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Original Research Article

A clinical study of pemphigus vulgaris and its variants, evaluation of safety and efficacy of glucocorticoids versus immunosuppressants at tertiary care hospital: a study of 75 cases

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ABSTRACT

Background: Pemphigus is an autoimmune blistering disorder affecting skin and mucous membranes. Autoantibodies target desmoglein proteins, leading to acantholysis. Glucocorticoids (GCs) are the primary treatment, but long-term use leads to side effects, prompting the use of other immunosuppressants like cyclophosphamide, rituximab, azathioprine, methotraxate for steroid-sparing effects.
Methods: Seventy-five pemphigus patients were included. Diagnoses were based on clinical and histopathological findings. Patients were treated with GCs alone or in combination with immunosuppressants like cyclophosphamide, rituximab, azathioprine, methotraxate. Clinical remission and adverse events recorded over an 18-month follow-up.
Results: The 46 patients were treated with GCs alone, while 19 received additional cyclophosphamide. 89.5% of patients treated with GCs and cyclophosphamide achieved remission within 4 months, compared to 73.9% with GCs alone.
Conclusions: Cyclophosphamide and other immunosuppressants enhances clinical outcomes by achieving earlier remission and reducing relapse rates in pemphigus patients compared to GCs alone. Its use as an adjunct may offer significant steroid-sparing effects.

Keywords: Pemphigus, Glucocorticoids, Cyclophosphamide, Other immunosuppressants

INTRODUCTION

Pemphigus is an autoimmune intraepidermal blistering disease that involves skin and mucous membrane.[1] Acantholytic cells and clefts or bullae are formed in the epidermis as a result of interaction of auto-antibodies with epidermal keratinocyte desmosomal cadherins (intercellular cement substance: desmoglein 1 and desmoglein 3).[2] In a majority of the cases, the diagnosis of pemphigus vulgaris (PV), pemphigus foliaceus (PF) and other variants, rests upon clinical and histological features.[3] With the combination of GCs and immunosuppressants, morbidity and mortality from pemphigus has decreased even further.[4,5]

Because of corticosteroid related side effects, immunosuppressants have been added to the treatment of pemphigus to attain a steroid- sparing effect.

METHODS

A total of seventy-five patients of different types of pemphigus having active skin or mucosal lesions were studied in department of dermatology, venereology and

leprosy at medical college and S.S.G. hospital, Vadodara, Gujarat from Jan 2012 and September 2013. Diagnosis was done through detailed history, clinical examination, and histopathological examination. Patients were followed up to 18 months after the initiation of treatment and evaluated for disease course. Patients were also clinically evaluated for development of adverse drug reaction,

Inclusion criteria

Patients above 18 years and below 70 years, clinically and histopathologically confirmed cases of various types of pemphigus and patient willing to give consent were included.

Exclusion criteria

Patient not willing to undergo necessary investigations, patients below 18 and above 70 years, pregnant woman and lactating mothers, couples planning for pregnancy and patient not giving consent were excluded. Permission from institutional ethical committee was taken.

All the eligible patient attending department of Skin-VD at tertiary care hospital during the above-mentioned time periods were included for the study. Seventy-five patients of different type of pemphigus having active skin or mucosal lesions were included in the study.

The complete clinical history was taken to record evolution and progression of the disease since its onset, response to the treatment received previously and to determine whether the patient suffering from any concomitant dermatologic or other disease. Complete physical examination was carried out to record the severity and extent of the cutaneous and mucosal involvement. Monitoring of treatment response and side effects of the different modalities was done in follow up visits of all the patients. The duration of follow up was from 6 to 18 months. The extent of skin involvement was noted according to "the rule of nine". The diagnosis of pemphigus was made on the basis of clinical criteria and confirmed by Tzanck smear and histopathology. Biopsy was taken from early intact bullae. Immunofluorescence studies were not done because of unavailability in the setup.

Table 1: Dosage and route of administration of drugs.

Treatment option	Dose
Oral prednisolone	0.5-1.0 mg/ kg/day in morning (as a initial dose up to 2 mg/ kg/ day)
IM dexamethasone	8 mg once day in morning in severe disease
Cyclophosphamide (oral)	1-3 mg/ kg/day early morning with plenty of water
Azathioprine (oral)	2-4 mg/ kg/day in three divided doses
Mycophenolate mofetil	2-3 mg/ kg/day in two divided doses
Dexamethasone-cyclophosphamide pulse therapy (IV)	100 mg IV dexamethasone with 500 mg cyclophosphamide in 500 ml of 5%, dextrose over 1-2 hr on day 1, f/by daily administration of 100 mg of Dexamethasone for next two days, repeated every monthly. And daily 50 mg cyclophosphamide given orally daily.
Rituximab infusion	500 mg IV slowly over 6-8 hours biweekly for 8 weeks in intensive care unit set up with vital monitoring (total 4 infusion)

Laboratory investigations included: complete blood count, erythrocyte sedimentation rate, blood glucose level (random blood sugar, fasting blood sugar, post prandial blood sugar), renal function test and liver function tests, serum electrolytes, urine routine, electrocardiogram, chest x ray (pa view), x-ray pelvis with both hips, x-ray dorso-lumbar spine ap lateral views, bone mineral density as and when required (dexa scan), ophthalmic examination monthly to rule out glucocorticoid induced cataract and other side effects and ENT surgeon reference for pharyngeal, nasal and oesophageal involvement.

In addition, periodic examinations for cataract, striae atrophicans, hypertension, epigastric tenderness to rule out peptic ulcer, weight change, hair loss and urinary symptoms were carried out to record side effects of systemic corticosteroids, cyclophosphamide and other treatment modalities.

Treatment protocol

Mild

Few skin lesion (less than 20% body surface area involvement) and no mucosal and the scalp involvement in mild treatment protocol.

Moderate

More skin lesion (twenty to forty percentages BSA involvement) and mucosal and scalp involvement in moderate.

Severe

More than 40% BSA involvement and mucosal and scalp involvement.

Treatment response

Treatment response judged by taking regular follow up of all the cases. When the patient had no new lesions for at least 2 months and healing of older lesions completely, he or she was considered to be in clinical remission. If any patient who had been in clinical remission and develops new lesions during the course of the treatment afterwards it was considered as relapse and the treatment was revised.

Table 2: Type of treatment given during study period.

Type of treatment	PV	PVg	PF	PE	IgA P	Total
GC	28	1	15	2	0	46
GCs+ cyclophosphamide	16	1	2	0	0	19
GCs+azathioprine	3	0	0	0	0	3
GCs+rituximab	4	0	0	0	0	4
GCs+methotrexate	1	0	0	0	0	1
GCs+dapsone	0	0	1	0	1	2
Total	52	2	18	2	1	75

RESULTS

In our study, daily GCs were the main stay of the treatment. All 75 cases had received GCs as prednisolone or dexamethasone in equivalent doses which were tapered gradually according to response in terms of clinical remission.

Out of 75 cases of pemphigus, 46 cases received daily GCs alone while other cases have received daily adjuvant immunosuppressants e. g. cyclophosphamide (19 cases), azathioprine (3 cases) and rituximab infusions intravenously (4 cases), methotraxate (1 case), dapsone (2 case) during the study period (Table 3).

Oral cyclophosphamide was given at a dose of 1-3 mg/kg/day early morning with plenty of water.

Among the cases treated with only daily GCs (46), 44 (95.65%) cases achieved clinical remission of the disease within 6 months of therapy, while 2 (4.34%) cases failed to achieve same at the end of 6 months.

All the cases treated with daily GCs with cyclophosphamide were in remission at the end of 6 months of therapy.

At the end of 4 months of treatment, 89.48% cases of pemphigus who received daily GCs with cyclophosphamide were in clinical remission which was earlier than those cases (73.9%) that were on daily GCs alone.

Cyclophosphamide has a role as an adjuvant in providing clinical remission early in pemphigus cases. At the end of 6 months, 2 cases failed to achieve clinical remissions that were on daily GCs only (Table 4).

In our study, the pemphigus cases on adjuvant drug along with GCs were having longer duration of remission than those who were only on GCs. All the cases who received daily GCs alone (100% cases) were remained under remission up to 8 months.

However, 6 (31.5%) cases out of 19 who received cyclophosphamide along with GCs were having remission lasting from 9 months up to 17 months. And out of them 4 (21.05%) cases were off medications till last follow up (18 months) (Table 5).

Addition of cyclophosphamide induced longer remission in our study.

During the follow up period of average 10-12 months per case, the relapse rate of pemphigus cases on daily GCs was 2.28 relapse/ case, while for the cases on cyclophosphamide along with daily GCs was 1.15 relapse per case (Table 6).

Use of cyclophosphamide along with GCs has reduced the number of relapses during the course of treatment in cases of pemphigus compared to the daily GCs (Table 7-9).

Rituximab therapy (500 mg-4 infusions at the interval of 15 days to one patient and 3 infusions at the interval of 15 days to other 3 patients) induced prolonged clinical remission in patients with PV.

Relapses could be managed with additional infusions administered on demand. All four patients were under remission in one month. They remained in remission for 3, 4, 6 and 18 months (till last follow up).

Out of three cases on daily GCs and azathioprine, one case unable to achieve clinical remission at the end of 6-month therapy while other two had achieved their remission at 3rd and 6th month of initiating treatment. And they remained in remission till 3rd and 5th month.

Table 3: Age and sex wise distribution of different types of pemphigus.

Age group (in years)	PV		PF		PVg		PE		IgA P		Total, N (%)
Sex	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**0**
<20	1	0	0	0	0	0	0	0	0	0	1 (1.3)
21-40	9	16	4	5	1	0	0	0	0	0	35 (46.7)
41-60	4	12	6	1	1	0	2	0	1	0	27 (36)
>60	4	6	1	1	0	0	0	0	0	0	12 (16)
Total	18	34	11	7	2	0	2	0	1	0	75

Table 4: Time to achieve clinical remission in cases on daily GCS alone and daily GCS with cyclophosphamide.

Time in weeks	GCs only, N (%)	GCs + cyclophosphamide, N (%)
Less than 1 month	2 (4.35)	1 (05.26)
1-2 months	12 (26.10)	7 (36.85)
3-4 months	20 (43.45)	9 (47.36)
5-6 months	10 (21.80)	2 (10.52)
No remission for more than 6 months	2 (4.35)	0
Total	46	19

Table 5: Duration of clinical remission daily GCs alone and daily GCs with cyclophosphamide.

Remission duration	GCs only, N (%)	GCs+cyclophosphamide, N (%)
Less than 1 month	2 (4.35)	1 (5.26)
1-4 month	27 (58.69)	6 (31.58)
5-8 month	17 (36.96)	6 (31.58)
9-12 month	0	3 (15.79)
13-18 month	0	2 (10.53)
>18 month	0	1 (5.26)
Total	46	19

Table 6: Relapse rate of daily GCs and GCs with cyclophosphamide (Average 10-12 months per case).

No. of relapse	GCs only, N (%)	GCs+ cyclophosphamide, N (%)
No relapse	13 (28.25)	3 (15.8)
1 relapse	14 (30.43)	11 (57.9)
2 relapses	15 (32.55)	4 (21.1)
3 relapses	13 (28.25)	1 (05.2)
4 relapses	3 (06.52)	0 (0)
Total	46	19
Relapse rate/case	2.28 relapse/case	1.15 relapse/case

Table 7: Adverse effects of GCs, (n=75).

Side effects	Total, N (%)
Moon faces	40 (53.3)
Weight gain >10%	20 (26.7)
Central obesity	18 (24)
Rise in blood pressure (HT)	13 (17.3)
Striae	12 (16)
Acneiform eruptions	9 (12)
Hyperglycemia (SDM)	9 (12)
Gastritis	9 (12)
Osteopenia	8 (10.7)
Cataract	8 (10.7)
Proximal muscle weakness	6 (8)
Disturbed sleep	4 (5.3)

Continued.

Side effects	Total, N (%)
Menstrual anomalies	4 (5.3)
Hypokalemia	3 (4)
Hair loss from scalp	3 (4)
Flushing of face	3 (4)
AVN of femur head	1 (1.3)

Table 8: Adverse effect of cyclophosphamide and GCs therapy (other than those mentioned in Table 7), (n=19).

Adverse effects	N (%)
Bone marrow suppression (pancytopenia)	3 (15.7)
Telogen effluvium/anagen effluvium	16 (84.2)
Hemorrhagic cystitis/hematuria	1 (5.26)
Darkening of skin (pigmentation)	11 (57.9)
Menstrual abnormality in females	2 (10.55)

Table 9: Dermatologic infections during the treatment of cases of pemphigus, (n=75).

Dermatologic infections	Daily GC (46)	Daily GCs+cyclo (19)	Daily GC + other immunosuppresants (10)	Total, N (%)
Dermatophytosis	3	1	0	4 (5.3)
Oral candidiasis (OC)	5	2	1	8 (5.3)
Herpes simplex (HSV)	1	2	1	4 (2.7)
Herpes zoster (HZ)	1	1	1	2 (2.7)
Kaposi's varicelliform eruption (KVE)	1	1	0	2 (2.7)

DISCUSSION

Pemphigus is an autoimmune intraepidermal blistering disease that involves skin and mucous membrane. It has high mortality rate if GCs not given early. PV is one of the dermatological emergencies just like burns. Various other immunosuppressants are tried as adjuvant therapies.

Cyclophosphamide is an alkylating agent and one of the potent immunosuppressants available today. Continuous oral cyclophosphamide has been used in dermatology for control of systemic lupus erythematosus and pemphigus.[6-8] However, serious side effects like hemorrhagic cystitis, bladder carcinoma and lymphoma can occur after a cumulative dose of 85 gm of cyclophosphamide.[9]

Pulse therapy

This source highlights dexamethasone-cyclophosphamide pulse (DCP) therapy, which involves administering high doses of dexamethasone intermittently, along with cyclophosphamide, followed by oral cyclophosphamide for maintenance. The DCP regimen is structured in four phases. Additional treatments, such as oral GCs or dexamethasone pulses, can be given to achieve quicker clinical recovery during the initial months.[10]

The source asserts that the DCP regimen can cure almost every pemphigus patient with strict adherence, leading to long-term remission even after treatment withdrawal. Relapses were more frequent in patients who did not adhere to the 28-day cycle.[10]

Current regimen of pulse therapy

This source details a dexamethasone cyclophosphamide pulse (DCP) therapy. The regimen consists of DCP/DP repeated in 28-day cycles, along with 50 mg of daily cyclophosphamide. The regimen is divided into four phases. [10]

Phase I: Continues until oral betamethasone and other drugs are completely tapered off. Additional daily doses of oral betamethasone are administered to control disease activity and then progressively tapered off. Systemic antibiotics are used for skin lesions and oral anti-candida drugs for oral ulcers until complete healing.

Phase II: Lasts nine months, with DCPs/DPs repeated every 28 days along with 50 mg of daily cyclophosphamide.

Phase III: Lasts nine months, with only 50 mg of daily cyclophosphamide.

Phase IV: Post-treatment follow-up.

In the study done by Pasricha et al DCP was given and it showed the following results: The DCP regimen aims for complete clinical remission in almost every patient, with a low tendency for relapse on prolonged follow-up, even

after complete withdrawal of treatment. The study reports that 84% of patients completed the treatment and remained disease-free, with follow-up periods ranging from 2 to more than 9 years. Relapses were mostly observed in patients who did not adhere to the prescribed schedule.[11]

The DCP regimen is noted for potentially fewer side effects compared to conventional daily corticosteroid regimens. Common corticosteroid side effects like weight gain, cushingoid obesity, and diabetes mellitus were generally absent or insignificant. However, pyogenic infections, candidiasis, and reactivation of tuberculosis were observed.

The study by Khandpur et al found that the time to achieve remission was significantly shorter in group B cyclophosphamide pulse and daily oral prednisolone (CP+P) than in group A dexamethasone-cyclophosphamide pulse and daily oral cyclophosphamide (DCP+C).[13] However, the number of patients achieving remission was comparable between the two groups. Relapse rates during the treatment and follow-up periods were also comparable in both groups and high (>60%) in both groups, suggesting a need for long-term maintenance therapy.

Both groups experienced immediate and delayed side effects.

Group A (DCP+C) experienced side effects such as dysgeusia, hiccups, palpitation, nail discoloration, bone pain, and urinary tract infection.[14-17]

Group B (CP+P) experienced nausea, flushing, menstrual irregularity, secondary amenorrhea, dyspnoea due to weight gain, and moon facies1. Steroid-associated side effects were more common in group B.[18,19]

Fleischli et al used intravenous pulse cyclophosphamide therapy in nine patients of severe, recalcitrant PV.[6] Six (66.67%) patients showed an excellent to good response, 2 (22.2%) had minimal or no response and one died. One (11.11%) patient relapsed. The total highest dose given was 2000 mg. The total number of pulses received by patients varied from 3 and 24.[6] In this study, the response was excellent to good in all patients. Two patients developed relapse, but the disease flares were not as severe as their previous disease and could be controlled with a short course of steroid. The total highest dose given at one time was 500 mg.

In the study by Fleischli et al 4 patients complained of severe nausea and two had serious side effects in the form of neutropenia or sepsis. In the study, seven patients complained of nausea, which was mild, except in one patient where it necessitated stopping treatment. None of our patients developed any severe adverse reaction.[19]

In our study, 95.65% of patients on daily GCs alone achieved clinical remission within 6 months, and all patients treated with daily GCs and cyclophosphamide were in remission at 6 months. However, the relapse rate was 2.28 relapses per case for GCs alone and 1.15 relapses per case with the addition of cyclophosphamide. This suggests that while initial remission rates are high, sustained treatment may be necessary to manage relapses.

The 19 patients were given GCs plus cyclophopsphomide. All the patients were in remission at the end of 6 months of therapy. Pemphigus cases on adjuvant drug along with GCs were having longer duration of remission than those who were only on GCs alone. All the cases who received daily GCs alone (100% cases) were remained under remission up to 8 months. However, 6 (31.5%) cases out of 19 who received cyclophosphamide along with GCs were having remission lasting from 9 months up to 17 months. And out of them 4 (21.05%) cases were off medications till last follow up (18 months).

In our study, 89.48% cases of pemphigus who received daily GCs with cyclophosphamide were in clinical remission which was earlier than those cases (73.9%) that were on daily GCs, at the end of 4 months of treatment.

In our study also there were fewer side effects with cyclophosphamide plus GCs as compared to GCs only because of the steroid sparing action of cyclophosphamide

In our study, GCs plus cyclophosphamide telogen effluvium (84.2%), darkening of skin (57.9%), bone marrow suppression (15.7%), menstrual abnormalities (10.55%) and hemorrhagic cystitis (5.26%) were common side effects.

Table 10: In our study, following infections occurred.

Dermatologic infections	Daily GC (46), N (%)	Daily GCs + cyclo (19), N (%)
Dermatophytosis	3 (6.52)	1 (5.26)
OC	5 (10.87)	2 (10.52)
HSV	1 (2.17)	2 (10.52)
HZ	1 (2.17)	1 (5.26)
KVE	1 (2.17)	1 (5.26)

In our study, common side effects noted in group of GCs only were moon facies (53.5%), weight gain (26.7%), central obesity (24%), high blood pressure (17.3%) and striae (16%) (Table 10).

CONCLUSION

Pemphigus is an autoimmune intraepidermal blistering disease that involves skin & mucous membrane. Pemphigus and all its variants lead to morbidity and mortality in the majority of the patients. So, prompt

diagnosis and initiation of treatment are of utmost importance. Though glucocorticoids remain the mainstay of treatment in this autoimmune disease, their long-term usage may cause a variety of side effects. Other immunosuppressants like cyclophosphamide and rituximab as adjuvants to glucocorticoids induced earlier remission with reduced relapse rates and acted as steroid-sparing agents.

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