activating the limit "Clinical Trial" and using the search field tag "Title/Abstract."
2. Cochrane Central Register of Controlled Trials: Search was performed for the above diseases separately in "Title, Abstract, or Keywords."

The search was first performed on November 9, 2010 and was repeated on November 28, 2010; both searches resulted in identical references. All the articles thus identified went into first-stage screening.

First-stage screening

Abstracts of all the articles identified in the above-mentioned databases were read. Only those abstracts were selected for the second-stage screening, which met all of the following three inclusion criteria: (a) human trial, (b) prospective trial, and (c) controlled trial.

Second-stage screening

This was performed on the full-text articles. Full-texts of the articles which met the first-stage screening criteria were obtained. Only those articles were selected which met both of the following selection criteria: (a) mention of randomization in methods and (b) mention in methods that at least one of the following three tests were performed: (i) direct immunofluorescence test for detection of immunoglobulin G (IgG) on keratinocyte cell surface, (ii) test for detection of antibodies against desmoglein 1 and/or 3, or (iii) indirect immunofluorescence test for detecting IgG in patient's serum, which binds the cell surface of normal keratinocytes.

Articles that met the above-mentioned criteria were the randomized controlled trials (RCTs) of interventions in patients with pemphigus and these went into the data extraction stage.

Data extraction

Full-texts of the articles were read and the data regarding the following variables was noted separately for each article: name of disease(s) with which the patients were affected, number of centers where the trial was conducted and name of the country, interventions, adverse events, efficacy, and conclusions.

Quality appraisal

Quality appraisal of the RCTs was done by using the Delphi List,[1] which was expanded with respect to item number 1a as explained in the Discussion [Table 1].

Summarizing the findings

Summary of the RCTs was presented in tabular format.

Table 1: The Delphi list*[1]

Item number	Item	Assessment
1	Treatment allocation (a) Was a method of randomization performed? (i) Correct randomization method described (ii) Inadequate randomization method described (iii) Randomization stated, but method not described. (b) Was the treatment allocation concealed?	i, ii, iii Yes/No/Unclear†
2	Were the groups similar at baseline regarding the most important prognostic indicators?	Yes/No/Unclear
3	Were the eligibility criteria specified?	Yes/No/Unclear
4	Were the outcome assessor blinded?	Yes/No/Unclear
5	Was the care provider blinded?	Yes/No/Unclear
6	Was the patient blinded?	Yes/No/Unclear
7	Were point estimates and measures of variability presented for the primary outcome measures?	Yes/No/Unclear
8	Did the analysis include an intention-to-treat analysis?	Yes/No/Unclear

*Item 1a was expanded as explained in Discussion, †In Tables 4 and 6, "Y" has been used for "yes", "N" for "no", and "U" for "unclear"

Bullous pemphigoid

The same research protocol was followed as described above for pemphigus, with the following changes: Databases were searched for the word "pemphigoid." In the second-stage screening, only the articles that met both of the following selection criteria were selected: (a) mention of randomization in methods and (b) diagnosis of bullous pemphigoid by at least one of the following tests: (i) positive direct immunofluorescence test for C3 and/or IgG at the dermoepidermal junction, (ii) serum IgG labeling epidermal roof by indirect immunofluorescence, (iii) detection of antibodies against BP180 and/or BP230 antigens, or (iv) demonstration by immunoelectron microscopy of deposition of IgG associated with basal cell hemidesmosomes.

Epidermolysis bullosa acquisita

The same research protocol was followed as described above for pemphigus. Databases were searched for the phrase "epidermolysis bullosa acquisita." PubMed search resulted in three references which were excluded in first-stage screening. Search of Cochrane Central Register of Controlled Trials did not result in any reference.

As no RCTs were available on epidermolysis bullosa acquisita, no RCT-based conclusions can be drawn about its treatment.

RESULTS

Pemphigus

Number of articles on pemphigus vulgaris selected at different stages of the review is shown in Table 2 and those related to other types of pemphigus in Table 3. On reading the full-texts of articles, it became clear that no RCTs of interventions exclusively in pemphigus vegetans, pemphigus foliaceus, or pemphigus erythematosus were available. Of the 12 selected RCTs, 8 included patients with pemphigus vulgaris only and 4 included patients with both pemphigus vulgaris and pemphigus foliaceus. None of the available RCTs were found to include patients with pemphigus vegetans or pemphigus erythematosus.

Table 2: Number of articles on pemphigus vulgaris selected at different stages of the review

Database	PubMed	Cochrane central register of controlled trials
References identified	59	32
Articles selected after first-stage screening	21	23 (18 in PubMed search, 3 conference abstracts later published as articles also in PubMed search, 2 unique to Cochrane search)
Full-texts obtained	20*	2
Articles selected after second-stage screening	12	0

*Full-text of one article[2] unobtainable

Summary of the selected articles[4-15] of interventions in pemphigus vulgaris and foliaceus is presented in Table 4.

Bullous pemphigoid

Number of articles on bullous pemphigoid selected at different stages of the systematic review is shown in Table 5. Seven articles[19-25] met the selection criteria of second-stage screening and were selected for final analysis. Results are presented in Table 6.

Table 3: Number of articles on pemphigus vegetans, pemphigus foliaceus, and pemphigus erythematosus selected at different stages of the review

Pemphigus vegetans		
Database	PubMed	Cochrane central register of controlled trials
References identified	3	1
Articles selected after first-stage screening	1 (article already selected in search for pemphigus vulgaris)	1 (same as in PubMed search)
Pemphigus foliaceus		
References identified	19	7
Articles selected after first-stage screening	5 (4 already included in pemphigus vulgaris search, 1 unique)	5 (3 already included in pemphigus vulgaris PubMed search, 1 in pemphigus foliaceus PubMed search, 1 unique*)
Full-texts obtained	1	0
Articles selected after second-stage screening	0	0
Pemphigus erythematosus		
References identified	4	2
Articles selected after first-stage screening	1 (already in PubMed pemphigus vulgaris search)	1 (already in PubMed pemphigus vulgaris search)

*Full-text of one article on South American pemphigus foliaceus in Portuguese[3] unobtainable

DISCUSSION

Pemphigus

In the present review, an attempt was made to find out the evidence-based treatment for pemphigus. Good quality evidence consists of results of randomized controlled trials (RCTs). When an initial search was made on the two databases by using the phrase "randomized controlled trial" and name of a disease (eg, pemphigus vulgaris), it was found that very few articles were identified. The reason for this finding was that usually the articles that reported RCTs did not have this phrase in the titles or abstracts. Therefore, the search strategy was modified and it included a two-stage screening. It appears that this modified plan led to the identification of most, if not all, of the relevant articles.

PubMed is a service of the United States National Library of Medicine and the National Institutes of Health and comprises more than 20 million citations for biomedical literature from MEDLINE, life science journals and online books. Approximately 5400 journals published in more than 80 countries are currently indexed in MEDLINE. The other database selected was the Cochrane Central Register of Controlled Trials. This database includes details of articles from MEDLINE and also from EMBASE and other published and unpublished sources. EMBASE currently has over 23 million indexed records from more than 7500 journals.

For the second-stage screening, full-texts of 23 of 25 articles on pemphigus vulgaris and pemphigus foliaceus selected after the first-stage screening were obtained, from which 12 articles were finally selected [Tables 2 and 3]. These 12 studies used randomization for allocating treatments to different groups of patients. Most of the articles used at least one of the three immunological tests mentioned in methods of this article for diagnosing pemphigus. Two articles,[5,15] which appeared to be relevant, mentioned that immunological tests (enzyme-linked immunosorbent assay [ELISA] for antidesmoglein 1 and 3 antibodies[5] and direct and indirect immunofluorescence assays[15]) were performed, but it was unclear to this reviewer how the results of these tests were used in making the diagnosis.

It may be very important to have clear-cut diagnostic criteria for pemphigus. This is relevant in individual patients as well as in a situation when a patient may be included in a clinical study. Using a uniform set of criteria will make it easier for results of different clinical studies to be compared. One of the articles selected in this review used a set of diagnostic criteria, which appear to be appealing.[6] These Japanese diagnostic criteria are as follows: pemphigus is diagnosed when at least one item from every three findings, or two items from clinical findings and one item from immunological findings are satisfied. The three groups of findings are:

1. Clinical findings (multiple, easily rupturing, flaccid blisters of the skin; subsequent progressive,

Table 4: Summary and quality appraisal of the identified randomized controlled trials of interventions in pemphigus vulgaris and pemphigus foliaceus

Reference	Patients/Centers/ Country	Interventions	Adverse events	Efficacy	Conclusions	Quality appraisal (the Delphi list)*
Beissert *et al*. 2010	Mild to moderate PV. International multicenter including India.	All patients prednisolone 1–2 mg/kg/d, tapered. Group 1: placebo (n=36) Group 2: MMF 2 g/d (n=21) Group 3: MMF 3g/d (n=37) Duration: 52 weeks	Treatment-related AE in 31%, 38%, and 43% patients, respectively. Most commonly infections, significantly more in MMF group. Serious AE less with MMF (7%) vs placebo (11%).	Primary efficacy variable (response = absence of new, persistent, oral or cutaneous lesions, and prednisolone dose ≤ 10 mg/d from weeks 48 to 52) Group 1: 23/36 (64%) Group2: 17/21 (81%) Group 3: 23/37 (62%) Combined MMF: 40/58 (69%) No significant difference placebo vs MMF, between 2 doses of MMF. Combined MMF: response more quickly (*P*=0.051) and lasted longer (*P*=0.03). Relapse rate at 24 weeks more with placebo (45% vs 22%, *P*=0.03)	No benefit of adding MMF for proportion of patients responding to treatment from 48 to 52 weeks. Beneficial effect of MMF for time to response and duration of response (longer time to relapse). Relapse rate less with MMF.	1a: i 1b: U 2: N (placebo-treated patients had milder disease) 3: Y 4 and 6: Blinded with respect to treatment allocation (MMF or placebo), open with respect to dosing regimen (4 or 6 tablets/d) 5: U 7: Y 8: Y
Sethy *et al*. 2009	PV. Single center, India.	Group A: dexamethasone 100mg 3 days every 4 weeks, cyclophosphamide 500 mg once in 4 weeks and 50 mg/d, and prednisolone 0.5–0.75 mg/kg/d after 2 weeks if 5 or more new lesions/d (n=15) Group B: Cyclophosphamide 15 mg/kg/d once in 4 weeks and prednisolone 1.5 mg/kg/d, tapered (n=13) Duration: 12 months	Dysgeusia significantly more common in group A, dyspnea due to weight gain and moon facies in Group B.	Time for initiation of cutaneous response and time to achieve complete remission significantly less in Group B vs A. Other efficacy parameters comparable (time for initiation of mucosal response, time for cutaneous remission, time for mucosal remission, number of patients achieving remission, recurrences during treatment, relapses).	Early remission achieved in Group B.	1a: i 1b: N 2: Y 3: Y 4: N 5: N 6: N 7: Y 8: N
Amagai *et al*. 2009	PV and PF not responding to prednisolone 20mg/d or more. Multicenter, Japan.	Group 1: Placebo (n=20) Group 2: IVIG 200mg/kg/d for 5 days (n=20) Group 3: IVIG 400mg/kg/d for 5 days (n=21)	In 25%, 35%, and 29%, respectively. Not significantly different.	Primary efficacy end point (time to escape from protocol [TEP]=time until additional treatment was not required): TEP significantly longer in 400mg vs placebo group, 200mg and placebo not significantly different. Disease activity significantly lower in 400 mg group vs others.	IVIG 400 mg/kg/d for 5 days is effective (with regard to TEP) and safe in pemphigus.	1a: i 1b: N 2: Y 3: Y 4: Y 5: N 6: Y 7: Y 8: Y

Contd...

Table 4: Contd...

Reference	Patients/Centers/ Country	Interventions	Adverse events	Efficacy	Conclusions	Quality appraisal (the Delphi list)*
Arnold *et al*. 2009	Single patient with severe PV. Single center, UK.	Two phases of 6 consecutive months of either placebo (first 6 months) or IVIG 1 g/ kg monthly (second 6 months). Patient also received prednisolone according to disease severity and azathioprine. Prior to initiation of the trial, the patient was on prednisolone and azathioprine probably for "years", exact duration not mentioned.	No AE secondary to IVIG.	Subjective patient severity scores and pemphigus autoantibody titers improved significantly on IVIG vs placebo.	IVIG has moderately beneficial effect as adjuvant in refractory pemphigus.	1a: iii 1b: N 2: NA 3: Y 4: Y 5: N 6: Y 7: Y 8: NA
Werth *et al* 2008	PV controlled with glucocorticoid and/or cytotoxic drugs, disease in maintenance phase. Further tapering of steroid not successful. Multicenter, US.	Placebo group (n=10) Dapsone group: dapsone started with 50 mg/d increased to 150 mg/d and to 200 mg/d in patients not responding (n=9). All patients received maintenance doses of steroid, attempts were made to taper it. Duration: 1 year after highest dapsone dose reached.	Dapsone-related AE in dapsone group.	Main outcome measure: Ability of patients to taper prednisolone to at least 7.5 mg/d in 1 year. Placebo 5/9 Dapsone 3/10, difference not significant. 3 of 4 patients failing placebo responded when switched to dapsone.	Trend to efficacy of dapsone as a steroid-sparing drug in maintenance phase PV.	1a: i 1b: N 2: Y 3: Y 4: Y 5: Y 6: Y 7: Y 8: Y
Chams-Davatchi *et al*. 2007	PV. Single center, Iran.	Group P: prednisolone (2mg/kg) daily Group P/A: prednisolone (2mg/kg) and azathioprine (2.5mg/kg) daily for 2 months then reduced to 50 mg daily. Group P/MM: prednisolone (2mg/kg) and mycophenolate mofetil (2g) daily. Group P/PC: prednisolone (2 mg/ kg) daily and monthly IV cyclophosphamide (1000 mg) for 6 m, then bimonthly. N=30 each group. Duration: 1 year	No significant differences among the 4 groups.	All patients completing treatment had complete remission. Mean total dose of prednisolone: 11631, 7712, 9798, 8276 mg, respectively. Significant difference in mean total dose of prednisolone: P vs P/A, and P/A vs P/MM.	Efficacy of prednisolone is enhanced when it is combined with a cytotoxic drug. Most effective cytotoxic drug to reduce steroid was azathioprine, followed by cyclophosphamide pulse, and mycophenolate mofetil.	1a: iii 1b: N 2: Y 3: Y 4: N 5: N 6: N 7: Y 8: Y

Contd...

Table 4: Contd...

Reference	Patients/Centers/ Country	Interventions	Adverse events	Efficacy	Conclusions	Quality appraisal (the Delphi list)*
Tabrizi *et al*. 2007	PV. Single center, Iran.	Left/right comparison of once daily application of epidermal growth factor (EGF) 10µg/g in 0.1% silver sulfadiazine cream vs 0.1% silver sulfadiazine cream (n=20) Patients also received systemic immunosuppressive treatment.	No intervention related AE.	Median time to healing less with EGF (9 days vs 15 days) (*P*=0.0003)	EGF can significantly reduce healing time of skin lesions in PV.	1a: i 1b: N 2: Y 3: Y 4: Y 5: Y 6: Y 7: Y 8: Y
Beissert *et al*. 2006	PV and PF. Multicenter, Germany	Group 1: methylprednisolone 2 mg/kg/d (tapered) and azathioprine 2 mg/kg/d (tapered) (n=18) Group 2: methylprednisolone 2 mg/ kg/d (tapered) and MMF 2 g/d (tapered) (n=21)	Not significantly different. Slight trend in favor of MMF for inducing fewer serious AE	Total methylprednisolone dose (primary endpoint) (median 8916 mg vs 9334mg) and remission rates (72% in group 1 and 95% in group 2) not significantly different	Azathioprine and MMF have similar efficacy, steroid-sparing effect and safety profile as adjuvants in PV and PF	1a: i 1b: N 2: U 3: Y 4: N 5: N 6: N 7: Y 8: Y
Mentink *et al*. 2006	PV. International European multicenter.	Group DP: Oral dexamethasone 300 mg 3 days per month. (n=11) Group PP: Placebo pulses. (n=9) Both group received prednisolone (80 mg/day tapered across 19 weeks) and azathioprine 3 mg/kg/ day for 1 year. Pulses continued till prednisolone tapered to 0. Duration: 1 year	One serious (EBV hepatitis) in DP. Weight gain significantly more frequent in DP.	DP: 8/11 remission. Mean time to remission 173 days. PP: 9/9 remission. Mean time to remission 176 days. No significant difference.	No benefit of adding dexamethasone pulse therapy to treatment with prednisolone and azathioprine.	1a: i 1b: Y 2: Y 3: Y 4: Y 5: U 6: Y 7: Y 8: Y

Contd...

Table 4: Contd...

Reference	Patients/Centers/ Country	Interventions	Adverse events	Efficacy	Conclusions	Quality appraisal (the Delphi list)*
Rose *et al*. 2005	PV and PF. Multicenter, Germany.	M/A: methylprednisolone (2 mg/kg) and azathioprine (2–2.5 mg/kg) daily, later tapered (n=11) D/C: IV 100 mg dexamethasone/ day on 3 days and cyclophosphamide 500mg on day 1 every 2-4 weeks initially, then longer intervals. Also between pulses, oral 50 mg cyclophosphamide daily for 6 m. (n=11) Duration: 24 m.	More in M/A group, but not significantly different.	M/A: 9/11 remission, 1/11 progression. Treatment stopped due to side effects 1. More relapses after remission than D/C. D/C: 5/11 remission, 6/11 progression. Differences not significant	No difference in efficacy and side effects. Results do not confirm the encouraging results of earlier case series about pulse dexamethasone/ cyclophosphamide therapy.	1a: i 1b: N 2: Y 3: Y 4: N 5: N 6: N 7: Y 8: Y
Ioannides *et al*. 2000	PV and PF. Single center, Greece.	Group 1: 1 mg/kg prednisolone equivalent, dose increased until disease activity controlled, tapered when lesions cleared 80%–90%. (n=17) Group 2: Above treatment and cyclosporine 5 mg/ kg/d, reduced to 3 mg/ kg/d when steroid dose 50% of maximum, then tapered. (n=16)	Cyclosporine-related AE more in group 2. Other AE similar incidence.	No significant difference between groups for time required to control activity, remissions, total corticosteroid given, and frequency of relapse.	Cyclosporine is ineffective as an adjuvant to corticosteroids in treatment of pemphigus.	1a: i 1b: N 2: Y 3: Y 4: N 5: N 6: N 7: Y 8: Y
Chrysomallis *et al*. 1994	Oral PV. Single center, Greece.	Group 1: 40 mg/d prednisolone equivalent (n=10) Group 2: 40 mg/d prednisolone equivalent and 100 mg/d cyclophosphamide (n=10) Group 3: 40 mg/d prednisolone equivalent and cyclosporine 5 mg/ kg/d (n=8) Treatment continued till 50% healing, then first steroid then adjuvants tapered.	Cyclosporine-related AE significantly more in group 3 vs other groups. Other AE similar among groups.	Time to achieve remission (mean 28, 24, 25 days, respectively) and relapse rates (2, 1, 2, respectively) not significantly different.	Moderate doses of steroids alone are effective in controlling oral pemphigus.	1a: iii 1b: N 2: Y 3: N 4: N 5: N 6: N 7: Y 8: Y

Articles are presented in order of their publication, with the latest article mentioned first, *Table 1, AE: Adverse events, IVIG: Intravenous immunoglobulin, MMF: Mycophenolate mofetil, NA: Not applicable, PF: Pemphigus foliaceus, PV: Pemphigus vulgaris, DP: Dexamethasone pulse

Table 5: Number of articles on bullous pemphigoid selected at different stages of the review

Database	PubMed	Cochrane central register of controlled trials
References identified	89	43
Articles selected after first-stage screening	11 (one conference abstract later published as article included as article only)	13 (2 conference abstracts later published as articles included as articles only, 11 in PubMed search, 2 unique)
Full-texts obtained	8*	2
Articles selected after second-stage screening	7	0

*Full-texts of one Chinese[16] and two French articles[17,18] unobtainable

refractory erosions or crusts after blisters; noninfectious blisters or erosions of visible mucosa including oral mucosa; Nikolsky sign)
2. Histologic findings (intraepidermal blisters caused by acantholysis).
3. Immunologic findings (IgG or complement deposition in the intercellular spaces of the lesional or normal-appearing skin and mucosa detected by direct immunofluorescence antibody assay; antidesmoglein antibody identified by indirect fluorescent antibody assay or ELISA).

In the immunologic findings, indirect immunofluorescence test for detecting IgG in patient's serum which binds the cell surface of normal keratinocytes may also be added. Scientifically, one would require a set of diagnostic criteria for which sensitivity and specificity have been worked out.

Assessment of the quality of the RCTs is a key step in a systematic review. Several quality scales have been developed for this purpose. In the present review, quality assessment was done using the Delphi list [Table 1], which is a criteria list for quality assessment of RCTs specially for conducting systematic reviews.[1] This list consists of eight items and item one was further elaborated for quality assessment in this review. The first item of the original Delphi list is as follows: Treatment allocation (a) was a method of randomization performed? (b) was the treatment allocation concealed? Item 1a was expanded to give three possible responses: (i) Correct randomization method described, (ii) Inadequate randomization method described, and (iii) Randomization stated, but method not described. This expansion provided a clearer picture about the randomization procedure. Treatment allocation concealment, which is considered to be the most important indicator of quality of a trial, was understood to have taken place only when there was a clear statement about it or when there was a statement which meant that treatment to be allocated was not known before the patient was entered into the study. Quality appraisal of RCTs is sometimes done to produce a quality score and a threshold score may be used for inclusion of RCTs in a systematic review. However, as there may be differences of opinion among the reviewers with regard to the relative importance of different items of quality, in the present review detailed data about different quality items of all selected articles was presented [Table 4].

The Cochrane Collaboration publishes high-quality systematic reviews. Its review on interventions for pemphigus vulgaris and pemphigus foliaceus[26] describes 11 RCTs, using a different search strategy. Eight of these RCTs were identified in the present review also; four articles identified in the present review[4-7] are not included in the Cochrane review. On the other hand, three articles[27-29] included in the Cochrane review were not identified in the database search for this review. These articles described the use of glucocorticoid alone versus glucocorticoid plus a traditional Chinese medicine,[27] low (0.5 mg/kg/day) versus high (1.0 mg/kg/day) initial doses of prednisolone,[28] and oral prednisolone versus oral prednisolone and plasma exchange.[29] All these studies had serious methodological problems and the effects of study interventions were considered inconclusive.[26]

Following general conclusions may be drawn about the evidence-based treatment of pemphigus from the present review:

1. Number of RCTs conducted on pemphigus is small. Common important shortcomings of these RCTs are: absence of blinding, no mention of treatment allocation concealment, and small sample size.
2. The diseases included in these RCTs are pemphigus vulgaris and pemphigus foliaceus.
3. Oral glucocorticoid along with a steroid-sparing agent appears to be the most effective treatment (two RCTs).[4,9]

Table 6: Summary and quality appraisal of the identified randomized controlled trials of interventions in bullous pemphigoid

Reference	Patients/ Centers/ Country	Interventions	Adverse events	Efficacy	Conclusions	Quality appraisal (the Delphi list)*
Joly *et al*. 2009	Moderate and extensive BP. Multicenter, France.	Standard regimen: CP 40 g/day, tapered over 12 months. (n=153) Mild regimen: CP 10-30 g/day tapered over 4 months. (n=159)	Mild regimen caused fewer treatment AE and a twofold reduction of risk of death or life-threatening treatment side effects in moderate BP. High rate of treatment AE in study mainly due to very old age of many patients and due to severe disease and poor general condition. Many deaths.	Disease control at day 21 (absence of new bullae for 3 consecutive days) similar (standard vs mild, 100% vs 98%). Mean time to achieve control similar. Strong beneficial effect of mild regimen observed in moderate BP. Slightly higher relapse rate with mild regimen (43% vs 35%). Mild regimen allowed 70% reduction in total CS dose.	Overall, mild regimen of topical CS as effective as the standard high dose topical CS regimen.	1a: i 1b: N 2: Similar for number of daily new bullae; mild regimen patients older, somewhat lower Karnofsky score. 3: Y 4: N 5: N 6: N 7: Y 8: Y
Beissert *et al*. 2007	BP. Multicenter, Germany.	Group 1: 0.5 mg/kg/d methylprednisolone and azathioprine 2 mg/kg/d. (n=38) Group 2: 0.5 mg/kg/d methylprednisolone and MMF 1000 mg/d. (n=35) First CS tapered and stopped then azathioprine or MMF.	Azathioprine caused significantly elevated liver function tests vs MMF.	Remission similar (Groups 1 vs 2, 92% vs 100%). Time to complete healing similar. Cumulative CS doses similar.	Adjuvant azathioprine and MMF are similarly effective for BP. MMF showed significantly less liver toxicity.	1a: i 1b: N 2: U 3: Y 4: N 5: N 6: N 7: Y 8: Y
Joly *et al*. 2002	Moderate and extensive BP. Multicenter, France.	Group 1: Oral prednisone 0.5 (moderate disease) or 1 mg/kg/d (extensive disease) (n=170). This dose continued for 15 days after disease control, then reduced by 15% every 3 weeks. Group 2: Topical CP daily dose 40g applied twice daily on entire body surface (n=171). This dose continued until 15 days after disease control, then 20 g daily for 1 month, 10 g daily for 2 months, 10 g every other day for 4 months, and 10 g twice a week for 4 months. Duration: 1 year.	No life-threatening AE with topical, oral 7 patients. Extensive disease: Severe AE less with topical, 29% vs 54%, (*P*=0.006). Moderate disease: Severe AE similar. 107 patients died. No difference in survival in moderate disease. Significantly longer survival in extensive disease with topical.	Primary endpoint: overall survival. Extensive disease: Overall survival significantly longer with topical CS (*P*=0.02). One year survival 76% vs oral 58% (*P*=0.009). Control at 3 weeks superior with topical, 99% vs 91%, (*P*=0.02). Moderate disease: No difference.	Topical CS therapy is effective for both moderate and extensive disease and is superior to oral CS for extensive disease.	1a: i 1b: N 2: Y 3: Y 4. N 5. N 6. N 7. Y 8. Y

Contd...

Table 6: Contd...

Reference	Patients/ Centers/ Country	Interventions	Adverse events	Efficacy	Conclusions	Quality appraisal (the Delphi list)*
Fivenson *et al*. 1994	Limited and extensive BP. Two centers, US.	Group 1: Nicotinamide 500 mg tid and tetracycline 500 mg qid (n=14) Group 2: Prednisone 40 to 80mg/day. (n=6) Fixed doses for 8 weeks, then medications tapered based on response.	Treatment-related AE in both groups. Less AE in group 1. 5/6 patients in group 2 major complications, 1 death due to sepsis.	At 8 weeks: 5 complete responses, 5 partial responses, 1 no response, 1 worsening in group 1. (2 drop-outs) 1 complete response, 5 partial responses in group 2. No difference.	Combination of nicotinamide and tetracycline appears to be a useful alternative to systemic steroids.	1a: iii 1b: N 2: U 3: Y 4: N 5: N 6: N 7: N 8: N
Guillaume *et al*. 1993	BP. Multicenter, France.	Group 1: Prednisolone 1 mg/ kg/d. (n=32) Group 2: Prednisolone 1mg/ kg/d and azathioprine 1 mg/kg/day. (n=36) Group 3: Prednisolone 1 mg/ kg/d and 4 large volume plasma exchanges. (n=32) In all groups, prednisolone tapered after 28 days.	Severe complications more common in group 2. 14 deaths, no difference among groups.	Complete remission similar at 28 days (71%, 80%, 71%, respectively), and 6 months (42%, 39%, 29%, respectively).	Neither azathioprine nor plasma exchange is effective enough to be used as an adjunct to corticosteroids.	1a: i 1b: Y 2: Y 3: Y 4: N 5: N 6: N 7: Y 8: Y
Roujeau *et al*. 1984	BP. Multicenter, France.	Group 1: Prednisolone 0.3 mg/ kg/d, later increased if necessary. (n=15) Group 2: Prednisolone 0.3 mg/ kg/d, later increased if necessary and 8 large volume plasma exchanges in 4 weeks. (n=22)	CS-related AE not reduced by plasma exchange. Group 2 patients had minor plasma exchange-related AE.	Cumulative dose for disease control and daily effective dose of CS significantly less in group 2.	Plasma exchange had a steroid sparing effect. However, considering cost and possible serious AE, cannot be recommended routinely.	1a: i 1b: N 2: Y 3: Y 4: N 5: N 6: N 7: Y 8: Y
Burton *et al*. 1978	BP. Single center, UK.	Group 1: Prednisone 30–80 mg/d, tapered. Group 2: Prednisone 30-80mg/d, tapered and azathioprine 2.5mg/kg/d, tapered after prednisone was stopped Initial no. not mentioned. 25 patients (13 group 1, 12 group 2) completed 3 years follow-up.	2 of 4 deaths in group 1 probably related to prednisone. 3 deaths in group 2 unrelated to treatment. AE due to azathioprine minimal.	Cumulative prednisone dose significantly less by about 45% in group 2 vs group 1 (P<0.01). Remission with no treatment: 3 patients group 1, 7 group 2.	Azathioprine plus prednisone is superior to prednisone alone.	1a: ii 1b: Y 2: U 3: Y 4: N 5: N 6: N 7: N 8: N

Articles are presented in order of their publication, with the latest article mentioned first, *Table 1, AE: Adverse events, BP: Bullous pemphigoid, CP: 0.05% clobetasol propionate cream, CS: Corticosteroid, MMF: Mycophenolate mofetil

4. Most effective steroid-sparing drug appears to be azathioprine (one RCT).[9]
5. Mycophenolate mofetil (MMF) may have similar (one RCT)[11] or less (one RCT)[9] steroid-sparing effect and similar safety profile compared to azathioprine (two RCTs)[9,11] or mild steroid-sparing effect (one RCT).[4]
6. There appears to be no benefit of adding dexamethasone pulse therapy to treatment with prednisolone and azathioprine (one RCT).[12]
7. Dexamethasone and cyclophosphamide pulse therapy as tested may be similar in efficacy to methylprednisolone and azathioprine regimen (one RCT).[13]
8. Intravenous immunoglobulin (IVIg) may have moderate effect as an adjuvant (one RCT)[7] or alone (one RCT)[6] on treatment-resistant pemphigus.
9. There may be a trend to some efficacy of dapsone as a steroid-sparing drug in maintenance phase pemphigus vulgaris (one RCT).[8]
10. Moderate doses of glucocorticoids without other immunosuppressive agent may be effective in controlling oral pemphigus (one RCT).[15]
11. Epidermal growth factor may reduce healing time of skin lesions in pemphigus vulgaris (one RCT).[10]
12. Cyclosporine may be ineffective as a steroid-sparing agent (one RCT).[14]

In view of the foregoing discussion, following suggestions may be made about future research on treatment of pemphigus:

1. Selection of patients for RCTs may preferably be based on uniform diagnostic criteria.
2. Selection criteria may preferably include severity assessment of the disease. Also, validated severity scale will help in assessing response to treatment. Two proposed scales, autoimmune bullous skin disorder intensity score (ABSIS)[30] and pemphigus disease area index (PDAI),[31] have recently been compared[32] for inter- and intra-rater reliability.
3. In an RCT, patients with one type of pemphigus may only be preferably included.
4. RCTs are required to compare the efficacy and safety of different doses of glucocorticoids used with different steroid-sparing agents.
5. Long-term follow-up of patients included in RCTs is important to find out relapse rate after remission with different treatments.
6. The issue of maintenance therapy to prevent relapse after remission may also preferably be addressed.
7. Effect of different treatments on the quality of life of patients with pemphigus may also be studied.

Bullous pemphigoid

In the second-stage screening, initially the first test in the second criteria was kept as follows: (i) positive direct immunofluorescence test for C3 and/or IgG on the epidermal roof of salt-split skin. This was done so that the patients with bullous pemphigoid are differentiated from those with EBA. But it was found that none of the articles in the second-stage screening met any of the criteria (ii), (iii), or (iv) and in only one article[20] the diagnosis was made by detection of autoantibody deposition at the blister roof on salt-split skin. Therefore, as a compromise, the wordings of the first test were changed to "positive direct immunofluorescence test for C3 and/or IgG at the dermoepidermal junction." It is to be clarified that in six[19,21-25] of the seven RCTs, which were selected for final analysis based on this criteria, the possibility of inadvertent inclusion of some patients with EBA cannot be ruled out.

This brings us to a situation similar to pemphigus. There are no uniform diagnostic criteria available for making diagnosis of bullous pemphigoid, which are used for individual patients and for their inclusion in clinical studies. It is important to have clear-cut diagnostic criteria for bullous pemphigoid, which include at least one positive immunological test from the following four tests: (i) positive direct immunofluorescence test for C3 and/or IgG on the epidermal roof of salt-split skin, (ii) serum IgG labeling epidermal roof by indirect immunofluorescence, (iii) detection of antibodies against BP180 and/or BP230 antigens, or (iv) demonstration by immunoelectron microscopy of deposition of IgG associated with basal cell hemidesmosomes.

Cochrane systematic review on interventions for bullous pemphigoid describes 10 RCTs.[33] The three extra articles in the Cochrane review were identified in search of databases for the present review also. One article was in Chinese[16] and the other two in French[17,18] and their full texts were unobtainable. These studies compared prednisolone alone versus prednisolone plus a Chinese medicine,[16] methylprednisolone versus prednisolone,[17] and higher versus lower doses of prednisolone.[18] All the three studies had important methodological problems and the results did not show statistically significant differences in any study.[33]

Following general conclusions may be drawn about the evidence-based treatment of bullous pemphigoid from the present review:

Table 7: Summary and quality appraisal of the additionally identified randomized controlled trial of interventions in pemphigus vulgaris

Reference	Patients/Centers/ Country	Interventions	Adverse events	Efficacy	Conclusions	Quality appraisal
Fiorentino *et al*. 2011	PV. Number of centers not mentioned. Authors from US and Canada.	Group 1: etanercept 50 mg subcutaneously once weekly. (n=6) Group 2: placebo. (n=2) Duration: 16 weeks. Patients were on immunosuppressive therapy at baseline, which was apparently continued.	Group 1: two drop-outs (1 PV flare, 1 hip fracture). No serious AE or laboratory abnormalities.	Primary end point (50% reduction in lesion number) 1 in Group 1, 2 in Group 2.	Results do not support previous case reports of uniformly effective results with etanercept. Small sample size precludes definitive conclusions.	1a: iii 1b: N 2. U 3. Y 4. Y 5. U 6. Y 7. Y 8. N

1. Number of RCTs conducted on bullous pemphigoid is small. None of the studies identified in this review were blinded and in only a few studies treatment allocation was concealed.
2. Topical corticosteroid therapy is effective for both moderate and extensive disease and appears to be superior to oral corticosteroid for extensive disease (one RCT).[21] Low doses of topical corticosteroid may also be effective (one RCT).[19]
3. Adding azathioprine to oral corticosteroid may (one RCT)[25] or may not (one RCT)[23] be superior to oral corticosteroid alone.
4. Adding plasma exchange to oral corticosteroid may (one RCT)[24] or may not (one RCT)[23] be superior to oral corticosteroid alone.
5. Adjuvant azathioprine and MMF may be similarly effective. MMF may have significantly less liver toxicity (one RCT).[20]
6. Combination of nicotinamide and tetracycline appears to be a useful alternative to systemic steroids (one RCT).[22]

In the light of the foregoing discussion, following suggestions may be made regarding future research on treatment of bullous pemphigoid:

1. Selection of patients for RCTs may preferably be based on uniform diagnostic criteria, which also enable exclusion of patients with EBA.
2. Selection criteria may preferably include severity assessment of the disease. Acceptable severity assessment scale may preferably be developed.
3. More RCTs are required to confirm the promising efficacy of different doses of topical corticosteroid therapy versus oral corticosteroid therapy.
4. Different doses of oral corticosteroids may be evaluated in RCTs to find out the safest effective dose.
5. RCTs are required to find out effective steroid-sparing agents with favorable toxicity profile.
6. Efficacy of combination of nicotinamide and tetracycline may be studied as a useful alternative to systemic corticosteroids.
7. Long-term follow-up of patients included in RCTs is important to find out relapse rate after remission with different treatments.
8. The issue of maintenance therapy to prevent relapse after remission may also preferably be addressed.
9. Effect of different treatments on the quality of life of patients with bullous pemphigoid may also be studied.

At the final proof reading stage, repeat search on June 10, 2011 found 3 new articles on pemphigus vulgaris in PubMed and Cochrane Central Register of Controlled Trials each. Two articles were same in both databases. Only one article[34] passed through the second-stage screening [Table 7]. One new article on bullous pemphigoid found in PubMed was excluded in first-stage screening. No new articles were found on other diseases.

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