

# The Demographic Attributes, Clinical Features, and Optimal Management of 143 Patients with Pemphigus: A Retrospective Observational Study from a Tertiary Care Center of India

## Abstract

**Background:** This retrospective study was to understand the clinico-epidemiologic and therapeutic aspects of pemphigus patients attending our clinic. **Methods:** We analyzed charts of 143 (M: F; 51:92) pemphigus patients having variable severity recorded between 2009 and 2019. Therapies were customized based on patient's age, disease severity, comorbidities, compliance prospects, and affordability. The patients were monitored monthly and as needed for therapeutic outcome in terms of disease control, reduced hospitalization, remission/relapse, and drug toxicity. **Results:** These patients were aged 15 to 86 years, the majority, 68 (47.5%), was 41 to 60 years of age. The pemphigus vulgaris in 83.9% patients was the commonest variant. Treatment regimens were; dexamethasone-cyclophosphamide-pulse (DCP) therapy in 51.2%, dexamethasone-azathioprine-pulse (DAP) therapy in 11%, dexamethasone-pulse (DP) therapy in 5.5%, rituximab in 24.4%, IVIg in 5.5% patients, and oral corticosteroids with or without adjuvant. Remission occurred after 2–17 (mean 5.8) DCP doses; 14 and 7 patients achieved remission for  $\geq 2$  y and  $\geq 5$  y, respectively. Rituximab was effective to treat both new and relapsed cases (n = 31). Additional treatment with another adjuvant prolonged remission in seven patients relapsed 12–16 months after treatment with rituximab alone. Overall, oral corticosteroids alone and DAP therapy showed unsatisfactory response. Adverse effects seen in 41.9% of patients were mainly corticosteroids related. **Conclusion:** The overall clinico-epidemiologic spectrum of pemphigus and therapeutic efficacy of DCP, DAP, or corticosteroids in this study was in sync with the literature. Combining rituximab and corticosteroids plus an immunomodulator initially (phase-1), followed by immunomodulator alone for one year (phase-2) will improve long-term (phase-3) therapeutic outcome. IVIg was effectively useful in patients with concurrent infections.

**Keywords:** Autoimmune bullous disease, azathioprine, cyclophosphamide, DAP therapy, DCP therapy, intravenous immunoglobulins, mycophenolate mofetil, OMP therapy, pemphigus, pemphigus foliaceus, pemphigus vulgaris, prednisolone, rituximab

## Introduction

Pemphigus is a group of autoimmune mucocutaneous blistering disorder with a protracted clinical course marked by remissions, relapses and a propensity to end fatally. Clinico-immunopathologically, the two commonest and distinct varieties include pemphigus vulgaris (PV) and pemphigus foliaceus (PF) with their variants pemphigus vegetans (PVeg) and pemphigus erythematosus (PE), respectively. However, with better understanding of immunopathogenesis uncommon variants such as pemphigus herpetiformis, IgA pemphigus, and paraneoplastic pemphigus having well-identified autoantigens too have been recognized.<sup>[1,2]</sup>

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Systemic corticosteroids with or without immunomodulators have been the mainstay of treatment and have substantially improved prognosis in an otherwise fatal disease.<sup>[3]</sup> After remission, achieved often by high-dose corticosteroids, the patient may need them for life because of chronic relapsing nature of pemphigus. The addition of immunomodulator agents such as cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin (IVIg), or other adjuvant(s) to corticosteroid regimens has significantly reduced adverse effects of prolonged

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corticosteroid therapy, morbidity and mortality in pemphigus.<sup>[3]</sup> In addition to oral corticosteroids, dexamethasone-cyclophosphamide pulse (DCP) therapy remains a standard therapeutic option for pemphigus, at least in India, for the last more than three decades.<sup>[3-10]</sup> Rituximab, an anti-CD20 monoclonal antibody, has been introduced lately to treat severe, recalcitrant or relapsing pemphigus.<sup>[11-15]</sup> In view of high efficacy, a recent consensus statement recommends rituximab as first-line steroid-sparing agent to treat moderate to severe pemphigus.<sup>[16]</sup> However, the selection of a treatment regimen is often dictated by age of the patient, the clinical type, severity and rate of progression of the disease, concurrent comorbidities, and very often cost and availability of therapy. While treatment strategies require customization for each patient, the choice of first-line corticosteroid and adjuvant differ substantially. Herein we share our clinico-therapeutic experience of 143 patients with pemphigus treated and followed up in our institution.

## Patients and Methods

The clinical records of all patients diagnosed with pemphigus between 2009 and 2019 in dermatology outpatient clinic were analyzed retrospectively for age, gender, age at onset and duration of disease, clinical variants and severity of pemphigus, concurrent comorbidities, and therapeutic outcome. The diagnosis of pemphigus was primarily clinical based on characteristic flaccid blisters and/or erosions, and confirmed by positive Tzanck smears and histopathology. The direct immunofluorescence (DIF) studies were undertaken for the affording patients. The disease severity was scored as mild (1+), moderate (2+), severe (3+) and extensive (4+) based on the extent of involvement and severity of the symptoms [Table 1].<sup>[8]</sup> All the patients were screened for diabetes, hypertension, autoimmune disorders, internal malignancy, and pulmonary tuberculosis (PTB). Detailed menstrual and obstetric history was obtained and absolute contraception advised for all female patients.

Lab investigations included complete blood counts, blood sugar, thyroid and hepato-renal function tests, urinalysis,

chest x-rays and ECG were carried out before, during and after the completion of treatment. Skin swabs and blood samples were subjected for aerobic culture and sensitivity for antimicrobials and repeated when indicated. Additionally, Mantoux test/computed tomography scan to exclude pulmonary tuberculosis, and echocardiography for cardiac fitness were performed before initiating treatment.

## Treatment protocols

Pending investigations all patients were initiated treatment with oral prednisolone 40-60 mg (1 mg/kg body weight) daily, amoxiclavunat 625 mg PO or 1 gm intravenously thrice daily, vaseline gauge dressings after cleansing of erosions with normal saline, and other supportive measures for fluid and electrolyte maintenance. Oral prednisolone was tapered off by 10 mg every month after initiation of selected therapy or after clinical remission when used in combination.

Various treatment protocols used are listed in Table 2. All patients were explained advantages, disadvantages and approximate cost of treatment options for an informed choice. The actual treatment was individualized for all patients on the basis of age, disease severity, compliance prospects for the selected regimen, and affordability. The decision to shift from one regimen to another was broadly on the basis of poor clinical response, noncompliance, intolerable adverse effects, and affordability.

The DCP therapy protocol used in our patients was without modifications and typically consists of a 4-phase treatment.<sup>[8,10]</sup> Children, young, unmarried adults and married patients yet to complete their family were treated with dexamethasone pulse alone or combined with daily PO azathioprine 50-100 mg/d, mycophenolate mofetil (MMF) 500 mg twice/d, or dapsone 100 mg/d. The patients who were intolerant or noncompliant to DCP therapy were treated with dexamethasone pulse (DP), oral prednisolone, or betamethasone oral mini-pulse (OMP) therapy alone or with an adjuvant as per protocol.<sup>[8-10]</sup>

After 2013 when rituximab became available, it was used as per rheumatoid arthritis protocol described previously.<sup>[17,18]</sup>

**Table 1: Disease severity score\***

Severity	Cutaneous involvement	Mucosal involvement
Mild (1+)	10% BSA involvement. Able to carry out daily routine without discomfort (or) localization to oral mucosa only.	Only localized to buccal mucosa. No difficulty in chewing or swallowing.
Moderate (2+)	10-25% BSA involvement along with oral mucosal involvement. Able to carry out daily routine with discomfort.	Buccal and gingivolabial mucosal involvement. Difficulty for solid food intake.
Severe (3+)	25-50% BSA involvement along with oral mucosal involvement. Unable to carry out daily routine.	Extensive oral mucosal involvement. Difficulty for semisolid food intake.
Extensive (4+)	>50% BSA involvement along with mucosal involvement. Bedridden or has complications.	Extensive oral mucosal lesions. Other mucous membranes involvement. Difficulty in swallowing liquids also (Unable to take anything orally).

\*Modified after Mahajan *et al.*<sup>[8]</sup>

**Table 2: Treatment protocols**

Treatment protocol	Treatment schedule				Remarks
	Phase 1	Phase 2	Phase 3	Phase 4	
DCP therapy	Dexamethasone 100 mg in 500 ml 5% dextrose by slow IV infusion over 3-4 h on three consecutive days given once in 28 days + cyclophosphamide 500 mg IV on 2nd day of pulse, and cyclophosphamide 50 mg/day PO intervening between two pulses. This comprised one dose of DCP	Six more doses were given as in phase 1	Cyclophosphamide 50 mg/day PO given for 1 year	Follow-up for clinical cure/relapse (if any) without any pharmacotherapy	In phase 1, prednisolone (40 mg/d, PO) and/or interval dexamethasone pulse 1 (100 mg in 500 ml 5% dextrose by slow IV infusion over 3-4 h) for two consecutive days at 2 weeks was given in patients with poor control of the disease. Blood pressure and pulse rate and were monitored at hourly interval.
DAP	Dexamethasone 100 mg in 500 ml 5% dextrose by slow IV infusion over 3-4 h on three consecutive days given once in 28 days + Azathioprine 100 mg/day PO in between two pulses. This comprised one dose of DCP	Six more doses were given as in phase 1	Azathioprine 100 mg/day PO given for 1 year	Follow-up for clinical cure/relapse (if any) without any pharmacotherapy.	In phase 1, oral dapsone 100 mg/d or azathioprine 100 mg/d or cyclophosphamide 50 mg/d was added in patients with poor control of the disease
DP therapy	Dexamethasone pulse without adjuvant immunomodulator given as above. This comprised one dose of DCP	Six more doses were given as in phase 1	Follow-up for clinical cure/relapse (if any) without any pharmacotherapy		Dapsone 100 mg/d, azathioprine 100 mg/d or cyclophosphamide 50 mg/d PO was added in patients with poor control of the disease
OMP	Betamethasone 5 mg given PO on 2 consecutive days every week.	Follow-up for clinical cure/relapse (if any) without any pharmacotherapy.			Dapsone 100 mg/d, azathioprine 100 mg/d or cyclophosphamide 50 mg/d PO was added in patients with poor control of the disease
Rituximab i.v. infusion	1 gm x 2 doses given 2 weeks apart	Follow-up for clinical cure/relapse (if any) without any pharmacotherapy			Prednisolone 40 mg/d, azathioprine 100 mg/d, cyclophosphamide 50 mg/d or mycophenolate 500 mg twice daily PO was added in patients with poor control or relapse of the disease
IVIg	0.4 g/kg bodyweight, given by IV infusion for 5 days	Follow-up for clinical cure/relapse (if any) without any pharmacotherapy			Prednisolone 40 mg/d, azathioprine 100 mg/d, cyclophosphamide 50 mg/d or mycophenolate 500 mg twice daily PO was added in patients with poor control or relapse of the disease

DCP, dexamethasone + cyclophosphamide pulse; DAP, dexamethasone + azathioprine pulse; DP, dexamethasone pulse; i.v., intravenous; IVIG, Intravenous immunoglobulin; OMP, oral mini pulse; PO, per oral. Note: Blood pressure and pulse rate were monitored at hourly interval in all patients treated with i.v. dexamethasone pulse with or without adjuvant

Briefly, premedication with IV pheniramine maleate 25 mg, hydrocortisone 100 mg, and oral paracetamol 500 mg was given half an hour prior to infusion. Two doses of 1 g of rituximab diluted in 250 mL of 5% dextrose were administered two weeks apart by slow IV infusion (10 mL/h) and increased by 10 mL/h every 20 min to a maximum of 80 mL/h. Blood pressure, pulse rate, and temperature were monitored at half hourly interval. In case of infusion reaction, after immediately stopping the infusion the patient was treated symptomatically with additional doses of premedication drugs. Rituximab infusion was resumed at a slower rate half an hour after infusion reaction subsided.

Patients having moderate to severe disease with clinical/laboratory evidence of cutaneous/systemic infection were treated with IVIg 0.4 gm/kg body weight/d for 5 days,

appropriate antimicrobials and other supportive treatments followed by oral prednisolone 40 mg/d with or without an adjuvant thereafter and monitored for remission/relapse.

### **Treatment outcome measures**

Patients were monitored every month for clinical activity of the disease and therapy-associated adverse effects until remission and once in three months thereafter or as and when needed/new lesions appeared. Early and late treatment endpoints, complete remission, relapse, and treatment failure were defined as per the recent consensus statement.<sup>[19]</sup> Persistence of old lesions or appearance of new lesions, presence of Tzanck cells, and positive Nikolsky's sign were considered signs of continued disease activity, poor therapeutic response, and relapse. All patients with poor response or relapse were retreated similarly with additional

intervening oral prednisolone with or without azathioprine/cyclophosphamide/mycophenolate mofetil or by switching over to a different regimen. Patients who relapsed after rituximab were retreated as earlier along with prednisolone 40 mg/d plus azathioprine 100 mg/d, cyclophosphamide 50 mg/daily, or MMF 500 mg twice/d for the next 6 months or until remission when the dose of prednisolone was tapered off by 10 mg every month. They received selected immunomodulator for one more year and remained under follow-up. Oral lesions persisting after skin lesions had healed were treated with intralesional triamcinolone 40 mg and clotrimazole + benzocaine + beclomethasone mouth paint after ruling out/empirically treating candidal/herpetic stomatitis.

### Statistical methods

MS Office™ Excel® software was used to tabulate and analyze the data. The continuous data are presented as mean, standard deviation and categorical variables are presented as frequencies and percentages. Median ± IQR was calculated for data having extreme values with wide and uneven distribution.

### Results and Observations

Table 3 depicts baseline characteristics of all patients. There were 143 newly diagnosed patients with pemphigus comprising 51 (35.7%) males and 92 (64.3%) females (M: F; 1:1.8) aged 15 to 86 years. The age at onset was 21 to 60 years in 109 (76.2%) patients with majority, 122 (85.3%) patients, having the disease for ≤1 year. DIF results available for 11 (PV 8, PF 3) patients showed features consistent with the clinical diagnosis. Overall, 30 patients had 39 systemic comorbidities.

### Disease profile

There were 120 (83.9%) patients with PV and 20 (11.9%) with PF. PVeg and PE were diagnosed in four and two patients, respectively. Of the PV patients, 49 (41.9%) had cutaneous lesions alone and 110 (91.7%) had mucocutaneous involvement. The mucosal lesions had preceded the skin involvement by 3–9 months in half of them. Three (2.1%) patients with gingival erosions remained undiagnosed for ≥10 years until skin lesions appeared. Exclusive mucosal involvement occurred in 10 (8.3%) patients only. Cutaneous involvement was mild (1+) in 73 (51%) and extensive (4+) in 5 (3.5%) patients. Severity of cutaneous disease was moderate (2+) in 38 (26.6%) and severe (3+) in 18 (12.6%) patients, respectively. Two patients with PF had extensive (4+) erythrodermic disease.

Mucosal involvement was mild (1+) in 68 (56.7%), moderate (2+) in 29 (24.2%), severe (3+) in 10 (8.3%), and extensive (4+) in 3 (2.5%) patients, respectively. Other than oral, ocular, genital and/or genital mucosae were also involved in 8 (6.8%) patients with severe or extensive mucocutaneous PV. While one patient each with Pveg

**Table 3: Baseline characteristics of patients with pemphigus**

Baseline Characteristics		Number of patients (%) <i>n</i> =143
Gender	Males	51 (35.7)
	Females	92 (64.3)
	Male: Female	1:1.8
Age	10-20 years	04 (2.8)
	Range (Mean)	21-40 years
	15-86 (48.5±14.8) y	41-60 years
		61-80 years
		>80 years
Age at onset	10-20 years	05 (3.5)
	Range (Mean)	21-40 years
	15-86 (47.6±15.3) y	41-60 years
		61-80 years
		>80 years
Duration of disease	<3 mo	69 (48.3)
	Range (Median±IQR)	>3 mo -6 mo
	1 week-27 y	>6 mo-1 year
	(0.3±0.2-0.7) y	>1-5 years
		>5-10 years
		>10 years
Disease profile	Pemphigus vulgaris	120 (83.9)
	Pemphigus vegetans	04 (2.8)
	Pemphigus foliaceus	17 (11.9)
	Pemphigus erythematous	02 (1.4)
Disease severity	<b>Cutaneous lesions</b>	<b>Mucosal lesions</b>
Mild (1+)	73 (51.0)	68 (56.7)
Moderate (2+)	38 (26.6)	29 (24.2)
Severe (3+)	18 (12.6)	10 (8.3)
Extensive (4+)	05 (3.5)	3 (2.5)
Comorbidities	Hypertension	14 (9.8)
	Diabetes mellitus	09 (6.3)
	Hypothyroidism	05 (3.5)
	Others*	11 (7.7)

\*Others include; Coronary artery disease (*n*=3), Pulmonary tuberculosis (*n*=3), HIV infection (*n*=1), Hepatitis C infection (*n*=1), Chronic kidney disease (*n*=1), Aortic valve replacement surgery (*n*=1), Chronic obstructive pulmonary disease (*n*=1)

had mild (1+) or severe (3+) orogenital or oral mucosal involvement, it was mild (1+) in 2 (11.8%) patients with extensive PF. None of the two patients with PE had mucosal involvement. Overall, the severity of mucosal and cutaneous lesions was not commensurate.

### Treatment outcome

Sixteen patients with mild (1+) PV on initial treatment with oral prednisolone or betamethasone OMP did not return after first or second monthly visit and are excluded from treatment outcome analysis. Table 4 depicts treatment status of 127 (88.8%) patients. Nineteen (11.5%) patients with mild (1+) PV continued oral corticosteroids with or



Table 4: Treatment status of 127 patients

Treatment regimen	Description	Number of patients at start of treatment phase	Number of patients at completion of treatment phase	Drop outs during the treatment phase	Number of patients shifted to other regimens
DCP therapy (n=65)	Phase 1	65	43	14	8
	Phase 2	43	36	4	3
	Phase 3	36	27	3	6
	Phase 4	27	21	6	-
DAP Therapy (n=14)	Phase 1	14	10	1	3
	Phase 2	10	5	3	3
	Phase 3	5	2	2	1
	Phase 4	2	0	0	0
DP Therapy (n=7)	First line therapy	7	Lost to follow-up, n=3; Shifted to DAP, n=3 (presently in phase 3) Shifted to Oral prednisolone + dapsone, n=1 (no follow-up)		
Oral corticosteroids with or without an adjuvant (n=19)	Betamethasone OMP	4	They received treatment for 8-12 mo and remained in remission with mild recurrences off and on.		
	Prednisolone	3	But have been irregular in follow-up.		
	Prednisolone + AZT	7			
	Prednisolone + CP	5			
Rituximab (n=31)	First line therapy	15	Relapsed (n=7) after 14-16 mo	Retreated with RTX + Prednisolone (tapering doses) + AZT, CP or MMF	
	Shifted from other treatments	16			
IVIg (n=7)	First line therapy	7	Follow on treatment for one year given includes: RTX (n=2), Prednisolone (tapering doses) + CP (n=2), MMF (n=1)		

AZT, azathioprine; CP, Cyclophosphamide; DAP, Dexamethasone azathioprine pulse; DCP; Dexamethasone cyclophosphamide pulse; DP, Dexamethasone pulse; IVIg, Intravenous immunoglobulin; MMF, Mycophenolate mofetil; mo, months; OMP, oral mini pulse; RTX, Rituximab

without an adjuvant; prednisolone + azathioprine (n = 7), prednisolone + cyclophosphamide (n = 5), OMP (n = 4), prednisolone (n = 3) for 8 to 12 months. They were continued treatment with adjuvant alone for another year and are in remission for  $\geq 2-3$  years reporting occasional lesions responding to topical corticosteroids. However, they remain irregular in follow-up.

Sixty five (51.2%) patients (PV n = 57, PVeg n = 1, PF n = 7) were initiated DCP therapy. Twenty-seven (41.5%) patients dropped out in various phases of DCP therapy. Eight patients were shifted to domiciliary treatment with oral prednisolone plus azathioprine or cyclophosphamide after seven DCP doses in phase 1 because of poor compliance imputed to frequent traveling, and in another patient the treatment was changed to OMP therapy because of mood disorder. They remained irregular in follow-up despite repeated counseling. Presently, 21 patients in phase-4, six patients in phase-3 and three patients in phase-2 remain under regular follow-up and are in remission. In phase-4, fourteen patients for  $\geq 2$  years and seven patients for  $\geq 5$  years have been in remission. In general, 2-17 (mean 5.8) DCP doses were needed in phase 1 to achieve remission. Patients with initial mild disease and good compliance needed less number of DCP doses. Only two patients, one with moderate mucocutaneous disease, hypertension and autoimmune hypothyroidism and another noncompliant patient needed maximum of 14

and 17 DCP doses in phase 1 for remission. Four patients with severe PV required intervening steroids between two DCP doses either as oral prednisolone/betamethasone OMP or 1-2 intervening DP(s). With counseling, six patients after one DCP dose, two patients with relapse in phase 2, and one patient with poor control even after 12 DCP doses opted for rituximab treatment and are in remission for  $\geq 3$  years thereafter.

Dexamethasone pulse therapy without any adjuvant was started in 7 (5.5%) PV patients having either mild disease or were young, unmarried individuals. Three patients did not continue the treatment after the first, second, and seventh DP without assigning any reason. Owing to a poor response to seven dexamethasone pulses, azathioprine was added for three patients. They achieved remission in the next 5-6 months and are presently in phase 3 of dexamethasone-azathioprine pulse (DAP).

Fourteen (11%) patients (PV n = 10, PVeg n = 2, PF n = 2) received DAP therapy as first-line treatment. Five patients, two patients each in phase 1 and one patient in phase 2 after receiving 1, 3, and 5 pulses respectively, were lost to follow-up. Two of them revisited a year later with relapse. One young PF patient with poor control even after ten DAP doses improved after azathioprine was switched with mycophenolate mofetil 500 mg twice/d. One patient each having CKD, hematemesis, or avascular necrosis of femoral head, two cases with relapse, and two patients

with poor control from DAP were treated successfully with rituximab + adjuvant regimens without relapse for two years now.

Apart from sixteen patients who were shifted from other regimens (DCP  $n = 9$ , DAP  $n = 7$ ), rituximab was opted as first-line treatment by 15 (11.8%) patients (PV  $n = 14$ , PF  $n = 1$ ). The oral prednisolone was tapered off by 10 mg every month after second dose of rituximab. No intervening immunomodulator was given. One patient, a 48-year-old woman with PV, died at home of unascertained cause 10 days after receiving first dose. Six patients with PV and one patient with erythrodermic PF relapsed after 12 to 16 months of treatment. They were re-treated with rituximab, oral prednisolone in tapering doses plus either azathioprine or MMF as per protocol. All these patients have been in remission for  $\geq 4$  years now.

IVIg was given in seven (5.5%) patients (PV  $n = 6$ , PF  $n = 1$ ) having severe (five patients) or extensive (one patient) disease, septicemia (four patients), or one patient each with past aortic valve replacement, mild aortic valve disease, and paraplegia. Extended treatment with rituximab (in two patients) alone, cyclophosphamide (in two patients), MMF (in one patient), or azathioprine (in one patient) given for one year was remittive for  $\geq 3$  years now.

In general, oral lesions were recurring, recalcitrant to treatment, or took a longer (mean 7.6 mo) to heal compared with cutaneous lesions (mean 5.4 mo).

### **Adverse effects and major complications of therapy**

All patients with pre-existing comorbidities were managed under expert supervision of concerned internists. The two or more adverse effects noted in 60 (41.9%) patients are tabulated [Table 5]. The transient hematological abnormalities were seen in 10 (16.7%) patients normalized after withdrawal of cyclophosphamide/azathioprine. The majority of the adverse effects were seen in patients receiving corticosteroids. Musculoskeletal symptoms in 33 (55%), gastrointestinal disturbances in 12 (20%), and neuropsychiatric abnormalities and weight gain/iatrogenic cushingoid in 14 (23.3%) patients each observed after approximately 8–10 months were normalized in 1–6 months after treatment cessation. Disturbed sleep was reported every time after DCP/DP by eight patients that normalized after withdrawal of dexamethasone in phase 3. Epigastric pain/dyspepsia and hiccups in two patients each and diarrhea in one case occurred every time on second day of DCP therapy. Hiccups were also encountered every time after OMP by one patient. These symptoms could be controlled with antacids and H<sub>2</sub> blockers. Transient hypertension, hyperglycemia, and tachycardia without ECG abnormalities in one patient each developing on second day of DCP or DAP normalized after oral nifedipine or insulin.

Irreversible amenorrhea, irregular and scanty menstrual cycles were reported by 12 (20%) women after 5–7 months of DCP therapy.

Post-treatment reactivation of PTB occurred in four patients (DCP,  $n = 2$ ; DAP,  $n = 1$ ; rituximab,  $n = 1$ ). Herpetic stomatitis in four and herpes zoster in two patients, respectively, occurred during DCP therapy. All these patients were treated appropriately. Avascular necrosis of femoral head in one patient after 8 doses of DAP was another notable adverse effect. One patient each died 2 weeks after first dose of DCP or rituximab therapy/hospital discharge. Except for infusion reaction in two, fatal septicemia, and reactivation of pulmonary tuberculosis in one patient each, rituximab was well tolerated. One 25-year-old male patient with PF relapsed within a year of treatment with rituximab and was retreated similarly. He was additionally prescribed MMF during intervening period but he did not follow-up further. While updating records recently, the parents revealed that the disease had relapsed again last year within 2 months after stopping MMF with fatal ending. No adverse effects were noted from IVIg.

### **Discussion**

Over all clinico-demographic features of pemphigus in our patients such as; it affecting both genders equally at any age particularly in their middle ages, PV and PF of variable severity being the commonest variants, oral lesions of severity disproportionate to that of skin lesions preceding by months in half of them, commonly complicated by herpetic stomatitis or oral candidiasis, and taking longer to heal were in sync with what is described in the literature.<sup>[5–9,20–24]</sup> Although seems fortuitous, the presence of hypertension, diabetes mellitus, hypothyroidism, CAD, AVR, COPD, HIV infection, hepatitis C virus infection, and past PTB in our patients reflects the significance of pre-treatment screening/management.

Treatment with systemic corticosteroids forms the mainstay of pemphigus treatment despite no consensus for the optimal dose for using a very high, intermediate, or low dose regimen.<sup>[25,26]</sup> Much of the pemphigus-related mortality currently is from complications of long-term corticosteroid therapy. However, strategies designed to reduce their adverse effects such as their use in intermittent high dose and addition of immunomodulator drugs as adjuvant, despite their own adverse-effects, has improved the prognosis in pemphigus. Since its introduction to treat pemphigus patients in the 1980s, DCP therapy had remained treatment of choice till date amongst Indian dermatologists. It showed advantage of rapid healing, reduced morbidity, and hospital stay with possibility of long-term remissions.<sup>[6–8,27]</sup> Similar advantages were observed in all our 65 patients who received DCP therapy but a dropout rate of 41.5% remains significantly high. Such a high dropout rate has been imputed mostly to high cost because of repeated hospitalization and investigations,

**Table 5: Adverse-effects and major complications of therapy noted in 60 patients\***

Adverse effects		DCP therapy	DAP therapy	DP therapy	Pred	OMP	Rituximab
Number of patients (%)		(n=38)	(n=11)	(n=3)	(n=4)	(n=1)	(n=3)
Hematological 10 (16.7)	Transient thrombocytopenia	4	1	–	–	–	–
	Transient leucopenia	3	–	–	–	–	–
	Anemia	2	–	–	–	–	–
Cardiovascular 3 (5)	Transient tachycardia	1	–	1	–	–	–
	Hypertension	1	–	–	–	–	–
Gastrointestinal 12 (20)	Altered taste	1	–	–	–	–	–
	Epigastric pain	2	–	–	–	–	–
	Anorexia	2	3	–	–	–	–
	Hematemesis	1	–	–	–	–	–
	Hiccups	2	–	–	–	1	–
	Diarrhea	1	–	–	–	–	–
	Neuropsychiatric 14 (23.3)	Sleep disturbances	5	3	–	–	–
	Psychosis	2	–	–	–	–	–
	Dizziness	3	–	1	–	–	–
Obstetrical 12 (20)	Menstrual irregularities	11	1	–	–	–	–
Musculoskeletal 33 (55)	Muscle weakness	7	2	–	–	–	–
	Arthralgia	1	1	–	–	–	–
	Malaise/Lethargy	18	3	–	–	–	–
	AVN (Femoral head)	–	1	–	–	–	–
Metabolic 15 (25)	Hyperglycemia	1	–	–	–	–	–
	Weight gain/Cushingoid habitus	7	3	1	2	1	–
Dermatological 8 (13.3)	Acneiform eruptions	1	–	–	2	–	–
	Facial hypertrichosis	2	–	–	2	–	–
	Hair loss	1	1	–	–	–	–
Infections 10 (16.7)	Pulmonary tuberculosis reactivation	2	1	–	–	–	1
	Herpes stomatitis	4	–	–	–	–	–
	Herpes zoster	2	–	–	–	–	–
	Fatal Septicemia	1	–	–	–	–	1
Others 8 (13.3)	Polyurea	1	–	–	1	–	–
	Dry cough	1	–	–	–	1	–
	Blurring of vision	1	1	–	–	–	–
	Infusion reactions	–	–	–	–	–	2

AVN, avascular necrosis; DCP, dexamethasone + cyclophosphamide pulse; DAP, dexamethasone + azathioprine pulse; DP, dexamethasone pulse; OMP, oral mini pulse; Pred, Oral prednisolone. \*Most of the patients had two or more adverse effects

frequent traveling to and fro to a treatment center, wage loss, and complacency of cure once the lesions heal.<sup>[8,27]</sup> We also encountered frequent requests from patients for shifting from center-specific treatment to a domiciliary treatment. However, unsatisfactory therapeutic response to DAP in few patients could be one of the reasons for dropouts.

Nearly, 70% of patients especially with severe disease may need extra doses of corticosteroids initially to achieve clinical remission as was also observed in our four patients with severe PV requiring intervening oral corticosteroids or 1-2 DP(s).<sup>[8]</sup> Due to the adverse effects of immunosuppressive agents, use of systemic corticosteroids alone as first-line therapy too has been advocated.<sup>[3]</sup> However, corticosteroid therapy alone in the form of dexamethasone pulse, prednisolone and betamethasone OMP used in our fewer patients were not

encouraging. Addition of azathioprine in three patients after seven DPs showed early and continued disease remission after 5-6 months. However, few patients treated with DAP in this study showed poor response necessitating switching to MMF or rituximab. Such low efficacy of azathioprine as adjuvant is perhaps from its suboptimal doses as was also noted previously.<sup>[8]</sup>

Rituximab is being used increasingly in the last few years both as first-line adjuvant or in relapsed cases. A rapid control of disease and re-epithelialization was observed as early as 1-3 months after initiation of treatment and long-term remission occurred in up to 58% of patients across studies.<sup>[11,28-30]</sup> We also made similar observations in our all 31 patients treated with rituximab as first-line treatment or who had failed DCP/DAP therapy. The response to rituximab alone was rapid and shortened the usually severe initial phase both in PV and PF. Although

7 (22.6%) patients relapsed within 1-1½ years, long-term remission could be maintained from re-treatment with rituximab + prednisolone along with MMF, azathioprine, or cyclophosphamide and given alone as follow-on therapy for one year thereafter. Treatment with IVIg in seven patients with septicemia and other comorbidities showed rapid healing of pemphigus lesions and follow on addition of an adjuvant was remittive for the long term.

The major corticosteroid therapy-associated adverse effects, bacterial wound infections, herpes zoster, and herpetic stomatitis complicating clinical course in our patients are well known.<sup>[3,8]</sup> Although adverse effects of immunomodulators were mild and transient in our patients, they warrant periodic screening and timely management. Reactivation of pulmonary tuberculosis and death following treatment with DCP, DAP, or rituximab in few patients signifies necessity of being vigilant.

### Limitations

A small number of patients in each group for stratification, lack of long-term follow-up, and retrospective study design remains major limitations. Being a retrospective study design the earlier pemphigus severity scale was used to maintain continuity of results. Because of poor affordability rituximab or IVIg was used in fewer patients only with the limited significance of long-term data analysis. DIF could not be performed in all patients and cyclophosphamide-induced gonadal toxicity was not assessed.

### Conclusion

The overall clinical spectrum of pemphigus in this study is not different from what is described in the literature. DCP or DAP therapy appears effective in achieving rapid healing of lesions and long-term clinical remission but requires careful patient selection in view of corticosteroids or immunomodulators associated adverse effects. However, frequent travel to treatment center, wage loss, cost of repeated hospitalization, and investigations remain an important cause of treatment non-adherence with resultant early relapses.

It will be pertinent to intensively treat patients with severe disease and concurrent infections with IVIg and appropriate antimicrobials prior to intended treatment with high dose corticosteroids or rituximab. Oral prednisolone and betamethasone OMP perhaps offer no extra advantage except oral administration and dosage convenience but chances of treatment default remain high.

Apart from rapid control of the disease and re-epithelialization, rituximab appears safe and preferred immunomodulator, especially after its FDA approval. Although it may prove economical in the long term, its availability and affordability remain precluding for most patients in our resource-poor setting. We feel that

combining rituximab with prednisolone and an adjuvant until healing of lesions (phase 1) followed by treatment with an adjuvant alone for one year (phase 2) will effectively put a stop to repeated hospitalization and frequent relapses during long-term follow-up (phase 3). However, few large well-designed, prospective studies to assess the efficacy of suggested treatment regimens are highly desirable for making any recommendation.

### Statement of Ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013. All patients were provided standard medical treatment and care.

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### Conflicts of interest

There are no conflicts of interest.

### References

1. Robinson DN, Hashimoto T, Amagai M, Chan LS. The new pemphigus variants. *J Am Acad Dermatol* 1999;40:649-71.
2. Yoshida K, Takae Y, Saito H, Oka H, Tanikawa A, Amagai M, *et al.* Cutaneous type pemphigus vulgaris: A rare clinical phenotypes of pemphigus. *J Am Acad Dermatol* 2005;52:839-45.
3. Kridin K. Emerging treatment options for the management of pemphigus vulgaris. *Ther Clin Risk Manag* 2018;14:757-78.
4. Pasricha JS, Srivastava G. Cure in pemphigus: A possibility. *Indian J Dermatol Venereol Leprol* 1986;52:185-6.
5. Pasricha JS, Thanzama J, Khan UK. Intermittent high-dose dexamethasone-cyclophosphamide therapy for pemphigus. *Br J Dermatol* 1988;119:73-7.
6. Kaur S, Kanwar AJ. Dexamethasone-cyclophosphamide pulse therapy in pemphigus. *Int J Dermatol* 1990;29:371-4.
7. Pasricha JS, Khaitan BK, Raman RS, Chandra M. Dexamethasone cyclophosphamide pulse therapy for pemphigus. *Int J Dermatol* 1995;34:875-82.
8. Mahajan VK, Sharma NL, Sharma RC, Garg G. A 12-year clinico-therapeutic experience in Pemphigus: A retrospective study of 54 cases. *Int J Dermatol* 2005;44:821-7.
9. Hassan I, Sameem F, Masood QM, Majid I, Abdullah Z, Ahmad QM. Non comparative study on various regimens (DCP, DAP and DMP) in pemphigus: Our experience. *Indian J Dermatol* 2014;59:30-4.
10. Narasimha Rao P, Lakshmi TS. Pulse therapy and its modifications in pemphigus: A six year study. *Indian J Dermatol Venereol Leprol* 2003;69:329-33.
11. Joly P, Mouquet H, Roujeau J-C, D'Incan M, Gilbert D, Jacquot S, *et al.* A single cycle of rituximab for the treatment of



- severe pemphigus. *N Engl J Med* 2007;357:545-52.
12. Cianchini G, Corona R, Frezzolini A, Ruffelli M, Didona B, Puddu P. Treatment of severe pemphigus with rituximab: Report of 12 cases and a review of the literature. *Arch Dermatol* 2007;143:1033-8.
  13. Lunardon L, Tsai KJ, Probert KJ, Fett N, Stanley JR, Werth VP, *et al.* Adjuvant rituximab therapy of pemphigus: A single-center experience with 31 patients. *Arch Dermatol* 2012;148:1031-6.
  14. Joly P, Maho-Vaillant M, Prost-Squarcioni C, Hebert V, Houivet E, Calbo S, *et al.* First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): A prospective, multicentre, parallel-group, open-label randomised trial. *Lancet* 2017;389:2031-40.
  15. Sharma VK, Gupta V, Bhari N, Singh V. Rituximab as an adjuvant therapy for pemphigus: Experience in 61 patients from a single centre with long-term follow-up. *Int J Dermatol* 2020;59:76-81.
  16. Murrell DF, Peña S, Joly P, Marinovic B, Hashimoto T, Diaz LA, *et al.* Diagnosis and management of pemphigus: Recommendations by an international panel of experts. *J Am Acad Dermatol* 2020;82:575-85.
  17. Kanwar AJ, Vinay K. Rituximab in pemphigus. *Indian J Dermatol Venereol Leprol* 2012;78:671-6.
  18. Sharma VK, Bhari N, Gupta S, Sahni K, Khanna N, Ramam M, *et al.* Clinical efficacy of rituximab in the treatment of pemphigus: A retrospective study. *Indian J Dermatol Venereol Leprol* 2016;82:389-94.
  19. Murrell DF, Dick S, Ahmed AR, Amagai M, Barnadas MA, Borradori L, *et al.* Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. *J Am Acad Dermatol* 2008;58:1043-6.
  20. Chams-Davatchi C, Valikhani M, Daneshpazhooh M, Esmaili N, Balighi K, Halaji Z, *et al.* Pemphigus: Analysis of 1209 cases. *Int J Dermatol* 2005;44:470-6.
  21. Khaled A, Ben Taazayet S, Ben Alaya N, Souissi A, Zegaloui F, Kaffel M, *et al.* The course and prognosis of pemphigus in 47 Tunisian patients. *J Eur Acad Dermatol Venereol* 2013;27:81-5.
  22. Ramassamy S, Agrawal P, Sathishkumar D, Mathew L, Peter JV, Mani T, *et al.* Clinical, immunological profile and follow-up of patients with pemphigus: A study from India. *Indian J Dermatol Venereol Leprol* 2018;84:408-13.
  23. Berger BW, Maler HS, Kantor I. Pemphigus vulgaris in 3½-year-old baby. *Arch Dermatol* 1973;107:433-4.
  24. Bastuji-Garin S, Souissi R, Blum L, Turki H, Nouria R, Jomaa B, *et al.* Comparative epidemiology of pemphigus in Tunisia and France: Unusual incidence of pemphigus foliaceus in young Tunisian women. *J Invest Dermatol* 1995;104:302-5.
  25. Werth VP. Treatment of pemphigus vulgaris with brief high dose intravenous glucocorticoids. *Arch Dermatol* 1996;132:1435-9.
  26. Ratnam KV, Phay KL, Tan CK. Pemphigus therapy with oral prednisolone regimens. *Int J Dermatol* 1990;9:363-7.
  27. Zivanovic D, Medenica L, Tanasilovic S, Vesic S, Skiljevic D, Tomovic M, *et al.* Dexamethasone-cyclophosphamide pulse therapy in pemphigus: A review of 72 cases. *Am J Clin Dermatol* 2010;11:123-9.
  28. Londhe PJ, Kalyanpad Y, Khopkar US. Intermittent doses of rituximab used as adjuvant therapy in refractory pemphigus. *Indian J Dermatol Venereol Leprol* 2014;80:300-5.
  29. Reguiai Z, Tabary T, Maizieres M, Bernard P. Rituximab treatment of severe pemphigus: Long-term results including immunologic follow-up. *J Am Acad Dermatol* 2012;67:623-9.
  30. Cho HH, Jin SP, Chung JH. Clinical experience of different schedules of rituximab in pemphigus with various disease severities. *J Eur Acad Dermatol Venereol* 2014;28:186-91.