Review of Systemic Treatment for Pemphigus

Supervisor: Assoc. Prof. Vesta Kucinskiene, MD, PhD

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Summary of Thesis:

Review of Systemic treatment of pemphigus

Ibrahim Almafreji

Aim: To conduct a systematic review of treatment for pemphigus in adults.

Objectives:

- To determine the most effective treatment regimens for pemphigus.
- To give an up-to-date coverage on newer therapies of pemphigus

Methods: The Medline (PubMed), the Cochrane Central Register of Controlled Trials (CENTRAL), Wiley Online Library and Science Direct databases were searched electronically for studies published in last thirty years for any treatment modality for Pemphigus Vulgaris (PV) and Pemphigus Foliaceus (PF). The PRISMA guidelines were followed to carry out this review. Quality was assessed according to the CONSORT statement.

Results: A total of 17 RCTs was identified from 120 abstracts obtained from 4 electronic databases. Interventions analysed included prednisolone, dexamethasone, azathioprine, mycophenolate mofetil, methotrexate, dapsone, cyclosporine, cyclophosphamide, rituximab and IV immunoglobulin. There was a lack of uniformity in outcome measures, some treatment types had superior outcomes, but it could not be concluded which was the most effective.

Conclusions: Current evidence is incomplete and inconclusive. The interventions which appear promising, but will require further evaluation include adjuvant azathioprine, mycophenolate mofetil, rituximab, intravenous immunoglobulin, methotrexate. Interventions with inconclusive effects requiring further evaluation include prednisolone dosage, pulsed dexamethasone, cyclophosphamide, cyclosporine, dapsone, infliximab.
Abbreviations:

1. - CENTRAL: Cochrane Central Register for Controlled Trials
2. - PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
3. - CONSORT: Consolidated Standards of Reporting Trials
4. - RCT: Randomized Controlled Trial
5. - AZT: Azathioprine
6. - MMF: Mycophenolate mofetil
7. - IVIG: Intravenous Immunoglobulin
8. - DCP: Dexamethasone Cyclophosphamide Pulse therapy
9. - DSG-3: Desmoglein 3
10. - DSG-1: Desmoglein 1
11. - PV: Pemphigus vulgaris
12. - PF: Pemphigus foliaceus
13. - ITT: Intention To Treat analysis
14. - TCA: Treatment completed analysis
15. - PVDAI: Pemphigus Vulgaris Disease Area Index
16. - PDAI: Pemphigus Disease Area Index
17. - MTX: Methotrexate
18. - CPT: Cyclophosphamide Pulse Therapy
19. - TEP: Time to Escape Protocol
20. - IFX: Infliximab
21. - ELISA: Enzyme-Linked Immunosorbent Assay
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Conflict of interest

The author declares no conflicts of interest.

Terms

Acantholysis: loss of keratinocyte to keratinocyte adhesion caused by binding of circulating autoantibodies.

Intention to treat analysis: ITT analysis means all patients who were enrolled and randomly allocated to treatment are included in the analysis and are analysed in the groups to which they were randomized.
**Introduction**

Pemphigus is a scarce lethal disorder that presents with mucosal erosions and/or flaccid bullae, erosions, or pustules on skin. Acantholysis is a characteristic feature of pemphigus. This process culminates in the formation of intraepithelial blisters in mucous membranes and skin [1-3]. The circulating autoantibodies, usually of the IgG class (to a lesser extent IgA), are directed against desmosomal glycoproteins present on the cell surface of the keratinocyte [4]. Desmoglein-3 (DSG-3) is one of the particular protein targets belonging to the desmosomal cadherine family. Desmoglein-1 (DSG-1) is present in all the layers of the epidermis, whereas DSG-3 is present in the basal and spinous layers.

The four main groups of the pemphigus include PV, PF, IgA pemphigus, and paraneoplastic pemphigus [5].

1) **PV**: Affects oral mucosa initially, then cutaneous. Autoantibodies against DSG-3 or both DSG-1 and DSG-3 [4].

2) **PF**: Involves the skin only. Autoantibodies against DSG-1 [4].

3) **IgA pemphigus**: Grouped vesicles or pustules and erythematous plaques with crusts, subcorneal or intraepidermal acantholytic blisters, autoantibodies against desmocollin 1 in subcorneal pustular dermatosis-type IgA pemphigus [6-9].

4) **Paraneoplastic pemphigus**: Extensive, intractable stomatitis and variable cutaneous findings; associated neoplastic disease and suprabasal acantholytic blisters with autoantibodies against desmoplakins or other desmosomal antigens.

The initial manifestation of the disease is seen in the oral mucosa in nearly 60% of cases and 80-90% of patients with PV present with oral lesions some stage during the disease. It is common for the oral lesions to be present up to 4 months before the appearance of skin lesions. If treatment is started within the 4 month period, the disease can be managed easier, and there is an increased chance of early remission. The lesions of PV can appear on any mucosal surface, however they most often affect the oral mucosa [10].

The treatment of autoimmune bullous diseases consists of a few phases: early observation points of disease activity is the baseline. Baseline is defined as the day that treatment is commenced by a physician. Endpoints define control of disease activity, the end of the consolidation phase, and remission [11].
Early Endpoints: Control of disease activity (disease control) is defined as the period of time from baseline to the time at which new lesions stop forming and established lesions start to heal. This is also known as the consolidation phase. Disease control is expected to be controlled within a number of weeks [11].

The End of the consolidation phase is defined as the time at which no new lesions have been formed for a minimum period of 2 weeks and most (approximately 80%) of the established lesions have healed. It is at this point that most clinicians begin to taper corticosteroid doses.

Late endpoints: Late endpoints of disease activity are identified as (1) complete remission off therapy and (2) complete remission on therapy, both of which only apply to patients who have had no new or established lesions for at least 2 months [11].

The primary aim in the therapy of pemphigus is to control the disease, prevent relapses, and avoid side effects affiliated with prolonged steroid use. Systemic corticosteroids are the primary agents of choice. Usually, steroid therapy is long-term and therefore results in severe adverse events. Adjuvants such as AZT and MMF are the main choices of steroid-sparing treatment. Rituximab is effective in refractory pemphigus, when other treatments are unsuccessful in controlling the disease. These newer agents, such as rituximab, are CD20 antibodies and may provide months of disease relief and reduce the need for the use of prednisolone.

Doses vary depending on the type of drug used, risk of adverse effects and treatment phase. This remains one of the main problems of pemphigus therapy. The optimal dose for steroid therapy and the regimen of adjuvant therapy is not conclusive. A few options are available in case of relapse; the steroid dose can be changed to a previous higher dose, immunosuppressants can be added if the patient is on steroid monotherapy, or if the patient is already combination therapy then the first-line immunosuppressant can be replaced with another [12].

Overall, there is a scarcity in high quality RCTs, partially due to the lack of previous validated outcome measures. Due to the majority of obtained data being limited to case reports and small case series, it is more difficult to assess the effectiveness of most treatments other than that of those using systemic steroids. This paper aims to evaluate and provide an updated review on the interventions for the treatment of pemphigus.
**Aim:** To conduct a systematic review of treatment for pemphigus in adults.

**Objectives:**

- To determine the most effective treatment regimens for pemphigus.
- To give an up-to-date coverage on newer therapies of pemphigus

**Materials and Methods**

The Medline (PubMed) and the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE databases were searched for studies of any treatment modality for the various types of pemphigus (vulgaris, foliaceus, IgA). Paraneoplastic pemphigus was not included in this review because of its different etiology, prognosis and treatment.

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.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [47] were followed in order to carry out this systematic review.

**Search strategy**

1. **PubMed:** This was searched for the phrases "pemphigus treatment," and phrases which combined 'Pemphigus' with words such as "Prednisolone", “Azathioprine”, “Mycophenolate mofetil”, “Methotrexate”, “Dapsone”, “Pulse Therapy”, "Rituximab," and "New Developments" 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."

3. The same search for the above diseases was performed separately in "Title, Abstract, or Keywords." In Science Direct and Wiley Online Library.
The quality of the studies were assessed according to the CONSORT (Consolidated Standards of Reporting Trials) statement [48]. The checklist includes method of randomization, allocation concealment, blinding, follow-up and statistical analysis.

The search was first performed on April 8 2017 and was repeated on December 18 2017; both searches resulted in almost identical references.

First-stage and Second-stage searches

During the first-stage of searching abstracts of all the articles identified in the above-mentioned databases were read.

Abstracts selected for second-stage screening were required to meet the following criteria; (a) P.V or P.F, (b) Treatment of pemphigus in adults, and (c) One or more of the following treatment modalities: prednisolone, dexamethasone, AZT, MMF, MTX, dapsone, cyclophosphamide, cyclosporine, IFX, rituximab or IVIG.

Furthermore, the studies cited in the articles were also scanned to find any more published research suitable for this review.

This was performed on the full-text articles that met the screening criteria, with the most appropriate selected for data extraction. Only patients with pemphigus diagnosed based on clinical features, histopathology and immunofluorescence studies were included.

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.

Evaluation of heterogeneity

Clinical heterogeneity was evaluated by checking study participants and regimens of interventions, including doses, route and tapering schedule. Methodological heterogeneity was assessed by inspecting methods of randomization, blinding, loss to follow-up and allocation concealment.
**Selection of articles:**

**Study flow chart.** Figure showing the manner in which this research was done to obtain final articles.

Total citations extracted from:
- PubMed,
- Cochrane,
- Science direct,
- Reference lists.
(n=120)

Excluded (n=62):
- Duplicates (6),
- Non-randomized controlled trials or ineligible study population (56)

Potentially relevant full-text articles (n=58)

Full-text articles excluded (37):
- Non-randomized controlled trials,
- Adjuvant agent not included in the predefined list,
- Articles older than 10 years old,
LITERATURE REVIEW

First-line therapy

1. Systemic Glucocorticoids

The use of systemic glucocorticoids is essential in pemphigus treatment due to their effectiveness in rapidly controlling the disease within a matter a weeks [13]. Despite this, two main problems remain associated with their use; first- the numerous adverse effects associated with their long-term use and the large dosages required to reach disease control. The second drawback is the necessity for an optimal systemic glucocorticoid regimen.

In a randomized open-label trial in which 30 patients with PV were treated with prednisolone alone (2 mg/kg per day), 23 of these patients (77 %) responded to treatment, with the average time to cessation of blistering was 18 days [14].

There were a few variations in which glucocorticoid therapy is administered. The most common approach consists of treatment with around 1 to 1.5 mg/kg per day of prednisone or prednisolone [15].

The initial prednisolone doses of low (45–60 mg daily) versus high (120–180 mg daily) was evaluated in one study involving only 22 participants [16]. Patients were followed up for 5 years. The study was inconclusive in determining the effect of varying prednisolone dose; being limited by its small sample size and lack of important outcome measures such as cumulative prednisolone dose. This is important as the long-term complications of glucocorticoids are most likely to be reflective of the cumulative dose rather than the initial starting dose [17].

Most clinicians, initiate therapy with doses ranging from 1 to 1.5 mg/kg per day. If the clinical response is inadequate, a quick increase in dose up to a maximum of 2 mg/kg per day is considered [18].

In most patients treated with glucocorticoid therapy, cessation of blistering occurred within 2-3 weeks and complete disease control is established within 6-8 weeks [18]. Once the disease activity is under control, glucocorticoid tapering should begin, with the goal of reaching the lowest dose needed to keep the disease under control. The ultimate goal is to withdraw all treatment.

The best way to taper glucocorticoids in patients with pemphigus has not been found.
Dexamethasone pulsed therapy (300 mg over 3 days, monthly) combined with the standard therapy of prednisolone and AZT, versus conventional therapy alone, was assessed in one study involving 20 participants [19]. The patients were followed up for 1 year. The effectiveness of dexamethasone pulsed therapy could not be determined in the study. In addition, the dexamethasone group experienced more side effects related to the high dosage of glucocorticoid.

**Adjuvant therapies**

Although systemic glucocorticoids are the mainstay of pemphigus treatment, the use of nonsteroidal immunomodulatory agents as adjuvant therapies has risen due to the risk of serious adverse effects related to prolonged, high-dose systemic glucocorticoid therapy [13].

AZT and MMF are two of the most common adjuvant agents used in the initial management of pemphigus. Based upon the available evidence, the major benefit of adjuvant therapy appears to be a glucocorticoid-sparing effect rather than a direct disease-modifying effect [20].

2. Azathioprine

Immunomodulatory agents such as AZT, have been considered as maintenance therapies for PV. Their steroid-sparing effects allow the reduction of cumulative systemic glucocorticoid used. The most effective systemic non-steroidal immunomodulatory agent is yet to be determined. AZT is a purine synthesis inhibitor initially used in organ transplantation, and now also as a first-line adjuvant therapy in PV.

2.1 Azathioprine Versus Glucocorticoid Alone

AZT (2.5 mg/kg daily) with prednisolone was compared to prednisolone alone, adjuvant cyclophosphamide and MMF in a 4-regimen study involving 120 participants altogether by Chams-Davatchi et al. [14]. The follow-up period was 1 year. The study showed that AZT has a steroid-sparing effect compared with prednisolone alone in 57 participants. No conclusive differences were found in all other reported outcome measures, including adverse events. The main limitation was the short follow-up period.

In another study involving 56 participants by Chams-Davatchi et al., adjuvant AZT (2.5 mg/kg daily) was compared to prednisolone alone [21]. The follow-up period was 1 year. The study demonstrated no conclusive differences in the individual visit PVDAI scores.
between the adjuvant AZT and the prednisolone alone group. Similarly, the cumulative glucocorticoid dose and the mean daily prednisolone dose showed no conclusive differences between the groups in the first 9 months, but favoured the AZT group in the last 3 months by ITT analysis and TCA analysis. The study’s conclusion was that AZT’s steroid-sparing effect was significant when used over a 1 year period, but inconclusive in the first 9 months.

Subsequently, a validation study of the PVDAI was conducted, finding that the PDAI was superior to it. [22,23].

2.2 Azathioprine Versus Other Immunomodulatory Agents

In the 4-regimen study by Chams-Davatchi et al. [14], AZT’s produced a greater steroid-sparing effect than MMF in 57 participants. The steroid-sparing effect of AZT was not significantly different to that of cyclophosphamide in 51 participants. No conclusive differences were found in all other reported outcome measures.

3. Mycophenolate Mofetil

MMF is an immunosuppressant frequently used for organ transplantation as well as dermatological diseases such as psoriasis and connective-tissue disorders. It is also a common adjuvant immunomodulatory agent for pemphigus.

3.1 Mycophenolate Mofetil Versus Glucocorticoid Alone

MMF versus glucocorticoid alone was analyzed in 2 studies [14, 24]. A randomized open-label trial was conducted on 120 patients with PV. Those given prednisolone (2 mg/kg per day up to a maximum of 120 mg per day followed by a taper) and MMF (2 g per day) presented with a lower average total dose of prednisolone than those treated with prednisolone alone after 1 year (9798 versus 11,631 mg, respectively)[14]. There wasn’t a significant difference in the rate of complete remission observed between the 2 groups (70 vs 77 %, respectively).

Another RCT of 94 patients with PV compared a treatment using oral prednisone (initial dose 1 to 2 mg/kg per day followed by a taper) plus MMF (2 or 3 g per day), with oral prednisone given plus a placebo pill. A significant difference wasn’t found in terms of response [25]. A significantly lower amount of total prednisone was consumed over the period of a year in the MMF group than those in the placebo group (3220 versus 4450 mg, respectively). Furthermore, relapse was considerably more delayed in the MMF group; 22 % of MMF-
treated patients versus 45% of placebo-treated patients relapsed by 24 weeks after an initial response. A quicker response was also noticed in the MMF group (24 vs 31 weeks to initial response). The follow-up period was 52 weeks.

3.2 Mycophenolate Mofetil Versus Other Immunomodulatory Agents

Chams-Davatchi et al. found that the steroid-sparing effect of MMF was lower to that of AZT in 57 participants, but inconclusive when compared with cyclophosphamide in 54 participants [14].

3.3 Low Dose Versus High Dose

According to Beissert et al., the effect of low/standard dose (2 g daily) versus high dose (3 g daily) MMF was ambiguous in his study of 96 participants [24].

4. Dapsone

Dapsone is an anti-inflammatory drug which has been used as a maintenance therapy in PV. Dapsone is utilized less due to the lack of literature on its use in comparison to AZT and MMF. Nevertheless, some physicians administer dapsone as adjuvant therapy in patients with pemphigus, especially for those with PF or IgA pemphigus, due to reports of efficacy in some patients and the positive results of dapsone as a nonimmunosuppressive therapy [25-27].

Adjuvant dapsone (50 mg daily) versus prednisolone alone was compared in a multicentre American study involving 19 participants [25]. The study assessed if tapering of steroids in relapsing PV patients was possible. The follow-up period was 1 year. Outcome measures including remission and drug safety demonstrated an inconclusive effect of dapsone. The small sample size and few outcome measures were the main trial’s main limitations.

5. Methotrexate (MTX)

MTX is an immunosuppressive drug that has been shown to be effective in autoimmune and chronic inflammatory diseases, mainly rheumatoid arthritis and psoriasis, but also ulcerative colitis and atopic dermatitis. Even though MTX is thought to be steroid sparing, evidence to support this idea was only found in a few early reports. The effectiveness of MTX as an adjuvant has not been analysed in a randomized trial. Data can only be obtained from uncontrolled studies and case series to support this drug [28].

S.Baum et al. carried out a retrospective study to analyse MTX as an adjuvant therapy in 30 patients with PV, which proposes that MTX is both effective and safe as an adjuvant
therapy[28]. Statistical analysis (paired t-test) demonstrated a considerable improvement in severity score at the six months of MTX treatment. While 22 patients improved on MTX treatment, 3 patients had a worsened disease state and 5 were stable. Patient follow-up was continued between 6 months and 2.5 years. 11 of the 30 patients were still taking the MTX treatment at the conclusion of this study. Four patients (13.3%) stopped the treatment because of remission in their disease or its lack of efficacy. The study is limited by the small patient sample and the absence of a placebo control group being used.

6. Cyclosporine

Cyclosporine has been reported to be somewhat effective in a case series of patients with pemphigus [29]. However, 1 randomized trial did not indicate an advantage of cyclosporine therapy [30].

Cyclosporine has been used in PV after other adjuvant immunomodulatory agents failed. Ioannides et al. [30] compared the efficacy and the adverse effects of 2 different regimens for the treatment of pemphigus: prednisolone alone compared with a treatment combination of corticosteroids and cyclosporine in a study involving 33 participants; 29 of them suffered from PV and 4 from PF.

The follow-up period was approximately 60 months. The study revealed the effect of cyclosporine was inconclusive in all outcome measures. It was both ineffective as an adjuvant therapy for pemphigus and less safe to use, having a higher incidence of adverse effects compared to prednisolone treatment alone.

**Management of refractory pemphigus**

Even though many patients with PV or PF (around 60 to 80 %) can achieve at least initial improvement with first-line therapies, other patients do not to respond or suffer frequent relapses whilst on these therapies. The first course of action for those who fail initial therapy is to optimize the dose of the systemic glucocorticoid (up to a maximum of 1.5 to 2 mg/kg per day of prednisone) and adjuvant agent, or to change the adjuvant therapy to a different first-line agent (e.g. change from AZT to MMF or the other way around). If a sufficient response continues to be unattained, other therapies are then initiated.

The main treatment options for a refractory disease include interventions that directly target the antibody-mediated pathogenesis of pemphigus (rituximab, IVIG and immunoadsorption) and cyclophosphamide; a drug that may be used as an alternative adjuvant
immunosuppressant. Concern for the high cost of rituximab, IVIG and immunoadsorption and the adverse effect profile of cyclophosphamide (eg, sterility, cytopenia, hemorrhagic cystitis) is the main reason why these methods are used for refractory pemphigus and not new-onset disease. [31]

Patients with pemphigus, including those that fail to respond to first-line regimens, may benefit may benefit from the therapies used for refractory disease. Treatments for refractory pemphigus may also aid patients with contraindications to initial therapies or who cannot tolerate initial treatments .[31]

7. Cyclophosphamide

Cyclophosphamide is an alkylating agent which selectively affects B-lymphocytes and antibody production while sparing haematopoietic cells. Cyclophosphamide has been used in a variety of autoimmune disorders including PV. Treatment regimens that include cyclophosphamide may be useful for inducing remission in pemphigus and reducing dependence on systemic glucocorticoids.

7.1 Cyclophosphamide Versus Glucocorticoid Alone

Cyclophosphamide versus glucocorticoid alone was evaluated in 3 studies [14, 32, 33]. Adjuvant oral cyclophosphamide (100 mg daily) was compared with prednisolone alone as well as adjuvant cyclosporine in a study involving 28 participants by Chrysomallis et al. [32]. The follow-up period was 5 years. Outcome measures including time until remission, number of relapses and incidence of complications demonstrated that the effect of cyclophosphamide was inconclusive when compared with prednisolone alone in 20 participants.

Adjuvant intravenous cyclophosphamide pulse therapy (CPT) (15 mg/kg monthly) versus prednisolone alone was analysed in a study involving 60 participants [35]. Patients were followed up for 1 year. Outcome measures including times until initial response/remission/relapse, remission and relapse rates, cumulative steroid doses and adverse events demonstrated that the effect of CPT was inconclusive.

Chams-Davatchi et al. [14] compared adjuvant CPT (1 g monthly for 6 months, then 1 g every 2 months) against prednisolone alone, AZT and MMF separately. Within a study involving 54 participants, the effect of CPT could not be concluded when compared with prednisolone alone.
7.2 Methylprednisolone Cyclophosphamide Pulse Therapy

There have been favorable results demonstrated in some patients in uncontrolled studies which are evaluating the effects of treatment regimens with cyclophosphamide specifically on patients with refractory pemphigus [34].

In a retrospective study, 21 patients with pemphigus refractory to prednisolone plus AZT or MTX (18 PV, 2 PF, 1 paraneoplastic pemphigus) were treated with 4-22 pulses of intravenous methylprednisolone (1 g per day for 3 consecutive days) together with 500 mg of intravenous cyclophosphamide on the second day of treatment [34]. Patients were given oral cyclophosphamide (50 mg per day) and prednisolone between the monthly pulse treatments. Continuation of adjuvant therapy with other immunosuppressants (mycophenolate mofetil and/or methotrexate) was allowed.

There was a statistically significant decrease in skin and oral disease scores after therapy. The median number of pulses given to patients who achieved an excellent response was 12 (ranging from 6-19). Moreover, 4 patients with excellent responses achieved clinical remissions (defined as complete resolution of blisters and erosions for at least 6 months) that lasted for 6 months to 6 years.

8. Intravenous Immunoglobulin (IVIG)

IVIG in high doses has been proven to be effective for various autoimmune conditions. It was also found to be promising in treatment of PV, with expanding interest in the last few years.

An 85-day multicenter, randomized, placebo-controlled, double-blind trial in 61 adults was done to analyse the effect of a single cycle of high-dose IVIG (400, 200, or 0 mg per kg per day) given over 5 consecutive days in patients relatively resistant to systemic steroids.[35] The follow-up period was 2 years. TEP was utilized as an efficacy indicator. It provided flexibility for physicians to rescue patients when needed and proved to be useful in evaluating efficacy of a single cycle of high dose IVIG in a double-blind comparison design.

The TEP was found to be significantly longer for patients in the 400 mg IVIG group compared with those in the placebo group [35], demonstrating the beneficial effect of the 400 mg dose of IVIG. There wasn’t a statistically significant discrepancy in the TEP for the 200 mg IVIG group and the placebo group. In addition, the pemphigus activity score was significantly lower at all study observation points for participants in the 400 mg IVIG group.
and at all study observation points after day 15 in the 200 mg IVIG group. There wasn’t a significant decrease in pemphigus activity score at any point in the placebo group.

There were a few limitations: prednisolone at 20 mg/d or more may not be high enough to define steroid resistance, limited number of patients.

Arnold et al. carried out a ‘n-of-1’ placebo-controlled crossover trial. It showed a beneficial effect of IVIG in therapy of refractory pemphigus [36]. However, the study was limited by its sample size of 1 and the lack of a validated outcome measure such as ABSIS, PDAI. This study's result need to be confirmed in a larger, multi-centre RCT with adequate follow up.

Several uncontrolled studies and case series provide additional support for the use of IVIG for refractory pemphigus [37-39]. In most of the series, patients received IVIG at a dose of 2 g/kg/cycle consisting of two to four consecutive treatment days, and IVIG cycles were repeated in 4-6 week intervals. In some studies, clinical improvement following IVIG has been found to correlate with decreasing titers of desmoglein-specific IgG autoantibodies [37,39].

9. Tacrolimus

Tacrolimus possesses similar but more potent immunosuppressant features compared with cyclosporine and is a novel macrocyclic lactone immunosuppressant. It inhibits cell mediated and humoral immune responses [40].

L. Dastgheib et al. carried out a RCT to assess the adjuvant effect of tacrolimus in the management of PV. Each patient was followed up and evaluated for 6 months. About 23 patients received prednisolone and AZT, and 23 patients prednisolone and tacrolimus. The restrictions include the study not being blinded, and that the titres of DSG-3 antibodies and thiopurine methyltransferase enzyme were not determined. The 6-month follow up could be extended in future studies with larger populations being included for a better conclusion [41].

10. Tumor Necrosis factor-a inhibitor

TNF-α has been shown to play a role in the pathogenesis of PV. Case reports have shown IFX to be beneficial in the treatment of PV.

10.1 Infliximab (IFX)

A double-blind, placebo-controlled trial of IFX with prednisone versus prednisone alone was conducted to determine if blockade of TNF-α would be a safe and effective treatment for
patients with PV. [42] The follow-up period was 26 weeks. IFX therapy was not shown to be beneficial in the treatment of patients with PV, inspite of trends suggesting some patients may derive benefit from this treatment approach. The small sample size of subjects was the main limitation of this study. The study was unable to evaluate efficacy endpoints despite very large differences between treatment and placebo groups.

11. Monoclonal antibody against the CD20 antigen - Rituximab

Rituximab is a monoclonal antibody that acts against the CD20 antigen on B lymphocytes. Reports have shown it to be effective in various autoimmune diseases, including autoimmune bullous dermatoses such as pemphigus [43]. The immunological effects of rituximab that contribute to its benefit in pemphigus may be complex; long-lasting B-cell depletion following rituximab treatment may be one significant factor [44]. Additional findings during rituximab therapy that may be involved in the treatment effect include a preferential decline in autoantibodies compared with pathogen-specific antibodies and a decline in autoreactive CD4+ T cells [44].

In the past, rituximab has been primarily used for recalcitrant pemphigus and for pemphigus in patients for whom severe adverse effects or contraindications prevent the use of conventional immunosuppressive therapies. Nevertheless, a prospective, multicentre, parallel-group, open-label, randomised trial in 25 dermatology hospital departments in France indicates that combination therapy with rituximab and prednisone can be an effective initial treatment for pemphigus that permits use of reduced doses of prednisone and is associated with lower rates of serious side effects compared with higher-dose, longer-term prednisone monotherapy. [45] This may be valuable for patients with moderate to severe disease or who are less suitable candidates for high-dose, long-term prednisone therapy.

The most supportive data regarding use of rituximab as an initial treatment for pemphigus comes from this trial. 90 patients with newly diagnosed PV or PF were randomly assigned to either intravenous rituximab (1000 mg on days 1 and 14, then 500 mg at months 12 and 18) plus oral prednisone (0.5 mg/kg per day for moderate disease and 1 mg/kg per day for severe disease) tapered over 3-6 months or prednisone alone (1 mg/kg per day for moderate disease and 1.5 mg/kg per day for severe disease) tapered over 12 to 18 months [45].

At month 24; 41 of 46 patients (89 %) in the rituximab plus prednisone group were in complete remission off therapy compared with 15 of 44 patients (34 %) in the prednisone only group. In addition, the rituximab plus prednisone group had a shorter median delay to
achieve complete remission off therapy (277 versus 677 days) as well as less common severe adverse events compared with the prednisone only group. The trial was limited in that it was not blinded and that the tapering of prednisone doses differed between the two treatment groups.

Both a case report of 17 patients and a multicenter retrospective study of 36 patients have stated that rituximab can be a safe and valuable treatment in the treatment of PV and PF. Additional data is required to define optimal dosing for initial treatment with rituximab and optimal method for use of rituximab in combination with systemic glucocorticoids and other immunosuppressive therapies.

12. Recent developments

There were some recent developments in treatment:

A retrospective study, in 9 patients, showed that a biweekly regimen of immunoabsorption in PV is safe and effective. An 80% decrease in autoantibody concentration was seen after 6 months of therapy and this resulted in clinical improvement of the disease. Steroid consumption was also lowered by 75% after 90 days. [50]

Another retrospective study treated 5 patients with drug resistant pemphigus with double-filtration plasmapheresis. The study exhibited a reduction in autoantibody titers and PDAI, clinical improvement and a reduction in steroid dose. [51]
Results

General Description

A grand total of 120 abstracts were identified from 4 electronic databases (Fig. 1). 58 studies were assessed for eligibility criteria. Altogether 17 RCTs were identified (Fig. 1). The interventions included glucocorticoids (prednisolone dosage, pulsed dexamethasone), AZT, MMF, cyclophosphamide, dexamethasone–cyclophosphamide pulse therapy (DCP), cyclosporine, MTX, dapsone, tumor necrosis factor (TNF)-a antagonists (rituximab, infliximab), IVIG and new modalities that could have a positive effect on pemphigus.

Overall, RCTs evaluating the treatment for PV were limited in numbers and poor in quality. Only 10 out of 17 RCTs had adequate blinding. The duration of follow-up ranged from 2 weeks to 5 years. The sample sizes of included studies were small, ranging from 1-120 participants. The outcome measures had large amounts of variation, ranging from antibody levels to self-designed severity scores. Therefore, the limited number of studies and varied outcome measures precluded meta-analysis of similar interventions.

The interventions which appear promising, but will require further evaluation include adjuvant MMF, AZT, IVIG, IFX, rituximab. Interventions with inconclusive effects requiring further evaluation include prednisolone dosage, pulsed dexamethasone, cyclophosphamide, DCP, cyclosporine, dapsone, MTX.

Outcomes

As mentioned above, there is a large amount of variation in the outcome measures used between different studies. The following criteria were commonly used to assess the results of the studies:

- Number of patient deaths
- Complications/Adverse events
- Number of relapses
- Remission
- Initial disease control
In case of studies analysing adjuvant therapies, there were various methods of assessing their steroid sparing effects. Total amount of corticosteroids taken or mean cumulative steroid dose were used to assess this aspect of treatment, although it was not seen in all studies [32,35,36,42].

One of the critical differences was the variation in assessment of disease activity. ABSIS, PVDAI and PDAI were rarely used [21]. Some studies used their own disease activity scores [24, 28, 36, 41]. Moreover, antibody titres were used as part of the criteria to express therapeutic response in some cases [34, 36, 42, 48].

Finally, complete remission on or off therapy, as well as partial remission, were used as one of the primary outcome measures to assess response [19, 21, 30, 32, 33, 34, 45, 48]. The 2008 consensus statement led to the progression in the assessment of therapeutic outcomes by integrating uniformity into the analysis of treatment responses. Thus improving the ease of which data from clinical trials could be interpreted, leading to further advancements in clinical trials [11].
Table No.1. Studies of the treatments for pemphigus identified in this systematic review

<table>
<thead>
<tr>
<th>First Author</th>
<th>Interventions Compared</th>
<th>Blinding</th>
<th>No. of subjects</th>
<th>Follow-up period</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ratnam (1990) {16}</td>
<td>Low prednisolone dose (45-60mg), High prednisolone dose (120-180 mg)</td>
<td>Not blinded</td>
<td>22</td>
<td>5 years</td>
<td>The effect of the different doses on death, disease control relapse and adverse events was inconclusive.</td>
</tr>
<tr>
<td>Chrysomallis (1994) {32}</td>
<td>Adjuvant oral cyclophosphamide, Adjuvant cyclosporine, Prednisolone alone.</td>
<td>Not blinded</td>
<td>28</td>
<td>5 years</td>
<td>The effect of all interventions on time until remission, relapse and complications was inconclusive.</td>
</tr>
<tr>
<td>Ioannides (2000) {30}</td>
<td>Cyclosporine &amp; Prednisolone</td>
<td>Not blinded</td>
<td>33</td>
<td>~60 months</td>
<td>Cyclosporine was ineffective as an adjuvant therapy of pemphigus. It was also less safe as the incidence of adverse effects was higher in cyclosporine group compared to that with prednisolone alone.</td>
</tr>
<tr>
<td>Mentink (2006) {19}</td>
<td>Adjuvant pulsed dexamethasone, Prednisolone and AZT alone</td>
<td>Double blinded</td>
<td>20</td>
<td>1 year</td>
<td>Dexamethasone group had more adverse events. Its effect on remission, death and relapse were inconclusive.</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention(s)</td>
<td>Trial Design</td>
<td>Duration</td>
<td>Endpoints</td>
<td></td>
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<tr>
<td>Chams-Davatchi (2007) {14}</td>
<td>Adjuvant MMF, Adjuvant CPT, Adjuvant AZT, Prednisolone alone.</td>
<td>Not blinded</td>
<td>120</td>
<td>1 year</td>
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<td></td>
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<td></td>
<td>MMF and AZT had steroid-sparing effects. AZT's steroid sparing effect was superior to MMFs. Cyclophosphamide's steroid sparing effect was inconclusive. The effect of all interventions on other efficacy measures and adverse events were inconclusive.</td>
<td></td>
</tr>
<tr>
<td>Werth (2008) {25}</td>
<td>Adjuvant Dapsone, Prednisolone alone.</td>
<td>Double blinded</td>
<td>19</td>
<td>1 year</td>
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<td></td>
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<td></td>
<td>The effect of dapsone on remission and drug safety was inconclusive.</td>
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<tr>
<td>Arnold (2009) {36}</td>
<td>IVIG, Placebo</td>
<td>Double blinded</td>
<td>1</td>
<td>1 year</td>
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<td></td>
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<td>The IVIG group had lower mean daily prednisolone doses and disease severity scores and lower monthly autoantibodies, Dsg1 and Dsg3 titres.</td>
<td></td>
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<tr>
<td>Amagai (2009) {35}</td>
<td>IVIG (High dose)</td>
<td>Double blinded</td>
<td>61</td>
<td>2 years</td>
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<td></td>
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<td>Disease activity and ELISA scores were significantly lower in the 400 mg group than in the other group. A single cycle of high dose IVIG for 5 days has a therapeutic effect to suppress the disease activity.</td>
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</tr>
<tr>
<td>Study (Year)</td>
<td>Treatment</td>
<td>Blinding</td>
<td>Duration</td>
<td>Outcome</td>
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<td>Saha (2010) [34]</td>
<td>IV Methylprednisolone &amp; IV Cyclophosphamide</td>
<td>Not blinded</td>
<td>21</td>
<td>PPC can be effective treatment in refractory pemphigus. A statistically significant decrease in skin and oral disease scores after therapy.</td>
<td></td>
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<tr>
<td>Beissert (2010) [24]</td>
<td>Adjuvant MMF (2g/day). Adjuvant MMF (3g/day). Prednisolone alone</td>
<td>Double blinded</td>
<td>96 weeks</td>
<td>The MMF group took shorter time to respond (MWD - 6.8 weeks), shorter time to reach a sustained response and longer time until relapse.</td>
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<tr>
<td>Kasperkiewicz (2011) [48]</td>
<td>Rituximab &amp; Prednisolone</td>
<td>Not blinded</td>
<td>25 months</td>
<td>Serum autoantibodies decreased at 3, 6 and 12 months after initiation of rituximab and at the end of follow-up time. 8 of the 17 patients showed a complete remission off therapy.</td>
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<tr>
<td>Baum (2012) [28]</td>
<td>MTX &amp; prednisolone</td>
<td>Not blinded</td>
<td>2-5 years</td>
<td>This series suggests that MTX is both effective and safe as an adjuvant therapy.</td>
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</tr>
<tr>
<td>Sharma (2013) [33]</td>
<td>Adjuvant CPT, Prednisolone alone.</td>
<td>Not blinded</td>
<td>1 year</td>
<td>The effect of CPT on time until response/ remission/ relapse, remission and relapse rates, cumulative steroid doses and adverse events was inconclusive.</td>
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</tr>
<tr>
<td>Study</td>
<td>Treatment</td>
<td>Blinding</td>
<td>Duration</td>
<td>Results</td>
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<tr>
<td>Chams-Davatchi (2013) [21]</td>
<td>Adjuvant AZT, Prednisolone alone</td>
<td>Double blinded</td>
<td>56</td>
<td>The effect of azathioprine on severity score, cumulative glucocorticoid dose and mean daily prednisolone dose was significant in the last 3 months of the 1 year trial. Its effect was inconclusive in the first 9 months of the trial.</td>
<td></td>
</tr>
<tr>
<td>Dastgheib (2014) [41]</td>
<td>Tacrolimus &amp; Prednisolone, AZT &amp; prednisolone</td>
<td>Not blinded</td>
<td>46</td>
<td>Pemphigus activity scores, cumulative steroid dosage, the time corticosteroid was tapered, etc. showed positive results without significant difference compared to AZT.</td>
<td></td>
</tr>
<tr>
<td>Hall (2015) [42]</td>
<td>IFX &amp; Prednisone, Prednisone alone</td>
<td>Double blinded</td>
<td>26 weeks</td>
<td>Infliximab therapy was not shown to be effective</td>
<td></td>
</tr>
<tr>
<td>Joly (2017) [45]</td>
<td>Rituximab &amp; Prednisone, Prednisone alone</td>
<td>Not blinded</td>
<td>90</td>
<td>First-line use of rituximab plus a short prednisone regimen was more effective than prednisone alone for patients with pemphigus on all primary and secondary endpoints.</td>
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</tr>
</tbody>
</table>


**Discussion**

Systemic glucocorticoids are the cornerstone of management of pemphigus. They have been shown to provide a rapid control of the disease. There was no benefit shown between low or high dose therapy[14]. Therefore, an RCT regarding the optimal dose regimen is needed. The effects of dexamethasone pulsed therapy were inconclusive.[16] Prednisone or prednisolone remains the first line treatment for pemphigus.

Patients require prolonged periods of steroid therapy. Consequently, they suffer from side effects of prednisolone therapy overtime, highlighting the need for adjuvant therapy. Several trials have been conducted on a variety of adjuvant agents testing their steroid sparing properties but the optimal agent has not yet been conclusively found. AZT and MMF have shown a beneficial effect in adjuvant treatment. They have decreased cumulative steroid doses and thus lessened the adverse effects of prolonged steroid use. According to Chams-Davatchi’s RCT [17], AZT’s steroid sparing effect was superior to that of MMF. However, additional trials would be useful for clarifying the efficacy of AZT as a glucocorticoid-sparing agent and for comparing this drug with other therapies.

Dapsone showed some efficacy in the maintenance phase in PV but its effects on remission and drug safety were inconclusive [25]. In Ioannides’ study, cyclosporine was ineffective as an adjuvant and was also less safe as cyclosporine produced more adverse events than prednisolone alone.[30] AZT and MMF are recommended above cyclosporine, dapsone or MTX as adjuvant therapy due to their efficacious steroid sparing properties and safety profile.

In terms of refractory pemphigus management, rituximab and IVIG have shown promising results. A single cycle of high-dose IVIG over 5 days showed some benefit in pemphigus resistant to systemic steroids in the form of longer TEP and a decrease in pemphigus activity score in the 400 mg IVIG group.[31] Rituximab was shown to be of some benefit in the treatment of severe pemphigus as 21 (58 %) pemphigus patients showed complete response to rituximab treatment and a decrease in visual analog scale was also observed [49].

There are many case reports and studies showing positive results in pemphigus therapy but without RCTs carried out to clarify their results. Tacrolimus has shown effects that compare to those of AZT[29]. However, it has not yet been determined which agent is more effective in treatment, this can only be concluded upon through further scientific research in the future. A retrospective study carried out by S.Baum showed MTX to be valuable in the treatment of
pemphigus, as demonstrated in its decrease of severity score and prednisolone dosage. This was limited by the fact that its an uncontrolled study and the small sample size.

In addition to those above, cyclophosphamide has received mixed results in its studies. RCTs demonstrated that its effect was inconclusive compared to prednisolone therapy. However, a recent retrospective study evaluating pulsed cyclophosphamide therapy showed that it can be of benefit in refractory pemphigus. In order for the results and conclusions to be conclusive, further clinical trials are required to be carried out with appropriate blinding, sample size, follow-up, common outcome measures and inclusion criteria.

Limitations of this review:

Overall, the evidence from the RCTs and other studies for the treatment of pemphigus is inconclusive and incomplete. There are many treatment modalities that are being used across the world that have not been evaluated in well-designed RCTs- this is one of many limitations of the conducted trials. The samples were also small and insufficient to yield results in many RCTs. Out of the 17 studies analysed, 10 did not have adequate blinding. This is an important factor in determining a study’s quality, as double-blind trials remove the effect of bias and placebo effects, giving more accurate measures in the clinical efficacy and safety of the drugs tested. Therefore this should be one of the aspects to improve on in future RCTs.

Moreover, there was a lack of uniformity in outcome measures, there is no common measure used to evaluate the efficacy of an intervention. For instance, some studies used antibody titres to assess disease severity, others used a variety of self-designed severity scores according to the numbers and sizes of clinical lesions. This variation poses a challenge to conducting a review and evaluating the most effective therapy. Recently, validated outcome measures such as PDAI for disease severity and consensus on disease definitions and end points have been developed. It is hoped that these will be utilized in future RCTs and bring uniformity to outcome measures.

The final limitation was the pooling of data from trials evaluating different adjuvant therapies and trials with varying treatment populations and treatment regimens. Additional trials evaluating adjuvant therapies will be useful for clarifying the impact of adjuvant therapy.
Conclusion:

Corticosteroids, namely prednisolone, alone or combined with a steroid-sparing immunomodulatory agent, such as AZT or MMF, remains the primary therapy for pemphigus. Newer secondary interventions include IVIG and rituximab are used for patients that are resistant to AZT or MMF. However, recent data suggests rituximab may be of use in initial treatment alongside steroid therapy.

The optimal treatment strategy for pemphigus remains unclear. Greater quality RCTs are needed to re-assess several interventions and to discover other unstudied modalities. These RCTs should use methods including adequate blinding, sample size, uniform outcome measures and act on various stages (and if possible types) of pemphigus disease. In order for this to be achieved, multi-centred international collaboration is of utmost importance.
References

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