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DEXAMETHASONE-AZATHIOPRINE PULSE THERAPY AS AN ALTERNATIVE TREATMENT MODALITY IN PEMPHIGUS WITH DEXAMETHASONE-CYCLOPHOSPHAMIDE PULSE THERAPY FAILURE: A RETROSPECTIVE OBSERVATIONAL STUDY

Dr. Deepak Dhadekar[1], Dr. Anand Asia[2], Dr. Girishkumar Ambade[3]

[1]Post Graduate Student, Department of Dermatology, Venereology and Leprosy, Government Medical College, Akola (Maharashtra),

[2]Professor, Department of Dermatology, Venereology and Leprosy, Government Medical College, Akola (Maharashtra),

[3]Former Assistant Professor, Department of Dermatology, Venereology and Leprosy, Government Medical College, Akola (Maharashtra).

Conflicts of Interest: Nil

Corresponding author: Dr. Deepak Dhadekar

Abstract:

Background: Dexamethasone Immunosuppressant Pulse therapy has been widely accepted as a promising treatment for treating Autoimmune Vesico-bullous diseases. Dexamethasone-Cyclophosphamide Pulse (DCP) therapy has been reported to have better remission rate in Pemphigus patients as compared to Dexamethasone-Azathioprine Pulse (DAP) and Dexamethasone-Methotrexate Pulse (DMP) therapy, but few cases may prove to be resistant to DCP therapy. Rituximab is one of the modalities preferred for treatment in such resistant cases.

Aim: To study role of DAP therapy in Pemphigus patients with DCP therapy failure.

Materials and Methods: Records of Pemphigus cases between January 2014 to December 2019 were analyzed retrospectively. Cases who received DAP therapy after failures to achieve remission inspite of receiving 12 DCPs earlier were included in the study.

Results: It was observed that after shifting on DAP therapy all 6 patients achieved clinical remission within mean duration of 4 months of phase-1. Presently all these patients are in phase-4 of DAP therapy without recurrence.

Conclusion: Treatment failure with Cyclophosphamide could be due to resistance to Cyclophosphamide which may occur due to decreased cellular penetration, improved DNA repair or increased drug metabolism. In such cases of failure, Azathioprine may be effective due to its structural similarity to endogenous purines. It incorporates into DNA and RNA, inhibiting purine metabolism and cell division. It also decreases antibody production by B-cells. Decreased antibody production due to different mechanism of action could be the reason for good response in patients with Cyclophosphamide resistance. In such cases DAP therapy can be considered for effective treatment of this disease in patients with financial constraints.

Keywords: Dexamethasone-Azathioprine Pulse(DAP), Dexamethasone-Cyclophosphamide Pulse(DCP), Pemphigus.

Introduction

Pemphigus are a group of chronic autoimmune bullous dermatoses that are characterized histologically by intraepidermal blister formation and immune-pathologically by the presence of bound and circulating autoantibodies against the intercellular adhesion structures. Dexamethasone immunosuppressant pulse therapy has been widely accepted as a promising treatment for treating Autoimmune Vesico-bullous diseases. Pemphigus has been treated with Dexamethasone Cyclophosphamide Pulse (DCP) Therapy since 1981 with several studies having reported its efficacy.[1-6] Various modifications have been suggested in the original regimen from time to time.[5-8] Other therapeutic regimens consist of Dexamethasone-Azathioprine Pulse (DAP) and Dexamethasone-Methotrexate Pulse (DMP) therapy. DAP therapy is recommended for unmarried patients who have not completed their family. DCP therapy has been reported to have better remission rate in Pemphigus patients as compared to DAP or DMP therapy.[9] Pemphigus cases resistant to treatment are now treated with Rituximab.[10] However, in non-affording patients DAP therapy may prove to be beneficial. With this background retrospective analysis was undertaken to observe the role of DAP therapy in Pemphigus patients with DCP therapy failure.

Materials and Methods:

Records of all Pemphigus patients attending Outpatient Department of Dermatology, Venereology and Leprosy at tertiary care centre between January 2014 to December 2019 were analyzed retrospectively after approval of the Institutional Ethical committee. Six diagnosed cases of pemphigus based on clinical features, Tzanck smear and histopathology who received DAP therapy after failure to achieve remission inspite of receiving 12 DCPs previously were included in study. Patient records were obtained from medical record section of Department of Dermatology, Venerology and Leprosy. Details of history, physical examination findings, laboratory data, treatment, clinical photographs and follow-up data were analyzed. Data of baseline investigations including complete blood counts, blood sugar level, liver and kidney function tests, serum electrolytes, routine urine, stool examinations with stool occult blood, chest X-ray and electrocardiogram and of follow-up visits including complete blood count, blood sugar level, liver and kidney function test was recorded. Monitoring of disease activity with pemphigus disease area index (PDAI)[11] was done at each follow up visit. In all these patients, due to failure to achieve remission, Cyclophosphamide was stopped after 12 DCPs and patients were shifted on DAP therapy. In phase-1 of DAP therapy patients received Injection Dexamethasone 100 mg in 500 ml of 5% Dextrose, intravenously over 2 hours with monitoring of pulse rate and blood pressure, on 3 consecutive days, every 4 weekly with oral Azathioprine 2 mg/kg/day. In phase-2 another nine dexamethasone pulses with same dose of Azathioprine were given and in phase-3 oral Azathioprine 2 mg/kg/day for nine months was continued. Withdrawal of oral Azathioprine and follow-up at every 2-3 months was done in phase-4. Patients received oral Prednisolone 30mg/day in first month, 20mg/day in second month and 10mg/day in successive months of phase-1 of DAP therapy. As and when required intralesional Triamcinolone/ topical corticosteroids and topical antibiotics were given. For oral erosions topical Triamcinolone oral paste/ gel was given.

Results and Discussion:

Out of six patients of Pemphigus with DCP failure, four patients were of Pemphigus vulgaris (3 females and 1 male) and two patients were of Pemphigus foliaceous (1 female and 1 male) (Table 1). Inspite of receiving 12 DCPs three patients continued to have new and persistent mucocutaneous lesion and three patients continued to have new and persistent cutaneous lesion (Table 1). After shifting on DAP therapy all 6 patients achieved clinical remission within mean duration of 4 months of phase-1 (Figure 1). Reduction in PDAI score was noted in all 6 patients while on DAP therapy (Figure 2). Presently all 6 patients are in phase-4 of DAP therapy without development of any new lesions and following up 3 monthly.

Remission on therapy is absence of new or established lesions while the patient is receiving minimal therapy and Control of disease activity (disease control) is defined as the time at which new lesions cease to form and established lesions begin to heal. [12] DCP remains the most effective regimen with quickest onset of remission and continuance of remission.[9] Varala et al in their study reported remission rate of 70.1% with DCP therapy and 63.6% with DAP therapy.[13] Failure of therapy is considered if there is continued development of new lesions, continued extension of old lesions or failure of established lesions to begin to heal despite 3 weeks of therapy on 1.5 mg/kg/day of Prednisone equivalent with or without any of the following agents: Cyclophosphamide 2 mg/kg/day for 12 weeks; Azathioprine 2.5 mg/kg/day for 12 weeks; Methotrexate 20 mg/week for 12 weeks; or Mycophenolate mofetil 3 g/day for 12 weeks.[12] Hence, failure to control disease activity (relapse/flare) with full therapeutic doses of systemic treatments is defined as 'Failure of therapy'. In a study based on the type of pulse therapy conducted by Roga et al the relapse rate was found to be 23.9% with DCP and 47.8% with DAP.[14] Hassan et al in their study observed that among 5 patients of pemphigus started on DMP in whom DCP phase-1 was more than 12 months, one patient relapsed in fifth month of phase-3 of DMP therapy while in other 4 patients disease activity was poorly controlled.[9] However, in 6 patients included in our study control of disease activity was not achieved even after receiving 12 DCPs with Cyclophosphamide 2 mg/kg/day and hence DCP therapy failure was considered. Adverse effects associated with prolonged Cyclophosphamide treatment like leucopenia, thrombocytopenia, hemorrhagic cystitis, gonadal failure and carcinogenesis urges the need for shift of treatment modality.

Treatment failure with Cyclophosphamide could be due to resistance to Cyclophosphamide which may occur due to decreased cellular penetration, improved DNA repair or increased drug metabolism.[15] Azathioprine has structural similarity to endogenous purines. It incorporates into DNA and RNA, inhibiting purine metabolism and cell division. It also decreases antibody production by B-cells. Decreased antibody production due to different mechanism of action of Azathioprine could be the reason for good response in such patients with Cyclophosphamide resistance in our study. The limitations of the study were small sample size of study and non-availability of data regarding Anti-Desmoglein antibody levels, indirect immunofluorescence findings and thiopurine s-methyltransferase levels.

Table 1: Information of patients before shifting on DAP therapy

Sr. No.	Age/ Gender	Diagnosis	Past treatment	Lesions before shifting on DAP therapy
1.	70yrs/ male	Pemphigus vulgaris	DCP therapy (12 pulses) with interpulse steroids	Cutaneous and mucosal
2.	68yrs/ female	Pemphigus vulgaris	DCP therapy (12 pulses) with interpulse steroids	Cutaneous and mucosal
3.	52yrs/ female	Pemphigus vulgaris	DCP therapy (12 pulses) with interpulse steroids	Cutaneous
4.	38yrs/ female	Pemphigus foliaceous	DCP therapy (12 pulses) with interpulse steroids	Cutaneous
5.	45yrs/ male	Pemphigus foliaceous	DCP therapy (12 pulses) with interpulse steroids	Cutaneous
6.	39yrs/ female	Pemphigus vulgaris	DCP therapy (12 pulses) with interpulse steroids	Cutaneous and mucosal

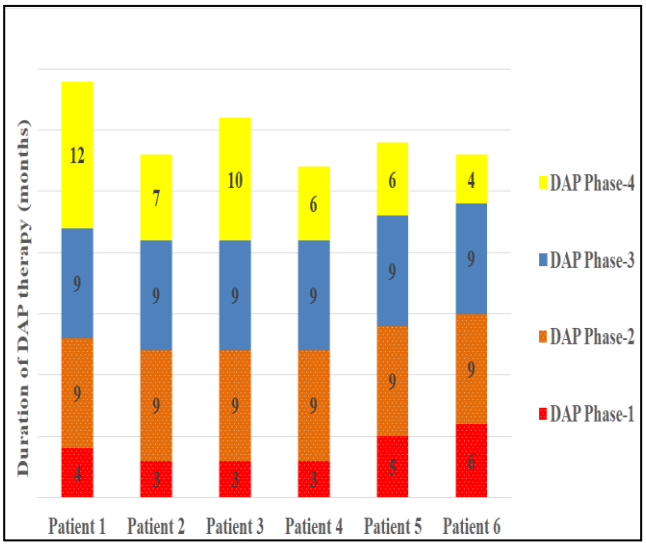


Figure 1: Duration of phases of DAP therapy

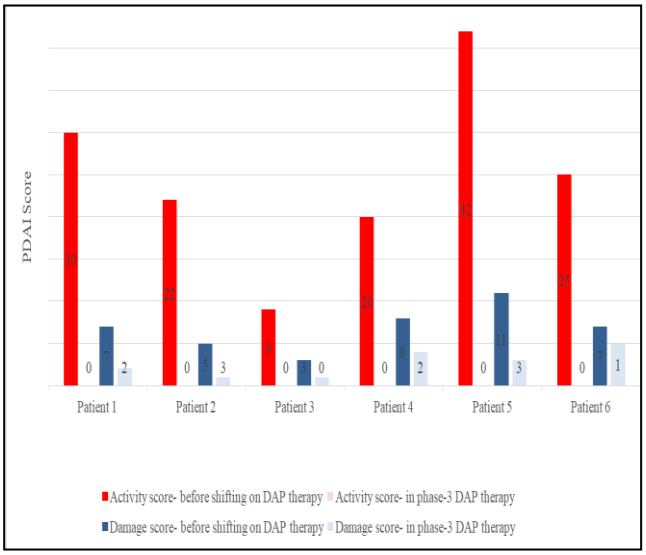
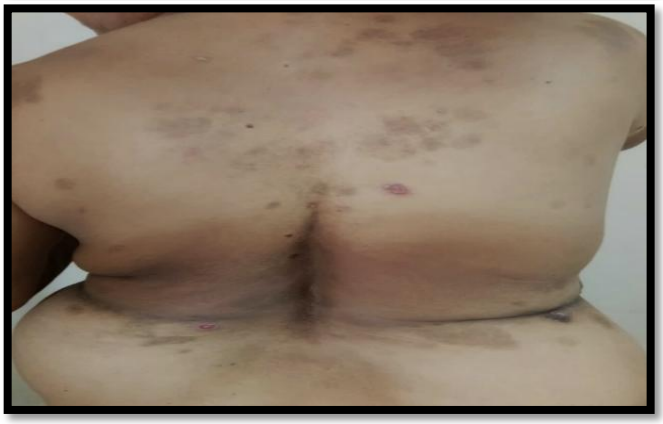
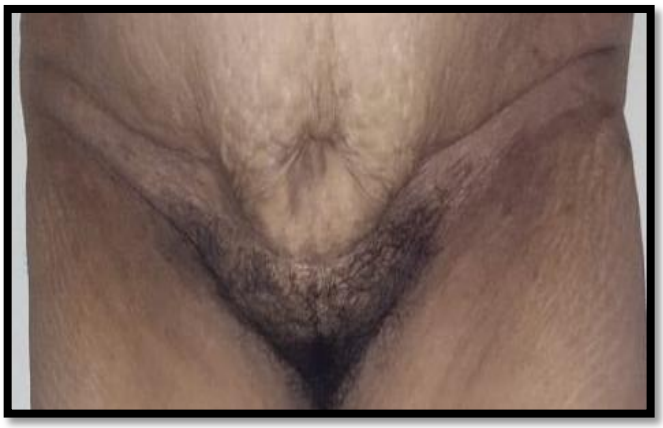
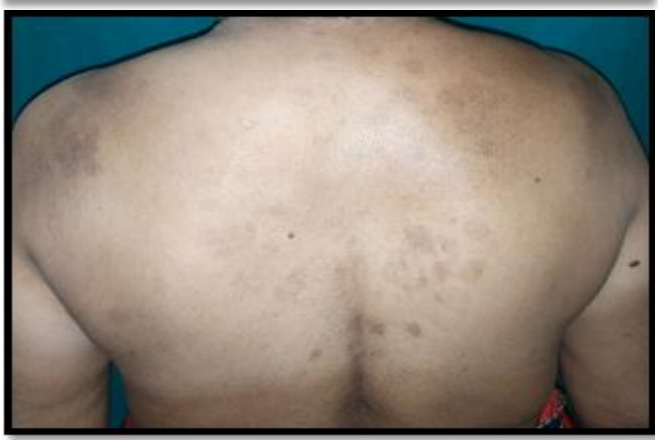


Figure 2: Pemphigus Disease Activity Index (PDAI)



Patient 2: before starting DAP





Patient 2: in pahse-4 DAP

Conclusion:

Although DCP therapy remains the effective treatment with quickest onset of remission and continuance of remission in pemphigus but, few cases may prove to be resistant to treatment. In such cases DAP therapy can be considered for effective treatment of this disease in patients with financial constraints. However, more studies with larger sample size and randomized controlled trials are required to establish beneficial role of DAP therapy in patients of pemphigus with DCP therapy failure.

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