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Original Research Article

A Study of Use of Immunosuppressant Drugs in Dermatology for Chronic Skin Diseases

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Abstract

Background: Autoimmune illnesses including psoriasis, pemphigus vulgaris, and systemic sclerosis are examples of chronic skin diseases that call for long-term pharmacological therapy. The goal of the current study was to track the effectiveness and unfavourable side effects of immunosuppressive medications used to treat chronic skin disorders.

Methods: N=50 patients with newly diagnosed chronic skin disorders were enrolled in the research. Methotrexate, Dexamethasone-Cyclophosphamide Pulse Therapy, Azathioprine, Folic Acid, Calcium, and Antiulcer Drugs were initiated in their treatment regimen. At the conclusion of the first, third, and sixth months of therapy, the response was evaluated. The Psoriasis Area Severity Index (PASI) score was used to track the effectiveness of therapy in psoriasis patients. The Pemphigus Area and Activity Score (PAAS) was used to measure therapy effectiveness in patients with pemphigus vulgaris, and modified Rodnan's skin scores were used to measure treatment effectiveness in patients with systemic sclerosis (MRSS). Haematological and clinical exams were used to evaluate tolerability.

Results: In this study out of n=50 cases 44% were males and 56% were females. Among the cases included in the study n=30(60%) patients were with psoriasis n=10(20%) cases of pemphigus vulgaris and n=10(20%) cases of systemic sclerosis. Among the n=30 psoriasis cases analyzed, most of the patients belonging to 40 - 50 years of age n=12 followed by patients in age of 31- 40 years n=8. The mean age of the subjects was 37.5 ± 6.5 years. Among the n=30 psoriasis cases n=18(60%) were males and n=12(40%) were females.

Conclusion: From the study we conclude that prolonged use of typical daily steroids frequently has negative, potentially life-threatening consequences. Immunosuppressive medications including methotrexate and dexamethasone-cyclophosphamide pulse treatment were well tolerated and effective when used together to treat autoimmune skin disorders.

Keywords: Immunosuppressive drugs, Methotrexate, Dexamethasone-cyclophosphamide pulse therapy, Adverse reactions, Chronic skin diseases

Introduction

The entry of microorganisms in the body is protected by the normal skin barrier. [1] The epidermal barrier function and antimicrobial peptide concentration may both be compromised in people with chronic skin disorders. In the general

population, 20 to 30% of people might suffer from skin problems at any given moment. Psoriasis, bullous disorders, systemic sclerosis, systemic lupus erythematosus, dermatomyositis, and inflammatory dermatoses such atopic and seborrheic dermatitis are examples of chronic skin diseases. [2] Specific immune responses that are directed against self-contained structures cause autoimmune disorders. The term "horror autotoxicus" was used by Paul Ehrlich at the beginning of the 20th century to describe an immune-mediated process that was capable of selectively harming the self. [3]

Women are more likely than males to suffer from several autoimmune illnesses. It begins pretty early on and lasts the rest of one's life. The majority of illnesses are chronic in nature and need for lifetime treatment. The development of autoimmune disorders is influenced by a confluence of environmental and genetic risk factors. [4, 5] Autoantibodies and inflammation, including mononuclear phagocytes, autoreactive T lymphocytes, and plasma cells, are characteristics of all autoimmune disorders. Nearly every organ in the body, including the heart, brain, nerves, muscles, skin, eyes, joints, lungs, and kidneys, are susceptible to it. Early on, corticosteroids are used to treat autoimmune skin conditions. In addition to growth retardation in children, poor wound healing, cataracts, hyperglycemia, hypertension, and an increased prevalence of cerebrovascular and cardiovascular illnesses related to atherosclerosis, the excessive use of steroids frequently has life-threatening and severe side effects. Immunosuppressive medications used concurrently have minimized the need of steroids in treating certain disorders, improved treatment outcomes, and lowered side effects from both medications. [6] Methotrexate, cyclophosphamide, azathioprine, and dexamethasone are the medications utilized.

Patients with psoriasis, a prevalent and persistent immune-mediated skin condition, have utilised methotrexate. It works by blocking the purine route and inhibiting the folic acid antagonist, which modulates the immune system and reduces inflammation in people with psoriasis. [7] The following benefits of pulse therapy with dexamethasone and cyclophosphamide over steroid-only therapy appear. (i.e.) improved disease management, almost no steroid side effects, and a shorter hospital stay. In the treatment of pemphigus, systemic lupus erythematosus, systemic sclerosis, and dermatomyositis, this regimen has proved effective. In bullous diseases, azathioprine can be administered instead of cyclophosphamide. Immunosuppressive medication has improved treatment outcomes, but it also causes serious side effects, including haemorrhagic cystitis, diminished immunological response, and bone marrow suppression. In order to evaluate the clinical response of south Indian patients with chronic skin disorders who are being treated at a tertiary care hospital, as well as the tolerance and safety of immunosuppressive medication in the aforementioned individuals, is the goal of this study.

Material and Methods

This cross-sectional study was conducted in the Department of Pulmonology, Prathima Institute of Medical Sciences, Naganoor, Karimnagar. Institutional Ethical approval was obtained for the study. In local vernacular, the study's goal, methodology, and potential adverse effects were described. Those who were willing to participate in the study voluntarily were provided their written informed permission in the required format and the local language.

Inclusion criteria

1. Newly diagnosed patients with Psoriasis, Pemphigus Vulgaris & Systemic sclerosis

2. Aged 18 years and above
3. Males and Females
4. Available for follow-up
5. Willing to participate in the study voluntarily

Exclusion criteria

1. Hepatic diseases
2. Renal diseases
3. Immunodeficiency diseases
4. Pregnant and lactating females
5. Diabetes mellitus
6. Chronic diseases such as tuberculosis etc
7. Malignancy
8. Hypertension and cardiovascular diseases
9. Use of other alternative medications
10. Lost in follow up

During the study comprised n=50 cases with persistent skin disorders who met all the inclusion and exclusion criteria were selected. At the initial visit, the socio-demographic information, including the patient's age, sex, address, educational background, occupation, and smoking and alcohol use, was gathered. Complete hemogram, erythrocyte sedimentation rate, liver function tests, renal function tests, blood sugar, lipid profile, and standard urine exams were performed as part of the evaluation. Prior to enrolment, the investigator informed the patients verbally and in writing about the purpose, importance, consequences, and risks of the trial. These were described by the investigator in terms and language that the patient could easily comprehend. Utilizing a grading system for the individual disorders, effectiveness was evaluated. Patients received information on medication therapy side effects as well as the investigator's contact information for reporting. Every two weeks, patients we asked for follow up with next dose of medication given at that time. Compliance was monitored during these visits by counting empty medicine packets, and patients with low compliance received counselling to keep up with therapy. Dose adjustments were made in response to the response.

Psoriasis, pemphigus vulgaris, and systemic sclerosis are the autoimmune illnesses examined in the study. Methotrexate was used to treat people with psoriasis, pemphigus vulgaris, and systemic sclerosis, whereas dexamethasone-cyclophosphamide pulse treatment was used to treat patients with such conditions. The Psoriasis Area Severity Index (PASI) score [8] was used to track the effectiveness of therapy in psoriasis patients. At the first, third, and sixth months of medication, the Pemphigus Area and Activity Score (PAAS) [9] was used to assess treatment efficacy in patients with pemphigus vulgaris, and the modified Rodnan's skin score (MRSS) [10] was used to assess treatment efficacy in patients with systemic sclerosis. By evaluating treatment compliance and adverse responses reported by patients, the tolerability of medications was kept under observation. At baseline, the first, third, and sixth months of treatment, lipid profiles, complete hemograms, erythrocyte sedimentation rates, liver and renal function tests, and urine routines were observed. The data was analyzed using descriptive statistics and the Friedman test for skewed data in the SPSS statistical software package (Version 19.0 SPSS Inc., Chicago, USA) on windows format. P values of <0.05 were considered significant.

Results

For the study, N=50 patients with chronic skin conditions were enrolled, and their pharmacological therapy responses and side effects were examined. All the cases were followed up till the end of the current study. The range of age of the cases was from 19.0 years to 62.0 years. The mean age of the sample was 37.5 ± 8.5 years. Most of the cases were belonging to the age group 31 – 40 years with 38% of all the cases followed by age group 21 – 30 years with 28% of all cases. The details of

age wise and sex wise distribution of the cases included in the study have been depicted in table 1.

Table 1: Age-wise and Sex wise distribution of cases in the study

Age (Years)	Male	Female	Total (%)
18 – 20	1	6	7 (14%)
21 – 30	6	8	14 (28%)
31 – 40	9	10	19 (38%)
41 – 50	4	3	7 (14%)
51 – 60	1	1	2 (4%)
> 61	1	0	1 (2%)
Total	22	28	50 (100%)

In this study out of n=50 cases 44% were males and 56% were females. Among the cases included in the study n=30(60%) patients were with psoriasis n=10(20%) cases of pemphigus vulgaris and n=10(20%) cases of systemic sclerosis. Among the n=30 psoriasis cases analyzed, most of the patients belonging to 40 - 50 years of age n=12 followed by patients in age of 31- 40 years n=8. The mean age of the subjects was 37.5 ± 6.5 years. Among the n=30 psoriasis cases, n=18(60%) were males and n=12(40%) were females.

Among the n=10 pemphigus vulgaris cases most of the cases were in the age group of 31 – 40 years (n=5) followed by the age group 41 – 50 years (n=3). The mean age of the cases was 39.55 ± 9.5 years. N=3 cases were males and n=7 cases were females. Among the n=10 cases of systemic sclerosis most of the patients belonged to age group 21 – 30 years with n=5 cases, followed by age group 41 – 50 years with n=4 cases. The mean age of the cases was 38.52 ± 11.5 years. Out of the n=10 cases n=9 cases were females and n=1 was male.

The PASI score for psoriasis is a valuable tool for tracking how well methotrexate medication is working to treat the condition. Decreasing PSAI indicates improvement of the condition. In this study we found decreasing PASI scores at the end of 6 months when compared with baseline values and first, second and third, months of treatment depicted in figure 1.

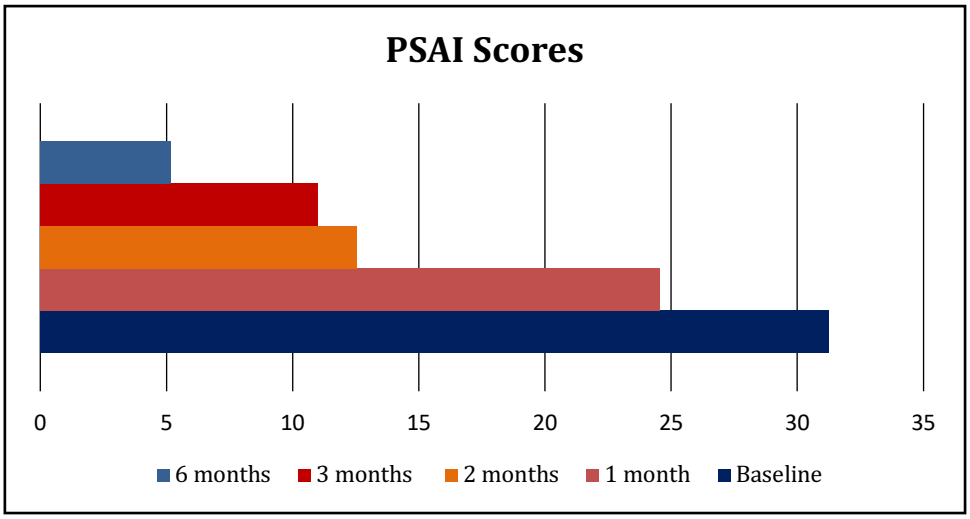

Figure 1: PSAI scores at the baseline and different intervals during follow-up

Friedman's test was used to determine whether there was a statistically significant difference between the PASI score of methotrexate-treated psoriasis patients

after one month (median = 24.55), Two months (12.54) three months (median = 10.99), and six months (median = 5.19) of treatment and the baseline score ($p < 0.0001$) and significant.

The Pemphigus Area and Activity Score (PAAS) is helpful for assessing how well medication is working to treat pemphigus vulgaris. As evidenced by the decreasing Pemphigus Area and Activity Score at the end of the first, third, and sixth months of treatment, drug therapy with dexamethasone – cyclophosphamide (pulse) has improved the lesions given in figure 2. In Pemphigus Vulgaris patients receiving Dexamethasone - Cyclophosphamide pulse therapy, Friedman's test reveals that there was a statistically significant decrease (P value 0.0001) in the Pemphigus Area and Activity Score after one month (median = 27.54), two months (median=18.66), three months (median = 13.24), and six months (median = 9.14) of treatment compared to the baseline score (median = 30.22).

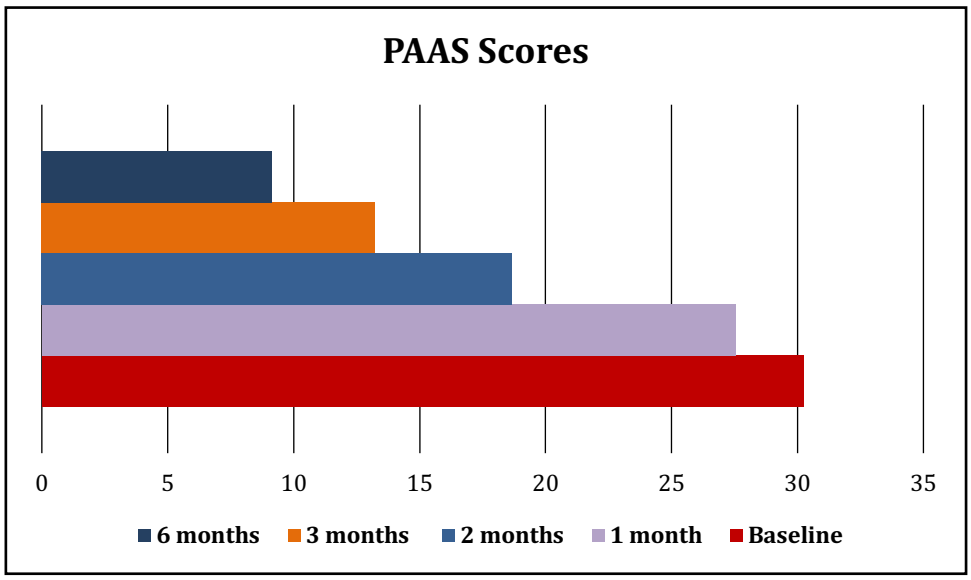

Figure 2: Pemphigus Area and Activity Score (PAAS) at different intervals during follow-up

The Modified Rodnan Skin Score (MRSS) is helpful for evaluating systemic sclerosis medication treatment. When the modified Rodnan Skin Score fell at the conclusion of the first, third, and sixth months of treatment, it indicated that the skin lesions had improved due to the drug therapy with dexamethasone - cyclophosphamide (pulse) treatment given in figure 3. When systemic sclerosis patients receiving Dexamethasone-Cyclophosphamide pulse therapy were compared to baseline scores (median = 15.52), there was a statistically significant ($p < 0.0001$) decrease in Modified Rodnan Skin Score after one month (median = 13.1), Two months (11.08), three months (median = 9.12), and six months (median = 6.87).

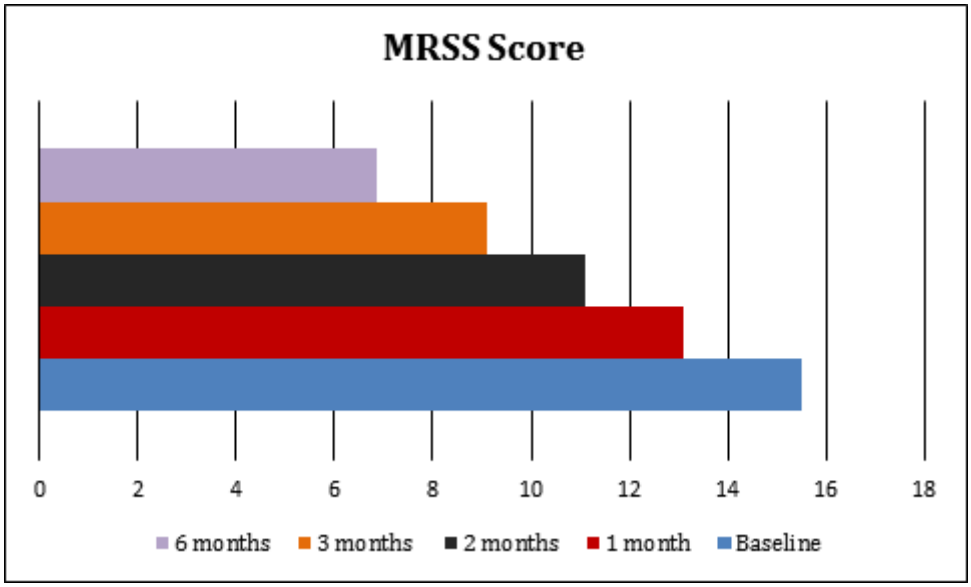

Figure 3: Modified Rodnan Skin Score (MRSS) at different intervals during follow-up

This was evaluated using periodic urine tests, complete hemograms, erythrocyte sedimentation rates, liver and renal function tests, lipid profiles, general examinations, systemic examinations, ophthalmological examinations, and laboratory investigations.

Psoriasis patients treated with methotrexate study group 23.33% reported with nausea/vomiting, 6.67% of gastritis, 3.33% of mucosal ulcer, 6.67% of alopecia, 16.67% microcytic anaemia with minimal side effects like liver enzyme elevation (6.67%) some of the cases have reported more than one adverse effect. Methotrexate induced adverse reactions reported in the study population of psoriasis was represented in the table 2.

Table 2: Adverse effects of methotrexate therapy

Adverse effects	Frequency (n=30)	Percentage
Nausea/vomiting	7	23.33
Gastritis	2	6.67
Mucosal ulcers	1	3.33
Alopecia	2	6.67
Anemia	5	16.67
LFT elevation	2	6.67

Note: more than one reaction has been reported in patients

The study group of pemphigus vulgaris patients treated with Dexamethasone – cyclophosphamide pulse therapy was found with commonest adverse reaction of nausea and vomiting in 40% and infections was also found in 40% cases other common adverse effects include weight gain, and leukopenia the other adverse effects have been depicted in table 3.

Table 3: Adverse effects of with Dexamethasone – cyclophosphamide pulse therapy in pemphigus Vulgaris

Adverse effects	Frequency (n=10)	Percentage
Nausea/vomiting	4	40
Gastritis	2	20
Weight gain	3	30
Alopecia	2	20

Infections	4	40
Anemia	2	20
Leukopenia	3	30
Menstrual irregularity	2	20
Pedal edema	1	10
Hypertension	1	10
Diabetes mellitus	1	10

Note: more than one reaction has been reported in patients

The study group of systemic sclerosis patients treated with DCP therapy, 30% reported with nausea/vomiting, 20% of gastritis, 10% alopecia, 30% microcytic anemia, 10% pedal edema, and 20% infection and others. DCP therapy induced adverse reactions reported in the study population of systemic sclerosis was represented in the table 4.

Table 4: Adverse effects of with Dexamethasone – cyclophosphamide pulse therapy in Systemic sclerosis

Adverse effects	Frequency (n=10)	Percentage
Nausea/vomiting	3	30
Gastritis	2	20
Weight gain	1	10
Alopecia	1	10
Infections	2	20
Anemia	3	30
Pedal edema	1	10
Hypertension	1	10

Note: more than one reaction has been reported in patients

Discussion

In the general population, 20 to 30% of people might suffer from skin problems at any given moment. Psoriasis, bullous disorders, systemic sclerosis, systemic lupus erythematosus, dermatomyositis, and inflammatory dermatoses such atopic and seborrheic dermatitis are examples of chronic skin illnesses. Early on, corticosteroids are used to treat autoimmune skin conditions. Excessive steroid usage frequently has fatal and permanently crippling side effects. Immunosuppressive medications used concurrently have minimized the need of steroids in treating certain disorders, improved treatment outcomes, and lowered side effects from both medications. [11] Therefore, the purpose of this study is to track the clinical progress of the south Indian population with chronic skin illnesses who visit a tertiary care facility. Commonly used systemic treatments for psoriasis include retinoids, methotrexate, and immunosuppressants such cyclosporine and PUVA therapy. [12] In 1958, methotrexate was first made available as a treatment for psoriasis, and it is now one of the most established and popular systemic treatments for all forms of psoriasis. [13] Dihydrofolatereductase is competitively inhibited, which is how it works. Methotrexate's intracellular polyglutamation and enhanced adenosine synthesis play a crucial role in the clinical effectiveness of this treatment for psoriasis because of its immunosuppressive, anti-inflammatory, and anti-proliferative effects. [14] Patients with psoriasis get doses of methotrexate ranging from 5 mg to 25 mg per week. Starting with a so-called test dosage of 5 or 7.5 mg for a week, the procedure is followed by the collection of blood samples for

comprehensive hemograms and liver function tests to check for potential adverse effects. Myelosuppression was the riskiest since it might be harmful to the patient. The dose of methotrexate may be raised if the results of the studies are within normal ranges. Complete blood count, liver enzymes, and renal parameters are regularly evaluated in the laboratory, and the patient is checked for any potential skin and mucous membrane adverse effects. The dosage is changed in accordance with the conditions.

The Psoriasis Area Severity Index (PASI) score was used to determine the effectiveness of the methotrexate medication treatment. Before beginning methotrexate medication as well as after the conclusion of the first, third, and sixth months of treatment, scoring was completed. According to this study, there was a statistically significant (p 0.001) drop in PASI score compared to baseline score after the first month, three months, and six months of methotrexate treatment. This conclusion confirms retrospective analysis indicating that methotrexate was extremely effective in their 75% psoriasis patients, and observation that > 75% of their 43 patients (100%) had a mean PASI score drop at 16 weeks. [15, 16] In the current study, methotrexate causes negative side effects such as nausea and vomiting (23.33%), 6.67% of gastritis, 3.33% of mucosal ulcer, 6.67% of alopecia, 16.67% microcytic anaemia with minimal side effects like liver enzyme elevation (6.67%). The drug in question directly stimulates the chemoreceptor trigger zone, causing nausea and vomiting, and the upper gastrointestinal tract also produces emetic impulses. Reduced dosage, the addition of antiemetics, and proton pump inhibitors were used to treat these adverse effects. The primary cause of microcytic anaemia is a decline in bone marrow function. Supplemental folic acid and iron were used to treat anaemia. After methotrexate dose is decreased, an elevated liver enzyme returns to normal.

The following common autoimmune skin disorder is pemphigus vulgaris. Systemic corticosteroids are the treatment's cornerstone. Pemphigus patient mortality decreased from 90% to 24% after corticosteroid therapy was introduced in the 1950s. [17] A long-term, high-dose corticosteroid regimen may cause a variety of negative side effects. To lessen the side effects of typical daily dosing regimens, corticosteroid pulse treatment and immunosuppressive medications were given this treatment has decreased the mortality. The goal of pulse treatment, which administers megadoses of immunosuppressants and steroids intravenously, is to fast achieve immunosuppressive effects without suffering from the negative side effects of long-term medication usage. Azathioprine (2 mg/kg) and cyclophosphamide (1-2 mg/kg) are the two immunosuppressive medications that are most frequently administered orally in between pulse treatments.

In 1982, Pasricha and Gupta incorporated DCP therapy into the pemphigus treatment plan, and they used it to treat pemphigus patients and obtain long-lasting remissions. [18] DCP is an intravenous infusion of 100 mg dexamethasone diluted in 500 ml of 5% dextrose administered over the course of two hours, repeated three times. The dexamethasone infusion was supplemented with 500 mg of cyclophosphamide on the second day for the patients. One DCP resulted from this. After exactly 28 days from the initial day of the drip, the DCPs were repeated. Any departure from the 28-day period was seen as an irregular course of therapy. Additionally, they got 50 mg of oral cyclophosphamide each day. Pemphigus Area and Activity Score was used to evaluate the effectiveness of DCP pulse treatment (PAAS). For cutaneous and mucosal lesions, the PAAS is computed

separately; the total score is obtained by adding the results. In extreme situations, PAAS scores might vary from 0.8 to 50. According to the current study, there is a statistically significant (p= 0.001) decrease in PAAS score compared to baseline score after one month, Two, three months, and six months of therapy. In other investigations, a significant clinical improvement has also been noted. In their research of 50 patients with auto immune bullous illness who had DCP therapy. Sacchidanand et al., [19] observed remission in 41 (82%) individuals. All 103 patients with pemphigus who had DCP treatment according to Pasricha et al., [20] study have also found similar results. The main side effects observed in the present study with dexamethasone – cyclophosphamide pulse therapy is nausea/vomiting. In the current study, nausea and vomiting were the most common adverse effects associated with dexamethasone-cyclophosphamide pulse treatment. The drug's activation of CTZ and the production of emetic impulses from the upper gastrointestinal tract are to blame for nausea and vomiting. Proton pump inhibitors were added to ondansetron (8 mg) for the treatment of nausea and vomiting, and gastritis. Folic acid treatment and iron therapy are used to treat anaemia. [21] Oral nystatin and systemic antibiotics are used to treat oral candidiasis and subsequent pyogenic skin infection. 5% of our patients had leukopenia, cyclophosphamide was stopped for two weeks while white blood cell levels rose, and cyclophosphamide was then reintroduced. The alkylating drug's myelosuppression causes leukopenia. Diabetes mellitus was discovered in one previously healthy person. The increased glucose production from the liver, insulin resistance, and the suppression of glucose uptake by peripheral tissues were the causes of the development of diabetes mellitus. A patient who acquired hypertension was treated with the appropriate antihypertensive medications.

An autoimmune disorder called systemic sclerosis is characterised by vascular abnormalities, connective tissue atrophy and sclerosis, and the presence of autoantibodies that cause fibrosis and vascular abnormalities. Similar to pemphigus vulgaris, systemic sclerosis patients also get monthly pulse treatment with dexamethasone and cyclophosphamide. By altering cellular components, the immunosuppressive alkylating drug cyclophosphamide inhibits and modifies lymphocytes. Patients were assessed once every two weeks for the first week, then once a month for the next six weeks. Before and after each DCP therapy, clinical and laboratory tests (complete blood counts, serum electrolytes, blood sugar, liver enzymes, and urine analysis) were used to evaluate the course of treatment. The Modified Rodnan Skin Score (MRSS), the most widely used scoring system, was used to determine the effectiveness of the DCP medication treatment in systemic sclerosis. According to the study, the Modified Rodnan Skin Value decreased statistically significantly (p 0.001) from the baseline score after the first, third, and sixth months of DCP treatment. The result confirms Steen and Medsger's observation that 90% of patients survived for at least five years in their research series of 278 patients with at least 25% skin score decrease from baseline. [20] Similar to this, Valentine et al series showed that cyclophosphamide was effective in treating cutaneous involvement in individuals with early illness, with an estimated reduction of 30% in the MRSS. Therefore, we concluded that cyclophosphamide decreased the severe dermal thickening in individuals with diffuse systemic sclerosis and may in the future minimise morbidity and death associated with the condition. In the current study, vomiting and nausea (30%) and gastritis (20%), three of the most

common side effects of DCP treatment in systemic sclerosis, were found.

Conclusion

In this study we found that all the patients responded well to medication as measured by appropriate scoring systems such as the Pemphigus Area and Activity Score for dexamethasone-cyclophosphamide pulse therapy in patients with pemphigus vulgaris, the PASI score for methotrexate therapy in patients with psoriasis, and the modified Rodnan skin score for DCP therapy in patients with systemic sclerosis. Therefore, in autoimmune skin disorders, the concurrent use of immunosuppressant medications such as methotrexate, dexamethasone, and cyclophosphamide pulse treatment were well tolerated and effective. However, minor side effects may be observed which can be easily managed.

References

1. Archer C.B. Functions of the skin. In: Burns, SM Breathnach, NH Cox and CEM Griffiths. Rook's textbook of Dermatology. 8th edition. John Wiley & sons Ltd, Wiley-Blackwell. 2010: 4.1-4.11.
2. Anne Braae Olesen. Chronic Skin Disease and Risk of Infection. The Open Infectious Diseases Journal.2012; 6 (Suppl 1: M6): 60-64.
3. Silverstein, Arthur. Horror autotoxicus, Autoimmunity, and Immunoregulation: The Early History. Transfusion Medicine and Hemotherapy - Transfus Med Hemother. 2005; 32. 296-302.
4. MatteoBellone, Arianna Brevi, Samuel Huber, Microbiota-Propelled T Helper 17 Cells in Inflammatory Diseases and Cancer, Microbiology and Molecular Biology Reviews. 2020; 84(2):00064-19.
5. Gregersen PK, Olsson LM. Recent advances in the genetics of autoimmune disease. Annu Rev Immunol. 2009; 27:363-91.
6. Wiseman AC. Immunosuppressive Medications. Clin J Am SocNephrol. 2016 Feb 5;11(2):332-43.
7. Tripathi K. D. Immunosuppressant drugs. In: Essential of Medical Pharmacology. 7th edition. New Delhi: Jaypee Brothers Medical Publishers Ltd. 2013: 878-885.
8. Ashcroft DM, Wan Po AL, Williams HC, Griffiths CE. Clinical measures of disease severity and outcome in psoriasis: a critical appraisal of their quality. *Br J Dermatol.* 1999;141(2):185–191.
9. Grover S. Scoring systems in pemphigus. Indian J Dermatol. 2011 Mar;56(2):145-49.
10. Khanna D, Furst DE, Clements PJ, Allanore Y, Baron M, Czirjak L, Distler O, Foeldvari I, et al. Standardization of the modified Rodnan skin score for use in clinical trials of systemic sclerosis. J Scleroderma RelatDisord. 2017 Jan-Apr;2(1):11-18.
11. Srinivas TR, Meier-Kriesche HU. Minimizing immunosuppression, an alternative approach to reducing side effects: objectives and interim result. Clin J Am SocNephrol. 2008 Mar;3Suppl 2(Suppl 2): S101-16.
12. Tariq Malik, AmerEjaz. Comparison of methotrexate and azathioprine in the treatment of psoriasis. A randomized controlled trial. Journal of Pakistan Association of Dermatologists 2010; 20: 152-157.
13. Czarnecka-Operacz M, Sadowska-Przytocka A. The possibilities and principles of methotrexate treatment of psoriasis - the updated knowledge. Postepy Dermatol Alergol. 2014 Dec;31(6):392-400.
14. Bedoui Y, Guillot X, Sélambarom J, Guiraud P, Giry C, Jaffar-Bandjee MC, Ralandison S, Gasque P. Methotrexate an Old Drug with New Tricks. Int J Mol Sci. 2019 Oct 10; 20(20):5023.

15. Ranjan N, Sharma NL, Shanker V, Mahajan VK, Tegta GR. Methotrexate versus hydroxycarbamide (hydroxyurea) as a weekly dose to treat moderate-to-severe chronic plaque psoriasis: a comparative study. J Dermatolog Treat. 2007; 18(5):295-300.
16. Montaudié H, Sbidian E, Paul C, et al. Methotrexate in psoriasis: a systematic review of treatment modalities, incidence, risk factors and monitoring of liver toxicity. J Eur Acad Dermatol Venereol. 2011; 25(Suppl 2):12–8.
17. Cholera M, Chainani-Wu N. Management of Pemphigus Vulgaris. Adv Ther. 2016 Jun; 33(6):910-58.
18. Pasricha JS, Khaitan BK, Raman RS, Chandra M. Dexamethasone-cyclophosphamide pulse therapy for pemphigus. Int J Dermatol. 1995 Dec; 34(12):875-82.
19. Sacchidanand S, Hiremath NC, Natraj HV, Revathi TN, Shobha Rani RH, Pradeep G, et al. Dexamethasone-cyclophosphamide pulse therapy for autoimmune-vesiculobullous disorders at Victoria hospital, Bangalore. Dermatology Online Journal 2003; 5(2).
20. Patricia Andrade de Macedo, Claudia Teresa Lobato Borges, Romy Beatriz Christmann de Souza. Cyclophosphamide: effective in the treatment of severe cutaneous involvement in systemic sclerosis. Bras J Rheumatol 2009; 49(3): 265-75.