ISSN 2515-8260 Volume 10, Issue 1, 2023

A CORRELATIVE RESEARCH OF METHOTREXATE AND APREMILAST'S EFFICACY IN THE MANAGEMENT OF MODERATE TO SEVERE PLAQUE PSORIASIS

Dr A Raj Pratheepa[1], Dr. P. Rukmini Reddy[2*]

[1]Assistant professor, Department of DVL, RVM Institute of Medical Sciences and Research Center, Laxmakkapally, Telangana, India.

[2]Assistant professor, Department of DVL, RVM Institute of Medical Sciences and Research Center, Laxmakkapally, Telangana, India.

[*]Corresponding author: Dr. P. Rukmini Reddy, Assistant professor, Department of DVL, RVM Institute of Medical Sciences and Research Center, Laxmakkapally, Telangana, India.

ABSTRACT

Background and objective: To evaluate the effectiveness of weekly Methotrexate versus everyday Apremilast in treating patients with moderate to advanced plaque psoriasis who visit the hospital dermatology OPD.

Methods: In a comparative analysis, the study included 50 people with moderate-to-severe plaque psoriasis. The diagnosis of psoriasis was made using clinical data. The psoriasis area and severity index (PASI) was used to evaluate the severity of the condition. Two groups of patients were formed; group A (25 patients) received methotrexate, while group B (25 patients) received apremilast. At the 0, 1, 2, and 4th treatment months, patients were evaluated using the Psoriasis Area and Severity Index (PASI) scores. The effectiveness of the medications was compared using PASI.

Results: 22 (61%), 11 (30.56%), 9 (25%), and 3 (8.34%) individuals had nail involvement. Group B patients with baseline PASI scores >25 experienced a substantial drop in PASI score after one month, compared to group A patients who did not. 9 of 13 patients had lower scores after 2 months. Three of four patients had lower PASI scores after three months. One patient never replied.

Conclusion: Methotrexate is a medication that is both cost-effective and efficient in our circumstance. With routine lab monitoring, low dose regimens, and folic acid supplements, it is safe to use despite having a number of harmful side effects and potentially fatal toxicities.

ISSN 2515-8260 Volume 10, Issue 1, 2023

Three patients who weren't able to reach PASI 75 with 7.5mg of methotrexate might have succeeded at higher doses.

Keywords: Plaque psoriasis, Apremilast, Methotrexate, PASI

INTRODUCTION

Psoriasis is an autoimmune skin condition where the cells buildup and form scales, dry to itchy patches. Here the skin cells multiply upto 10 times faster than normal cells. Most commonly appear on the scalp, elbow, knees, and lower back. It cannot be transmitted from person to person. More than 80% of psoriasis cases are plaque psoriasis. Types of psoriasis are plaque psoriasis, inverse psoriasis, guttate psoriasis, pustular psoriasis, nail psoriasis, erythrodermic psoriasis. The majority of patients have mild symptoms and respond well to topical medication, but 10–20% of patients have moderate to severe disease and need phototherapy or systemic therapy. Well-known systemic treatments for moderate-to-severe chronic plaque psoriasis include methotrexate and apremilast [1,2,3]. The immunosuppressive and anti-proliferative drug methotrexate shares structural similarities with folic acid. It prevents DNA Synthesis in the S phase of the cell cycle and competitively inhibits the enzyme dihydrofolate reductase. The side effects of MTX, which include myelosuppression, pulmonary fibrosis, and digestive issues, have the potential to be very serious. Hepatotoxicity is the main long-term side effect. Weekly oral doses of methotrexate are efficient [4,5].

The US Food and Drug Administration (FDA) has approved the oral PDE4 inhibitor apremilast for the treatment of psoriasis. Its oral route of administration gives it an advantage over biologics and other systemic antipsoriatic medications in that its use does not require laboratory monitoring [6,7]. By inhibiting PDE4, which is highly expressed in dentritic cells, monocytes, neutrophils, and keratinocytes, the medication controls immune reactions related to psoriasis by preventing the breakdown of cyclic adenosine monophosphate (cAMP). Diarrhoea, nausea, upper respiratory tract infection, nasopharyngitis, and headache are the most frequently reported adverse reactions [8, 9].

MATERIAL AND METHODS

The study comprised 50 individuals with moderate-to-severe plaque psoriasis in a comparative analysis at DVL Department, RVM Institute of Medical Sciences and Research Center, from November 2021 to October 2022. Psoriasis was identified based on clinical

ISSN 2515-8260 Volume 10, Issue 1, 2023

evidence. The patient's occupation, co-morbidities, use of other drugs, family history, and length of the disease were all noted in detail. Physically examined thoroughly for severity of psoriasis and other skin conditions. The psoriasis area and severity index were used to assess the psoriasis severity (PASI). Initial baseline assessments were completed prior to beginning the treatment. The patients were split into two groups; group A (25 patients) received methotrexate at a dose of 7.5 mg weekly following a 2.5 mg test dose the first week [10,11].

The dosage of apremilast was started at 10 mg in group B (25 patients) and increased up to 30 mg twice daily. For 16 weeks, a regular biweekly visit was performed to examine for clinical improvement and negative effects. Psoriasis area and severity index (PASI) scores were used to assess patients at the 0, 1, 2, and 4th treatment months. There was a 6-month post-treatment follow-up period during which the patient's length of remission and likelihood of relapse were assessed [12,13]. Using PASI, the medicines' efficacy was compared.

INCLUSION CRITERIA:

- Individuals with plaque psoriasis both female and male
- Between 15 to 70 years age
- Participants who are available for follow up

EXCLUSION CRITERIA:

- Pregnancy
- Lactating
- DM
- Obesity
- Active pulmonary TB
- Immunosuppressed
- Alcohol dependency participants
- Hematologic/hepatic/renal disorders

RESULTS

TABLE 1. AGE DISTRIBUTION

The range of age in our study was from 23 yrs to 70 yrs. The p value not significance indicates that there is no significant difference observed between the two groups.

ISSN 2515-8260 Volume 10, Issue 1, 2023

The mean age in the study was

Group A (Methotrexate): 45

Group B (Apremilast) : 45.65

AGE	METHOTREXATE	APREMILAST
< 30	5	3
31 – 45	9	12
46 – 60	9	7
> 60	2	3
TOTAL	25	25
Mean	45	45.65
SD	11.074	11.811
P-value	(Not significant)	

TABLE 2. GENDER DISTRIBUTION.

Males outnumbered females in both the groups.

Gender	METHOTREXATE	APREMILAST
MALE	17	17
FEMALE	8	8
TOTAL	25	25
P-value	0.73 (Not significant)	

ISSN 2515-8260 Volume 10, Issue 1, 2023

TABLE 3. DISEASE DURATION

The range of duration of illness was from one month to 40 yrs. The mean duration of illness was as follows,

Group A (Methotrexate): 72.45

Group B (Apremilast): 89.95

Disease duration (MONTHS)	METHOTREXATE	APREMILAST
< 25	14	11
> 25	11	14
TOTAL	25	25
Mean	72.45	89.95
SD	89.67	113.009
P-value	0.591 (Not significant)	

TABLE 4. ONSET AGE

The range varies from 15 years to 52 years. The mean age of onset was

Group A (methotrexate) -36.55

Group B (Apremilast) - 35.15

AGE OF ONSET	METHOTREXATE	APREMILAST
< 30	10	9
31 - 45	9	10
46 - 60	6	6
TOTAL	25	25
Mean	36.55	35.15
SD	10.231	10.946
P'value	0.678 (Not significant)	

ISSN 2515-8260 Volume 10, Issue 1, 2023

TABLE 5. SITE OF ONSET

The commonest site of onset is the scalp followed by back.

No. of patients with scalp as site of onset-25

No. of patients with back as site of onset-5

SITE OF ONSET	METHOTREXATE	APREMILAST
ABDOMEN	1	1
BACK	4	1
BOTH KNEES	2	1
LIMBS	2	0
LEGS	0	1
LEFT LEG	0	1
LOWER LIMBS	0	1
LUMBOSACRAL AREA	3	0
NAILS	0	1
RIGHT FOREARM	1	1
RIGHT LEG	0	1
SCALP	10	15
TRUNK	1	1
UPPER LIMBS	1	0
TOTAL	25	25
P-value	0.325 (Not significant)	

TABLE 6. INVOLVEMENT OF SCALP

Scalp involvement of psoriatic lesions was seen as a site of onset or through following the course of disease.

No of patients with scalp involvement - 36

ISSN 2515-8260 Volume 10, Issue 1, 2023

SCALP INVOLVEMENT	METHOTREXATE	APREMILAST
YES	18	18
NO	7	7
TOTAL	25	25
P-value	0.658 (Not significant)	

TABLE 7. INVOLVEMENT OF NAIL

Totally 36 (72%) patients had nail involvement, out of which

22(61%) patients had nail pitting [P]

11(30.56%) patients had onycholysis [O]

9 (25%) patients had subungual hyperkeratosis [SUH]

3 (8.34%) patients had nail dystrophy [D]

NAIL INVOLVEMENT	METHOTREXATE	APREMILAST
YES	17	19
NO	8	6
TOTAL	25	25
P-value	0.715 (Not significant)	

TABLE 8. PALMS AND SOLES INVOLVEMENT

Totally 17 patients (34%) had palms and soles involvement

PALMS AND SOLES	METHOTREXATE	APREMILAST
YES	8	9
NO	17	16
TOTAL	25	25
P-value	1.0 (Not significant)	

ISSN 2515-8260 Volume 10, Issue 1, 2023

TABLE 9. GENITAL INVOLVEMENT

Total no of patients with psoriatic lesions involving external genitalia – 8 (16%)

Genital involvement	Methotrexate	Apremilast
Yes	5	3
No	20	22
Total	25	25
P-value	0.658 (Not significant)	

TABLE 10. MUCOSAL INVOLVEMENT

Only 2 patient (4%) presented with geographic tongue in the study

MUCOSAL	METHOTREXATE	APREMILAST
YES	2	0
NO	23	25
TOTAL	25	25
P-value	1.0 (Not significant)	

TABLE 11. AGGRAVATING FACTORS

Only few patients had the history of aggravating/precipitating factors in which alcohol is the most common factor seen in 7 patients (14%).

Other precipitating factors are smoking, meat, sunlight, trauma, non-vegetarian food items.

Aggravating factors	Methotrexate	Apremilast
Alcohol	1	2
Alcohol, smoking	1	2
Alcohol, smoking, meat	1	0
Sunlight	1	0
Trauma	1	0

Trauma, food	0	1
Nil	20	20
Total	25	25
P-value	0.229 (Not significant)	

TABLE 12. ASSOCIATED DISEASES

In this study a 23 yrs female with psoriatic vulgaris had associated Down syndrome. A 61 yr old male with psoriasis vulgaris had associated facial nerve palsy and another patient of 35 yrs old male had associated kyphosis, genu valgum.

Associated disease	Methotrexate	Apremilast
Down syndrome	0	0
Facialnervepalsy	0	1
Kyphosis,genu valgum	0	1
Nil	25	23
Total	25	25
P-value	Not significant)	

TABLE 13. JOINT INVOLVEMENT

Only 6(12%) patients had joint involvement out of which 3 patients had symmetrical polyarthritis, 3 patients had asymmetrical oligoarthritis involving both hands.

JOINT INVOLVEMENT	METHOTREXATE	APREMILAST
YES	3	3
NO	22	22
TOTAL	25	25
P-value	.0 (Not significant)	

ISSN 2515-8260 Volume 10, Issue 1, 2023

TABLE 14. PASI 0

Most of the patients had initial PASI score above 25.

The mean PASI Score at week 0

Group A (Methotrexate): 25.6

Group B (Apremilast): 24.5

PASI0	METHOTREXATE	APREMILAST
< 15	6	2
16 - 25	4	8
> 25	15	15
TOTAL	25	25
Mean	25.605	24.585
SD	8.498	5.103
P'value	0.648(Not significant)	

TABLE 15. PASI 1

The mean of 1st month was as follows

Group A (Methotrexate): 21.2

Group B (Apremilast): 20.3

PASI 1	METHOTREXATE	APREMILAST
< 15	4	2
16 - 25	3	17
> 25	13	1
TOTAL	20	20
Mean	21.21	21.13
SD	7.382	5.8
P-value	0.965 (Not significant)	

ISSN 2515-8260 Volume 10, Issue 1, 2023

TABLE 16. PASI 2

PASI 2	METHOTREXATE	APREMILAST
< 15	9	6
16 - 25	11	19
> 25	5	0
TOTAL	25	25
Mean	17.905	18.16
SD	7.567	5.67
P-value	(Not significant)	

TABLE 17. PASI 3

PASI 3	METHOTREXATE	APREMILAST
< 15	8	14
16 - 25	15	11
> 25	2	0
TOTAL	25	25
Mean	15.935	15.69
SD	5.918	4.94
P'value	0.868 (Not significant)	

TABLE 18. PASI 4

PASI 4	METHOTREXATE	APREMILAST
< 15	18	20
16 - 25	5	5
> 25	2	0
TOTAL	25	25
Mean	12.925	11.72

SD	4.846	4.71
P'value	(not significant)	

TABLE 19. MEAN PASI REDUCTION

Comparing the mean PASI score at the end of each month throughout the study showed close similar values.

PASI	METHOTREXATE	APREMILAST
PASI0	25.605	24.585
PASI1	21.21	21.13
PASI2	17.905	18.16
PASI3	15.935	15.69
PASI4	12.925	11.72

TABLE 20. PASI 75

8 (16%) patients didn't achieve the PASI 75 out of which 3 patients (6%) were in Group A and 5 patients (10%) were in Group B. In those 3 patients from Group B was defaulted.

PASI 75	METHOTREXATE	APREMILAST
ACHIEVED	17	17
DEFAULT	0	3
NOT ACHIEVED	3	2
TOTAL	25	25
P-value	Not significant)	

TABLE 21. ADVERSE EFFECTS

ADVERSE EFFECTS	METHOTREXATE	APREMILAST
HEADACHE, LOWER ABDOMEN PAIN	0	2

ISSN 2515-8260 Volume 10, Issue 1, 2023

NAUSEA, HEADACHE	0	4
NIL	25	19
TOTAL	25	25
P-value	Not significant)	

TABLE 22. TREATMENT RESPONSE RATE

At the end of 1 month 8(6%) patients from each group attained PASI 75.

At the end of 2 months 12 (35%) patients receiving methotrexate achieved PASI 75 whereas 9 patients (27.5%) achieved PASI 75 apremilast.

At the end of 3 months 4 more patients achieved PASI 75 in group A and 8 more patients in group B.

At the end of 4 months 2 patient each in both the groups had not achieved PASI75.

PASI75 achieved	METHOTREXATE	APREMILAST
1st month	4	4
2nd month	12	9
3rd month	4	8
4th month	3	0
Not achieved	2	2
Default	0	2
Mean	4.5	4.25

TABLE 23. TREATMENT RESPONSE (PASI 75) WITH APREMILAST

During 1st month 4 patients with PASI score of >25 achieved PASI75.

Majority of people irrespective of their initial PASI score, achieved PASI 75 at the end of 2nd month (10 patients).

Though more number of patients in the Apremilast group showed reduction in the PASI score only 4 attained PASI75 at end of one month, Methotrexate group also showed 3 patients achieved the similar result.

ISSN 2515-8260 Volume 10, Issue 1, 2023

	1st month	2nd month	3rd month	4th month
<15	0	2	3	0
15 - 25	0	8	5	0
>25	4	0	0	0

TABLE 24. TREATMENT RESPONSE (PASI75) WITH METHOTREXATE

None of the patients with initial PASI score >25 achieved PASI 75 in 1st month; only on 2nd month of treatment they achieved it.

The Majority of people irrespective of initial PASI score attained PASI 75 at end of 2nd month (10 patients).

3 patients in this group have not achieved PASI75.

	1st month	2nd month	3rd month	4th month
<15	2	4	1	0
15 – 25	1	4	3	1
>25	0	2	0	0

TABLE 25. TREATMENT RESPONSE IN SCALP LESIONS

In methotrexate:

Initial PASI score	0 month	1st month	2nd month	3rd month	4th month
<15	2	2	3	4	11
15-25	3	7	8	11	5
>25	11	8	5	2	1

In Apremilast:

Initial PASI score	0 month	1st month	at 2nd month	at 3rd month	at 4th month
<15	1	1	1	6	14
15-25	6	15	14	7	1
>25	10	2	0	0	0

3 Patients with methotrexate not achieved PASI75.

Majority of patients (23/34) are seen with PASI score >25. The reduction in PASI score at the end of one month is higher in Apremilast (1/11) compared with methotrexate (6/12).

Three patients were default in treatment with Apremilast. One of them default at 1st month and other two at 2nd month.

TABLE 26. TREATMENT RESPONSE IN NAIL LESIONS

In methotrexate:

Initial PASI score	0 month	1st month	2nd month	3rd month	4th month
<15	1	3	4	5	9
15-25	4	5	5	9	4
>25	8	5	4	1	1

In Apremilast:

Initial PASIscore	0 month	1st month	2nd month	3rd month	4th month
<15	1	1	3	9	13
15-25	7	15	13	7	2
>25	11	1	0	0	0

3 patients with nail changes not achieved PASI75 at the end of treatment.

More than half of patients with nail changes (18/30) are seen with PASI Score >25, out of which 16 patients undergone treatment with apremilast and remaining 14 patients with methotrexate.

One default patient was noted Apremilast group at 2nd month.

More number of patients with nail changes (9/10) treated with Apremilast having PASI score >25 showed good and response to treatment which was comparatively higher than methotrexate undergoing patients (3/8).

TABLE 27. TREATMENT RESPONSE IN PALMOPLANTAR LESIONS

In methotrexate:

Initial PASIscore	0 month	1st month	2nd month	3rd month	4th month
<15	1	3	2	1	5
15-25	1	1	1	3	1
>25	4	2	2	0	0

In Apremilast:

Initial PASIscore	0 month	1st month	2nd month	3rd month	4th month
<15	1	2	2	4	5
15-25	1	7	6	2	3
>25	6	0	0	0	0

All the cases undergone Apremilast therapy with PASI score >25 showed response at 1st month of treatment (0/5), but the patients on methotrexate showed slow response (1/4).

Table 28. TREATMENT RESPONSE IN JOINT INVOLVED PATIENTS

In methotrexate:

Initial PASIscore	0 month	1st month	2nd month	3rd month	4th month
<15	1	2	1	0	1
15-25	0	0	0	3	1
>25	1	1	2	0	0

In Apremilast:

Initial PASIscore	0 month	1st month	2nd month	3rd month	4th month
<15	0	0	0	1	1

15-25	0	1	2	0	0
>25	1	0	0	0	0

One patient in each group has joint involvement with PASI score >25

TABLE 29. PASI75 ANALYSIS

INITIAL PASI score	No.of patients in group A (methotrexate)	PASI75 not achieved in group A	No of patients in group B (Apremilast)	PASI75 not achieved in group B
<15	3	2	1	0
16-25	8	0	5	1
>25	13	1	11	0

All the patients with PASI score >25 in Group B achieved PASI 75, but in group Aon methotrexate one patient didn't achieved it.

Even though with initial PASI score <15 noted in 4 patients in group A, two of them did not achieve PASI75 at the end of the treatment.

All the patients with PASI initial score 16 – 25 achieved PASI75 in group A, but one patient in group B didn't achieved it.

TABLE 30. TREATMENT RESPONSE ANALYSIS

In group A [Methotrexate]

PASISCORE	No.of patients in	1st month	2nd month	3rd month	4th month
	0 MONTH				
<15	5	4	8	6	16
16-25	4	3	10	13	5
>25	13	13	4	2	1

In Group B [Apremilast]

PASISCORE	0 month	1st month	2nd month	3rd month	4th month
<15	1	2	5	12	18
16-25	6	17	16	8	3

>25	12	1	0	0	0

Majority of the patients in group B (11/12) who had initial PASI score >25 showed reduction in PASI score at the end of one month which was significant compared with patients in group A who did not show much response after one month (13/13). But at the end of 2nd month 9 out of 13 patient showed reduction in the score. At the end of 3rd month three out four remaining patient showed reduction in PASI score. One patient never responded till the end.

One patient in Apremilast group reached the PASI 75 at 1stmonth but on 3rd month of visit the patient had new lesions and the PASI score was raised following intake of alcohol.

Similarly two patients in methotrexate group achieved PASI 75 at the end of 2 months of treatment, then on next visit they showed exacerbation of lesions and PASI score was raised. The reason for exacerbation after the initial response could not be found.

DISCUSSION

The medicine methotrexate has been on the sale for even more than 50 years. There aren't many research that clearly contrast the effectiveness of Apremilast and methotrexate. Methotrexate is typically recommended as the initial course of treatment by doctors. For the treatment of moderate to severe persistent plaque psoriasis, apremilast was recently approved by the FDA in 2014 [14,15,16]. It is also employed as an option to medications like methotrexate, cyclosporine, and biologicals, that have undesirable side effects and necessitate ongoing monitoring, including a higher chance of infections, liver damage, etc. In this study, the median age at which psoriasis first appears is 35.85. According to Faber et al study, average age of onset was reported to be 28 years while other studies done in UK about Psoriasis in a community by Dr. Nevitt and Dr. Hutchinson showed the mean age of onset as 33 years. whereas the mean duration of psoriasis was around 13-14 years in the Shetty et al study done in Indian population in 2018 [17,18,19]. In our study 34 patients had psoriatic lesions over scalp. Only 4 patients didn’t achieve remission of scalp lesions even after treatment which included 2 patients from group A and other 2 from group B.

Only 4 patients had joint involvement, two from each group. Asymmetrical oligo arthritis and symmetrical polyarthritis were the findings seen in these patients. Out of the four patients, two patients, one from each group showed poor response to treatment at the end of 4 months. Thirteen patients in our study had palmoplantar involvement and all patients responded to both methotrexate and Apremilast [20,21]. This study is a randomized study, comparing the

ISSN 2515-8260 Volume 10, Issue 1, 2023

efficacy of methotrexate and apremilast clinically by evaluating the PASI score. The treatment response of this study is measured by PASI 75. PASI 75 is a reduction in 75% of initial PASI score (PASI 0). In our study 34 patients (85%) achieved the PASI 75. Only 6 (15%) patients didn't achieve the PASI 75, out of which3 patients (7.5%) were in Group A and 3 patients (7.5%) were in Group B. Out of the three patients in group B two defaulted. Where as in a study by Nicoloff et al, only 75% patients achieved PASI 50 with 15mg/week. All the 3 patients belonged to the Apremilast group. Headache was the most common side effect followed by nausea and lower abdominal pain. Many trials reported that diarrhea and nausea as the major adverse effects [22,23]. None of the patients taking methotrexate developed adverse effects. The probable reason for absence of side effects may be due to the low dosage of Methotrexate and folic acid supplementation. Defaulters are more in Apremilast than methotrexate probably again due to low dosage regimen and supplement folic acid therapy. Aggravating factors includes Alcohol is the most common aggravating factor seen in 5 patients (12.5%) in our study. Even though we excluded the alcohol dependent patients in our study the adverse effects are seen in the above patients who had occasional drinking. (who were excluded from the alcohol dependence criteria). The PASI 75 was not achieved by this patient at the end of treatment. Follow up: The methotrexate and Apremilast drugs were stopped for all the patients in the study after 4 months of treatment. All patients were followed for 6 months period. During the follow up period two of the patients in methotrexate group had relapse after 2 months then they were treated with methotrexate in higher doses [24,25]. Four patients in Apremilast group showed exacerbation of lesions out of which One patient developed relapse after 3 months was switched to methotrexate. One patient had relapse within one month started with cyclosporine. And other two had minimal scaling in 2 months and were treated symptomatically and with topical emollients.

CONCLUSION

In the treatment of moderate to severe plaque psoriasis, methotrexate and apremilast both demonstrated equal efficacy. When compared to Apremilast at the end of 16 weeks, methotrexate has a low or nonexistent incidence of side effects. beginning of observable remission in both groups following initiation. Compared to methotrexate, apremilast demonstrated a much better response to nail psoriasis. For scalp lesions, methotrexate and apremilast both demonstrated comparable results. Both medications worked well on palmoplantar lessions. When compared to methotrexate, the apremilast group experienced a

ISSN 2515-8260 Volume 10, Issue 1, 2023

minimal reduction in initial PASI score earlier, but only 3 patients reached PASI 75, which was comparable to the methotrexate group. At the end of four months, there was no discernible difference between the two groups in terms of their PASI 75 scores.

Headache, nausea, and lower abdominal pain were the most frequent side effects of apremilast. Ours is the only comparative study using a low dose of methotrexate, or 7.5 mg/week, as far as we are aware. While the starting dose for all other studies was 15mg/week. In our setting, methotrexate is a drug that is both affordable and effective. Despite the fact that it has a number of negative side effects and potentially fatal toxicities, it can be used safely with regular lab monitoring, low dose regimens, and folic acid supplements. With higher doses of methotrexate, three patients who failed to achieve PASI 75 with 7.5mg of the drug might have succeeded.

Funding support:

Nil

Conflict of interest:

None

REFERENCES

1. Schmitt, J., & Wozel, G. (2005). The psoriasis area and severity index is the adequate criterion to define severity in chronic plaque-type psoriasis. *Dermatology*, *210*(3), 194-199.
2. AbuHilal, M. D., Walsh, S., & Shear, N. (2016). Use of apremilast in combination with other therapies for treatment of chronic plaque psoriasis: a retrospective study. *Journal of Cutaneous Medicine and Surgery*, *20*(4), 313-316.
3. Menting, S. P., Dekker, P. M., Limpens, J., Hooft, L., & Spuls, P. I. (2016). Methotrexate dosing regimen for plaque-type psoriasis: a systematic review of the use of test-dose, start-dose, dosing scheme, dose adjustments, maximum dose and folic acid supplementation. *Acta dermato-venereologica*, *96*(1), 23-8.
4. Armstrong, A. W., Betts, K. A., Sundaram, M., Thomason, D., & Signorovitch, J. E. (2016). Comparative efficacy and incremental cost per responder of methotrexate versus apremilast for methotrexate-naïve patients with psoriasis. *Journal of the American Academy of Dermatology*, *75*(4), 740-746.

5. Smith, C. H., & Barker, J. N. W. N. (2006). Psoriasis and its management. *Bmj*, *333*(7564), 380-384.
6. Holubar, K. (1998). Robert Willan's description and treatment of cutaneous diseases 1797/1798: a bicentennial. *Journal of Investigative Dermatology*, *110*(1), 101-101.
7. Brajac, I., & Gruber, F. (2012). History of Psoriasis. In *Psoriasis-A Systemic Disease* (pp. 57-68). Intechopen.
8. Potter, B. S. (2003). Bibliographic landmarks in the history of dermatology. *Journal of the American Academy of Dermatology*, *48*(6), 919-932.
9. Ichihashi, M., Fujiwara, Y., Uehara, Y., & Matsumoto, A. (1985). A mild form of xeroderma pigmentosum assigned to complementation group G and its repair heterogeneity. *Journal of investigative dermatology*, *85*(3), 284-287.
10. Eder, L., & Gladman, D. D. (2013). Psoriatic arthritis: phenotypic variance and nosology. *Current rheumatology reports*, *15*(3), 1-8.
11. Dogra, S., & Yadav, S. (2010). Psoriasis in India: Prevalence and pattern. *Indian journal of dermatology, venereology and leprology*, *76*(6), 595.
12. Parisi, R., Symmons, D. P., Griffiths, C. E., & Ashcroft, D. M. on behalf of the Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team, Identification, Management of P, Associated ComorbidiTy project t (2013) Global epidemiology of psoriasis: a systematic review of incidence and prevalence. *J Invest Dermatol*, *133*, 377-385.
13. Henseler, T., & Christophers, E. (1985). Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *Journal of the American Academy of Dermatology*, *13*(3), 450-456.
14. Lowes, M. A., Russell, C. B., Martin, D. A., Towne, J. E., & Krueger, J. G. (2013). The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses. *Trends in immunology*, *34*(4), 174-181.
15. Bos, J. D., De Rie, M. A., Teunissen, M. B. M., & Piskin, G. (2005). Psoriasis: dysregulation of innate immunity. *British Journal of Dermatology*, *152*(6), 1098-1107.
16. Lomholt, G. (1963). Psoriasis: prevalence, spontaneous course, and genetics. A census study on the prevalence of skin disease on the Faroe Island. Copenhagen. *GEC Gad*, 31-33.
17. Robinson, A., Van Voorhees, A. S., Hsu, S., Korman, N. J., Lebwohl, M. G., Bebo Jr, B. F., & Kalb, R. E. (2012). Treatment of pustular psoriasis: from the Medical Board of the

National Psoriasis Foundation. *Journal of the American Academy of Dermatology*, *67*(2), 279-288.

18. Gupta, A., Sardana, K., Bhardwaj, M., & Singh, A. (2018). Methotrexate cutaneous toxicity following a single dose of 10 mg in a case of chronic plaque psoriasis: A possible idiosyncratic reaction. *Indian dermatology online journal*, *9*(5), 328.
19. Ighani, A., Georgakopoulos, J. R., Zhou, L. L., Walsh, S., Shear, N., & Yeung, J. (2018). Efficacy and safety of apremilast monotherapy for moderate to severe psoriasis: retrospective study. *Journal of Cutaneous Medicine and Surgery*, *22*(3), 290-296.
20. Papadavid, E., Rompoti, N., Theodoropoulos, K., Kokkalis, G., & Rigopoulos, D. (2018). Real- world data on the efficacy and safety of apremilast in patients with moderate- to-severe plaque psoriasis. *Journal of the European Academy of Dermatology and Venereology*, *32*(7), 1173-1179.
21. Snehalatha, K., Ravindranathan, R., Sriram, D. K., & George, M. (2018). Utility of apremilast in the treatment of psoriasis.
22. Farber, E. M., & Nall, L. (1974). The natural history of psoriasis in 5,600 patients. *Dermatology*, *148*(1), 1-18.
23. Nevitt, G. J., & Hutchinson, P. E. (1996). Psoriasis in the community: prevalence, severity and patients' beliefs and attitudes towards the disease. *British Journal of Dermatology*, *135*(4), 533-537.
24. Nickoloff, B. J., Mitra, R. S., Green, J., Zheng, X. G., Shimizu, Y., Thompson, C., & Turka, L. A. (1993). Accessory cell function of keratinocytes for superantigens. Dependence on lymphocyte function-associated antigen-1/intercellular adhesion molecule-1 interaction. *The Journal of Immunology*, *150*(6), 2148-2159.
25. Langley, A., & Beecker, J. (2017). Management of Common Side Effects of Apremilast. *Journal of Cutaneous Medicine and Surgery*, *22*(4), 415-421.