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REVIEW

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

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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 immunofluoresence 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 NFkappa B 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

Table 1 Corticosteroids

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
	1	2	3	4	5	6	7
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 At initiation of therapy—61.6 ± 8.1 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 = 3.5 mo)	Prednisone = 20–120 mg/day in 29 pts. No Rx in 1 pt

Table 1 continued

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
	1	2	3	4	5	6	7
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 CyclP 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 I.M. 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 Range/mean (years)	Type of pemphigus vulgaris	Previous Rx	Duration of disease symptoms before CS were started	CS dose
	1	2	3	4	5	6	7
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 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	NM	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, 5.44 pulse courses PP (placebo pulse therapy) (*N* = 9) 6 Placebo tablets 3 days/mo, 6.44 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

Table 1 continued

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
	1	2	3	4	5	6	7
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) Pred (30) 11631 mg (2 mg/kg/day) Pred/AZA (30) 7712 mg (2 mg/kg/day P + 2.5 mg/kg/day AZA Pred/MMF (30) 9798 mg (2 mg/kg/day P + 2 g/d MMF) Pred/CyclP (30) 8276 mg (2 mg/kg/day P + 1 g iv CyclP monthly)
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, IVIg, etanercept, chlorquine	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 + PITAinjections (*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)

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[a]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11	12	13	14
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	DM, 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	NM	Cushingoid symptoms, Infections, GI tract ulceration, CHF, HTN, Diabetes, Osteporosis, 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

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[a]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11	12	13	14
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)	Rx d/c in 2 pts after CR in 1 mo and 1 years 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
Lamey et al. [16]/1992	4–8 weeks	5–20 years	AZA, Cyclp 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

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[a]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11	12	13	14
Werth [46]/1996	NM	At least 500 days	AZA, MTX, CyclP, 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 septicemia = 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 CyclP = 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, CyclP, dapsone	Death = 2, Relapses and still being treated at time of publication = 21, PR on = 4, CR off = 5pts 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	NM	2–19/Mean = 7.7 years	AZA, CyclP, 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	NM

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[a]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11	12	13	14
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 / Pred/ iv bms Symptom resolved: 15 d / 12 d Clinical resolution: 30 d / 25 d	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 4.5 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	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	NM

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[a]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11	12	13	14
Yazganoglu et al. [39]/2006	NM	4 pts were followed for 2–4 years. 1 patientt was lost to F/U	MMF in1 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	1 year	AZA = 3 mg/kg/day, Pred = 80 mg/day	CR on = 8 in DP within 173.2 days of starting therapy, CR on = 9 in PP within 175.6 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	NM	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	NM	1 year Nine were lost to F/U	MMF, AZA, CyclP	CR on; failures; complications (Rx d/c) Pred 23, 6, 1 Pred/AZA 24, 1, 2 Pred/MMF 21, 8, 1 Pred/CyclP 22, 2	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	NM	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	NM	NM	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

Table 1 continued

Author/year	Duration to initial improvement in symptoms after CS 8	Follow up period 9	Concomitant Rx 10	Outcome 11	Duration on medication (corticosteroid) and adjunct[a] 12	PV antibody titer changes after Rx 13	Adverse effects 14
Mignogna et al. [55]/ 2010	NM	Mean = 5.3 years	PITA grp: AZA 50–150 mg/day; CyclP 50–100 mg/day. No PITA grp: AZA 100 mg/day; CyclP 50 mg/day	Death 3 years after CR = 1; CR on = 21; CR off = 13; complete clinical remission within mean 126.6 days of starting therapy in grp with PITA. Complete clinical remission within mean 153.2 days of starting therapy in grp without PITA	NM	NM	Candidiasis in 3 pts, yellowish gingival pellets, gingival neurovascularization in PITA pts. Candidiasis in 7 pts without PITA

Pred prednisone, *CS* corticosteroid, *MMF* mycophenolate mofetil, *AZA* azathioprine, *MTX* methotrexate, *DCP* dexamethasone cyclophosphamide pulse, *IVIg* intravenous immunoglobulin, *Rtx* rituximab, *CydP* 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, *wks* weeks, *d* days, *NM* not mentioned, *PITA* perilesional/intralesional triamcinolone acetonide

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

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 ($n = 20$ and $n = 120$), and five retrospective cohort studies ($n = 15$, $n = 16$, $n = 23$, $n = 32$, 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 erythematous. 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

Author/year	Type of study	*N* M/F	Age range/ mean (years)	Type of pemphigus vulgaris	Previous Rx	Duration of disease before AZA	AZA dose, prednisone dose		
	1	2	3	4	5	6	7		
Mourellou et al. [56]/1995	Retrospective analysis	*N* = 48	NM	NM	NM	NM	40–100 mg Pred	>100 mg Pred	40 mg Pred + 100 mg AZA
							25 pts	8 pts	15 pts
Chaidemenos et al. [1]/2010	Retrospective bi center comparative study	*N* = 36 M/F = 16/20	Mean = 54	Mucosal	NM	4 mo	Monotherapy of Pred (*N* = 17)		Alternate day Pred + daily AZA (*N* = 19)
							Starting dose = 1.5 mg/kg/day		40 mg Pred every other day + 100 mg/d AZA
Chams-Davatchi et al. [57]/2013	Randomized double blind controlled study	*N* = 56 M/F = 23/33	10–75	Mucocutaneous = 33; mucosal = 15; cutaneous = 8	None	5–10 mo	Placebo grp (Pred + placebo)		AZA grp (Pred + AZA)
							Pred: 2 mg/kg up to 120 mg/day		Pred: 2 mg/kg up to 120 mg/day
							Placebo: 2.5 mg/kg		AZA: 2.5 mg/kg

Author/year	Duration to initial improvement of symptoms after AZA	Follow up period	Concomitant Rx	Outcome				Duration on all medications[a]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11				12	13	14
Mourellou et al. [56]/1995	NM	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
				14/15 pts treated effectively in AZA + Pred grp. No deaths in that grp						
Chaidemenos et al. [1]/2010	Monotherapy grp = mean 19. 2 days; Pred + AZA grp = mean 58.53 days	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
				PR on	3	PR on	4	CR and PR on therapy in mean 119.6 days and off therapy in 234.4 days		
				PR off	2	PR off	2			
				CR on	9	CR on	7			
				CR off	1	CR off	2			
				Death	1	Death	0			
				Rx failure	1	Rx failure	4			
Chams-Davatchi et al. [57]/2013	NM	12 mo	Pred	Placebo		AZA		Medications given for 5–22 mo.	NM	Abnormal liver function test, sepsis, abnormal CBC
				CR on (6–11 months)	13	CR on (8–11 months)	16			
				NR	11	NR	6			
				Dropped	4	Dropped	6			

Pred prednisone, *AZA* azathioprine, *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, *R* relapse, *NR* no response, *F/U* follow-up, *d/c* discontinue, *mo* months, *d* days, *pts* patients, *NM* not mentioned

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

Table 3 Mycophenolate mofetil

Author/year	Type of study 1	*N* M/F 2	Age range/mean (years) 3	Type of pemphigus vulgaris 4	Previous Rx 5	Duration of disease before MMF[a] 6	MMF dose 7
Enk and Knop [58]/1999	Case series	*N* = 12 M/F = 5/7	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 M/F = 4/8	41–78	Mucocutaneous = 8; mucosal = 4	AZA, Pred, MTX, CyclP, 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 PV + 11 PF M/F = 21/21	6–74 (Mean = 47.2)	NM	Pred, AZA	NM	35–45 mg/kg per day
S. Beissert et al. [61]/2006	Multicenter randomized controlled non-blinded clinical trial	N = 33 PV + 7 PF; 21 PV pts treated with MMF M/F = 16/23	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 M/F = 8/10	29–67/52	Mucocutaneous = 12, mucosal only = 6	Pred, Pred + MMF in 1 pt only	1–6 yrs	2–3 g/day
S. Beissert et al. [63]/2010	Multicenter placebo controlled non-blinded trial	*N* = 94 M/F = 38/56 75 completed study	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 M/F = 5/4	18–75	NM	Pred + AZA	14.4 mo	Enteric coated—mycophenolate sodium 1440 mg/day (given in 2 divided doses)
Ionnaides et al. [65]/2011	Randomized prospective non-blinded clinical trial	*N* = 36 PV + 11 PF M/F = 18/29	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

Table 3 continued

Author/year	Duration to initial improvement in symptoms after MMF	Follow up period	Concomitant Rx	Outcome	Duration on all medication[b]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11	12	13	14
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[b]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11	12	13	14
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: 24.1 week; Placebo grp: 31.3 week	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

Table 3 continued

Author/year	Duration to initial improvement in symptoms after MMF	Follow up period	Concomitant Rx	Outcome	Duration on all medication[b]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11	12	13	14
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 diseases 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

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

Table 4 Intravenous immunoglobulin

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
	1	2	3	4	5	6	7
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
Amagai et al. [67]/2009	Multicenter randomized controlled double-blind trial	*N* = 40 PV + 21 PF M/F = NM	Mean: placebo grp = 53.1 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 Placebo grp 13 pts 200 mg grp 14 pts 400 mg grp 13 pts
Stojanovic et al. [68]/2009	Case report	1/F	44	NM	Pred, CyclP	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
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

Author/year	Duration to initial improvement in symptoms after IVIg	Follow up period	Concomitant Rx	Outcome	Duration on medication (IVIg)[a]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11	12	13	14
Bystryn et al. [66]/2002	Within 2 wks skin lesions healed by 80 % and oral lesions by 40 %	2–4 mo	Prednisone, CyclP (100–150 mg/day)	Controlled disease activity in all 6 pts. Additional details on duration NM.	Medications given for 2 mo to 5.4 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	8–15 days	After Rx = 90 days; Total = 2 years	Prednisone	10 pts withdrawn. 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 in 90 days	Headache, hepatitis C, lymphopenia, constipation, nausea, abdominal discomfort, palpitations etc
Stojanovic et al. [68]/2009	NM	NM	CyclP, pyridiostigmine bromide for concomitant myasthenia gravis	Stable Remission[b]	1 year	NM	NM
Stojanovic et al. [68]/2009	NM	NM	Pred, pyridiostigmine bromide for concomitant myasthenia gravis	Stable remission after last infusion[b]	6 months	NM	NM

Pred prednisone, *AZA* azathioprine, *IVIg* intravenous immunoglobulin, *CyclP* cyclophosphamide, *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, *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

[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
	1	2	3	4	5	6	7
Lever and Goldberg et al. [69]/1969	Case series	*N* = 5 M/F = 4/1	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][b]/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)[a]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11	12	13	14
Lever and Goldberg et al. [69]/1969	NM	5–7 years	Pred	CR on = 4, improvement = 1. additional details NM	Pred d/c in 1 patientt at fifth year. Tapered in rest on clinical improvement. MTX continued In all patients at end of f/u	IIF: Pt1—1:640 to 1:80 to 1:10 to neg Pt2—1:40 to 1:10 Pt3—1:40 to 1:10 Pt4—1:20 to 1:40 to 0 Pt5—1:80 to 1:40 to 0 to 1:10	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)[a]	PV antibody titer changes after Rx	Adverse effects
	8	9	10	11	12	13	14
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, necrtotizing 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 flare-ups were seen within 23 days of discontinuing MTX at end of f/u	NM	Nausea, mild elevations of transaminase
Baum et al. [76][b]/2012	NM	NM	Pred	Improvement in 21 pts at 6 mo of treatment. Additional details NM	Pred dose tapered	NM	Mild adverse effects

Pred prednisone, *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, *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

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

[b] Only abstract is available for Baum et al. [75]/2012

Table 6 Rituximab

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
	1	2	3	4	5	6	7
Salopek et al. [77]/2002	Case report	1/F	29	Mucocutaneous	Pred, AZA, Pulsed iv CyclP, Pl, IVIg, MMF	9 mo	375 mg/m^2 BSA—6 infusions over 8 weeks
Cooper et al. [78]/2002	Case report	1/M	54	Cutaneous	Pred, AZA, MMF, Pl, IVIg, CyclP	20 mo	375 mg/m^2 BSAonce weekly for 4 weeks
Espana et al. [79]/2003	Case report	1/M	39	Mucocutaneous	Pred, AZA, Pl, CyclP	NM	375 mg/m^2 BSAonce weekly for 4 weeks
Morrison et al. [80]/2004	Case report	1/M	51	Mucocutaneous	Pred, MTX, Dapsone, AZA, minocycline, IVIg MMF, CyclP	56 mo	375 mg/m^2 BSAonce weekly for 4 weeks
Morrison et al. [80]/2004	Case report	1/M	37	Cutaneous	CyclP, Pred, Pl, Dapsone, IVIg	70 mo	375 mg/m^2 BSAonce weekly for 4 weeks
Morrison et al. [80]/2004	Case report	1/F	47	Mucocutaneous	AZA, MMF, IVIg, CyclP,	30 mo	375 mg/m^2 BSA once weekly for 4 weeks
Virgolini Marzocchi [25]/ 2007	Case report	1/F	53	Cutaneous	Pred, CyclP, MTX	120 mo	375 mg/m^2 BSA once weekly for 4 weeks
Wenzel et al. [81]/2004	Case report	1/F	55	Cutaneous	Pred, AZA, CyclP, MTX, MMF, IVIg	156 mo	600 mg (corresponding 375 mg/m^2 BSA) once weekly within 5 weeks
Dupuy et al. [82]/2004	Case report	1/F	34	Mucocutaneous	Pred, CyclP	144 mo	(375 mg/m^2 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/m^2 BSA once weekly for 4 weeks) ×2 at 6 mo interval
Dupuy et al. [82]/2004	Case report	1/M	20	Cutaneous	Pred, dapsone, gold compounds, MMF, IVIg, Pl	24 mo	375 mg/m^2 BSA once weekly for 4 weeks
Kong et al. [83]/2005	Case report	1/F	17	Mucocutaneous	Pred, AZA, MMF, MP, IVIg, Pl	84 mo	375 mg/m^2 BSA once weekly for 4 weeks
Arin et al. [34]/2005	Case report	1/F	60	Mucocutaneous	Pred, MMF, AZA	8 years	375 mg/m^2 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/m^2 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/m^2 BSA once weekly for 4 weeks

Table 6 continued

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
1		2	3	4	5	6	7
Arin et al. [34]/2005	Case report	1/F	57	Mucocutaneous	Pred, MMF, AZA	14 years	375 mg/m^2 BSA once weekly for 4 weeks
Schmidt et al. [84]/2005	Case report	1/M	14	Mucocutaneous	Pred, AZA. Dapsone, MMF, CyclP, staphyloccocal protein A immunoadsorption	2.5 years	375 mg/m^2 BSA once weekly for 4 weeks
Schmidt et al. [85]/2006	Case report	1/F	17	Mucocutaneous	Pred, IVIg, AZA, MMF, MTX	30 mo	375 mg/m^2 BSA once weekly for 4 weeks
Schmidt et al. [85]/2006	Case report	1/F	39	Mucocutaneous	Pred, IVIg, AZA	79 mo	375 mg/m^2 BSA once weekly for 4 weeks
Schmidt et al. [85]/2006	Case report	1/F	68	Mucocutaneous	Pred, IVIg, MMF, dexamethasone-cyclP pulse	64 mo	375 mg/m^2 BSA once weekly for 4 weeks
Schmidt et al. [85]/2006	Case report	1/F	81	Mucocutaneous	Dexamethasone-cyclP pulse	7 mo	375 mg/m^2 BSA once weekly for 4 weeks
Ahmed et al. [86]/2006	Case series	$N = 11$ M/F = 5/6	15–68	Mucocutaneous	Pred, MMF, AZA, MTX, Dapsone,		
Gold,CyclP,Cyclosporine, colchine, tacrolimus	31–219 mo (mean = 68.8 mo)	375 mg/m^2 BSA once weekly for 3 weeks; fourth week—IVIg; 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	Mucocutaneous	AZA, MMF, IVIg, Pl, iv cyclP, cyclosporine, gold	2–96 mo	375 mg/m^2 BSA once weekly for 4 weeks
Marzano et al. [88]/2007	Case series	$N = 3$ M/F = 2/1	Pt1: 51 Pt2: 50 Pt3: 55	Mucocutaneous	AZA, MMF, IVIg, Pred, CyclP	Pt 1: 6 years; Pt 2: 5 years; Pt 3: 4 years	375 mg/m^2 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	Mucocutaneous = 2 Cutaneous = 3	AZA, MMF, IVIg, Pred, CyclP, MTX Pl, Cyclosporine	3–7 years	375 mg/m^2 BSA once weekly for 4 weeks
Cianchini et al. [90]/2007	Case series	$N = 10$ M/F = 5/5	27–63	Mucocutaneous	Pred, AZA, MMF, Pl, CyclP, cyclosporine, extracorporeal photopheresis	1–9 years	375 mg/m^2 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	Mucocutaneous	Pred, IVIg, AZA, MTX, MMF, cyclosporine	4–168 mo (mean = 70.2 mo)	375 mg/m^2 BSA once weekly for 4 weeks

Table 6 continued

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
	1	2	3	4	5	6	7
Shimanovich et al. [92]/2007	Case series	*N* = 5 M/F = 1/4	37–71	Mucocutaneous	Pred, AZA, MMF, Pl, MTX, cyclosporine, Cyclp dexamethasone, dapsone	3–76 mo	375 mg/m^2 BSA once weekly for 4 weeks
Eming et al. [93]/2008	Case series	*N* = 11 M/F = 5/6	37–70/52.1	Mucocutaneous = 7, mucosal = 2; cutaneous = 2	Ped, AZA, MMF	NM	375 mg/m^2 BSA once weekly for 4 weeks
Faurschou and Gniadecki [94]/2008	Case report	1/M	68	Mucocutaneous	Pred, MMF, IVIg	3 years	(375 mg/m^2 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, IVIg	NM	(375 mg/m^2 BSA once weekly for 4 weeks) × 2 at 6 mo interval
Pfutze et al. [95]/2009	Case series	*N* = 5 M/F = 2/3	Mean = 55	Mucosal dominant	CS, MMF	NM	375 mg/m^2 BSA once weekly for 4 weeks
Fuertes 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	*N* = 17 M/F = 8/9	38–75/ mean = 55	Mucocutaneous = 7; mucosal = 6; cutaneous = 4	AZA, cyclosporine, CyclP, MTX, MMF, dapsone, IVIg, PAIA, Pl, Pred, dexamethasone, hydroxychlorquine	3–144 mo	Two infusions of 1000 mg 2 wks apart. Additional Rtx cycle in 2 pts
Craythorne et al. [98]/2011	Case series	*N* = 6 M/F = 3/3	45–71	Mucocutaneous	Pred, AZA, MMF, cyclosporine	0–13 years	375 mg/m^2 BSA once weekly for 8 weeks then monthly ranging from 4 to 10 mo in all pts
Kasperkiewicz et al. [99]/ 2011	Case series	*N* = 8 M/F = 4/4	43–65	Cutaneous = 1; Mucosal = 7	AZA, MMF, Pred, dapsone, cyclosporine, dexamethasone	3–72 mo	375 mg/m^2 BSA once weekly for 4 weeks = 3 pts; 1000 mg twice 2 wks apart = 5
Kim et al. [100]/2011	Retrospective study	*N* = 25 PV + 2 PF M/F = 12/13	24–83	Mucocutaneous = 20; cutaneous = 3; mucosal = 2	AZA, MMF, IVIg, CyclP, steroid pulse therapy, cyclosporine	12–15.5 mo	(375 mg/m^2 BSA once weekly) 2 wks 11 pts 3 wks 11 pts 4 wks 1 pt 5 wks 2 pts
Reguiai et al. [101]/2011	Case series	*N* = 9 M/F = 3/6	14–61	Mucocutaneous	Pred, IVIg, AZA, MMF	NM	375 mg/m^2 BSA once weekly for 4 weeks

Table 6 continued

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
1		2	3	4	5	6	7
Horvath et al. [102]/2011	Case series	$N = 12$ M/F = 8/4	34–80	Mucocutaneous	AZA, Pred, MMF, dapsone, doxyycline, CyclP, 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 analysis	$N = 19$ M/F = 14/5	Mean = 52	Mucocutaneous = 14; mucosal only = 5	Pred with or without immunosuppressive agent	NM	375 mg/m^2 BSA once weekly—12 infusions over 6 mo period
Leshem et al. [104]/2012	Case series	$N = 42$ PV + 3 PF	18–83	Mucosal only = 40	Pred, MTX, AZA, IVIg, Dapsone, Rtx (lymphoma protocol), CyclP	0–163 mo (mean = 25 mo)	Two infusions of 1000 mg 2 wks apart
Cianchini et al. [37]/2012	Case series	$N = 37$ PV + 5 PF M/F = 13/29	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	$N = 24$ M/F = 13/11	26–86/50	Mucocutaneous	Pred, AZA, MMF, Dapsone, CyclP, IVIg, Cyclosporine	3–234 mo (mean = 41 mo)	(375 mg/m^2 BSA once weekly for 4 weeks) ×13 pts. (Two infusions of 1000 mg 2 wks apart) × 11 pts. 1 Rtx cycle = 6 pts 2 Rtx cycle = 8 pts 3 Rtx cycle = 7 pts 4 Rtx cycle = 2 pts 6 Rtx cycle = 1 pt
Kasperkiewicz and Eming et al. [106]/2012	Case series	$N = 33$ PV + 3 PF M/F = 16/20	15–76/52	Mucosal = 29	Pred, AZA, MMF, Pl, MTX,PAIA, IVIg, CyclP, chloroquine, leflunomide	0.1–16 years (mean = 4)	4 × 375 mg/m^2 = 9 pts. 2 × 1000 mg = 25 pts. Two cycles of 4 × 375 mg/m^2 = 1 pt. 7 × 375 mg/m^2 = 1 pt
Balighi et al. [107]/2013	Phase 2 clinical trial	$N = 40$ M/F = 33/7	40–50	Mucocutaneous	Pred, AZA, MMF, Dapsone, IVIg, CyclP	Mean = 35 ± 32 mo	375 mg/m^2 BSA once weekly for 4 weeks

Table 6 continued

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
	1	2	3	4	5	6	7
Kanwar et al. [108]/2013	Open label pilot study	*N* = 9 M/F = 5/4	9–60	Mucocutaneous	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 × 1000 mg + 1 × 140 mg = 1 pt
Kolesnik et al. [109]/2014	Case series	*N* = 6 M/F = 3/3	48–81	Mucocutaneous	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	Mucocutaneous = 61, mucosal = 20, cutaneous = 11	Pred, AZA, MMF, IVIg, MTX, dapsone, CyclP, gold, cyclosporine, cyclosporine, 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	Mucocutaneous	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)	Mucosal = 14;	MMF, AZA, Pred	NM	Two infusions of 1000 mg 2 wks apart; 375 mg/m^2 BSA once weekly for 4 weeks

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)[a]	PV Antibody titer changes after Rx (U ml^{-1})	Adverse effects
	8	9	10	11	12	13	14
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	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 wks 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, IVIg, 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. IVIg d/c before starting Rtx; Pred and Cyclp 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 CyclP 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)[a]	PV Antibody titer changes after Rx (U ml^{-1})	Adverse effects
	8	9	10	11	12	13	14
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 1in 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: 1:4616 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)[a]	PV Antibody titer changes after Rx (U ml^{-1})	Adverse effects
	8	9	10	11	12	13	14
Arin et al. [34]/2005	Pred, MMF	NM	After Rtx = 36 mo; total = 204 mo	CR on	Medication given for 17 years and Pred contd 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 contd 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 contd 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 73 mo. MMF contd at end of f/u	ELISA: Anti Dsg3: 877 to 27	None
Schmidt et al. [85]/ 2006	Dexamethasone-cyclP 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 Dsg3:222 to 0 Anti Dsg1:985 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, 1:60,1:10, to 0 in 16 to 18 mo after Rtx in all 5 pts	Transient fatigue in 3 pts, neutropenia, 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: 24 mo; Pt 2: 21 mo; Pt 3: 2 mo	Pt 1: CR on; Pt 2: PR; 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

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)[a]	PV Antibody titer changes after Rx (U ml^{-1})	Adverse effects
	8	9	10	11	12	13	14
Antonucci et al. [89]/2007	Pred	Pt1: 2 wks after last rtx infusion; Pt2: 4 wks after last Rtx infusion. Pt3: 3 wks afterlast Rtx infusion Pt4: 8 wks after first Rtx infusion Pt5: 5 wks after last Rtx infusion	After Rtx = 11–13 mo	Pt 1: R after 12 mo of CR; CR off again after second cycle of Rtx with no relapse Pt2: CR off in 4 weeks after Rtx therapy Pt3: CR on Pt4: CR off in 12 mo after Rtx therapy Pt5: CR on	Pt1: 6–7 years. Pred d/c 1 mo after end of Rtx therapy. Pt2: 4.1 years. Pred tapered and d/c after 1 mo of Rtx. Pt 3: 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 Rtx infusion = 2 CR on within 2 mo after Rtx infusion = 2 CR on within 1 mo after Rtx infusion = 2 CR on within 1 yr after Rtx infusion = 2 PR within 6 mo after Rtx infusion = 2	Medication given for 1.1–9.1 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 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	Medication given for (range = 4–213 mo) mean 52.1 mo. Corticosteroids tapered by 10 % twice a month after Rtx started controlling disease. 8/21 pts with PV and PF d/c Rx	Reduction in 9/14 pts with CR. High titers even on CR in 5 pts	Headache, asthenia, fever, chills, nausea, pyelonephritis

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)[a]	PV Antibody titer changes after Rx (U ml^{-1})	Adverse effects
	8	9	10	11	12	13	14
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	Between 6 and 12 mo of Rtx therapy CR on = 8 and *R* = 3	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
Pfutze 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

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)[a]	PV Antibody titer changes after Rx (U ml^{-1})	Adverse effects
	8	9	10	11	12	13	14
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 Immunosuppressant withdrawn	NM	Nausea, cough, chills
Kasperkiewicz et al. [99]/2011	AZA, CyclP, MMF, Pred, Dexamethasone, clobetasol propionate, IVIg, 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 Rtx infusion before CR = 4	Medication given for 3–99 mo. Rx d/c in 12 mo in 3 CR off pts. Rx contd 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 Rtx 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 Rtx 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 Rtx cycle.	After Rtx = 12–71 mo (mean = 41 mo); total = 81 mo	CR on minimal therapy for mean 27 mo after last Rtx cycle = 4; CR under Pred 3 mo after last Rtx cycle = 1. CR off, mean duration of f/u after d/c of medication was 31 mo after last Rtx cycle = 4	Pred discontinued 12 mo after last Rtx 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)	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 34.5 median wks	Medication given for 2–13.5 years. 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

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)[a]	PV Antibody titer changes after Rx (U ml^{-1})	Adverse effects
	8	9	10	11	12	13	14
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 years. Immunosuppressant d/c with start of Rtx therapy. Pred tapered gradually	NM	None
Lunardon et al. [105]/2012	Pred, AZA, MMF, Dapsone, CyclP, 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 years	Anti Dsg1: returned to normal in 14/24 pts Anti Dsg3: returned to normal in 11/32 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 Final, CR = 40 within mean 10.13 mo (between 0.5 and 23 mo) after start of therapy	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

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)[a]	PV Antibody titer changes after Rx (U ml^{-1})	Adverse effects
	8	9	10	11	12	13	14
Kanwar et al. [108]/2013	Pred in 8 pts, P + MMF in one pt	Within 5 weeks (5–12 weeks)	24–48 weeks. (Mean = 33.4 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: 1372-0.12 Pt2: 327-0.73; Pt3: 34.69- 10.01; Pt3: 32.55-2.2; Pt4: 1517.2-23.05; Pt5: 95.7-0; Pt6: 117.3-14.15. Anti Dsg3: Pt1:888-42; Pt2: 872-82; pt3: 1162-3; pt4: 124-132; Pt5: 63-0.97; Pt6: 25-0; pt7: 839-138	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
Heelan 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

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)[a]	PV Antibody titer changes after Rx (U ml^{-1})	Adverse effects
	8	9	10	11	12	13	14
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 Low dose grp: Anti Dsg1: 310 to 60 in 48 wks Anti Dsg3: 180 to 70 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, *CyclP* 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

[a] 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/m^2 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, CyclP, 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

Other Less Commonly Used Adjuvants from Studies Listed in Table 1

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 sulfhydryl 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 phosphoramide mustard. 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 ($\geq$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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