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COMPARATIVE STUDY OF EFFICACY AND SAFETY OF DCP VS RITUXIMAB IN PEMPHIGUS GROUP OF DISORDERS

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ABSTRACT: Background: Pemphigus group disorders, presents clinically as flaccid blisters over skin and (or) mucosa and show acantholytic cells on tzanck smear. This condition requires longer duration of treatment, currently systemic steroids, immunosuppressant's, DCP and biologicals etc are in use. In this study we compare the efficacy and safety of DCP vs rituximab therapy in pemphigus group of disorders. **Objectives:** To compare the Efficacy and safety of rituximab vs DCP in pemphigus group of disorders**. Method:** Present study is prospective study included 20 patients of pemphigus group presented to opd of DVL department, clinically presented with flaccid bulla, on tzanck acantholytic cells and Direct immunofluorescence (DIF) proved cases included in study. These patients were divided randomly into two groups. Group A includes 10 patients Receiving DCP pulse, group B includes 10 patients receiving rituximab injection, follow up is done for 24 months. **Results:** Out of 20 patients, group A with 10 patients receiving rituximab showed better improvement with no recurrence during the follow up period of 24 months, while group B with 10 patients receiving DCP pulse showed recurrence in 2 patients**. Conclusion:** Rituximab has the advantage of prolonged, immediate response with fewer side effects when compared to DCP pulse therapy.

INTRODUCTION: Pemphigus group of disorders includes *Pemphigus vulgaris*, *Pemphigus foliaceus*, *Paraneoplastic pemphigus* and IgA pemphigus, patients present clinically with flaccid blisters over skin and (or) mucosa, on tzanck smear shows acantholytic cells. The incidence of these diseases varies in different countries and has been reported as 4.4 cases per million population per year in India [1]. Pemphigus has equal preponderance in male and females; the mean age of onset is approximately 50–60 years [2].

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Patients suffer with pain over lesions, difficulty to eat and swallow, in severe cases fatal outcome is seen due to skin failure. It also affects psychologically by social stigma and personal acceptance. Various modalities of treatments like steroids, azathioprine, cyclophosphamide, DCP, biologics like rituximab etc. are available.

All these treatment modalities require longer duration, further use of systemic corticosteroids, immunosupressants for longer duration causes side effects such as hypertension, diabetes mellitus, cushings syndrome, recurrence of disease is seen immediately after stopping the treatment. To avoid the above adverse effects newer modalities of treatment like DCP, Rituximab are in use. Dexamethasone cyclophosphamide pulse therapy (DCP) was introduced in management of PV in the Department of Dermatology, All India Institute of

Medical Sciences by Pasricha in 1982 [3]. The advantages of DCP or other pulse protocol include faster healing of lesions, faster control of disease activity especially in extensive disease, reduction in total cumulative corticosteroid dose, and longterm complete remission or cure with minimal corticosteroid induced side effects. The advantages of DCP are most evident on long-term follow-up of "disease free, drug-free" period for more than 15 years. Rituximab is a chimeric monoclonal antibody that targets CD20+ B cells causing their depletion and decreasing production of autoantibodies. Rituximab was used for the first time in the treatment of autoimmune bullous diseases by Heizmann *et al.*,[4] who reported a case of paraneoplastic pemphigus successfully treated by rituximab. It has been recommended for the treatment of new cases of PV as well as patients not responding to conventional therapy

This study aimed to compare the efficacy, side-effect profile and safety of rituximab vs DCP therapy in 20 cases of pemphigus group of disorders.

MATERIAL AND METHODS: This is the prospective study including 20 patients with clinical presentation with flaccid bulla over body and/or mucus membrane with tzanck smear showing acantholytic cells are included in study, attended to DVL department in MNR medical college and hospital. Approval was sought from the institutional ethics committee, informed and written consent was obtained from each patient. Data regarding the disease, previous treatments received, response to treatment, and any adverse events were recorded.

Inclusion Criteria Includes: (i) Patients with flaccid blisters with confirmed diagnosis on histopathology (PV, PF). (ii) Age group 20 to 80 years (iii) Patients who are willing to give written and informed consent for treatment.

Exclusion criteria therapy were: (i) pregnancy; (ii) breastfeeding; (iii) history of sensitization to murine protein; (iv) active and/or severe infections (including tuberculosis, sepsis, and hiv); and (v) severe cardiac disease [5].

In each patients complete history, thorough clinical examination was done. Diagnosis of *Pemphigus vulgaris*, *Pemphigus foliaceous* was done based on clinical presentation, tzanck smear shows neutrophils and eosinophilic infiltrates with large, round acantholytic cells with larger nucleus than cytoplasm in pemphigus vulgaris, small diamond shaped acantholytic cells, in pemphigus foliaceus, histopathology of *Pemphigus vulgaris* shows supra basal split in *Pemphigus vulgaris* and subcorneal split in *Pemphigus foliaceous*. Direct immunofluorescence findings of *Pemphigus vulgaris* shows IgG antibodies seen in the intercellular space of epidermis giving green colored "fish-net" appearance. Patients advised admission and categorized based on severity of disease assessed according to the revised severity index for pemphigus described by Ikeda *et al* [14]. Each item in the severity index was scored from aminimum of 0 to maximum of 3 and included: (i) the ratio of the affected area of skin to the total skin area as a percentage (0-none, 1-<5%, 2-5%–15%, and 3->15%) (ii) the presence or absence of the Nikolsky phenomenon (0-none, 1-only focal, 2-positive, and 3- distinct) and routine investigations, such as complete blood picture (CBP), random blood sugar (RBS), liver function test (LFT), renal function test (RFT), electrocardiogram (ECG), chest x-ray, TB gold quantiferon assay, and serology for viral hepatitis (HbsAg, HCV) and human immunodeficiency virus were performed. All the patients were randomly divided into two groups, 10 in each group, group A includes patients receiving DCP and group B includes patients receiving rituximab infusion.

Standard DCP therapy consists of four phases.

Phase I: Dexamethasone 100 mg is given intravenously dissolved in 500 mL of 5% dextrose over 3 hours on 3 consecutive days. Cyclophosphamide 500 mg is dissolved in the same infusion on the second day. The same cycle is repeated again at 28 days (4 weeks). Daily dosage of oral cyclophosphamide 50 mg is also given

In phase 1 these cycles are given till all the lesions are healed.

Phase II: In phase II, DCP is continued for another 9 months after complete healing of lesions and stopping of oral steroids.

Phase III: In phase III, monthly DCPs are stopped and cyclophosphamide 50 mg is continued for another 9 months and then stopped.

Phase IV: It is the "disease-free, drug-free" period of observation where patient is off all medications and is just kept under follow-up to note for any recurrences.

Rituximab was administered using a fixed-dose (rheumatoid arthritis) protocol, 1 g intravenously at 2 weeks interval under strict monitoring over a period of 5–6 hours [6]. Before infusion of Rituximab pre-medications (i.v methylprednisolone, i.m pheniramine, and paracetamol) was given, Initial infusion is started at a rate of 50 mg/hr, in the absence of infusion toxicity, increased by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr, any changes in vitals or hypotension drip rate is slowed down or stopped. Maintenance dose of 500mg infusion is given at 6, 12 and 18 months respectively where ever necessary. All the patients were evaluated initially every 2 weeks for a month followed by monthly intervals for at least 24 months. Improvement at each visit was noted based on the lesions clinically. Indirect immunofluorescence circulating IgG autoantibody titers were evaluated on human skin sections by serial serum dilutions made at 1:10, 1:40 and 1: 160. Decreased antibody titer at each visit, correlates with disease severity

RESULTS: Out of 20 patients in present study, most common age group affected in group A(DCP)is 50 years, in group B(rituximab) is 55 years with maximum age is 60 years, lowest age is 25years, as shown in **Fig. 1**, most common gender affected is female i.e 12 patients. Male to female ratio in both the groups is 2:3, as shown in **Fig. 2**. There were 12 cases of *Pemphigus vulgaris* (6 in each group), 8 cases of *Pemphigus foliaceous* (4 in each group), average duration of the disease seen is <6 months in both the groups. Treatment history of the patients includes 6 patients already used medication of oral corticosteroids, whereas 14 patients did not take any treatment as shown in **Table 1.** All the patients have mucocutaneous involvement.

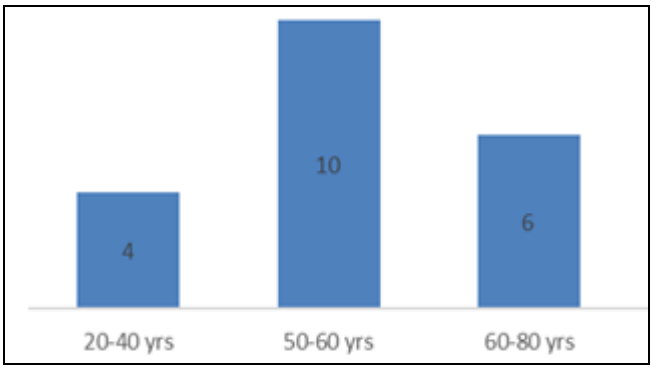

FIG. 1: AGE GROUPS AFFECTED IN PEMPHIGUS GROUP OF DISORDERS

TABLE 1: SHOWING DISTRIBUTION OF PATIENTS IN BOTH THE GROUPS

	Group (A) (DCP)	Group B (rituximab)
Age (mean)	50 years	55 years
Male: female	2:3	2:3
Pemphigus vulgaris	6	6
Pemphigus foliaceous	4	4
Average duration of disease	6 months	6.5 months
Prior treatment	4	2
Improvement	80%	100%
Recurrence	20%	0

FIG. 2: GENDER AFFECTED IN PEMPHIGUS GROUP OF DISORDERS

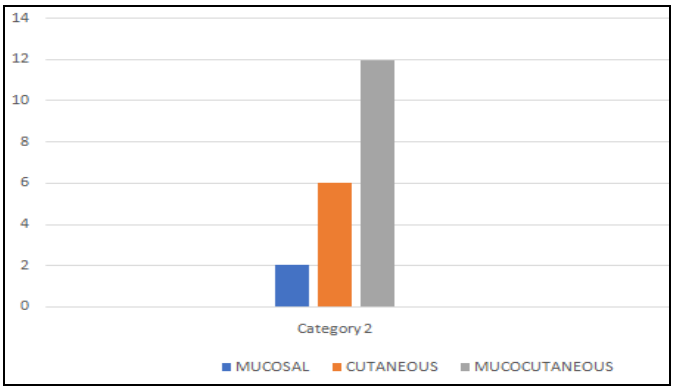

FIG. 3: SITE OF INVOLVEMENT OF LESIONS

Follow up at 4 weeks after treatment showed improvement in existing lesions, at 8 weeks showed all the lesions healed with formation of crust, follow up for 6 months showed complete

healing with no new lesions, follow up at 24 months, showed all the lesions healed completely with post inflammatory hyper pigmentation few with milia formation, 100 % improvement is seen in patients received rituximab infusion with no recurrences, as shown in **Table 2**. 80 % improvement is seen in patients receiving DCP pulse, but recurrence is seen in 20% patients as shown in **Table 3**. Indirect immunofluorescence shows positive antibody titers initially before giving therapy in all the cases, during follow up in group A patients receiving DCP therapy, response is seen with decreasing titers at 12 month sonly 40% shows positive titers, at 18 and 24 months only 20% patients with positive titers are seen as shown in **Table 2**. In group B patients receiving rituximab therapy decrease in titers are seen in 40% and 20% patients during follow up of 12 and 18 month with all patients showing negative titers at the end of 24 months as shown in **Table 3.**

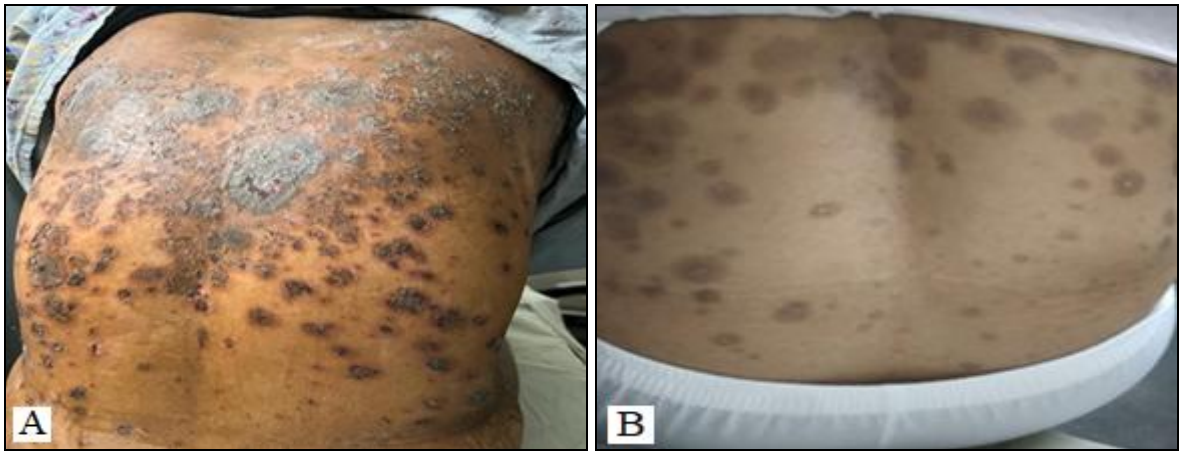

FIG. 4A AND B: SHOWS THE IMAGES OF PATIENTS BEFORE AND AFTER TREATMENT WITH DCP THERAY IN GROUP A PATIENTS

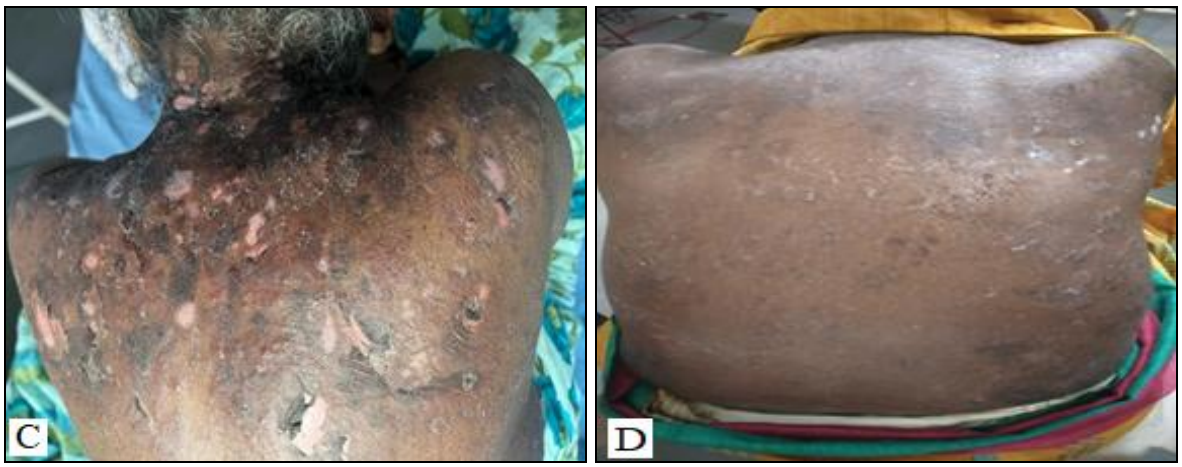

FIG. 4C AND D: SHOWS IMAGES OF PATIENTS BEFORE AND AFTER TREATMENT WITH RITUXIMAB THERAPY IN GROUP B PATIENTS

TABLE 2: SHOWING IMPROVEMENT IN GROUP A PATIENTS DURING FOLLOW UP PERIOD

Months	Existing lesions	New lesions	IIF
6 months	Healed in 80%	No new lesions	Positive in all cases
12 months	Healed	No new lesions	Positive in 40% cases
18 months	Healed	No new lesions	Positive in 20% cases
24 months	Healed	2-3 new lesions seen in 20%	Positive in 20% cases

TABLE 3: SHOWING IMPROVEMENT IN GROUP B PATIENTS DURING FOLLOW UP PERIOD

Months	Existing lesions	New lesions	IIF
6 months	Healed in 90% cases	No new lesions	Positive in all cases
12 months	Healed	No new lesions	Positive in 40% cases
18 months	Healed	No new lesions	Positive in 20% cases
24 months	Healed	No new lesions	Negative in all cases

The common adverse effects are seen in 40% of patients in group A(DCP) during infusion include headache, chills, fever, nausea, changes in blood pressure, and pain during infusion seen in 30% patients at phase I of DCP. Early post infusion reactions such as weakness and vomiting is seen in 5% of patients. Late post infusion side effects such as oral candidiasis, upper respiratory tract infections are seen in 5% patients during follow up as shown in **Table 4.**

The common adverse effects are seen in 30% of patients in group B(rituximab) during infusion include headache, chills, fever, nausea, changes in blood pressure, and pain during infusion seen in 20% patients at first exposure of rituximab. Early post infusion reactions such as weakness, vomiting is seen in 5% of patients. Late post infusion side effects such as oral candidiasis, upper respiratory tract infections are seen in 5% patients during follow up as shown in **Table 4.**

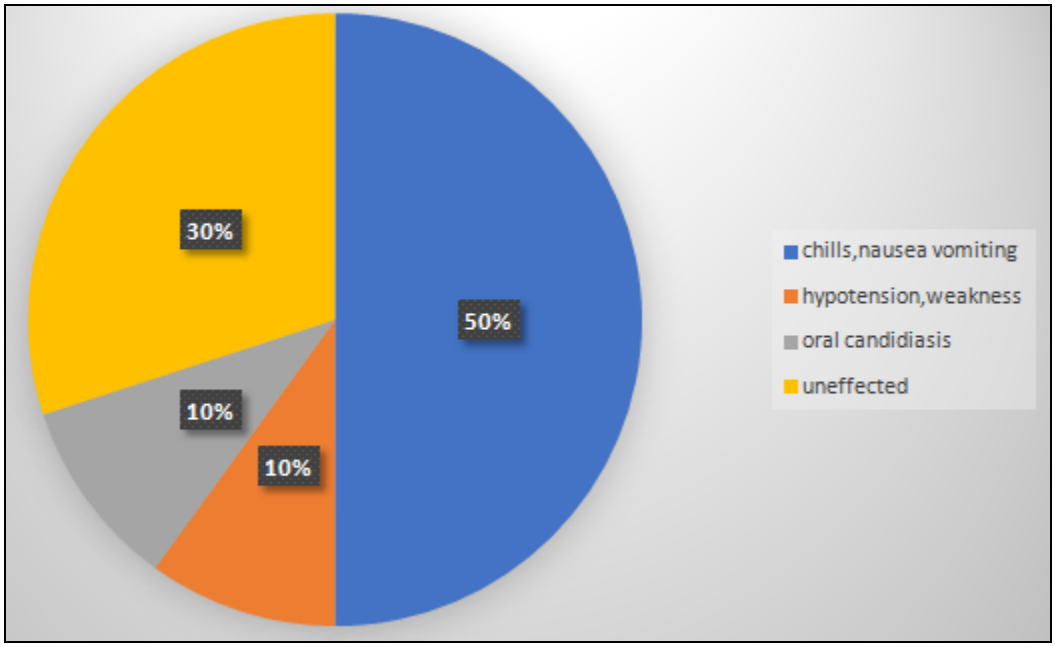

FIG. 5: ADVERSE EFFECTS DUE TO TREATMENT

TABLE 4: SHOWING ADVERSE EVENTS FOLLOWING THERAPY IN BOTH THE GROUPS

Adverse effects	Group A	Group B	Total
Chills, fever, nausea, changes in blood pressure	30%	20%	50%
weakness	5%	5%	10%
Oral candidiasis	5%	5%	10%

DISCUSSION: Pemphigus group of immunobullous disorders includes PV, PF, paraneoplastic pemphigus, IgA pemphigus. associated antibodies against the desmosome antigens, causing acantholysis resulting in bullous lesions, most of the blistering diseases shows the chronic course, variety of treatment modalities are available like long term steroids, azathioprine, MMF etc, most of the times lesions are recurrent after tapering the treatment.

Considering high morbidity and mortality in PV, treatment strategies need to be well defined. DCP revolutionized PV treatment in India, however, frequent hospital visits and a few distressing symptoms are its limitations. Rituximab is effective in severe and refractory PV with limited hospital visits. It has been found to significantly reduce the time to attain disease remission with a significantly greater proportion of patients achieving remission and also a decrease in total cumulative steroid dose when compared with oral corticosteroids or nonsteroidal conventional immunosuppressants [7, 8]. However, its high cost may be a limiting factor in resource-limited settings, necessitating comparison between the two agents.

In present study, most common age group affected were 50 to 60 years which is in concordance with study conducted by Ozge Askin *et al* [9], which is discordant with the study conducted by Nanda *et al* [10], may be because of limited sample size in our

study, Most common gender effected were females which is concordance with study conducted by Kianfer N *et al* [11]. The average duration of disease is 6 months to 1 year which is concordance with study Hicham T *et al* [12] and discordance with study Askin O *et al* [9] may be because of later study was done in recalcitrant cases of pemphigus. Among the pemphigus group of disorders, the most commonly occurring is pemphigus vulgaris which is in concordance with Kridin K *et al* [13]. In pemphigus vulgaris the mucocutaneous type of lesions are most common, which is in concordance with Porro A M *et al* [14]. 90% of patients showed excellent results after receiving 2 doses, 10% of patients showed improvement after receiving maintenance dose after 6 months study in concordance with Dipankar De *et al* [15]. There is no significant association with family history is seen. Most of the pemphigus patients are associated with comorbidities which is in concordance with the study done by Anna pankakoski *et al* [16]. pemphigus patients having comorbidities such as hypertension, diabetes mellitus, etc are common because of their age, treatment in these patients becomes difficult, in this situation rituximab is considered as mainstay of treatment,

Rituximab is a chimeric monoclonal antibody that targets CD20+ B cells causing their depletion and decreasing production of autoantibodies, 100% patients showed improvement in group B, with no recurrence rates, during the follow up, where as 80% showed improvement in group A, with 20 % recurrence rate in 1st 6 months of follow up which is in concordance with study done by Das S *et al* [17], discordant with the study done by Leshem YA *et al* [18]. There is no significant association with family history is seen.

Most frequent side effects seen were chills, nausea, vomiting's seen in 40% patients receiving rituximab which is in concordance with the study done by Feuring Buski M *et al* [19] followed by infusion reaction in 5% patients, followed by opportunistic infections in 5% patients during follow up. In patients receiving DCP 30% showed side effects of generalized weakness, nausea, most of the side effects are seen during the phase I therapy which is in concordance with the study done by Varala S *et al* [20]. Infusion and post infusion adverse effects are managed by continuous monitoring during infusion and careful follow up. Rituximab is FDA approved for the treatment of immunobullous disorders showing complete remission it can also be used in Non hodgkins lymphoma (NHL), Chronic lymphocytic leukemia (CLL), Refractory Rheumatoid arthritis, granulomatous polyangitis, Microscopic polyangitis etc. Numerous case series and case reports explore the efficacy of rituximab in PNPB cell lymphoma, vasculitis, and dermatomyositis [20].

It is advisable to give rituximab as 1st line medicine over DCP therapy considering there is 100% remission and no recurrence for any form of Pemphigus group because of complete remission and minimal side effects.

CONCLUSION: Rituximab was significantly better than conventional therapy such as DCP as it has complete remission and no recurrences are seen. It has few transfusion reactions as side effects and under careful monitoring it can be considered as 1st line agent in treating pemphigus group of disorder

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CONFLICT OF INTEREST: Nil

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