National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Impact of immunosuppressive drugs in the therapeutic efficacy of autoimmune skin diseases

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Received: October 08, 2020; **Accepted:** October 30, 2020

ABSTRACT

Background: Autoimmune skin diseases such as pemphigus vulgaris and psoriasis and systemic sclerosis require long-term treatment. Immunosuppressive drug therapy is a gold standard treatment choice in the management of autoimmune skin disease. **Aim and Objective:** The aim of the study was to assess the efficacy of immunosuppressive drugs in the management of chronic skin diseases. **Materials and Methods:** A total of 120 cases of both genders (75 males and 45 females), above 18 years and newly started with immunosuppressant drugs for psoriasis (methotrexate therapy-weekly once), Pemphigus Vulgaris and Systemic Sclerosis (pulse therapy – monthly once) were recruited. The clinical response of drugs was assessed by psoriasis area severity index score (PASI), modified Rodnan Skin Score (MRSS), and Pemphigus Area and Activity Score (PAAS). **Results:** The PAAS score, PASI score, and MRSS scores were significantly decreased from the beginning to the end of the 6th month and the difference was statistically significant ($P < 0.005$). Nausea/vomiting were the common adverse effects in all groups followed by gastritis and weight gain. **Conclusion:** The usage of immunosuppressant drugs such as methotrexate in the management of psoriasis and dexamethasone-cyclophosphamide therapy in the management of pemphigus vulgaris and systemic sclerosis is effective and did not show any major adverse effects.

KEY WORDS: Methotrexate Drug Therapy; Dexamethasone-cyclophosphamide Pulse Therapy; Autoimmune Skin Diseases

INTRODUCTION

Skin is the largest organ in the human body; it is most frequently strained by autoimmune disorders.[1] Managing autoimmune skin conditions periodically requires trial and error. Treatment requires a close monitor to determine whether treatment is working or not.[2] Autoimmune skin diseases were usually managed with corticosteroids. However, boundless use of corticosteroids leads to debilitating adverse drug events.[3] In modern days, adjunctive use of immunosuppressive drugs has diminished the usage of steroids and is corresponded with less adverse drug events and better therapeutic outcome.

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2020.10.10292202030102020	

Methotrexate (4-amino-10-methylfolic acid, MTX) is an antagonist of folic acid used as a therapeutic choice in malignant and non-malignant diseases.[4] MTX is a safe and effective systemic drug for the ministration of all forms of psoriasis and is administered in weekly doses.[5-7] Dexamethasone-cyclophosphamide pulse therapy along with corticosteroids and immunosuppressive drugs is reported to decrease the morbidity and mortality from pemphigus vulgaris.[8,9] As per literature, immunosuppressive therapy

is an effective therapeutic choice with better treatment outcomes but has severe adverse events. This study was designed to assess the efficacy of immunosuppressive drugs in the management of chronic skin diseases.

MATERIALS AND METHODS

The present prospective observational study was conducted in the Department of Pharmacology in association with the Department of Dermatology at Kamineni Academy of Medical Sciences and Research Centre, Hyderabad during January 2019 to February 2020. A total of 120 cases of both sexes attending to dermatology department fulfilling the study criteria were recruited. Cases above 18 years of age, newly started with immunosuppressant drugs for psoriasis, pemphigus vulgaris, and systemic sclerosis, were included in the study. Case with hypertension, diabetes, tuberculosis, pregnancy, chronic liver diseases, chronic renal complications, and immunodeficiency was excluded from the study. Written informed consent was obtained from all the study participants and the study protocol was approved by the institutional ethics committee.

Study participants were undergone to general examination, complete hemogram, and other routine diagnostic procedures. During the study, drugs used were Tab. Methotrexate 5 mg – 25 mg orally weekly once, Inj. cyclophosphamide 500 mg iv monthly once – pulse therapy, Inj. dexamethasone 100 mg iv for 3 consecutive days at 28 days interval (pulse therapy), Tab. paracetamol 500 mg as required, Tab. ranitidine 150 mg twice daily or C. omeprazole 20 mg once daily, Tab. calcium once daily, Tab. B. complex, folic acid, and ferrous sulfate orally in case of anemia. The clinical response of drugs was assessed by the scoring system. The efficiency of methotrexate drug therapy in psoriasis management was evaluated by psoriasis area severity index score (PASI). The efficiency of dexamethasone-cyclophosphamide pulse (DCP) drug therapy in the management of systemic sclerosis was evaluated by the modified Rodnan Skin Score (MRSS). The efficiency of dexamethasone-cyclophosphamide pulse therapy in the management of pemphigus vulgaris was evaluated by Pemphigus Area and Activity Score (PAAS). The SPSS version 23 software was used to carry out statistical analysis relevant to the study. $P < 0.05$ was considered statistically significant.

RESULTS

Majority cases were in between 4th (31.6%) and 5th decade (28.3) with more male participants (62.5%). Among the study cases 45% had Pemphigus vulgaris, 30% had psoriasis and 25% systemic sclerosis [Table 1].

The PASI score was significantly decreased from the beginning to the end of the 6th month and the difference was statistically significant ($P < 0.004$). The MRSS score difference was statistically significant ($P < 0.002$). The PAAS score was significantly decreased from the beginning to the end of the 6th month and the difference was statistically significant ($P < 0.004$) [Table 2].

Nausea/Vomiting was most common adverse effects noticed in all the study groups, followed by mucosal ulcers and gastritis [Table 3].

DISCUSSION

The management of autoimmune skin diseases with corticosteroids reduces morbidity. Athough higher doses can be given for short periods, prolonged course can lead to major adverse effects such as hypertension, diabetes mellitus, and osteoporosis etc.[3] In recent days, with the advancement of therapeutic options, the management of skin diseases with immunosuppressive drugs substitutes the usage of steroids. This study was designed to assess the efficacy of immunosuppressive drugs in the management of chronic skin diseases. A total of 120 cases of both sexes (75 males and 45 females), above 18 years and newly started with immunosuppressant drugs for psoriasis, pemphigus vulgaris, and systemic sclerosis were recruited. Among the participants, 45% of cases had pemphigus vulgaris, 30% of cases had psoriasis, and 25% cases had systemic sclerosis [Table 1]. The efficiency of methotrexate drug therapy in psoriasis management was evaluated by psoriasis area severity index score. The score at the beginning was 28.76, at the end of 1st month 24.28, at the end of 3rd month 11.06, and at the end of 6th month 5.18. The PASI score was significantly decreased from the beginning to the end of the 6th month and the difference was statistically significant ($P < 0.004$). The efficiency of dexamethasone-cyclophosphamide pulse

Table 1: Age, gender, and disease wise distribution of study participants

Parameters	Study participants	
	Number	Percentage
Age (In years)		
18–30	26	21.6
31–40	38	31.6
41–50	34	28.3
51–60	12	10
Above 60	10	8.33
Gender		
Male	75	62.5
Female	45	37.5
Disease wise distribution		
Pemphigus vulgaris	54	45
Psoriasis	36	30
Systemic sclerosis	30	25

therapy in the management of pemphigus vulgaris was evaluated by Pemphigus Area and Activity Score. The PAAS score was significantly decreased from the beginning to the end of the 6th month and the difference was statistically significant ($P < 0.004$). Nausea/vomiting (38.8%) were common adverse events noticed in methotrexate drug therapy, followed by mucosal ulcers (22.2%), gastritis (16.6%), microcytic anemia (11.1%), and alopecia (11.1%). The above adverse events were managed by the addition of anti-emetics and proton pump inhibitors and decreasing drug dose. Folic acid and iron supplementations were used to manage anemia. Nausea and vomiting (33.3%) were the common adverse events in dexamethasone-cyclophosphamide pulse therapy in the management of pemphigus vulgaris, followed by gastritis (7.4%), weight gain (7.4%), alopecia (7.4%), and menstrual irregularities (7.4%). Hypertension, mucosal ulcers, and diabetes mellitus were noticed in 5.55% cases uniformly.

A study by Heydendael *et al*. measured disease severity by PASI score found no statistical significance and found >75% reduction in the mean PASI score at 16 weeks in 100% of study participants.[10] Heydendael *et al*. stated that methotrexate is an efficient agent in 75% of psoriasis cases.[11] A study by Ranjan *et al*. noticed that 66.66% cases showed >75% reduction in PASI score and remaining 33.33% cases showed >50–75% reduction in PASI score at the end of 12th week.[12] A study by van Dooren-Greebe *et al*. found that prolonged use of methotrexate reduces psoriasis in 81% cases.[13] The efficiency of DCP drug therapy in the management of systemic sclerosis was evaluated by the MRSS. The MRSS score at the beginning was 15.22, although the score was reduced to 7.04 at the end of 6th month. The difference was statistically significant ($P < 0.002$) [Table 2]. Heydendael *et al*. notified adverse events in 67.44% of total study participants. Among them, 44.19% cases complained with nausea.[11] A study by Ranjan *et al*. noticed nausea/vomiting, dizziness, lesional erythema in 46.67% cases, and gastrointestinal tract (GIT) related side effects were predominant while complete therapy.[12] Similarly, van Dooren-Greebe *et al*. noticed more side effects in liver function tests (44%) followed by nausea (43%) and over 73% of cases were reported adverse events.[13] A study by Duhra stated that the occurrence of adverse effects depended on a weekly dose but on a complete dose or duration of therapy.[14]

Straight away stimulating chemoreceptor trigger zone and provokes impulses in the upper GIT leading to nausea and vomiting, which was administered by proton pump inhibitors and by decreasing prostaglandin synthesis drug leads to gastritis. Olszewska *et al*. stated that monotherapy of cyclophosphamide is not beneficial in the management

Table 2: Drug efficacy in the management of various autoimmune skin disease

Time	Pemphigus vulgaris (PAAS score)		Psoriasis (PASI score)		Systemic sclerosis (MRSS score)	
	Median	SD	Median	SD	Median	SD
At beginning	28.76	6.98	29.14	7.23	15.22	6.28
1 month	24.28	5.32	25.72	7.09	12.64	5.92
3 months	11.06	2.56	14.01	4.38	9.56	4.46
6 months	5.18	1.84	9.28	2.66	7.04	3.62
P-value	0.004		0.004		0.002	

PASI: Psoriasis area severity index score, MRSS: Modified Rodnan skin score

Table 3: Adverse drug events noticed in various drug therapies

Adverse drug events	Pemphigus vulgaris (*n*=54)		Psoriasis (*n*=36)		Systemic sclerosis (*n*=30)	
	Number	Percentage	Number	Percentage	Number	Percentage
Diabetes mellitus	3	5.55	-	-	2	6.67
Hypertension	3	5.55	-	-	-	
Weight gain	4	7.4	-	-	4	13.3
Gastritis	4	7.4	6	16.6	4	13.3
Infection	2	3.7	-	-	2	6.67
Nausea/vomiting	18	33.3	14	38.8	8	26.67
Menstrual irregularity	4	7.4	-	-	-	-
Hematuria	1	1.85	-	-	-	-
Microcytic anemia	3	5.55	4	11.1	3	10
Mucosal ulcers	3	5.55	8	22.2	-	-
Pedal edema	3	5.55	-	-	2	6.67
Alopecia	4	7.4	4	11.1	3	10
Leukopenia	2	3.7	-	-	2	6.67

of pemphigus vulgaris.[15] A study by Kandan and Thappa noticed leukocytosis in 15 cases, followed by hyperglycemia in 10 cases, hypocalcemia in 6 cases and eosinophilia in 6 cases, anemia in 4 cases, leukopenia, elevated aspartate aminotransferase in 2 cases, and alanine aminotransferase in 2 cases.[16] The main adverse event noticed in the management of systemic sclerosis by DCP drug therapy was nausea and vomiting (26.67%), followed by gastritis (13.3%), weight gain (13.3%), microcytic anemia (10%), and alopecia (10%) [Table 3]. A study by Sakshi *et al*. stated during the management of systemic sclerosis by DC, pulse therapy did not find any major adverse effects.[17] Sakshi *et al*. stated that DC pulse therapy can reduce disease progression but cannot cure the whole systemic sclerosis.[17] In the present study, methotrexate drug therapy in the management of psoriasis showed a better outcome with minimal side effects. Whereas DC pulse therapy in the management of pemphigus vulgaris and systemic sclerosis showed notable outcomes with adverse effects. Kandan and Thappa stated that DC pulse therapy has a high degree of a positive outcome in the management of pemphigus vulgaris.[16] The present study was limited to less number of cases and conducted in less duration.

CONCLUSION

The results of this study concluded that boundless consumption of steroids leads to severe adverse events. The usage of immunosuppressant drugs such as methotrexate in the management of psoriasis and dexamethasone-cyclophosphamide therapy in the management of pemphigus vulgaris and systemic sclerosis is effective and did not show any major adverse effects. Hence, the usage of immunosuppressant drug therapy in the management of autoimmune skin disease is more effective than conventional steroids.

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How to cite this article: Jillella A, Zaman SU, Banothu VP. Impact of immunosuppressive drugs in the therapeutic efficacy of autoimmune skin diseases. Natl J Physiol Pharm Pharmacol 2020;10(12):1110-1113.

Source of Support: Nil, **Conflicts of Interest:** None declared.