Management of Pemphigus Vulgaris

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ABSTRACT

Introduction: Pemphigus vulgaris (PV) is a chronic, autoimmune, vesiculobullous disease. As a result of the relative rarity of PV, published randomized controlled trials (RCTs) are limited, which makes it difficult to evaluate the efficacy of different treatment regimens in this disease. This also precludes conduct of a meta-analysis.

Methods: English-language publications describing treatment outcomes of patients with PV were identified by searches of electronic databases through May 2015, and additionally by review of the bibliography of these publications. A total of 89 papers, which included 21 case reports, 47 case series, 8 RCTs, and 13 observational studies, were identified. The findings from these publications, including information on disease course and prognosis, medications used, treatment responses, and side effects, are summarized in the tables and text of this review.

Results: Prior to availability of corticosteroid therapy, PV had a high fatality rate. Early publications from the 1970s reported high-dose, prolonged corticosteroid use and significant associated side effects. Later reports described use of corticosteroids along with steroid-sparing adjuvants, which allows a reduction in the total dose of corticosteroids and a reduction in observed mortality and morbidity. For the majority of patients in these reports, a long-term course on medications lasting about 5–10 years was observed; however, subgroups of patients requiring shorter courses or needing longer-term therapy have also been described. Early diagnosis of PV and early initiation of treatment were prognostic factors. In recent publications, commonly used initial regimens include corticosteroids in combination with mycophenolate or azathioprine; whereas, for patients with inadequate response to these regimens, adjuvants such as intravenous immunoglobulin (IVIg) or rituximab are used.

Conclusion: The review findings emphasize the importance of early diagnosis, early initiation of
treatment, and use of steroid-sparing adjuvants to allow a reduced total dose and duration on corticosteroids. Also highlighted is the need for more RCTs.

**Keywords:** Autoimmune vesiculobullous disease; Azathioprine; Corticosteroids; Methotrexate and IVIg; Mycophenolate mofetil; Pemphigus vulgaris; Rituximab

**INTRODUCTION**

Pemphigus vulgaris (PV) is a chronic, autoimmune, mucocutaneous, vesiculobullous disease [1].

The word pemphigus comes from the Greek word *pemphix*, which means blister [2]. It is a rare disease with estimated worldwide annual incidence of 0.1–0.5 per 100,000 [3]. It occurs in all racial and ethnic groups with the highest incidence seen in Ashkenazi Jews [4]. Occurrence is most common during the fifth and sixth decades of life, although a few cases have been reported in children [5].

In the majority of cases, PV initially presents with lesions on the oral mucosa [3]. Often the first sites affected are those exposed to frictional trauma including the buccal and lateral tongue mucosa along the occlusal level, or the gingiva, but PV can occur on any oral site particularly if exposed to sharp or acidic foods. The lesions start as vesicles which rupture easily leaving erosions and ulcers.

The pathogenesis of pemphigus involves the presence of circulating and tissue-bound autoantibodies to the keratinocyte cell surface desmosomal molecules desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1). Dsg3 and Dsg1 belong to the cadherin superfamily involved in cell–cell adhesion. These autoantibodies cause loss of cell–cell adhesion between epithelial cells, which results in suprabasilar intraepithelial vesicle formation [4, 6].

Diagnostic tests include perilesional mucosal or skin biopsy for histologic examination and direct immunofluorescence testing. Histologic findings include presence of intraepithelial blisters and suprabasilar acantholysis; direct immunofluorescence findings include IgG deposits and less commonly IgM and C3 deposits in intercellular spaces in the epithelium. Blood tests include ELISA testing for Dsg3 and Dsg1 autoantibodies [7].

Prior to availability of corticosteroid therapy in the 1950s, PV had a very high fatality rate. While many treatment options are now available, corticosteroids in combination with other drugs still form the mainstay of treatment. Mortality from pemphigus has decreased significantly in the last half century and is now usually due to adverse effects of the medications used [8, 9].

As a result of the relative rarity of pemphigus, there are very few randomized controlled trials. However, numerous observational studies, case reports, and case series have been published that report on the treatment of pemphigus. The objective of this review was to summarize the findings from all of the reported human studies including observational studies and case reports.

**METHODS**

Publications relating to treatment of PV were identified by searches of electronic databases including PubMed, Cochrane, and Google Scholar through May 2015. Keywords used included pemphigus vulgaris, autoimmune vesiculobullous disease, corticosteroids, azathioprine, rituximab, mycophenolate mofetil, methotrexate, and IVIg. The full-text
versions of the papers identified were obtained. The bibliography of these papers was also reviewed to identify any additional papers that did not appear in the electronic search. Only English-language papers describing treatment outcomes of patients with PV were included in this review. A total of 89 papers, which included 21 case reports, 47 case series, 8 RCTs, and 13 observational studies, were included. These papers were reviewed to obtain information on publication date, type of study done, age of the patients, extent of lesion involvement (skin and mucosa), previous treatments if any, medications used, duration of use of previous medications before new ones were started, duration to first improvement after the start of medications, follow-up duration, concomitant medication used along with main drug, outcome, duration on medication, adverse effects of drugs, and antibody titer changes after treatment. This information is summarized in Tables 1, 2, 3, 4, 5 and 6.

Definitions for some of the terms relating to treatment outcomes listed in the tables are described in a consensus statement published in 2008 [10] as follows:

Complete remission off therapy: Absence of new and/or established lesions while the patient is off all systemic therapy for at least 2 months.

Complete remission on therapy: Absence of new or established lesions while the patient is receiving minimal therapy.

Minimal therapy: Less than, or equal to, 10 mg/day of prednisone (or the equivalent) and/or minimal adjuvant therapy for at least 2 months.

Minimal adjuvant therapy: Half of the dose required to be defined as treatment failure.

Failure of therapy: Failure to control disease activity (i.e., relapse/flare) with full therapeutic doses of systemic treatments.

Partial remission off therapy: Presence of transient new lesions that heal within 1 week without treatment and while the patient is off all systemic therapy for at least 2 months.

Partial remission on minimal therapy: Presence of transient new lesions that heal within 1 week while the patient is receiving minimal therapy, including topical steroids [10].

However not all papers included in this review have described their specific definition for these terms. If these terms were mentioned in the publication, we have listed them in the tables as mentioned in the publication.

This article is based on previously conducted studies and does not involve any studies of human or animal subjects performed by any of the authors.

RESULTS

Corticosteroids (CS)

Since the time of their approval in the 1950s, corticosteroids have been the mainstay of treatment of PV.

Mechanism of Action

Corticosteroids have strong anti-inflammatory and immunosuppressive effects. They affect almost every aspect of the immune system. They are potent inhibitors of NFκB activation and have effects on leukocyte movement, leukocyte function, and humoral factors. In addition they have inhibitory effects on many known cytokines [11].

The first case series on corticosteroid use in PV was published in 1972.

The publications reporting use of corticosteroids in PV are summarized in Table 1. This table includes papers that had systemic corticosteroids as the primary
| Author/year | Type of study  | N M/F | Age at the beginning of follow-up period (years) | Type of pemphigus vulgaris | Previous Rx | Duration of disease symptoms before CS were started | CS dose |
|-------------|----------------|-------|--------------------------------------------------|---------------------------|------------|---------------------------------------------------|---------|
| Ryan [40]/1972 | Case series | N = 41 M/F = 23/18 | 26–80 | Mucocutaneous | NM | NM | 500–1000 mg cortisone equivalents |
| Berger et al. [41]/1973 | Case report | 1/M | 3.5 | Oral mucosal lesions | NM | NM | Prednisone = 15–120 mg/day |
| Rosenberg et al. [42]/1976 | Case series | N = 85 PV + 5 P vegetans | 14–88 | Oral mucosa = 80, Skin = 52 | NM | NM | Prednisone = 60–180 mg/day |
| Lozada, Silvermann, Cram [14]/1982 | Case series | N = 6 M/F = 3/3 | 24–89 | Mucocutaneous = 6 | Pred | NM | Prednisone = 40–80 mg/day |
| Lever and Schaumburg-Lever et al. [12,13]/1984 | Case series | N = 84 | 20–79/mean = 51 | Mucocutaneous | NM | NM | Prednisone = 40–350 mg/day |
| Aberer et al. [43]/1986 | Case series | N = 29 M/F = 12/17 | At onset of disease—mean 59.9 ± 9.0 years | Mucocutaneous | Pred, MTX | NM | Prednisone = 80–200 mg/day |
| Seidenbaum et al. [44]/1988 | Case series | N = 88 PV + 27 (PF, PE, P vegetans) M/F = 46/69 | 40–60 | Oral mucosa = 50; Cutaneous = 33; Mucocutaneous = 32 | NM | NM | Prednisone = 60–120 mg/day |
| David et al. [15]/1988 | Case series | N = 4 M/F = 2/2 | 11–17 | Mucocutaneous = 3, Oral mucosa = 1 | NM | NM | Prednisone = 60–80 mg/day |
| Laskaris and Stoufi [45]/1990 | Case report | 1/F | 6 | Extensive oral mucosal lesions | None as no diagnosis was made when symptoms were first noted at age of 2 | 4 | Prednisolone = 30 mg/day for 3 weeks. Prednisolone maintained to 10 mg/day every other day after clinical improvement |
| Lamey et al. [16]/1992 | Case series | N = 30 M/F = 10/20 | 24–68/ Mean = 48.1 | Cutaneous = 4; Mucosal = 26 (Oral mucosa = 25) | NM | 2–9 mo (Mean = 35 mo) | Prednisone = 20–120 mg/day in 29 pts. No Rx in 1 pt |
| Author/year | Type of study | N/M/F | Age at the beginning of follow-up period Range/mean (years) | Type of pemphigus vulgaris | Previous Rx | Duration of disease symptoms before CS were started | CS dose |
|-------------|---------------|-------|-------------------------------------------------------------|-----------------------------|-------------|-------------------------------------------------|---------|
| Werth [46]/1996 | Retrospective case controlled study | N = 15 M/F = 10/5 | 28–72 | Mucosal = 6; Cutaneous = 1; Mucocutaneous = 8 | None | Mean. Control grp = 3.1 ± 1.2 mo; Pulsed grp = 4.1 ± 1.0 mo | Control grp (N = 6); Pulsed grp (N = 9). Methylprednisolone sodium succinate pulse Pred = 95 ± 22.5 mg Pred before pulse = 82 ± 15.8, after pulse = 78 ± 7.6 mg/d. Pulse dose = 250–1000 mg/24 h |
| Robinson et al. [47]/1997 | Case series | N = 12 M/F = 3/9 | 3–66/ Mean = 32 | Oral mucosa = 12, Cutaneous = 7 | NM | NM (Newly diagnosed pts) | Prednisone = 10–80 mg/day |
| Kaur and Kanwar et al. [17]/1990 | Case series | N = 45 PV + 5 PF M/F = 24/21 | 15–55 | NM | NM | 3 mo to 5 years | Dexamethasone = 136 mg dissolved in 5 % dextrose given by a slow iv drip over 1–2 h and repeated on 3 consecutive days |
| Mignogna et al. [48]/1999 | Retrospective analysis | N = 16 M/F = 5/11 | 26–76/ Mean = 51 | Oral mucosa = 16, Cutaneous = 6 | NM | 1–3 mo (Mean = 55 days) | Deflazacort = 120 mg/daily |
| Scully et al. [49]/1999 | Case series | N = 32. Additional 23 pts referred to dermatology and with limited available data M/F = 22/23 | 16–83/ Mean = 50.2 | Mucosal = 55, cutaneous lesions later developed = 13 | NM | 3–192 weeks (Mean = 27.2 weeks) from 42 patients with available data | Prednisolone = 20–80 mg/day |
| Herbst and Bystryn et al. [29]/2000 | Case series | N = 40 M/F = 15/25 | 14–73/ Mean = 51 | Mucocutaneous | NM | NM | Prednisone = 15–90 mg/day |
| Kanwar et al. [18]/2002 | Retrospective analysis | N = 32 | 21–75/ Mean = 49 | Mucocutaneous = 27; Mucosal = 1; Cutaneous = 4 | NM | NM | 136 mg iv Dexamethasone for 3 consecutive days (2–8 pulses required for PR) and (8–32 pulses required for CR) + 500 mg CycIP on day 2 |
| Ljubojevic et al. [50]/2002 | Retrospective analysis | N = 154 M/F = 57/97 | 19–89/ Mean = 53 | Mucocutaneous | NM | >5 years | Prednisone = 100–150 mg daily for first 4–6 weeks. Then gradually tapered to maintenance dose of 5–20 mg. In 14 pts with refractory PV LM, gold given up to 50 mg per week |
Table 1 continued

| Author/year | Type of study | N/M/F | Age at the beginning of follow-up period | Type of pemphigus vulgaris | Previous Rx | Duration of disease symptoms before CS were started | CS dose |
|-------------|---------------|-------|-----------------------------------------|---------------------------|-------------|-----------------------------------------------|---------|
| Femiano et al. [51]/2002 | Case series | N = 20 |
| | | M/F = 8/12 |
| | | 35–57/Mean = 43 |
| | | Mucocutaneous |
| | | NM |
| | | NM |
| | | Oral Pred (N = 10) |
| | | 125 mg/day to 5 mg once a week for 1 mo |
| | | Oral Pred alternated with iv betamethasone (N = 10) |
| | | Pred 50 mg/day to 5 mg/d once a week for 1 week/20 mg/d iv to 8 mg/d iv for 4 days |
| Robinson et al. [32]/2004 | Case report | 1/M |
| | | 47 |
| | | Oral lesions |
| | | NM |
| | | 3 mo |
| | | Prednisolone = 1 mg/kg/day (80 mg); topical 0.1 % triamcinolone acetonide |
| Chams davatchi et al. [38]/2005 | Case series | N = 1111 M/F = 492/717 |
| | | 4–82/Mean = 42 |
| | | Mucocutaneous = 782; Mucosal = 200; Cutaneous = 129; Oral cavity involved in 978 pts |
| | | None |
| | | NM |
| | | Prednisone dose NM |
| Alonso et al. [33]/2005 | Case series | N = 14 |
| | | M/F = 4/10 |
| | | 21–87 |
| | | Oral mucosa = 9; Mucocutaneous = 5 |
| | | 0.75–72 mo (Mean = 11.66 mo) |
| | | 0.5 % Triamcinolone corticosteroids + 60 mg/day systemic Pred in 12 pts for 1 mo/Intralesional corticoid infiltration (parametasone) in 1 pt every 15 days during 45 days of therapy |
| Ben lagha et al. [31]/2005 | Case report | 1/F |
| | | 71 |
| | | Mucocutaneous |
| | | NM |
| | | 4 mo |
| | | Prednisone = 0.5 mg/kg/d; 20–40 mg/day |
| Ariyawardana et al. [5]/2005 | Case report | 1/F |
| | | 14 |
| | | Oral mucosal lesions |
| | | None |
| | | 10 days |
| | | Systemic Prednisolone = 10 mg/day; 0.1 % triamcinolone acetonide in orabase twice a day maintenance dose for 3 mo |
| Yazganoglu et al. [39]/2006 | Case series | N = 5 |
| | | M/F = 3/2 |
| | | 7–15 years |
| | | Mucocutaneous |
| | | NM |
| | | NM |
| | | Prednisolone = 1–2 mg/kg/day |
| Mentink et al. [19]/2006 | Randomized controlled trial | N = 20 |
| | | M/F = 13/7 |
| | | 26–71/Mean = 49 |
| | | Mucocutaneous |
| | | Systemic and topical CS, AZA, antibiotics |
| | | NM |
| | | DP (Dexamethasone pulse therapy) (N = 11) |
| | | Oral dexamethasone in 300 mg pulses 3 days/mo, 5/4 pulse courses |
| | | PP (placebo pulse therapy) (N = 9) |
| | | 6 Placebo tablets 3 days/mo, 6.4 pulse courses |
| Chaidemenos et al. [52]/2007 | Prospective cohort study | N = 74 |
| | | Studied = 68 |
| | | M/F = 21/47 |
| | | 24–83 years |
| | | Oral mucosa = 68; cutaneous = 33; genital and nasal lesions = 14 |
| | | NM |
| | | 0.15–18 mo/mean = 3.6 mo |
| | | Prednisone = 40 mg/day |
| Author/year | Type of study | NM/F | Age at the beginning of follow-up period | Type of pemphigus vulgaris | Previous Rx | Duration of disease symptoms before CS were started | CS dose |
|-------------|--------------|------|------------------------------------------|---------------------------|-------------|-----------------------------------------------|---------|
| Chams davatchi et al. [53]/2007 | Randomized controlled open label trial | N = 120 M/ F = 71/40 | Mean = 40 years | Mucocutaneous = 74; mucosal = 29; cutaneous = 8. Oral cavity involved in 76 pts | None | 3–12 mo/1 year | Mean total dose (P = Prednisolone) |
| Dagistan et al. [30]/2008 | Case report | 1/F | 35 | Oral lesions | Sultamisilin, flurbiprofen | 2 mo | Prednisolone = 80 mg/day initially for 14 days and increased to 100 mg for a period of 14 days |
| Tran et al. [54]/2013 | Retrospective chart | N = 23 M/F = 11/12 | 26–72/Mean = 54 | Mucosal = 19, cutaneous = 4 | Pred, AZA, MMF, dapsone, Rtx, IVlg, etanercept, chloroquine | 2 mo to 10 years (Mean = 23 mo) | Prednisone = 35 mg/daily (mean dose) |
| Mignogna et al. [55]/2010 | Case series | N = 35 M/F = 13/22 | 17–72/Mean = 45 | Oral pharyngeal | NM | NM | Total CS + immunosuppressive therapy + PITA injections (N = 16) |

4894 mg (75–100 mg/day) + 2–8 sessions of PITA injections
Total CS + Immunosuppressive therapy only (N = 19)
5312 mg (75–100 mg/day)
| Author/year | Duration to initial improvement in symptoms after CS  | Follow up period | Concomitant Rx | Outcome | Duration on medication (corticosteroid) and adjuncts | PV antibody titer changes after Rx | Adverse effects |
|-------------|-----------------------------------------------------|-----------------|----------------|---------|--------------------------------------------------|-----------------------------------|----------------|
| Ryan [40]/1972 | NM | Variable F/U periods, maximum = 20 years | MTX, Mechlorethamine hydrochloride | Death = 24 pts; CR off = 5 which lasted for 2–156 mo before relapse; 11 pts were on long term medication with occasional flares; Lost to follow-up = 1 | 1–18 years | NM | Cushingoid features, furuncles, hyperkalemia, osteoporosis, melena, purpura, hypocalcemia, acidosis, electrolyte imbalance, phlebitis |
| Berger et al. [41]/1973 | NM | 7.5 years | None | Patient was treated with prednisone intermittently during the F/U period. Controlled activity of disease at the last F/U visit | 6.5 years | IIF was positive intercellularly at 1:10 before and after treatment | Cushingoid, retarded bone age, osteoporosis of long bone |
| Rosenberg et al. [42]/1976 | NM | 1 to >15 years | AZA or MTX in 3 pts | Death related to PV or drug = 28; Death unrelated to PV = 9 | 48 survivors. Many d/c therapy and fewer required 15 mg of Pred | NM | Cushingoid symptoms, infections, GI tract ulceration, CHF, HTN, Diabetes, Osteoporosis, thromboembolic phenomenon, etc |
| Lozada, Silvermann, Cram [14]/1982 | 2–8 weeks | 9–27 months | Levamisole = 100–200 mg/week | Symptoms of pain resolved = 6, PR (oral lesions) = 3, PR (skin lesions) = 2, CR (oral lesions) = 3, CR (skin lesions) = 4 | 1.5–13 years | NM | Chills, malaise which disappeared on d/c levamisole and did not recur on restart |
| Lever and Schaumburg-Lever et al. [12, 13]/1984 | NM | 5–22 years | AZA, MTX in 3 pts which was replaced by AZA | Death = 15; still being treated = 11; CR off = 47; CR on = 11 | 5 months to 8 years in CR off pts | NM | No significant |
| Author/year | Duration to initial improvement in symptoms after CS | Follow up period | Concomitant Rx | Outcome | Duration on medication (corticosteroide) and adjunct* | PV antibody titer changes after Rx | Adverse effects |
|-------------|-------------------------------------------------------|------------------|----------------|---------|---------------------------------------------------|-----------------------------------|----------------|
| Aberer et al. [43]/1986 | NM | 4–16 years (29 Pts) | AZA = 2–3 mg/kg body weight | Still being treated = 5; CR on = 11 pts, mean duration of Pred use before taper to low dose was 6 months (10 mg QOD); CR off = 13 pts, mean duration of F/U after d/c of medication was 4 years without relapse | AZA tapered to 1–2 mg/kg in 6 months. Pred and AZA D/c in 13 pts after maintenance therapy from 6 months to several years. Mean duration of therapy = 6.9 ± 3.8 years | Antibody titers before treatment were >160 monitored by IIF. After treatment: Negative in 13 CR off pts. >80 in 6 pts despite good clinical response | Leukopenia, herpes simplex, bacterial infection |
| Seidenbaum et al. [44]/1988 | NM | 4–24 years | AZA 100–150 mg/day | Death = 25 (11 PV); Still treated = 45, CR on = 10, CR off = 35 | NM | NM | NM |
| David et al. [15]/1988 | 1 months | 4–19 years | None | CR on = 1, mean duration of Pred use before taper to low dose was 4 years after 2 relapses. CR off = 1 within 1 year of medication, mean duration of F/U after d/c of medication was 6 years without relapse. CR off = 1 within 1 mo of medication, mean duration of F/U after d/c of medication was 4 years without relapse. (PR = 1 on homeopathy, did not take Pred) | Rs d/c in 2 pts after CR in 1 mo and 1 year after gradually tapering Pred | NM | NM |
| Laskaris and Stoufi [45]/1990 | NM | Lost to follow up after 2 years | None | Clinical improvement | 2 years until last F/U. Pred tapered and maintained to 10 mg/day from 30 mg/day | NM | NM |
| Lamy et al. [16]/1992 | 4–8 weeks | 5–20 years | AZA, Cyd in 3 pts. Gold in diabetes mellitus pt | CR on = 27 within 4–8 weeks of start of therapy. Pred tapered to 10 mg/day or on alternate days in other patients | NM | NM | Diabetes mellitus, HTN, duodenal ulcers |
| Author/year                  | Duration to initial improvement in symptoms after CS | Follow up period | Concomitant Rx                                                                 | Outcome                                                                 | Duration on medication (corticosteroid) and adjunct$^a$ | PV antibody titer changes after Rx | Adverse effects                                                                 |
|-----------------------------|------------------------------------------------------|------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------|----------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------|
| Werth [46]/1996             | NM                                                   | At least 500 days| AZA, MTX, CycP, Dapsone, Gold                                                  | Pulsed grp: Improvement = 6, CR off = 4 within mean 269 days of start of therapy and mean duration of f/u after d/c of medication was 714 days without any relapses Control grp: No remission in any 6 pts | NM                                                       | NM                               | Well tolerated. Transient increase in blood glucose levels treated successfully with insulin |
| Robinson et al. [47]/1997   | NM                                                   | 8–11 years (Mean = 4.5) | AZA, levamisole, cyclosporine, MTX, dapsone, topical dexamethasone, fluocinonide, clobetasol, clotrimazole | PR on = 3; CR on = 9, within 1.5–42 mo of start of therapy                                                                 | All pts were on medication at the end of f/u | NM                               | Cushingoid symptoms, Infections, GI upset, weight gain, fatigue, mood changes, constipation, osteoporosis, diabetes, insomnia, acute psychosis |
| Kaur and Kanwar et al. [17]/1990 | 3–4 days                                             | 2 years          | CyclP 500 mg added to dexamethasone and 50 mg orally each day, Pred (30–40 mg) in 7 pts | Still being treated = 28; death due to sepsis = 3 pts; lost to F/U = 13; no improvement & hence Rx changed = 6 | All pts were on medication at the end of f/u | NM                               | Cardiac arrhythmia in 1 pt and Ischemic heart disease in 1 pt                   |
| Mignogna et al. [48]/1999   | NM                                                   | NM               | AZA = 50–100 mg/d or CycP = 50 mg daily                                       | PR within 2–8 weeks of start of therapy = 14, CR off = 2                                                             | 1–8 years                                               | NM                               | Cushingoid symptoms, Infections, GI upset, weight gain, fatigue, mood changes, constipation, diabetes, osteoporosis, insomnia, psychosis |
| Scully et al. [49]/1999     | NM                                                   | At least 3 months | AZA (1–3 mg/kg/day), MTX, CycP, dapsone                                       | Death = 2. Relapses and still being treated at time of publication = 21. PR on = 4, CR off = 5 pts within 3 mo of start of therapy. (NM whether on or off of therapy) | NM                                                       | NM                               | Lethargy, cushingoid faces, adrenal suppression, candidiasis, HTN               |
| Herbst and Bystryn et al. [29]/2000 | 2–19/Mean = 7.7 years                                | 2–19/Mean = 7.7 years | AZA, CycP, dapsone, gold, cyclosporine, Pl                                   | Death = 2; PR = 8; CR off = 30, within 18–35 mo of start of therapy                                               | Rx for 2–19 years (mean = 7.7 years)                    | NM                               |                                                                                |
| Author/year | Duration to initial improvement in symptoms after CS | Follow up period | Concomitant Rx | Outcome | Duration on medication (corticosteroid) and adjunct* | PV antibody titer changes after Rx | Adverse effects |
|-------------|---------------------------------|-----------------|----------------|---------|-----------------------------------------------|----------------------------------|----------------|
| Kanwar et al. [18]/2002 | NM 2–12 years (Mean = 4.2) | 50 mg orally each day, Pred | CR off = 32 within 20–32 mo (Mean = 24 mo) of start of therapy | 1 year (Pulse therapy for 6 mo followed by oral CyclP 50 mg orally for 1 year | NM HTN, pulmonary tuberculosis, leucopenia, diarrhea, cataract, oligomenorrhea, sinus bradycardia |
| Ljubojevic et al. [50]/2002 | 19 years | NM AZA (100–150 mg); Pl in 5 pts with NR to AZA and Pred | Death = 14; PR on = 15; CR off = 5, mean duration of f/u after d/c of therapy was 5 mo to 5 years without relapse. Complications due to Pred, Rx d/c = 74, lost to follow up = 46 | NM | NM Sepsis, arterial HTN, cardiorespiratory diseases, skin infections |
| Femiano et al. [51]/2002 | NM NM | 150 mg/d Ranitidine, 1 ml Nystatin suspension bid | Oral Pred | NM | NM Gastritis, hyperglycemia, HTN, increased body weight, mood change, altered Ca and P levels |
| Robinson et al. [32]/2004 | 2 weeks | 8 mo Cimetidine, nystatin, calcium supplements | CR on within 3 mo of start of therapy | Pred tapered over 8 mo to 10 mg/day | NM | None |
| Chams davatchi et al. [38]/2005 | NM | 3.8 years, lost to F/U = 200 MMF/AZA, CyclP/Gold/ Dapsone | Death = 66; Still being treated = 350. Maintenance Rx = 471; CR off = 112 (Nothing else mentioned about duration to achieve remission and duration on medication) | Mean 45 years | NM | Candidiasis, HTN, osteoporosis, abnormal liver function test, infection, diabetes mellitus |
| Alonso et al. [33]/2005 | NM NM | None | Improvement in all pts. Additional details were NM | 45 days | NM | |
| Ben lagha et al. [31]/2005 | NM | 12 mo MTX 10–20 mg/week | CR on within 9 mo of start of therapy. Therapy was stopped at sixth mo after starting Pred and resumed after healing of fracture of femur | Rx contd at dose of 10 mg/d at the end of f/u | NM Stress fracture in neck of femur |
| Ariyawardana et al. [5]/2005 | 1 mo | 12 mo Dapsone 100 mg/day | CR off within 4 mo of starting therapy. No relapses | Systemic Pred. d/c at 1 mo and topical d/c in 3 mo after that | NM | |

* Duration to initial improvement in symptoms after CS is defined as the time it takes for symptoms to improve after the start of corticosteroid therapy. Follow up period is the duration of observation after the initial improvement. Concomitant Rx includes any other medications used in addition to corticosteroids. Outcome describes the response to therapy, including clinical improvement and relapse rates. Duration on medication refers to the time on corticosteroids after remission. PV antibody titers are changes observed in these antibodies after Rx. Adverse effects list the complications associated with corticosteroid use.
Table 1 continued

| Author/year | Duration to initial improvement in symptoms after CS | Follow up period | Concomitant Rx | Outcome | Duration on medication (corticosteroid) and adjunct* | PV antibody titer changes after Rx | Adverse effects |
|-------------|-----------------------------------------------------|------------------|----------------|---------|-----------------------------------------------------|-----------------------------------|-----------------|
| Yazganoglu et al. [39]/2006 | 4 pts were followed for 2–4 years. 1 patient was lost to F/U | MMF in 1 patient, dapsone in 1 patient | Relapses in all 4 cases which were controlled with Pred and MMF in 1 case | Treatment continued in all pts at end of f/u | NM | Cushingoid appearance and acneiform eruption in 2 pts |
| Mentink et al. [19]/2006 | 19 wks in 4 DP and 6 PP pts | AZA = 3 mg/kg/day, Pred = 80 mg/day | CR on = 8 in DP within 17 ± 2 days of starting therapy, CR on = 9 in PP within 17.56 days of starting therapy | Pred tapered to 0 from 80 mg/day over 19 weeks and treatment was given for 1 year | NM | Weight gain, increased blood glucose, wound infection, HTN, candidiasis, myopathy, diarrhea, leukopenia etc |
| Chaidemenos et al. [52]/2007 | 26–180 mo | AZA (100 mg/day) | Death = 2; CR on = 57; mean duration of f/u after d/c of medication was 27 ± 29 mo without relapses; Dropped out = 6; Rx changed = 9 | 2–138 mo. In 6–14 mo Pred tapered at a rate of 5 mg/mo and AZA tapered until 0 in 1 year | NM | Tuberculosis reactivation, toxic hepatitis, bone marrow depression, disturbed WBC counts |
| Chams davatchi et al. [53]/2007 | 1 year | MMF, AZA, CyclP | CR on; failures; complications (Rx d/c) | Duration on Rx = 1 year Tapering of Pred started in mean 17.2 ± 7.2 days until it was reached 7.5 mg/day | NM | Candidiasis, hyperlipidemia, herpes simplex, hyperglycemia, fungal and viral skin infections, gastritis, cataract, psychosis, infections |
| Dagistan et al. [30]/2008 | 1 year | AZA 50 mg twice a day | CR on (Additional details NM) | Pred tapered at end of 7 weeks by 30 mg/day. Treatment lasted for 1 year | NM | Hepatitis C |
| Tran et al. [54]/2013 | Mean MTX = 18.9 (15–25) mg/week | Rx d/c in 2 due to adverse events. Lost to f/u = 4. Still being treated = 4; clinical improvement in 21 pts of which pred d/c in 16 pts. CR off = 3, mean duration of f/u after d/c of medication = 26 mo until end of f/u | Pred d/c in mean 18 mo in 16 pts. In other five patients low dose pred in range of 2–10 mg/day was given. MTX d/c in 3 pts and tapered in 8 pts | NM | Fatigue, GI side effects |
medication used. Topical steroids were also used in many of the reports. In addition, adjuvant drugs were added in most cases. These adjuvants included azathioprine, methotrexate, cyclophosphamide, dapsone, gold, levamisole, cyclosporine, and mycophenolate. Adjuvants were usually administered one at a time; however, they were changed when lack of response was noted, and therefore some patients had multiple adjuvants used sequentially over the period of treatment.

**Publication Type, Patient Profiles, and Sample Sizes**

Seventeen case series were found, with the number of cases included in the individual papers ranging from 4 to 1111 cases (a total of 1704 patients were included in the 17 case series, of which 1681 had PV and 23 had either pemphigus foliaceous, pemphigus vegetans, or pemphigus erythematous). Six case reports describing single patients, one prospective cohort study \((n = 74)\), two randomized controlled trials \((n = 20 \text{ and } n = 120)\), and five retrospective cohort studies \((n = 15, n = 16, n = 23, n = 32, \text{ and } n = 154)\) are summarized in the Table 1. In all, the total number of cases in these 31 publications was 2164 out of which 2141 were PV patients, and the rest had pemphigus foliaceous or pemphigus vegetans or pemphigus erythematosus. These 31 reports originated from the USA, Israel, Iran, Sri Lanka, India, Scotland, Italy, Greece, Spain, the Netherlands, Germany, France, Singapore and Turkey.

Age at initial diagnosis of PV in these publications ranged from 4 to 89 years.

**Medication Use**

Prednisone and prednisolone were the most commonly used corticosteroids. Starting doses
ranged from 15 to 180 mg prednisone equivalent daily in all but one of the reports where doses as high as 400 mg daily were used [12, 13].

**Duration of PV Before Corticosteroids Were Started**
This ranged from 0.15 months to 6 years.

**Duration of Total Follow-up**
Duration of total clinical follow-up of the individual patients ranged from 9 months to 22 years.

**Duration Before Any Clinical Improvement Was Noted**
Seven publications reported on the duration before any clinical improvement after the start of corticosteroids was apparent, and this ranged from 3 days to 19 weeks [14–20].

**Duration to Start of Taper of Corticosteroids**
Information regarding tapering of corticosteroids was reported in seven publications. The duration before the start of taper of corticosteroids ranged from 0.5 to 12 months in these seven publications comprising of 156 patients.

**Duration to Complete Remission (On and Off Therapy)**
Duration to complete remission on therapy was reported in 15 articles, and ranged from 1.5 to 42 months (3.5 years), in 797 patients.

Duration to complete remission off therapy was reported in 15 articles, and ranged from 4 to 120 months (10 years) in 321 patients.

**Remission**
Of a total of 2141 patients reported on in Table 1, at the end of follow-up 97 patients had achieved partial remission on therapy, 797 patients had achieved complete remission on therapy, and 321 patients had achieved complete remission off therapy. A total of 485 patients were still being treated at the time of publication, 156 patients were lost to follow-up, death occurred in 177 patients, and 47 patients were classified as non-responders and referred elsewhere for treatment.

**Duration of Medication Use**
Total duration of medication use for all reported patients including those still on therapy at the time of publication ranged from 1.5 to 240 months (20 years).

**Follow-up Duration After Discontinuation of Medications**
Follow-up ranged from 2 to 156 months (13 years) after discontinuation of treatment in the 321 patients with complete remission off therapy, during which time there was no recurrence.

**Mortality**
Death occurred in a total of 177 of 2141 patients (8.26 %) with PV in all reports. These included deaths from all causes. Of these, the reports published between 1970 and 1980 included 127 patients with 61 deaths (48.03 %), between 1981 and 1990 included 183 patients with 26 deaths (14.2 %), between 1991 and 2000 included 190 patients with 7 deaths (3.6 %), and those published between 2001 and 2010 included 1589 patients with 83 deaths (5.2 %).

**Adverse Effects**
Adverse effects from corticosteroids reported in these papers included Cushingoid symptoms, diabetes mellitus, osteoporosis, hypertension, insomnia, GI upset, increased weight, candidiasis, tuberculosis, mood change, abnormal liver function test, fungal and viral infection, fatigue, acute psychosis,
hyperglycemia, electrolyte imbalance, hypocalcemia, acidosis, hyperkalemia, phlebitis, herpes simplex, hyperlipidemia, bone marrow depression, cataract, and myopathy.

Azathioprine (AZA)

Azathioprine was approved by the US Food and Drug Administration (FDA) in 1968 as an immunosuppressant to prevent organ transplant rejection.

Mechanism of Action
This drug restricts synthesis of DNA, RNA, and proteins by inhibiting metabolism of purine. It also interferes with cellular metabolism and mitosis [8].

Publication Type, Patient Profiles, and Sample Sizes
The studies reporting use of AZA in PV are summarized in Tables 1 and 2. Of the 31 papers in Table 1, 17 had included azathioprine as one of the treatment modalities. Table 2 includes only those publications that reported on comparative analyses of outcomes for patients on prednisone alone vs. those on prednisone in combination with azathioprine. The first case series on use of AZA in PV was published in 1986.

One randomized double blind controlled study (n = 56) and two retrospective cohort studies (n = 48 and n = 36) are summarized in Table 2. In all, a total of 140 patients were included in these three reports.

Age at initial diagnosis of PV in these publications ranged from 16 to 83 years.

Medication Use
The dosage of azathioprine used was 40 mg/day up to 3 mg/kg/day in all reports. Prednisone was used concomitantly with azathioprine in all reports. Azathioprine was added at the onset of treatment in the three reports in Table 2 and sometime after onset of corticosteroid use in the reports in Table 1.

Duration of PV Before Azathioprine Was Started in the Reports Summarized in Table 2
This ranged from 4 to 10 months.

Duration of Follow-up in the Reports Summarized in Table 2
Duration of clinical follow-up of the individual patients on azathioprine in these reports ranged from 12 months to 10 years.

Duration to Complete Remission (On and Off therapy) for the Azathioprine Plus Prednisone Group in Table 2
Duration to complete remission on therapy was reported in three articles and, ranged from 6 to 12 months, in 67 patients.

Duration to complete remission off therapy was reported in two articles and, ranged from 6 to 12 months, in eight patients.

Patients on prednisone and azathioprine had better responses as compared to patients on prednisone alone, with more patients achieving remission, and with fewer side effects.

Remission
Of a total of 140 patients, at the end of follow-up 11 patients had achieved partial remission and mean duration to achieve that was 234.4 days, 67 patients had achieved complete remission on therapy, and eight patients had achieved complete remission off therapy. Six patients were still being treated at the time of publication. No response was seen in 17 patients. Treatment failed in five patients. Death occurred in 13 patients and 13 patients were lost to follow-up.
Table 2 Azathioprine

| Authors/year | Type of study | $N$ | M/F | Age range/ | Type of pemphigus vulgaris | Previous Rx | Duration of disease before AZA | AZA dose, prednisone dose |
|--------------|---------------|-----|-----|------------|----------------------------|-------------|--------------------------------|--------------------------|
| Mourellou et al. [56]/1995 | Retrospective analysis | $N = 48$ | NM | NM | NM | NM | 40–100 mg Pred | >100 mg Pred |
| Chaidemenos et al. [1]/2010 | Retrospective bi center comparative study | $N = 36$ | Mean = 54 | Mucosal | NM | 4 mo | Monotherapy of Pred ($N = 17$) | Alternate day Pred + daily AZA ($N = 19$) |
| Chams-Davatchi et al. [57]/2013 | Randomized double blind controlled study | $N = 56$ | M/F = 23/33 | Mucocutaneous = 33; mucosal = 15; cutaneous = 8 | None | 5–10 mo | Placebo grp (Pred + placebo) | AZA grp (Pred + AZA) |

| Authors/year | Duration to initial improvement of symptoms after AZA | Follow up period | Concomitant Rx | Outcome | Duration on all medications* | PV antibody titer changes after Rx | Adverse effects |
|--------------|---------------------------------|-----------------|---------------|---------|----------------------------|-------------------------------|----------------|
| Mourellou et al. [56]/1995 | Up to 10 years | Pred | CR off = 5; CR on = 22; death = 12, still being treated = 6, lost to follow-up = 3 | Total duration on medications NM. Therapy d/c once patient was in remission for 6 mo | NM | NM |
| Chaidemenos et al. [1]/2010 | 24 mo | Pred | Monotherapy | Alternate day Pred + daily AZA | 24 mo | NM | Weight gain, GI disturbances, hair loss, HTN, arrhythmias, eye disease, internal infection, muscle weakness, redistribution of body fat etc |
| Chams-Davatchi et al. [57]/2013 | 12 mo | Pred | Placebo | AZA | CR on (6–11 months) | 13 | Medications given for 5–22 mo | NM | Abnormal liver function test, sepsis, abnormal CBC |

* Duration on medication included the time period on medication prior to the start of follow-up to this paper.

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Pred prednisone, AZA azathioprine, CR off complete remission off therapy, CR on complete remission on therapy, PR on partial remission on therapy, PR off partial remission off therapy, R relapse, NR no response, F/U follow up, d/c discontinue, mo months, d days, pts patients, NM not mentioned.
| Author/year | Type of study | N  | Age range/mean (years) | Type of pemphigus vulgaris | Previous Rx | Duration of disease before MMF | MMF dose |
|-------------|---------------|----|------------------------|-----------------------------|-------------|-------------------------------|----------|
| Enk and Knop [58]/1999 | Case series | N = 12 | 42–64 | NM | Pred, AZA | 4–8 mo | 2 g/day |
| Grundmann-Kollmann et al. [59]/1999 | Case report | 1/F | 76 | NM | Pred, AZA | 7 years | 2 g/day |
| Grundmann-Kollmann et al. [59]/1999 | Case report | 1/F | 66 | Cutaneous | Pred, AZA | 2 years | 2 g/day |
| Powell et al. [21]/2002 | Case series | N = 12 | 41–78 | Mucocutaneous = 8; mucosal = 4 | AZA, Pred, MTX, CycP, IVIg, dapsone, gold, thalidomide, minocin | 6–168 mo | 750 mg to 3.5 g (Mean = 2.5 g/day) |
| Mimouni et al. [60]/2003 | Case series | N = 31 | 6–74 (Mean = 47.2) | NM | Pred, AZA | NM | 35–45 mg/kg per day |
| S. Beisert et al. [61]/2006 | Multicenter randomized controlled non-blinded clinical trial | N = 33 | Mean = 56.5 | Cutaneous = 39; mucosal = 28 | NM | NM | MMF = 1 g twice daily AZA = 2 mg/kg/d |
| Strowd et al. [62]/2010 | Retrospective chart review | N = 18 | 29–67/52 | Mucocutaneous = 12; mucosal only = 6 | Pred, Pred + MMF in 1 pt only | 1–6 yrs | 2–3 g/day |
| S. Beisert et al. [63]/2010 | Multicenter placebo controlled non-blinded trial | N = 94 | 18–70/45.5 | Mucocutaneous | NM | Mean = 4 mo | Placebo + Pred 36pts MMF2 g/ d + Pred 21 pts MMF3 g/ d + Pred 37 pts |
| Bongiorno et al. [64]/2010 | Case series | N = 9 | 18–75 | NM | Pred + AZA | 14.4 mo | Encrier coated—mycophenolate sodium 1440 mg/day (given in 2 divided doses) |
| Ionnaides et al. [65]/2011 | Randomized prospective non-blinded clinical trial | N = 36 | Mean = 53 | Cutaneous = 47; oral = 24 | NM | Monotherapy = 4.35 mo; combination = 4.04 mo | Pred alone 1 mg/kg Pred + MMF 1 mg/kg + 3 g/day |
| Author/year | Duration to initial improvement in symptoms after MMF | Follow up period | Concomitant Rx | Outcome | Duration on all medication* | PV antibody titer changes after Rx | Adverse effects |
|-------------|--------------------------------------------------------|------------------|----------------|---------|-----------------------------|-----------------------------------|----------------|
| Enk and Knop [58]/1999 | NM | 9–12 mo | Prednisone | CR on = 11 within 2 months of start of therapy; one pt opted out of study | Medication given for 4–20 mo. Pred tapered to median dose of 2.5 mg/day, MMF was contd at last f/u | NM | Mild GI symptoms and mild lymphopenia |
| Grundmann-Kollmann et al. [59]/1999 | 10 days | 8 mo | Prednisone | CR on within 9 weeks of start of therapy | Total duration on medication = 7 years and 8 mo. Pred tapered and stopped after 4 weeks of starting therapy, MMF continued at last f/u | NM | None |
| Grundmann-Kollmann et al. [59]/1999 | 3 weeks | 8 mo | None | CR on within 8 weeks of start of therapy | Total duration on medication = 2 years and 8 mo. MMF continued at last f/u | NM | None |
| Powell et al. [21]/2002 | Within average 15 mo of therapy | 27 mo | Prednisone | Still being treated = 1, flare = 1, opted out = 2, CR on = 4 Controlled = 3, CR off = 1 | Medication given for 6–195 mo. Pred tapered at 12 and 18 mo. MMF d/c in CR off patient at 24 mo | ELISA: Negative in 5 pts and IIF: Negative in 6 pts after Rx. Gradually decreasing in rest other pts with Rx | Lymphopenia, nausea, depression |
| Mimouni et al. [60]/2003 | NM | 6–49 mo (Mean = 22 mo) | Prednisone | Rx failure; 8; PR = 1; CR on = 22 within mean 9 mo of start of therapy | Duration on medication = mean 22 mo (6–49 mo) | Rapid decrease in titers | GI symptoms, cytopenia, musculoskeletal pain |
| S. Beissert et al. [61]/2006 | Within 30 ± 7 days in MMF and AZA grp | 24 mo | Prednisone = 2 mg/kg/daily | MMF grp: NR = 1. CR on = 20 within 91 ± 113 days of start of therapy AZA grp: Rx d/c due to side effects = 2. NR = 2, lost to f/u = 1, CR on = 13 within 74 ± 127 days of start of therapy | Duration on medication was at least 720 days | NM | Infection, dizziness, nausea, diarrhea, blood pressure, hyperglycemia, cushing syndrome |
Table 3 continued

| Author/year          | Duration to initial improvement in symptoms after MMF | Follow up period | Concomitant Rx                           | Outcome                          | Duration on all medication * | PV antibody titer changes after Rx | Adverse effects |
|----------------------|--------------------------------------------------------|------------------|-----------------------------------------|----------------------------------|-------------------------------|------------------------------------|-----------------|
| Strowd et al. [62]/2010 | 75 % clearance within 1–18 mo (mean = 4.5 mo)         | Total = 5–130 mo (mean = 35.2 mo); after CR = 1–74 mo (mean = 23 mo) | Prednisone = 35–100 mg/day (mean = 60 mg/day) | CR on = 14; MMF failed in 4 pts of which Rtx given to 2 of which CR on = 1; CR off = 1; referred elsewhere = 2; Total CR off = 3/18 pts eventually after therapy | Medications given for 1 mo to 8 years. Pred and MMF d/c in 3 CR off patients after an average 3 years and are in CR for > than 1 year without relapse. Prednisone and MMF dose tapered with improvement in rest others | NM                                       | NM                      |
| S. Beissert et al. [63]/2010 | MMF grp Placebo grp                                     | 52 week          | Prednisone = 1–2 mg/kg/day              | Death = 1; lost to f/u = 6; NR = 4 due to adverse effects. Rx withdrawn = 22, Improvement in 40/58 pts of MMF combined grp; in 23/36 pts of placebo grp | Prednisone dose tapered to 10 mg/day every 4 weeks up to 52 weeks | Dsg1 and Dsg3 decreased in both grps. Dsg 3 decreased more in placebo grp | Pyrexia, nausea, cough, oral candidiasis, arthralgia, headache, upper respiratory tract infection |
| Bongiorno et al. [64]/2010 | 30–45 days                                             | 18 mo            | Prednisone = 75 mg once daily           | No response = 1. CR on = 6, mean duration of therapy before taper to low dose was 18 mo. CR off = 2 at mean duration of f/u after d/c of therapy was 16 mo without any R | Medications given for 32.4 mo. Pred and EC- MPS dose tapered at 6 mo and at 18 mo. Pred was again tapered at 18 mo. EC-MPS was d/c in 2 pts at 16 mo | Reduced Dsg 1 and Dsg 3 in 8/9 pts | Headache, increased fasting blood glucose |

*Note: MMF = mycophenolate mofetil, PV = pemphigus vulgaris, CR = complete remission, Rtx = retreatment, DM = dermatomyositis, Dsg = desmoglein, EC-MPS = etanercept, f/u = follow-up.
Mycophenolate used in patients with refractory pemphigus vulgaris (previous treatment with corticosteroids and azathioprine was unsuccessful in achieving remission) are reported in Table 3.

Pred prednisone, MMF mycophenolate mofetil, AZA azathioprine, MTX methotrexate, IVIg intravenous immunoglobulin, CyclP cyclophosphamide, Pl plasmapheresis, CR off complete remission off therapy, CR on complete remission on therapy, PR partial remission, R relapse, F/U follow-up, d/c discontinue, mo months, d days, NM not mentioned

*a* Most patients had been previously treated with other medications before MMF was started.

*b* Duration on medication included the time period on medication prior to the start of follow-up to this paper.

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| Author/year | Duration to initial improvement in symptoms after MMF | Follow up period | Concomitant Rx | Outcome | Duration on all medication | PV antibody titer changes after Rx | Adverse effects |
|-------------|-----------------------------------------------------|-----------------|---------------|---------|----------------------------|-------------------------------|----------------|
| Ionnaides et al. [65]/2011 | Mean 12 days in monotherapy mean 11.79 days in combination | 12 mo | Methylprednisone | Monotherapy: CR on within 144.5 days = 12; CR off within 186.83 days = 6; PR on within 132 days = 2; PR off within 150 days = 3 Combination: CR on within 141.9 days = 13; CR off within 175 days = 7; PR on within 144.5 days = 2; PR off within 129.6 days = 2 | Duration on medication was at least 12 mo. MMF and Pred tapered gradually every 2 weeks as per the control of disease activity. MMF reduced to 2 g/day | NM | Weight gain, muscle weakness, fatigue, GI disturbances, glycaemia, HTN, redistribution of body fat, eye disease, Internal infection |
| Author/year | Type of study | N/M/F | Age range/mean (years) | Type of pemphigus vulgaris | Previous Rx | Duration of disease before IVIg | IVIg dose | Duration to initial improvement in symptoms after IVIg | Follow up period | Concomitant Rx | Outcome | Duration on medication (IVIg) | PV antibody titer changes after Rx | Adverse effects |
|-------------|---------------|-------|------------------------|---------------------------|-------------|-------------------------------|-----------|---------------------------------|----------------|----------------|---------|-----------------------------|-----------------------------|----------------|
| Bystryn et al. [66]/2002 | Case series | N = 6 | M/F = 5/1 | 57–78 | Mucocutaneous = 1; cutaneous = 3; mucosal = 2 | Pred | 2 mo to 5 years | 400 mg/kg/day for 5 days, 1–3 courses | 2–4 mo | Prednisone, CydP (100–150 mg/day) | Controlled disease activity in all 6 pts. Additional details on duration NM. | Medications given for 2 mo to 3.4 years. Pred tapered in median 16 days after start of IVIg 1–3 courses given | IIF: IC IgG Reduced by 72%. At 2 weeks total IgG reduced to normal levels and 1.7% below baseline | Mild stroke in 1 pt with HTN |
| Amagai et al. [67]/2009 | Multicenter randomized controlled double-blind trial | N = 40 PV + 21 PF | M/F = NM | Mean: placebo grp = 55.1 yrs 200 mg grp = 57 yrs 400 mg grp = 50.1 yrs | Mucocutaneous Pred | Mean 24 mo | IV infusion 200 or 400 mg/kg/day in divided doses over 5 days. IV saline for 5 days in Placebo grp | 8–15 days | After Rx = 90 days; Total = 2 years | Prednisone | Significant Improvement in 400 and 200 mg grp pts by day 85. No significant Improvement in placebo group from baseline. Additional details NM | Up to 2 years | ELISA: Anti Dsg1 (%): Placebo grp: remained same; 200 mg grp: 100–60; 400 mg grp: 100–60 Anti Dsg3 (%): Placebo grp: 100–75; 200 mg grp: 100–70; 400 mg grp: 100–50 | Headache, hepatitis C, lymphopenia, constipation, nausea, abdominal discomfort, palpitations ex |
| Stojanovic et al. [68]/2009 | Case report | 1/F | 44 | NM | Pred, CydP | 3 years | 400 mg/kg/day for 5 days followed by long term single doses of 400 mg/kg every 6 weeks for 1 year | Stable Remissionb | 1 year | NM | Stable remission after last infusionb | 6 months | NM | NM |
| Stojanovic et al. [68]/2009 | Case report | 1/F | 64 | NM | Pred, AZA | NM | 400 mg/kg/day for 5 days followed by long term single doses of 400 mg/kg every 6 weeks for 6 mo | Stable Remissionb | 1 year | NM | Stable remission after last infusionb | 6 months | NM | NM |

Pred prednisone, AZA azathioprine, IVIg intravenous immunoglobulin, CydP cyclophosphamide, CR off complete remission off therapy, CR on complete remission on therapy, PR partial remission, PR off partial remission off therapy, R relapse, NR no response, FU follow-up, d/c discontinue, mo months, d days, pts patients, NM not mentioned, IIF indirect Immunofluorescence, ELISA Enzyme linked immunosorbent assay, Dsg1 and Dsg3 desmoglein 1 and 3

a Duration on medication included the time period on medication prior to the start of follow-up to this paper

b Not mentioned whether on medication or not
### Table 5 Methotrexate

| Author/year | Type of study | N M/F | Age range/mean (years) | Type of pemphigus vulgaris | Previous Rx | Duration of disease before MTX | MTX dose |
|-------------|---------------|-------|------------------------|----------------------------|-------------|--------------------------------|----------|
| Lever and Goldberg et al. [69]/1969 | Case series | N = 5 | 26–79 | Mucocutaneous | Pred | 11 mo to 7 years | 25–150 mg/week |
| Jablonska et al. [70]/1970 | Case series | N = 10 | 32–83 (mean = 58.8) | NM | Pred, triamcinolone | NM | 25 mg/week |
| Piamphongsant and Sivayathorn et al. [71]/1975 | Case series | N = 3 | 33–48 (Mean = 43.8) | NM | Pred, MTX in 1 pt | NM | 12.5–25 mg/week |
| Lever and Schaumburg-Lever, Lever et al. [72, 73]/1977 | Case series | N = 41 | 20–79 (mean = 51) | Mucocutaneous | None | NM | 20–50 mg/week |
| Mashkilleyson et al. [74]/1988 | Case series | N = 53 | 26–75 (mean = 56) | NM | Pred | NM | 25–50 mg/week |
| Smith and Bystryn et al. [75]/1999 | Case series | N = 9 M/F = 8/1 | Mean = 59 | NM | Pred | NM | 12.2 mg/week (13 courses) |
| Baum et al. [76]/2012 | Retrospective study | N = 30 | NM | NM | NM | NM | 15 mg/week |

| Author/year | Duration to initial improvement in symptoms after MTX | Follow up period | Concomitant Rx | Outcome | Duration on medication (MTX)* | PV antibody titer changes after Rx | Adverse effects |
|-------------|------------------------------------------------------|------------------|---------------|---------|-------------------------------|----------------------------------|----------------|
| Lever and Goldberg et al. [69]/1969 | 5–7 years | Pred | CR on = 4, improvement = 1. additional details NM | Pred d/c in 1 patient at fifth year. tapered in rest on clinical improvement. MTX continued in all patients at end of f/u | IIF Pr1—1:640 to 1:80 to 1:10 to neg | Nausea, lassitude |
| Jablonska et al. [70]/1970 | 1–30 weeks | NM | Pred, triamcinolone | Improvement in 8.9 pts after 1–30 weeks of treatment. Death = 1 due to bronchopneumonia. Whether PR or CR—NM | Duration of MTX 1–7.5 mo. MTX discontinued in six patients due to its side effects | NM | Bronchopneumonia, cerebral thrombosis, septicemia, bronchitis, anemia, diarrhoea, leucopenia, bacterial infection |
| Piamphongsant and Sivayathorn et al. [71]/1975 | NM | NM | Pred | Death = 1 due to Pred side effects CR on = 2 | Duration of MTX 33–78 days maintenance dose contd at end of f/u | NM | NM |
### Table 5 continued

| Author/year | Duration to initial improvement in symptoms after MTX | Follow up period | Concomitant Rx | Outcome | Duration on medication (MTX) | PV antibody titer changes after Rx | Adverse effects |
|-------------|------------------------------------------------------|------------------|---------------|---------|------------------------------|-----------------------------------|----------------|
| Lever and Schaumburg-Lever, Lever et al. [72, 73]/1977 | NM | 11–15 years | Prednisone = 40–360 mg/day | Death = 4 unrelated to MTX; CR on = 8, PR on = 15, CR off = 14 | MTX D/c in 14 pts with CR off therapy, mean duration of f/u after d/c of medication was mean 2.6 years (3 mo to 8 years) without any relapse. Rx contd in others at end of f/u | NM | Nausea, leucopenia, pyoderma |
| Mashkilleyson et al. [74]/1988 | 2–3 days | NM | Pred | Not effective in nine patients, CR on = 31; PR on = 11 | MTX discontinued in two patients due to its side effects | NM | Pneumonia, exacerbation of gastric ulcer, pyoderma, moniliasis, necrotizing gingivitis, TB of larynx |
| Smith and Bystryn et al. [75]/1999 | NM | NM | Prednisone = 3–40 mg/day | CR on = 6 pts within 6 mo of start of therapy. Additional details NM | Pred d/c in 6 pts within 6 mo after start of MTX therapy. MTX continued in all as flares were seen within 23 days of discontinuing MTX at end of f/u | NM | Nausea, mild elevations of transaminase |
| Baum et al. [76]/2012 | NM | NM | Pred | Improvement in 21 pt at 6 mo of treatment. Additional details NM | Pred dose tapered | NM | Mild adverse effects |

*Pred prednisone, MTX methotrexate, CR complete remission off therapy, CR on complete remission on therapy, PR partial remission, PR on partial remission on therapy, PR off partial remission off therapy, R relapse, NR no response, F/U follow-up, d/c discontinue, mo months, d days, pt patient, NM not mentioned, IIF indirect immunofluorescence, Dsg1 and Dsg3 desmoglein 1 and 3

* Duration on medication included the time period on medication prior to the start of follow-up to this paper

* Only abstract is available for Baum et al. [75]/2012
| Author/year | Type of study | M/F | Age range/ mean (yrs) | Type of pemphigus vulgaris | Previous Rx | Duration of disease before Rtx | Rituximab dose |
|-------------|---------------|-----|----------------------|---------------------------|-------------|-------------------------------|----------------|
| Salopek et al. [77]/2002 | Case report | 1/F | 29 | Mucocutaneous | Pred, AZA, Pulsed iv Cyclophosphamide, Pl, IVIg, MMF | 9 mo | 375 mg/m² BSA—6 infusions over 8 weeks |
| Cooper et al. [78]/2002 | Case report | 1/M | 54 | Cutaneous | Pred, AZA, MMF, Pl, IVIg, Cyclophosphamide | 20 mo | 375 mg/m² BSA once weekly for 4 weeks |
| Espana et al. [79]/2003 | Case report | 1/M | 39 | Mucocutaneous | Pred, AZA, Pl, Cyclophosphamide | NM | 375 mg/m² BSA once weekly for 4 weeks |
| Morrison et al. [80]/2004 | Case report | 1/M | 51 | Mucocutaneous | Pred, MTX, Dapsone, AZA, minocycline, IVIg, MMF, Cyclophosphamide | 56 mo | 375 mg/m² BSA once weekly for 4 weeks |
| Morrison et al. [80]/2004 | Case report | 1/M | 37 | Cutaneous | Cyclophosphamide, Pred, Pl, Dapsone, IVIg | 70 mo | 375 mg/m² BSA once weekly for 4 weeks |
| Wenzel et al. [81]/2004 | Case report | 1/F | 70 | Cutaneous | AZA, MMF, IVIg, Cyclophosphamide | 30 mo | 375 mg/m² BSA once weekly for 4 weeks |
| Dupuy et al. [82]/2004 | Case report | 1/F | 34 | Mucocutaneous | Pred, Cyclophosphamide | 144 mo | (375 mg/m² BSA once weekly for 4 weeks) ×2 at 6 mo interval |
| Dupuy et al. [82]/2004 | Case report | 1/F | 42 | Mucocutaneous | AZA, MTX, Pred, MMF, IVIg, extracorporeal photopheresis, cyclosporine | 60 mo | (375 mg/m² BSA once weekly for 4 weeks) ×2 at 6 mo interval |
| Kong et al. [83]/2005 | Case report | 1/F | 17 | Mucocutaneous | Pred, AZA, MMF, MP, IVIg, Pl | 84 mo | 375 mg/m² BSA once weekly for 4 weeks |
| Arin et al. [34]/2005 | Case report | 1/F | 60 | Mucocutaneous | Pred, MMF, AZA | 8 years | 375 mg/m² BSA once weekly for 4 weeks |
| Arin et al. [34]/2005 | Case report | 1/F | 26 | Mucocutaneous | Pred, MMF, AZA, MTX | 3 years | 375 mg/m² BSA once weekly for 4 weeks |
| Arin et al. [34]/2005 | Case report | 1/F | 27 | Mucocutaneous | Pred, MMF, AZA, MTX | 3 years | 375 mg/m² BSA once weekly for 4 weeks |
| Author/year       | Type of study | N   | M/F | Age range/mean (yrs) | Type of pemphigus vulgaris | Previous Rx                                                                 | Duration of disease before Rtx | Rituximab dose                                                                 |
|-------------------|---------------|-----|-----|----------------------|-----------------------------|------------------------------------------------------------------------------|--------------------------------|--------------------------------------------------------------------------------|
| Arin et al. [34]/2005 | Case report   | 1/F | 57  |                      | Muocutaneous                | Pred, MMF, AZA                                                               | 14 years                       | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Schmidt et al. [84]/2005 | Case report   | 1/M | 14  |                      | Muocutaneous                | Pred, AZA, Dapsone, MMF, CydP, staphylococcal protein A immunoadsorption     | 2.5 years                      | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Schmidt et al. [85]/2006 | Case report   | 1/F | 17  |                      | Muocutaneous                | Pred, IVlg, AZA, MMF, MTX                                                   | 30 mo                          | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Schmidt et al. [85]/2006 | Case report   | 1/F | 39  |                      | Muocutaneous                | Pred, IVlg, AZA                                                             | 79 mo                          | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Schmidt et al. [85]/2006 | Case report   | 1/F | 68  |                      | Muocutaneous                | Pred, IVlg, MMF, dexamethasone-cyclP pulse                                  | 64 mo                          | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Schmidt et al. [85]/2006 | Case report   | 1/F | 81  |                      | Muocutaneous                | Dexamethasone-cyclP pulse                                                   | 7 mo                           | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Ahmed et al. [86]/2006 | Case series   | N = 11 | M/F = 5/6 | 15–68 | Muocutaneous          | Pred, MMF, AZA, MTX, Dapsone                                              |                                |                                                                                |
| Gold,CydP,Cyclosporine, colchicine, tacrolimus | 31–219 mo (mean = 68.8 mo) | 375 mg/m² BSA once weekly for 3 weeks; fourth week—IVlg. 10 infusions of Rtx in 9 pts |
| Goh et al. [87]/2007 | Open label pilot study | N = 5 | M/F = 3/2 | 46–62/57 | Muocutaneous          | AZA, MMF, IVlg, Pl, iv cyclP, cyclosporine, gold                            | 2–96 mo                        | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Marzano et al. [88]/2007 | Case series   | N = 3 | M/F = 2/1 | Pt1: 51 | Muocutaneous          | AZA, MMF, IVlg, Pred, CydP                                                  | Pt 1: 6 years; Pt 2: 5 years; Pt 3: 4 years | 375 mg/m² BSA once weekly for 4 weeks; 2 more infusions for pt 3 (one each mo) |
| Antonucci et al. [89]/2007 | Case series   | N = 5 | M/F = 4/1 | 28–35 | Muocutaneous = 2 Cutaneous = 3 | AZA, MMF, IVlg, Pred, CydP, MTX Pl, Cyclosporine                           | 3–7 years                      | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Cianchini et al. [90]/2007 | Case series   | N = 10 | M/F = 5/5 | 27–63 | Muocutaneous          | Pred, AZA, MMF, Pl, CydP, cyclosporine, extracorporal photopheresis          | 1–9 years                      | 375 mg/m² BSA once weekly for 4 weeks. Additional Rtx infusion in only one patient |
| Joly et al. [91]/2007 | Case series   | N = 14 | M/F = NM | Mean = 53.7 | Muocutaneous          | Pred, IVlg, AZA, MTX, MMF, cyclosporine                                   | 4–168 mo (mean = 70.2 mo)      | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Author/year                | Type of study | N   | M/F  | Age range/mean (yrs) | Type of pemphigus vulgaris | Previous Rx                                                                 | Duration of disease before Rtx | Rituaximab dose                                                                 |
|---------------------------|---------------|-----|------|----------------------|----------------------------|------------------------------------------------------------------------------|--------------------------------|--------------------------------------------------------------------------------|
| Shimanovich et al. [92]/2007 | Case series   | 5   | 1/4  | 37–71                | Mucocutaneous              | Pred, AZA, MMF, Pl, MTX, cyclosporine, Cyelp, dexamethasone, dapsone          | 3–76 mo                        | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Eming et al. [93]/2008     | Case series   | 11  | 5/6  | 37–70/52.1           | Mucocutaneous = 7, mucosal = 2, cutaneous = 2 | Pred, AZA, MMF               |                               | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Faurschou and Gniadecki [94]/2008 | Case report  | 1/M | 68   | Mucocutaneous        | Pred, MMF, IVlg             | 3 years                        |                               | (375 mg/m² BSA once weekly for 4 weeks) × 2 at 6 mo interval                  |
| Faurschou and Gniadecki [94]/2008 | Case report  | 1/F | 46   | Mucosal              | Pred, MTX, MMF, IVlg        | NM                            |                               | (375 mg/m² BSA once weekly for 4 weeks) × 2 at 6 mo interval                  |
| Pfutze et al. [95]/2009    | Case series   | 5   | 2/3  | Mean = 55            | Mucosal dominant            | CS, MMF                        |                               | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Fuji et al. [96]/2010      | Case report   | 1/M | 1.5  | Mucocutaneous        | Pred, AZA, cyclosporine, Dapsone, Gold | Newly diagnosed               |                               | Mucocutaneous                                                                 |
| Kasperkiewicz et al. [97]/2011 | Pilot study  | 17  | 8/9  | 38–75/ mean = 55     | Mucocutaneous = 7, mucosal = 6, cutaneous = 4 | AZA, cyclosporine, Cyelp, MTX, MMF, dapsone, IVlg, PAIA, Pl, Pred, dexamethasone, hydroxychloroquine | 3–144 mo                       | Two infusions of 1000 mg 2 wks apart. Additional Rtx cycle in 2 pts           |
| Craythorne et al. [98]/2011 | Case series   | 6   | 3/3  | 45–71                | Mucocutaneous              | Pred, AZA, MMF, cyclosporine   | 0–13 years                     | 375 mg/m² BSA once weekly for 8 weeks then monthly ranging from 4 to 10 mo in all pts |
| Kasperkiewicz et al. [99]/2011 | Case series   | 8   | 4/4  | 45–65                | Mucosal = 1; Mucosal = 7    | AZA, MMF, Pred, dapsone, cyclosporine, dexamethasone | 3–72 mo                       | 375 mg/m² BSA once weekly for 4 weeks = 3 pts; 1000 mg twice 2 wks apart = 5   |
| Kim et al. [100]/2011      | Retrospective study | 25 PV + 2 PF | 12/13 | 24–83                | Mucocutaneous = 20; cutaneous = 3; mucosal = 2 | AZA, MMF, IVlg, Cyelp, steroid pulse therapy, cyclosporine | 12–15.5 mo                     | (375 mg/m² BSA once weekly) 2 wks = 11 pts 3 wks = 11 pts 4 wks = 1 pt 5 wks = 2 pts |
| Reguizai et al. [101]/2011  | Case series   | 9   | 3/6  | 14–61                | Mucocutaneous              | Pred, IVlg, AZA, MMF          | NM                            | 375 mg/m² BSA once weekly for 4 weeks                                          |
| Author/year                        | Type of study      | N  | M/F | Age range/mean (yrs) | Type of pemphigus vulgaris | Previous Rx                                                                 | Duration of disease before Rtx | Rituximab dose                                                                 |
|-----------------------------------|--------------------|----|-----|----------------------|-----------------------------|------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------------------------------------|
| Horvath et al. [102]/2011         | Case series        | 12 | M/F | 34–80                | Mucocutaneous               | AZA, Pred, MMF, dapsone, doxycycline, CycP, IVIg, dexamethasone, nicotinic acid, mycophenolic acid | 2–12 years                    | Two Rtx infusions of 500 mg at interval of 2 weeks in 10 pts and at an interval of 4 and 3 weeks in 2 pts |
| Feldman et al. [103]/2011         | Retrospective      | 19 | M/F | Mean = 52            | Mucocutaneous = 14; mucosal only = 5 | Pred with or without immunosuppressive agent                                | NM                            | 375 mg/m² BSA once weekly—12 infusions over 6 mo period                           |
| Leshem et al. [104]/2012          | Case series        | 42 | M/F | 18–83                | Mucosal only = 40           | Pred, MTX, AZA, IVIg, Dapsone, Rtx (lymphoma protocol), CycP                 | 0–163 mo (mean = 25 mo)       | Two infusions of 1000 mg 2 wks apart                                             |
| Cianchini et al. [37]/2012        | Case series        | 37 | M/F | 27–75                | Mucous or mucocutaneous involvement. No’s NM                               | Pred, immunosuppressants                                                   | 1–13 years; (mean = 4.2 years)       | Two infusions of 1000 mg 2 wks apart. Additional 500 mg Rtx infusion on PR or no response 6 mo after initial infusion |
| Lunardon et al. [105]/2012        | Case series        | 24 | M/F | 26–86/50             | Mucocutaneous               | Pred, AZA, MMF, Dapsone, CycP, IVIg, Cyclosporine                           | 3–234 mo (mean = 41 mo)        | (375 mg/m² BSA once weekly for 4 weeks) × 13 pts. (Two infusions of 1000 mg 2 wks apart) × 11 pts |
| Kasperkiewicz and Eming et al. [106]/2012 | Case series        | 33 | M/F | 15–76/52             | Mucosal = 29                 | Pred, AZA, MMF, Pl, MTX, PAIA, IVIg, CycP, chloroquine, Iefanamide         | 0.1–16 years (mean = 4)        | 4 × 375 mg/m² = 9 pts. 2 × 1000 mg = 25 pts. Two cycles of 4 × 375 mg/m² = 1 pt. |
| Baligh et al. [107]/2013          | Phase 2 clinical    | 40 | M/F | 40–50                | Mucocutaneous               | Pred, AZA, MMF, Dapsone, IVIg, CycP                                        | Mean = 35 ± 32 mo              | 375 mg/m² BSA once weekly for 4 weeks                                           |
| Author/year | Type of study | $N$ | M/F | Age range/mean (yrs) | Type of pemphigus vulgaris | Previous Rx | Duration of disease before Rtx | Rituximab dose |
|-------------|---------------|-----|-----|---------------------|---------------------------|-------------|-------------------------------|----------------|
| Kanwar et al. [108]/2013 | Open label pilot study | $N = 9$ | M/F = 5/4 | 9–60 | Macucutaneous | Pred, AZA, dapsone, dexamethasone pulse | 4–72 mo (mean = 18 mo) | 375 mg/m$^2$ BSA once weekly for 4 weeks = 1 pt; Two infusions of 1000 mg 2 wks apart = 7 pts; 1 x 1000 mg + 1 x 140 mg BSA = 1 pt |
| Kolesnik et al. [109]/2014 | Case series | $N = 6$ | M/F = 3/3 | 48–81 | Macucutaneous | Pred, AZA, MMF, dapsone, PAIA, Rtx in 1 pt | 1–240 mo | 375 mg/m$^2$ BSA once weekly for 3 to 6 weeks in combination with PAIA |
| Heelan et al. [35]/2014 | Case series | $N = 84$ PV + 8 PF | M/F = 37/55 | 13–77/43 | Macucutaneous = 61, mucosal = 20, cutaneous = 11 | Pred, AZA, MMF, IVIg, MTX, dapsone, Cclop, gold, cyclosporine, cyclophosphamide, mycophenolate sodium | 0–256 (mean = 24 mo) | Two infusions of 1000 mg 2 wks apart; 1000 or 500 mg 6 mo or more after induction if required |
| Kanwar et al. [110]/2014 | Randomized, comparative, observer-blinded study | $N = 15$ | M/F = 8/7 | Mean = 33 years | Macucutaneous | Dexamethasone pulse therapy, AZA, Pred, IVIg, MMF | 0.3–6 years | High dose grp: Two infusions of 1000 mg 2 wks apart = 7 pts Low dose grp: Two infusions of 500 mg 2 wks apart = 8 pts |
| Ojami et al. [111]/2014 | Case series | $N = 14$ | M/F = 7/7 | 30–75 (mean = 54.3) | Macucal = 14; | MMF, AZA, Pred | NM | Two infusions of 1000 mg 2 wks apart; 375 mg/m$^2$ BSA once weekly for 4 weeks |
| Author/year | Concomitant Rx | Duration to initial improvement in symptoms after Rtx | Follow up period | Outcome | Duration on medication (Rituximab and previous)* | PV Antibody titer changes after Rx (U ml⁻¹) | Adverse effects |
|-------------|----------------|-----------------------------------------------------|-----------------|---------|-----------------------------------------------|---------------------------------------------|---------------|
| 8           | 9              | 10                                                  | 11              |         |                                               |                                             |               |
| Salopek et al. [77]/ 2002 | Pred 1 mg/kg daily | 92 days after last infusion | After Rtx = 6.3 mo, total = 18.9 mo | PR occasional minor flare ups | 18.9 mo. Rx continued with IVIg and CyclP at end of f/u | 1:4000 to 0 at 5 mo after first infusion; and at 8 mo from 0 to 1:1000 | NM |
| Cooper et al. [78]/ 2002 | Pred, MMF | 1 in 2 weeks after first infusion | After Rtx = 6 mo, total = 26 mo | PR. Clinical improvement | 20 mo. Pred tapered over 3 mo; MMF d/c after 4 mo of start of therapy | IIF: No change in titer. Stable at 1:1280 | NM |
| Espana et al. [79]/ 2003 | Pred | 6 weeks after first infusion | 40 weeks | CR on | Duration on medication NM. Pred tapered; AZA d/c before Rtx infusion | Anti Dsg1: 77 to 7; Anti Dsg3: 160 to 90 at 28 wks., ICS = 1:160 to 1:10 | NM |
| Morrison et al. [80]/2004 | Pred, CyclP | 4 wk after first infusion 95 % re-epithelization | After Rtx = 18 mo | CR on. Mean duration of medication use before taper to low dose was 18 mo | 66 mo. Pred d/c 9 mo after Rtx; CyclP d/c 10 mo after Rtx | IIF: 1:2560 to 1:640 to 1:40 in 10 mo | NM |
| Morrison et al. [80]/2004 | CyclP, IVlg, Pred | 4 mo after last infusion—free of all lesions | After Rtx = 4 mo, total = 52 mo | Death in 5 mo after Rtx from Pneumocystis carinii pneumonia | 6 years. IVlg d/c before starting Rtx; Pred and CycP were not changed and contd at end of f/u | IIF: 1:320 to 1:160 | Pneumocystis carinii pneumonia |
| Morrison et al. [80]/2004 | CyclP | After last infusion and contd to improve over next 9 mo | After Rtx = 9 mo; total = 35 mo | PR | 39 mo and CycP d/c twice but restarted and contd at low doses at end of f/u | IIF: 1:2560 to 1:640 to 1:320 | NM |
| Virgolini Marzocchi [25]/2007 | Pred, CyclP | 3 mo after last infusion complete healing of lesions | After Rtx = 10 mo; total = 130 mo | CR on within 3 mo of start of therapy | About 121 months. | NM | None |
| Wenzel et al. [81]/2004 | Pred | Between second and sixth wk after last infusion | After Rtx = 3 mo | CR on | 159 mo and Rx contd. With prednisone at end of f/u | IIF: 1:640 to 1:40 | None |
| Dupuy et al. [82]/2004 | Pred, AZA | third wk after first infusion improvement was noticed; second course due to worsening of lesions | After Rtx = 9.8 mo, total = 35 mo | No significant improvement | 152 mo. Pred tapered by fifth mo after first infusion but increased again due to flare up and maintained | IIF: 1:500 to 1:200 | Community acquired pneumonia after first course. None after second course |
## Table 6 continued

| Author/year | Concomitant Rx | Duration to initial improvement in symptoms after Rtx | Follow up period | Outcome | Duration on medication (Rituximab and previous) | PV Antibody titer changes after Rx (U ml⁻¹) | Adverse effects |
|-------------|----------------|------------------------------------------------------|------------------|---------|-----------------------------------------------|---------------------------------------------|----------------|
| Dupuy et al. [82]/2004 | Pred, MMF cyclosporine | First course: improvement from second wk after first infusion; second course: improvement in 3 wks after first infusion | After Rtx = 17 mo, total = 77 mo | CR within 4 mo after first course with a flare up at sixth mo; after second course CR on therapy at 6 mo of therapy | Pred tapered from week 10 after first infusion but increased again during second course due to flare up | IIF: first course: 1:200 to 0 in 2 mo to 1:500 in 11 mo second course: 0 in 6 mo | Facial edema, P aeruginosa hip arthritis |
| Dupuy et al. [82]/2004 | Pred | Clinical improvement observed from week 7 after starting Rtx infusion | After Rtx = 9 mo, total = 33 mo | CR on within third month after first Rtx infusion | 30 mo and Pred tapered and contd. at sixth mo after Rtx therapy at end of f/u | IIF: 1:1600 to 1 in 3 mo and 0 until end of F/U | NM |
| Kong et al. [83]/2005 | Pred | Clinical improvement in 10 days after starting Rtx | After Rtx = 17 mo, total = 101 mo | CR off | Total duration on medication = 101 mo. 17 mo of Rtx therapy. Pred tapered over 2 wks after 10 days of remarkable improvement on Rtx therapy and d/c. But maintenance infusions of Rtx contd every 8–12 weeks at end of f/u | Anti Dsg 1: 1:2079 to 1:33 Anti Dsg3: 1:8616 to 1:564 | NM |
| Arin et al. [34]/2005 | Pred, MMF | NM | After Rtx = 24 mo; total = 120 mo | CR on | Medication given for 10 years and MMF continued at end of f/u | Anti Dsg1: 0–20 Anti Dsg3: 100 to 75 to 100 again | No serious events. Nausea, vomiting, chills or cough, facial edema |
| Arin et al. [34]/2005 | Pred, MTX | NM | After Rtx = 10 mo; total = 46 mo | PR | Medication given for 46 mo and MTX + Pred contd at end of f/u | Anti Dsg1: 15 to 0 to 15 Anti Dsg3: 100 to 0 | No serious events. Nausea, vomiting, chills or cough, facial edema |
| Arin et al. [34]/2005 | Pred, MTX | NM | After Rtx = 10 mo; total = 46 mo | PR | Medication given for 46 mo and MTX + Pred contd at end of f/u | Anti Dsg1: 20 no change Anti Dsg3: 100 to 75 to 100 again | No serious events. Nausea, vomiting, chills or cough, facial edema |
Table 6 continued

| Author/year | Concomitant Rx | Duration to initial improvement in symptoms after Rtx | Follow up period | Outcome | Duration on medication (Rituximab and previous) | PV Antibody titer changes after Rx (U ml⁻¹) | Adverse effects |
|-------------|----------------|------------------------------------------------------|------------------|---------|-----------------------------------------------|---------------------------------|---------------|
| Arin et al. [34]/2005 | Pred, MMF |NM |After Rtx = 36 mo; total = 204 mo |CR on |Medication given for 17 years and Pred continued at end of f/u |Anti Dsg1: 200 to 100 Anti Dsg3: 175 to 8 |No serious events. Nausea, vomiting, chills or cough, facial edema |
| Schmidt et al. [84]/2005 | Pred, MMF, IVIg (after first and fourth infusion) |Improvement 10 wks after first infusion and CR in 9 mo |After Rtx = 24 mo; total = 54 mo |CR off |Medication given for 4.5 years. Pred and MMF d/c after 18 and 21 mo of starting Rtx therapy, respectively |Anti Dsg3 and Dsg1: 875 to 0 in 7 mo and stable at 0 after that |Hypergammaglobulinemia after first infusion |
| Schmidt et al. [85]/2006 | Pred, MMF |PR after 6 mo of Rtx |After Rtx = 7 mo |PR |Medication given for 37 mo. MMF + Pred continued at end of f/u |ELISA: Anti Dsg3: 7708 to 517 |None |
| Schmidt et al. [85]/2006 | AZA, Pred |PR after 3 mo of Rtx |After Rtx = 21 mo |PR |Medication given for 100 mo. AZA + Pred continued at end of f/u |ELISA: Anti Dsg3: 806 to 108 |None |
| Schmidt et al. [85]/2006 | MMF, Pred |PR after 3 mo of Rtx |After Rtx = 9 mo |CR on |Medication given for 75 mo. MMF continued at end of f/u |ELISA: Anti Dsg3: 877 to 27 |None |
| Schmidt et al. [85]/2006 | Dexamethasone- cycloP pulse |PR after 3 mo of Rtx |After Rtx = 68 mo |CR off at 12 mo F/U |Rx d/c after 12 mo |ELISA: Anti Dsg3: 322.2 to 0 |Bacterial pneumonia, pulmonary embolism |
| Ahmed et al. [86]/2006 | NM |Within 3–6 wks (mean = 4 wks) |After Rtx = 15–37 mo; (mean 32.5 mo) |CR off = 9 within 7–9 wks after Rtx infusion between seventh and ninth infusion; R = 2 at 6 mo after tenth Rtx infusion and recent CR in 15 and 24 mo resp |Medication given for mean 50.6 mo (range = 31–225 mo) and prednisone continued at end of f/u |Antikeratinocyte antibodies: reduced from Mean 1:1280 (1:5120 to 1:320) to 1:40 |None |
| Goh et al. [87]/2007 | Pred, AZA, MMF, cyclosporine |Clinical response ranged between 2 and 8 mo |After Rtx = 13–18 mo |CR off = 1 CR on = 2 PD = 2; CR within 13–18 mo after start of Rtx therapy |Medication given for 2–114 mo. Rx d/c after 13 mo of start of therapy in CR off pt |IIF: 1:1280, 1:640, 1:160, 1:80 to 0 in 16 to 18 mo after Rtx in all 5 pts |Transient fatigue in 3 pts, neuropathy, community acquired pneumonia |
| Marzano et al. [88]/2007 | Pred |Pt 1: 2 wks after last Rtx infusion. Pt 2: 5 mo after last Rtx infusion. Pt 3: 3 mo after first Rtx infusion, total 6 Rtx infusions for third pt |Pt 1: CR on; Pt 2: CR; Pt 3: MR (minimal response) |Medication given for 8 years (Pt1). 6.8 years (Pt2). 4.2 years (Pt3) and Rx continued in all patients at end of f/u |Pt1: Anti Dsg1: 125 to 0; Anti Dsg3: 175 to 125. Pt2: Anti Dsg1: 50 to 0; Anti Dsg3: 225 to 25 at end of F/U. Pt3: NM |Facial edema, chills, precordial pain only in first and second infusion |
| Author/year                | Concomitant Rx | Duration to initial improvement in symptoms after Rtx | Follow up period | Outcome | Duration on medication (Rituximab and previous) | PV Antibody titer changes after Rx (U ml⁻¹) | Adverse effects |
|----------------------------|----------------|------------------------------------------------------|------------------|---------|-----------------------------------------------|---------------------------------------------|----------------|
| Antonucci et al. [89]/2007 | Pred           | Pt1: 2 wks after last rtx infusion; Pt2: 4 wks after last Rx infusion; Pt3: 3 wks after last Rx infusion; Pt4: 8 wks after first Rx infusion; Pt5: 5 wks after last Rx infusion | After Rtx = 11–13 mo | Pt 1: R after 12 mo of CR; CR off again after second cycle of Rx with no relapse; Pt2: CR off in 4 weeks after Rx therapy; Pt3: CR on; Pt4: CR off in 12 mo after Rx therapy; Pt5: CR on | Pt1: 6–7 years. Pred d/c 1 mo after end of Rx therapy. Pt2: 4.1 years. Pred tapered and d/c after 1 mo of Rx. Pt3: 4.1 years. Pred tapered and contd. Pt4: 8 years. Pred d/c in 10 weeks. Pt5: 3.2 years | ELISA: Anti Dsg 3: Pt1: 200 to 60 in 24 mo; Pt2: 200 to 55 in 24 mo; Pt3: 200 to 60 in 24 mo; Pt4: 180 to 175 in 48 mo; Pt5: 200 to 100 in 24 mo | None |
| Cianchini et al. [90]/2007  | Pred, AZA, CyclP | NM | 16–18 mo | CR on within 6 mo after Rx infusion = 2 | Medication given for L1–9.1 years. Prednisone maintenance dose continued in all patients at end of f/u | Anti Dsg1: Pt1: 125-0 in 18 mo; Pt2: stable at 0; Pt3: 175-10 in 12 mo; Pt4: 150-0 in 12 mo; Pt5: 200-100 in 12 mo; Pt6: 240-140 in 6 mo; Pt7: 260-75 in 6 mo; Pt8: 250-0 in 6 mo; Pt9: 210-75 in 6 mo; Pt10: 25-0 in 6 mo; Anti Dsg3: Pt1: 290-75 in 18 mo; Pt2: 175-0 in 18 mo; Pt3: 120-0 in 15 mo; Pt4: 140-25 in 15 mo; Pt5: 120-25 in 15 mo; Pt6: 200-50 in 6 mo; Pt7: 150-0 in 6 mo; Pt8: 100-25 in 6 mo; Pt9: 200-50 in 6 mo; Pt10: 140-60 in 6 mo | Tachycardia in one patient |
| Joly et al. [91]/2007       | Prednisone in all but 3 pts | NM | 26–45 mo (mean = 34 mo) | CR on = 14 PV pts within 3 mo in 12 pts; within 6 mo in 1 pt; within 12 mo in 1 pt; R in 6 pts after a mean of 18.9 mo. CR at end of F/U in 18/21 pts with PV and PF | Reduction in 9/14 pts with CR. High titers even on CR in 5 pts | Headache, asthenia, fever, chills, nausea, pyelonephritis | |

Table 6 continued
Table 6 continued

| Author/year      | Concomitant Rx | Duration to initial improvement in symptoms after Rtx | Follow up period | Outcome | Duration on medication (Rituximab and previous) | PV Antibody titer changes after Rx (U ml⁻¹) | Adverse effects |
|------------------|----------------|-----------------------------------------------------|------------------|---------|-----------------------------------------------|---------------------------------------------|-----------------|
| Shimanovich et al. [92]/2007 | PAIA, IVIg | Within 4 weeks of Rx | 13–30 mo | 2 pts failed to show improvement with Rtx who improved on subsequent IVIg; CR on = 4; CR off = 1 within 6 mo of start of therapy | Medication given for 6 mo up to 106 mo Rx d/c within 6 mo of start of therapy in CR off pt | ELISA: Anti Dsg1: Negative in all 5 pts at end of F/U Anti Dsg3: Pt1: 465-neg in 27 mo Pt2: 1179-40 in 30 mo Pt3: 1170-44 in 21 mo Pt4: 257-neg in 13 mo Pt5: 230-23 in 27 mo | Staphylococcus aureus bacteremia, deep venous thrombosis, P. carinii pneumonia. Resolved with appropriate management |
| Eming et al. [93]/2008 | Prednisone | Within 6 mo after Rtx therapy | >12 mo in 10 pts, 3 mo in 1 pt | CR on after second course which was 6 mo after first course | Pred tapered acc to clinical response; MMF or AZA given for 6 mo after Rtx and tapered acc to clinical remission | Anti Dsg3 IgG: 100 to 25 in 12 mo in 8 CR pts 60 to 25 in 6 mo to 75 in 12 mo in 3 R pts | NM |
| Faurschou and Gniadecki [94]/2008 | Pred, MMF | 6 wks after first Rtx infusion | 6 mo after second course | CR on after second course which was 6 mo after first course | Medication given for 3.8 years. Pred tapered, MMF continued at end of F/U | IIF: 1:1280 to 1:640 | NM |
| Faurschou and Gniadecki [94]/2008 | Pred | 3 wks after first Rtx infusion | Total = 4 years | CR on after second course which was 6 mo after first course | Medication given for 4 years. Pred tapered, MMF continued at end of F/U | NM | NM |
| Pfütze et al. [95]/2009 | Pred, MMF | 1 mo and 6 mo after Rtx therapy in 4 and 1 pt resp. And improved over 12 mo | After Rtx = 12 mo | CR on = 5 within 12 mo of start of therapy | Pred tapered and d/c by 12 mo. MMF continued at end of F/U | Anti Dsg1: 40 ± 9.5 % to 6.1 ± 11.5 % in 12 mo Anti Dsg3: 44 ± 34.7 % to 8.3 ± 22.1 % in 12 mo | NM |
| Fuertes et al. [96]/2010 | None | 1 mo after start of Rtx therapy | After Rtx = 18 mo; total = 16 years | CR off started within 6 mo of start of Rtx therapy. No relapse | No other drugs other than Rtx | Anti Dsg1: reduced to 2U/ml. Anti Dsg3: reduced to 11 U/ml | None |
| Kasperkiewicz et al. [97]/2011 | PAIA, AZA, MMF, dexamethasone pulses | Mean 2.7 wks after therapy | 11–43 mo; mean = 29 mo | PR = 2; MD = 1; CR on = 8; CR off = 6; R before CR = 4; CR within mean 8.4 mo | Medication given for 3–183 mo. d/c of Rx in 6 CR off pts in 6–39 mo. Rx continued in rest others at end of F/U | Anti Dsg 1 and 3: Mean: 100 to 0 at last testing of F/U | NM |
| Author/year | Concomitant Rx | Duration to initial improvement in symptoms after Rtx | Follow up period | Outcome | Duration on medication (Rituximab and previous) | PV Antibody titer changes after Rx (U ml⁻¹) | Adverse effects |
|-------------|----------------|------------------------------------------------------|-----------------|---------|-----------------------------------------------|---------------------------------------------|----------------|
| Craythorne et al. [98]/2011 | Immunosuppressant | NM | 20–35 mo | CR off = 6 within 5–20 weeks of start of therapy | Medication given for 1 mo to 13.2 years | NM | Nausea, cough, chills |
| Kasperkiewicz et al. [99]/2011 | AZA, CycIP, MMF, Pred, Dexamethasone, clobetasol propionate, IVlg, PAIA | NM | 12–59 mo/mean = 24.9 mo | CR off = 6 within 12–59 mo (mean 18.6 mo); CR on = 1 within 26–28 mo (mean 5.4 mo); PR = 1 within 27 mo; R in 9–24 mo after first Rx infusion before CR = 4 | Medication given for 3–99 mo. Rx d/c in 12 mo in 3 CR off pts. Rx coned in others at end of f/u | Anti Dsg1 and 3: Decreased by ~49–100 % (mean 90 %) at end of F/U | Dyspnea, hypotonia, vomiting |
| Kim et al. [100]/2011 | NM | 4 wks after last Rx infusion | 3–43 mo; mean = 15.7 mo | CR off = 16 within 186 days; PR = 5 within 135 days; R = 8 within 11.5 mo F/U in pts with 2 Rx infusions. Death = 1 | Medication given for 3 mo to 71 mo. | Anti Dsg1: 176.2–18.9 Anti Dsg3: 189.2–66.3 | None |
| Reguiai et al. [101]/2011 | Prednisone | Within 3 mo after Rx cycle. | After Rx = 12–71 mo (mean = 41 mo); total = 81 mo | CR on minimal therapy for mean 27 mo after last Rx cycle = 4; CR under Pred 3 mo after last Rx cycle = 1. CR off, mean duration of f/u after d/c of medication was 31 mo after last Rx cycle = 4 | Pred discontinued 12 mo after last Rx cycle | Moderate to high titers of Abs even though pts were in CR in 6/9 pts | None |
| Horvath et al. [102]/2011 | Mycophenolic acid, AZA, Pred, MMF | Within 2–24 weeks (median = 7 weeks) | 32–152 weeks (mean = 94 weeks) | PR on = 4; PR off = 2; CR on = 3; CR off = 3; R = 5 (CR within 36 wks after re-treatment). CR in median 51 wks, PR in 345 median wks | Medication given for 2–13.5 yrs. Rx d/c in CR off pts at 39–64 weeks | Anti Dsg3: Decreased in all but Relapsed pts. Anti Dsg1: 5 pts with positive titers before Rx showed decrease. *One pt with CR off had high titers throughout the Rx period | Nausea, fatigue, neutropenia, sepsis, herpes zoster, flu like symptoms |
| Author/year | Concomitant Rx | Duration to initial improvement in symptoms after Rtx | Follow up period | Outcome | Duration on medication (Rituximab and previous) | PV Antibody titer changes after Rx (U ml⁻¹) | Adverse effects |
|-------------|----------------|-----------------------------------------------------|-----------------|---------|------------------------------------------------|-----------------------------------------------|----------------|
| Feldman et al. [103]/2011 | IVIg | NM | Long term CR pts = 29.6 ± 11.2 mo; R = 40 ± 7 mo | Long term CR off = 11; R = 8 (total 15 relapses) retreatment in R grp lead to long term CR | Pred and immunosuppressive agents tapered and d/c long before Rtx therapy ended | Anti Dsg1 levels increased during relapse in pts with mucocutaneous lesions | NM |
| Leshem et al. [104]/2012 | Pred, AZA, MMF | Mean within 4 mo of first Rtx cycle | Mean = 18 ± 12 mo | No Remission = 4. PR on = 5; PR off = 2; CR on = 15; CR off = 19; CR in median time of 1–4 mo after start of therapy | Medications given for 0–181 mo. d/c in few months after achieving CR | NM | Infusion reaction with first Rtx infusion cycle which could be managed well |
| Cianchini et al. [37]/2012 | Pred | NM | 12–51 mo (mean = 26.5 mo) | PR = 6; CR on = 7; CR off = 29; (CR within 30–150 days, mean = 70 days); R = 20 within 8–64 mo (CR in all PR and R pts with additional 500 mg infusion of Rtx 6 mo after initial infusion) | Medications given for 1–14 yrs. Immunosuppressant d/c with start of Rtx therapy. Pred tapered gradually | NM | None |
| Lunardon et al. [105]/2012 | Pred, AZA, MMF, Dapsone, Cyclop, MTX, IVIg | NM | 12–80 mo | PR on = 7; PR off = 3; CR on = 3; CR off = 11; CR in mean 19 mo | Medication given for 3–251 mo. Concomitant drugs d/c after first Rtx infusion | Data of only 10 pts available. Titer decreased by median—80% | Perirectal phlegmon and intrapelvic abscesses in one pt |
| Kasperkiewicz and Eming et al. [106]/2012 | Pred, AZA, MMF, MTX, PAIA, IVIg | NM | 1–37 mo (mean = 11) | No response = 2; PR = 11; CR on = 20 | Medications given for 0.1–16.6 yrs | Anti Dsg1: returned to normal in 14/24 pts | Infusion related reactions, allergic reactions and infections |
| Balighi et al. [107]/2013 | Pred | 1–20 week. At mean 6.35 weeks | 3–46 mo. (mean = 12 mo) | Initial PR = 21, CR on = 19, R = 21 in mean 8 mo | Medication given for 3–46 mo after starting Rituximab. Duration on medication before Rituximab: NM. All immunosuppressant d/c 1 week prior to start of Rtx therapy. Pred tapered gradually as per improvement | NM | Lung abscess, deep vein thrombosis, pneumonia, sepsis, cavernous sinus thrombosis, generalized arthralgia, Steven Johnson’s syndrome |
| Author/year                  | Concomitant Rx                          | Duration to initial improvement in symptoms after Rtx | Follow up period | Outcome                     | Duration on medication (Rituximab and previous) | PV Antibody titer changes after Rx (U ml \(^{-1}\)) | Adverse effects |
|-----------------------------|----------------------------------------|------------------------------------------------------|------------------|-----------------------------|-----------------------------------------------|-----------------------------------------------|----------------|
| Kanwar et al. [108]/2013    | Pred in 8 pts, P + MMF in one pt        | Within 5 weeks (5–12 weeks)                          | 24–48 weeks.     | Death due to sepsis = 1; PR on = 2; CR on = 3; CR off = 3; CR within mean 8 weeks after start of therapy | Medications given for 2–21 mo. D/c in 8 weeks in CR off pts | ELISA Index values: Anti Dsg1: Pt1: 1372.00; Pt2: 327.07; Pt3: 34.69; Pt4: 32.55; Pt5: 151.23; Pt6: 95.72; Pt7: 117.30; | Infusion related angioedema and sepsis |
| Kolesnik et al. [109]/2014  | PAIA, Pred, AZA, Dapsone               | Within first 4 weeks of therapy                      | 0–45 mo (mean = 22 mo) | PR = 1; CR on = 4; mean duration of therapy use before taper to low dose was 3 to 12.5 mo; CR off = 1, mean duration of f/u after d/c of medication was 34 mo, No relapse. CR within 6.6 mo after first Rtx infusion | Medications given for 1–252 mo             | Anti Dsg1: decreased by 3–85 %; Anti Dsg3: decreased by 0.3–107 % | None |
| Hedin et al. [35]/2014      | Prednisone, immunosuppressant agents   | NM                                                   | 45–78 mo (mean = 51 mo) | PR on = 2; CR on = 26; CR off = 64; mean duration of f/u after d/c of medication was 51 mo with multiple R transformed into CR on retreatment. Median time to R = 15 mo | Medications given for 0–334 mo             | NM                                           | No serious events. Infusion reactions |
| Author/year | Concomitant Rx | Duration to initial improvement in symptoms after Rtx | Follow up period | Outcome | Duration on medication (Rituximab and previous)* | PV Antibody titer changes after Rx (U ml⁻¹) | Adverse effects |
|-------------|----------------|----------------------------------------------------|-----------------|---------|-----------------------------------------------|-------------------------------------------|----------------|
| Kanwar et al. [110]/2014 | AZA | Within 4–16 weeks | 48 weeks | PR = all 15 pts in 4 to 24 wks; R in 4 high dose grp pt and 7 low dose grp pt in 32–36 wks of therapy; CR off = all 15 pts mean duration of f/u after d/c of medication was 4–40 wks subsequent to PR without relapse | Medications given for 0.3 to 7 years. All Immunosuppressant agents d/c 4 weeks prior to Rtx therapy | ELISA Index values: High Dose grp: Anti Dsg1: 400 to 150 in 48 wks; Anti Dsg3: 90 to 20 in 48 wks | Mild Infusion reaction, upper respiratory infection, diarrhea, striae, acneiform eruptions |
| Ojami et al. [111]/2014 | MMF, Pred | Within 3 mo | NM | R = 1; Controlled (PR) = 9 within 3–24 mo after start of therapy; CR on = 4 within 24–36 mo of start of therapy | Medications given for 0.4–10 years. Pred tapered to 10 mg/day | NM | Post infusion febrile reaction |

*Rtx rituximab, Pred prednisone, AZA azathioprine, IVIg intravenous immunoglobulin, CycP cyclophosphamide, Pl plasmapheresis, MTX methotrexate, CR off complete remission off therapy, CR on complete remission on therapy, PR partial remission, PR on partial remission on therapy, PR off partial remission off therapy, CI (PR) clinical Improvement (PR) on doses greater than minimal therapy, R relapse, NR no response, F/U follow-up, d/c discontinue, mo months, d days, pts patients, NM not mentioned, IIF indirect immunofluorescence, ELISA enzyme linked immunosorbent assay, Dsg1 and Dsg3 desmoglein 1 and 3

*Duration on medication included the time period on medication prior to the start of follow-up to this paper.
Adverse Effects Reported in Table 2
Adverse effects in patients on azathioprine and corticosteroids reported in these publications included leukopenia, anemia, thrombocytopenia, pancytopenia, hepatotoxicity, hypertension, gastrointestinal problems, lethargy, weight gain, muscle weakness, adrenal suppression, alopecia, and rash-like skin disorders.

Mycophenolate Mofetil (MMF)

Mycophenolate Mofetil was approved by the FDA in 1995 as an immunosuppressant to prevent organ transplant rejection.

Mechanism of Action
After oral administration, mycophenolate is absorbed rapidly and then gets converted to the active metabolite mycophenolic acid (MPA). This active metabolite inhibits inosine monophosphate dehydrogenase selectively and hence inhibits de novo pathway of purine synthesis in T and B cells, which results in inhibition of T and B cell proliferation [20].

Publications reporting use of MMF as an adjuvant to corticosteroids in PV were included in Table 1. Additional papers which have reported on the use of mycophenolate in patients with refractory PV (previous treatment with corticosteroids and azathioprine was unsuccessful in achieving remission) are summarized in Table 3. Of 31 papers in Table 1, three had included MMF as one of the treatment modalities.

Publication Type, Patient Profiles, and Sample Sizes
The first case series on use of MMF in PV patients was published in 1999.

Four case series were included, with the number of cases included in the individual papers ranging from 9 to 31 cases (a total of 64 patients in four case series); two were case reports describing single patients and two were randomized prospective trials \((n = 94\) and \(n = 21\), respectively). One additional randomized clinical trial enrolled both PV and PF patients \([n = 36\) (PV) + 11 (PF); results were not reported separately for the PV and PF patients in this study] and one retrospective analysis \((n = 18)\) is summarized in the tables. The total number of patients treated with MMF in these 10 reports was 247.

Age at initial diagnosis of PV in these publications ranged from 6 to 78 years.

Medication Use and Duration of PV Before MMF Was Started
Medication use and duration of PV before MMF was started ranged from 1 month to 14 years. During this period patients were on a combination of corticosteroids and azathioprine. At the time mycophenolate was added, the azathioprine was discontinued; however, the patients continued to be on corticosteroids. One publication (Powell et al.) reported on patients in whom multiple medications like methotrexate, cyclophosphamide, IVIg, dapsone, gold, thalidomide, and minocycline along with azathioprine and corticosteroids were tried prior to addition of mycophenolate [21].

The starting dosage of mycophenolate mofetil used was 2–3 g/day in all reports.

Duration of Follow-up
Duration of clinical follow-up of the individual patients after the start of MMF therapy ranged from 5 to 130 months.

Duration Before Any Clinical Improvement Was Noted
First improvement in lesions was noted after 2–24 weeks after addition of mycophenolate to the existing medication regimen.
**Duration to Complete Remission (On and Off Therapy) After Addition of MMF**

Duration to complete remission on therapy was reported in six articles and, ranged from 2 to 16 months, in 104 patients.

Duration to complete remission off therapy was reported in one article and, ranged from 24 to 36 months, in 17 patients.

**Remission**

Of a total of 247 patients, 104 patients achieved complete remission on therapy and 17 patients achieved complete remission off therapy. A total of 76 patients achieved partial remission, and the duration to achieve that ranged from 129 to 150 days after the start of therapy. Failure of MMF was mentioned in four reports (N = 176) in 18 patients who were referred for treatment with rituximab or IVIg. Two patients were still being treated at the time of publication, 29 patients were lost to follow-up or withdrawn from study, and death occurred in one patient.

**Adverse Effects**

Adverse effects in patients on mycophenolate and corticosteroids reported in these publications included gastrointestinal problems, myalgia, neutropenia, and lymphopenia, which were the most common side effects reported. Headache, increased fasting blood glucose level, and hypertension, nausea, depression, pyrexia, redistribution of body fat, eye disease, weight gain, fatigue, and arthralgia were also reported.

In the one publication where enteric coated mycophenolate sodium was used, the side effects reported were headache and increased fasting blood glucose level.

**Intravenous Immunoglobulin (IVIg)**

IVIg was approved by the FDA for primary immune deficiency in 1952 [22].

**Mechanism of Action**

Intravenous immunoglobulins (IVIg) are obtained from a plasma pool of thousands of donors [22].

These immunoglobulins neutralize and slow down the production of circulating pemphigus antibodies [23].

**Publication Type, Patient Profiles, and Sample Sizes**

The studies reporting use of IVIg in PV are summarized in Table 4. The first case series on IVIg in PV was published in 2002.

One case series (n = 6), two case reports describing single patients, and one randomized placebo-controlled double-blind trial (n = 40) are summarized in Table 4, with a total of 48 patients included in these four papers. These reports included patients previously treated with corticosteroids, cyclophosphamide, azathioprine, and methotrexate without adequate response, prior to start of IVIg.

Age at initial diagnosis of PV in these publications ranged from 41 to 78 years.

**Medication Use**

The dosage of IVIg used was 400 mg/kg/day for 5 days followed by long- or short-term single doses of 400 mg/kg/day every 6 weeks for 6 months to 1 year. Concomitant drugs mainly used were corticosteroids in the published studies.

**Duration of PV Before IVIg Was Started**

This ranged from 2 months to 5 years.

**Duration of Total Follow-up**

Duration of total clinical follow-up of the individual patients ranged from 2 months to 2 years.
Duration Before Any Clinical Improvement Was Noted
First improvement in lesions was reported within 2–3 weeks of first IVIg infusion in all 48 patients.

Duration to Start of Taper of Corticosteroids
Only one case series of six patients described the duration to the start of taper of corticosteroids and only mentioned that the median time was 16 days after the start of IVIg infusions.

Duration to Complete Remission (On and Off Therapy)
This information was not available from the publications. However, all reports discussed improvement in all patients treated with IVIg; in six patients this was achieved within 3 weeks and in 29 patients within 3–12 months. Thirteen patients in the placebo group had no improvement.

Adverse Effects in Patients on IVIg Reported in Table 4
Headache, abdominal discomfort, nausea, constipation, lymphopenia, hepatitis C, and palpitations.

Methotrexate
Methotrexate was approved by the FDA for psoriasis in 1971 and for rheumatoid arthritis in 1988.

Mechanism of Action
Methotrexate inhibits the metabolism of folic acid and is used as a chemotherapeutic and immunosuppressive agent. Methotrexate allosterically inhibits dihydrofolate reductase, which plays a role in tetrahydrofolate synthesis. As folic acid is essential for normal cell growth and replication, methotrexate is effective against malignant cell growth and has anti-inflammatory effects [24].

Publication Type, Patient Profiles, and Sample Sizes
The studies reporting use of methotrexate in PV are summarized in Table 5. The first case series on MTX in PV was published in 1969.
Publications reporting use of methotrexate in PV were included in Table 1 (7 of 31 papers included methotrexate), and additional papers that reported on the use of methotrexate as the initial adjunctive treatment to corticosteroids are summarized in Table 5.

Six case series were included, with the number of cases included in the individual papers ranging from 3 to 53 cases (total of 121 patients in six case series), and one retrospective cohort study (n = 30) are summarized in the tables. In all, a total of 151 patients treated with MTX are reported in seven studies.

Age at initial diagnosis of PV in these publications ranged from 20 to 83 years.

Medication Use
The dosage of MTX used in these publications ranged from 12.5 to 150 mg/week. Concomitant drug used along with methotrexate was prednisone.

Duration of PV Before Methotrexate Was Started
This ranged from 11 months to 7 years.

Duration of Follow-up
Duration of clinical follow-up of the individual patients after the start of MTX ranged from 5 to 15 years.

Duration Before Any Clinical Improvement Was Noted
First improvement in lesions was reported within 1–30 weeks after the start of methotrexate therapy.
Duration to Complete Remission (On and Off Therapy)
Duration to complete remission on therapy was reported in six articles and, ranged from 1 to 30 weeks, in 51 patients.
Duration to complete remission off therapy was reported in one article and, ranged from 3 months to 8 years, in 14 patients.

Remission
Of a total of 151 patients, at the end of follow-up, 56 patients had achieved partial remission and the duration to achieve that was within 6 months after the start of MTX therapy; 51 patients had achieved complete remission on therapy; and 14 patients had achieved complete remission off therapy. Twelve patients were lost to follow-up. Treatment was not effective in nine patients. Death unrelated to MTX occurred in six patients.

Adverse Effects in Patients on MTX Reported in Table 5
Nausea, leukopenia, GI upset, fatigue, bacterial infection, bronchopneumonia, septicemia, necrotizing gingivitis, diarrhea, and pyoderma.

Rituximab
Rituximab was approved in 1997 by the FDA to treat B cell non-Hodgkin lymphoma and in 2006 to treat rheumatoid arthritis.

Mechanism of Action
Rituximab is a human–mouse chimeric monoclonal antibody to CD20 antigen on B cells. CD20 is a membrane protein that is involved in activation and proliferation of B cell [25].

Publication Type, Patient Profiles, and Sample Sizes
The studies reporting use of rituximab in PV are summarized in Table 6. The first case series on PV treated by rituximab was published in 2002.
Publications which have reported on the use of rituximab in patients with refractory PV (previous treatment with corticosteroids, azathioprine, methotrexate, mycophenolate, IVIg, and cyclophosphamide were unsuccessful in achieving remission) are summarized in Table 6.
Nineteen case series were included, with the number of cases included in the individual papers ranging from 3 to 84 cases (total of 339 patients in 19 case series), 24 were case reports describing single patients, three open label pilot studies (n = 5, n = 9, and n = 17), one randomized prospective trial (n = 15), two retrospective analysis (n = 25 and n = 19), and one phase 2 clinical trial (n = 40) are summarized in the tables. In all, a total of 493 patients were treated with rituximab.
Age of patients treated with rituximab for PV in these publications ranged from 15 to 86.

Medication Use
The dosage of rituximab used was 375 mg/m² body surface area (BSA) once weekly for 4 weeks or two infusions of 1000 mg at 2 weeks apart. Previously failed treatments before rituximab were prednisone, MMF, AZA, IVIg, MTX, dapsone, CycL, plasmapheresis, protein A immunoadsorption, cyclosporine, dexamethasone, and gold. Concomitant drug used was prednisone, MMF, AZA, and IVIg.

Duration of PV Before Rituximab Was Started
This ranged from 1 months to 23 years.
**Duration of Follow-up**
Duration of clinical follow-up of the individual patients after the start of rituximab therapy ranged from 6 to 80 months.

**Duration Before Any Clinical Improvement Was Noted**
First improvement in lesions was reported within 2 weeks to 8 months after the first rituximab infusion.

**Duration to Complete Remission (On and Off Therapy)**
Duration to complete remission on therapy was reported in 32 articles and, ranged from 1 to 36 months, in 184 patients.

Duration to complete remission off therapy was reported in 22 articles and, ranged from 2 to 59 months, in 229 patients.

**Remission**
Of a total of 493 patients reported in Table 6, at the end of follow-up, 80 patients had achieved partial remission, and duration to achieve that ranged from 3 to 27 months; 184 patients achieved complete remission on therapy; and 229 patients achieved complete remission off therapy. Death due to sepsis occurred in three patients. Relapses were seen in nine patients. No response to rituximab was seen in 11 patients. However, these patients had response after addition of IVIg or additional cycles of rituximab.

**Adverse Effects in Patients on Rituximab Reported in Table 6**
Local pain, nausea, cough, chills, sepsis, and angioedema related to infusion.

**OTHER MEDICATIONS**

**Gold salts** These are widely used in treatment of rheumatoid arthritis. Their action is related to their T cell-mediated immunosuppressive properties [23].

**Plasmapheresis** This is used for removing antibodies from the circulation. Reduction in antibodies triggers production of new antibodies as a result of a feedback mechanism [23].

**Immunoadsorption** With plasmapheresis protective immunoglobulins, albumin, and clotting factors are removed along with harmful pemphigus antibodies. Immunoadsorption selectively traps the harmful pemphigus antibodies through the sulphhydryl filtering membrane. Thus, protective antibodies and plasma components are returned [23].

**Cyclophosphamide** It has been widely used in the treatment of cancer and also as an immunosuppressant. This drug is converted in the liver to its active metabolites aldophosphamide and phosphoramidemustard. These bind to DNA and inhibit its replication, which leads to cell death. It can be given orally as well as intravenously. One report described cyclophosphamide use in seven patients for treating PV in combination with corticosteroids and azathioprine [26].

**Nicotinamide and tetracycline** These were used as steroid-sparing agent in combination with corticosteroids and azathioprine in one study of six patients with PV. Their mechanism of action is unclear [27].
DISCUSSION

In this paper, we have summarized the published literature on the management of PV. The published papers were mostly case reports, case series, observational studies, and only eight randomized controlled trials. As a result of the relative rarity of pemphigus, published randomized trials are limited, which makes it difficult to evaluate the efficacy of different treatment regimens in this disease. This also precludes conduct of a meta-analysis. A Cochrane review published in 2009 concluded that “there is inadequate information available at present to ascertain the optimal therapy for pemphigus vulgaris” [28]. While this remains the case, a summary of the literature provides information on disease course and prognosis as well as medication options, treatment responses, and side effects, which are of relevance to clinicians who treat this disease and patients who suffer from it.

The treatment options for PV have increased over the years. The early publications from the 1970s reported use of high corticosteroid doses over prolonged intervals and significant associated side effects. Later reports on PV management described use of corticosteroids along with steroid-sparing adjuvants, which allows a reduction in the total dose of corticosteroids used over the course of the treatment with a reduction in observed morbidity. The more commonly used steroid-sparing medications in the published reports include azathioprine, methotrexate, and mycophenolate mofetil. More recently, IVIg and rituximab have been used, mainly in patients with recalcitrant PV.

Overall, the mortality and morbidity from PV and the medications used in its treatment are considerably lower in the more recent publications than in the early reports.

The reported treatment response in patients with PV has varied significantly. Prognostic factors that have been identified include initial severity and extent of disease, with higher severity being predictive of poorer prognosis. [29]. Perhaps related to this is the fact that early initiation of treatment before the disease becomes too severe or widespread has been associated with improved prognosis [30, 31]. Once treatment is initiated, good initial response to treatment has also been found to be indicative of a better prognosis [32].

Most reports described medication courses of long duration before remission off therapy was achieved (between 5 and 10 years in the majority of patients with the range across all studies being 3 months to 27 years). However, Herbst and Bystryn described a group of 40 patients in whom 10 (25 %) patients achieved complete and long-lasting remission within 2 years of treatment; a subgroup of patients with PV, with a mild course of the disease requiring short courses of systemic medications or topical medication alone to induce remission [5, 32, 33]; and at the other extreme a subgroup that is resistant to treatment and required high doses and prolonged therapy have also been described [29, 32, 35].

The role of baseline laboratory tests, such as quantification of antibodies as predictors of disease course, has not been established. A recent study reported that a higher level of anti-Dsg1 autoantibodies (≥100 U/mL) at diagnosis was associated with poorer prognosis
in univariate analyses; however, this did not remain significant after adjustment for age [36].

Periodic antibody titers measured by indirect immunofluorescence or ELISA testing have not consistently shown correlation with clinical activity of PV [37]. Most authors in the listed papers reported using clinical response alone to guide medication taper.

Reports using rituximab described remission off therapy in a shorter time frame (ranging from 2 months to 5 years) as compared to other medication combinations; this observation suggested that while the initial side effects may be significant, a shorter total duration of therapy may be possible with use of rituximab. Because rituximab is a more recent drug, first introduced in 1997, long-term side effects are not well characterized at this time.

CONCLUSION

The findings from this review emphasize the importance of early diagnosis of PV, early initiation of treatment, and use of a treatment regimen which includes a steroid-sparing adjuvant to allow a reduced total dose and duration on corticosteroids. For the majority of patients in these reports, a long-term course on medications lasting about 5–10 years was observed; however, subgroups of patients requiring shorter courses or those needing longer-term therapy were also described. In recent publications, commonly used initial regimens include corticosteroids in combination with mycophenolate or azathioprine; whereas, for patients with inadequate response to these regimens, adjuvants such as IVIG or rituximab were used [21, 38, 39]. This review also highlights the need for more controlled trials to determine optimal treatment regimens for patients with PV.

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