Background: Popular treatment modalities for pemphigus vulgaris are dexamethasone cyclophosphamide pulse (DCP) therapy and rituximab. However, no previous studies are available which have compared the efficacy of the two modalities. Aim: This study aims to study the response of pemphigus vulgaris to DCP and rituximab therapy and to compare the efficacy and safety of the two modalities over a period of 1½ years. Materials and Methods: This was an observational retrospective study. The medical records of a total of 14 pemphigus vulgaris patients from July 2016 to July 2018 were retrieved for analysis who were treated with either DCP therapy or rituximab (7 in each group). Patients treated with any other modality except DCP/rituximab were excluded from the study. The pemphigus disease area index (PDAI) scores at baseline, 1 month, 6 months, 12 months, and 18 months were analyzed using statistical software (Stata Corp. 2013. Stata Statistical Software: Release 13. College Station, TX, Stata Corp. LP, Texas, USA). Outcome Measures: Time to achieve the end of consolidation phase, improvement in PDAI scores, adverse effects, and relapse. Results: Rituximab group achieved early remission; however, there was no statistically significant difference in the two groups in the time when they reached the end of consolidation phase. Repeated measure anova showed significant difference in PDAI scores within the two groups over time. One patient in DCP group relapsed following discontinuation of cyclophosphamide due to complications. Overall, the scoring of disease severity was markedly reduced in both the groups. Conclusion: Both DCP therapy and rituximab were found to be extremely and equally effective in inducing and maintaining remission.

Keywords: Comparison, cyclophosphamide dexamethasone pulse, pemphigus, rituximab

Introduction

Pemphigus vulgaris is a group of rare autoimmune blistering diseases which affect the skin and mucosa characterized by mucocutaneous blisters and erosions clinically and intraepidermal acantholysis histologically. The main causative factor implicated is formation of autoantibodies against the cell adhesion molecules called desmosomes.[1] Various treatment modalities have been tried for treatment of pemphigus with variable results. The factors governing the adoption of a particular treatment modality include the patient profile including the age, reproductive potential, other comorbidities, cost factor as well availability of the drug.

Initially considered fatal, the advent of corticosteroids revolutionized the course of the disease; however, their long-term usage was associated with various metabolic complications. Next milestone was the usage of
dexamethasone cyclophosphamide pulse (DCP) therapy by Pasricha et al. in 1984.[3] It continues to be one of the cheapest and most popular modality of treatment in India. It is administered in a total of 4 phases. In Phase 1 (induction phase – DCP monthly plus oral cyclophosphamide and adjuvant oral corticosteroids), which is the variable phase, treatment is continued till clinical remission. In Phase 2 (monthly DCP and tablet cyclophosphamide) and Phase 3 (tablet cyclophosphamide daily), treatment is given for a fixed duration of 9 months each, and Phase 4 is for follow-up to look for any relapse.[3]

Newer drugs targeted at the molecular level are like rituximab, a chimeric monoclonal antibody against CD20 expressing B-cells, which secrete the autoantibodies responsible for disease causation. Its use in pemphigus was a serendipitous discovery by Heizmann et al. while treating a patient of non-Hodgkin’s lymphoma with concomitant paraneoplastic pemphigus.[4] It has been used with two main protocols in India – lymphoma protocol and the rheumatoid arthritis (RA) protocol.[5]

Many studies are available which have compared the efficacy of the two protocols of rituximab and also compared its efficacy versus steroids.[3] However, only few studies are available which have compared the efficacy or side effect profile of this drug with the age-old popular DCP therapy.

The disease activity in pemphigus is assessed by different scoring systems, few of them being autoimmune bullous skin disorder intensity score, pemphigus disease area index (PDAI), pemphigus area and activity score, Ikeda index, Saraswat oral pemphigus scoring, and Harman pemphigus grading.[6,7]

We used the PDAI scoring system for evaluating the response to therapy in our patients.

**Materials and Methods**

**Aim**
The aim of this study is to study the response of pemphigus vulgaris to DCP therapy and rituximab therapy and to compare the efficacy of the two modalities over a period of 1½ years.

**Objective**
The primary objective was to assess the efficacy and adverse effects of rituximab and DCP in pemphigus vulgaris. The secondary objective was to compare the efficacy of the two modalities over a period of 18 months.

**Methods**
It is an observational retrospective study conducted in a tertiary care centre of Maharashtra. All biopsy confirmed patients of pemphigus vulgaris treated with either DCP therapy or rituximab over a period of 2 years were included in the study. DCP was given as per the standard protocol of monthly doses over a period of 3 days (dexamethasone infusion 100 mg on day 1, 2, and 3 and cyclophosphamide infusion 500 mg on day 2). Rituximab was given as per RA protocol (2 doses 15 days apart of 1000 mg/dose).

A total of 14 pemphigus patients (clinically and histopathologically) were included in the study. The patients were divided into two groups based on patient profile and affordability such that 7 patients were started on DCP therapy and 7 on rituximab therapy. The medical records of these 14 patients from July 2016 to July 2018 were retrieved for analysis. Patients of pemphigus who were treated with any other modality except DCP/rituximab were excluded from the study.

The disease scoring was done using PDAI which was calculated out of 250 without including the damage score. The score was retrieved from each patient’s record, being determined by the lesion extent and severity that was documented in the patient record template. PDAI values at baseline before treatment, 1 month, 6 months, 12 months, and 18 months were recorded in Excel database format. The scores were then analyzed using survival analysis, log-rank test to compare time to event, and repeated measurement anova for change in PDAI score over period of time. P = 0.05 was taken as significant. Stata Corp. 2013. Stata Statistical Software: Release 13. College Station, TX: Stata Corp., LP, Texas, USA was used for statistical analysis.

**Outcome measures evaluated**

Time to reach end of consolidation phase (the time at which no new lesions have developed for a minimum of 2 weeks, approximately 80% of lesions have healed, and when most clinicians start to taper steroids), improvement in PDAI (PDAI out of 250 max score) scores, adverse effects, and relapse if any. Ethical approval for the study was obtained from the Institutional Review Board of AFMC Pune (Letter number IEC 2018/62, 07-08-2018).

**Results**

A total of 14 patients were included in the study with a mean age of 39.14 ± 9.7 years. Of these, 9 patients were males and 5 were females. The mean PDAI score before treatment was 45.21 ± 15.23. Six of 7 patients in each group had involvement of the oral mucosa and 2 patients in DCP group while 1 in rituximab group also had involvement of the genital mucosa. None of the patients had anal mucosal/conjunctival involvement. None of the patients had a family history of bullous disorders. The duration of disease before treatment was ranging from 3 to 42 months, of which 6 patients had taken no prior
treatment while 8 patients had taken either azathioprine or intermittent oral steroids or both.

The mean time taken to achieve end of consolidation phase by the DCP group was 5.28 ± 2.28 months while that for the rituximab group was 3.57 ± 1.90 months; however, the difference between the two groups was not statistically significant. Five patients were given concomitant prednisolone, 1 was given azathioprine, while 2 were given both prednisolone and azathioprine. Remaining 6 patients did not require any concomitant therapy.

Two patients from the DCP group discontinued therapy due to complications and were shifted to plain dexamethasone pulse. These two patients developed a relapse 2–3 months after discontinuation of cyclophosphamide. One of these patients was in 5th cycle of Phase 2 and just developed a few breakthrough oral erosions which were controlled with adjuvant azathioprine and the patient was continued in Phase 2 and other had a severe relapse in the 7th cycle of Phase 2 and was shifted back to Phase 1 and is presently planned for rituximab [Table 1]. At the end of 18 months, in the DCP group, 1 patient was in Phase 1, one in Phase 2, while 5 patients were in remission on therapy (absence of new or established lesions while the patient is receiving minimal therapy) in Phase 3 [Figure 1].

In the rituximab group, of 7 patients, 5 patients achieved end of consolidation phase after 2 doses of rituximab while 2 patients had to be given an additional third dose after which they reached the end of consolidation phase [Figure 2]. There were no reported side effects of treatment.

The repeat PDAI scores were retrieved from records 1 month, 6 months, 12 months, and 18 months for both the groups and were analyzed using statistical software (STATA 13 IC). There was a drop in PDAI scores at the end of 18 months to 4.0 ± 8.94 in DCP group and 1.85 ± 3.18 in the rituximab group which were significantly low compared to the baseline; however, the difference between the two groups was not statistically significant [Figures 3 and 4].

There was no episode of relapse apart from the 2 cases mentioned in the period of observation.

**DISCUSSION**

DCP being cheap and easily available continues to be a popular modality for the treatment of pemphigus in India even in the present era of modern molecules.

**Table 1: Distribution of cases with their characteristics**

| Characteristics                  | DCP pulse (n=7) | Rituximab (n=7) | P     |
|----------------------------------|----------------|----------------|-------|
| Age years, mean±SD              | 41.3±10.3      | 37±9.4         | 0.4   |
| Sex (female), n (%)             | 2 (28.6)       | 3 (42.9)       | 0.6   |
| PDAI score pretreatment         | 44.4 (13.9)    | 47.9 (17.9)    | 0.7   |
| PDAI score 1 month              | 23.3 (10.24)   | 24.9 (11.3)    | 0.8   |
| PDAI score 6 months             | 8.4 (9.2)      | 6.9 (7.2)      | 0.7   |
| PDAI score 1 year               | 7.1 (11.3)     | 2.4 (1.6)      | 0.3   |

SD: Standard deviation, PDAI: Pemphigus disease area index, DCP: Dexamethasone cyclophosphamide pulse

**Figure 1:** Decrease in pemphigus disease area index scoring in a patient on dexamethasone cyclophosphamide pulse therapy
Furthermore, various anti-CD-20 antibodies are being explored for the treatment of various B-cell-mediated diseases like pemphigus, the most common being rituximab. The choice of treatment has to be tailor made according to the patient profile, comorbidities, cost, efficacy, and adverse effects. Both these modalities are being used very frequently as the first-line treatment of many patients.\cite{8,9}

DCP and rituximab are the two most common treatment regimens being followed in the hospital where the study was undertaken. Furthermore, no previous studies could be found which directly compared the efficacy of these two treatment modalities. The study was thus carried out with an attempt to compare the various outcome parameters associated with treatment with the two modalities.

Our findings were similar to the results reported by various previous studies as per which both DCP and rituximab have been found to be extremely efficacious. In a case series by Horváth et al., 8 of 15 patients achieved complete remission with two doses of rituximab in a median period of 5 weeks, while remaining 7 patients achieved partial remission in a median period of 34.5 weeks.\cite{10}

Kanwar et al. treated 10 pemphigus patients by RA protocol.\cite{11} At a mean follow-up of 33.4 weeks, three patients had achieved complete remission off all
treatment and four patients had achieved complete remission on minimal therapy, and mean time to disease control was 8 weeks. In a 6-year study by Rao and Lakshmi, 29 of the 30 patients in whom DCP was instituted showed a good response and completed Phase I in an average of 8 pulses.\textsuperscript{[12]} In a study by Roga and Augustine, mean time taken for control of activity was 6.7 months with DCP.\textsuperscript{[13]} However, no study or case series has been reported which has compared both these modalities head to head.

We also found similar excellent results like in above studies in the disease control with both the modalities. Rituximab therapy was found to be extremely effective in inducing early remission in cases of pemphigus. However, longer follow-up is required to ascertain maintenance of remission.

Pulse therapy was found to be equally effective in inducing and maintaining remission in the treatment of pemphigus. It takes a longer time to remission compared to rituximab, however forms a cheaper alternative. Relapses occurred in patients who had to discontinue cyclophosphamide component.

**CONCLUSION**

Both DCP therapy and rituximab were found to be extremely and equally effective in inducing and maintaining remission. A larger sample size with a longer follow-up would have added to the findings. The retrospective nature of the study, small sample size, and unavailability of follow-up anti-desmoglein autoantibodies levels were limitations of this study.

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

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