Original Research Article

A comparative study of the efficacy and safety of oral apremilast versus oral methotrexate in patients with moderate to severe chronic plaque psoriasis

Vinma H. Shetty*, Saumya Goel, Amita Murali Babu, Hafsia Eram

Department of Dermatology, Venereology and Leprosy, A. J. Institute of Medical Sciences, Kuntikana, Mangalore, Karnataka, India

Received: 24 August 2018
Accepted: 22 September 2018

*Correspondence:
Dr. Vinma H. Shetty,
E-mail: vinma_shetty@yahoo.co.in

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ABSTRACT

Background: Psoriasis is a chronic, inflammatory systemic disease. Methotrexate acts by inhibiting dihydrofolic reductase enzyme. Apremilast is an oral PDE4 inhibitor approved by US Food and Drug Administration for treatment of psoriasis.

Methods: This is hospital based comparative study conducted from February 2018 to August 2018. Seventy patients above 18 years of age with chronic plaque psoriasis were divided into 35 patients in each group and were treated with oral Apremilast (30 mg twice daily) and oral methotrexate (15 mg per week in three divided doses with a 12-hour interval between doses and folic acid on methotrexate free days) and were evaluated every 4 weeks for a period of 16 weeks and followed-up at 24th week. Outcome was assessed on basis of psoriasis area-and-severity index score (PASI), psoriasis disability index (PDI) and clinical photographs.

Results: % of improvement in Group-A patients (76.8%) after 16 weeks of treatment was relatively more (p<0.05) as compared to group B (71.5%). At the end of 16 weeks PASI score in methotrexate group was statistically significant (p<0.05) as compared to group B, PDI became 17.90±3.87 in group A and was statistically significant (p<0.05) as compared to group B which was 20.34±2.98. Side effects observed were comparatively less in group A patients.

Conclusions: On comparing the two drugs, methotrexate was comparatively better tolerated and had better efficacy and safety. More studies are required to further prove the efficacy of Apremilast in treatment of psoriasis.

Keywords: Apremilast, Methotrexate, Psoriasis, PDI

INTRODUCTION

Psoriasis is a chronic, inflammatory systemic disease which is characterized by erythematous, scaly patches, or plaques over the skin which occurs due to hyper-proliferation of epidermal keratinocytes.1,2 It usually affects approximately 1–3% of the world population.3-6 Around 30% of patients of psoriasis have first-degree relative with the disease, and those with early-onset disease have history of similar complaints in the family.7,8 The disease is not only genetic but various environmental factors also play a major role in development of this disorder.

Methotrexate is an antimetabolite drug which was initially used for treatment of cancer. In the 1950s it was found to be also effective in clearing psoriasis and was thereby approved for its use by the FDA in 1970s. It mainly acts as an inhibitor of DNA synthesis by blocking dihydrofolic reductase enzyme so that it helps to prevent
reproduction of the cells in the lesions and thus the function of the skin returns back to normal. It has a very long half-life and thus drug is given as an weekly administration and is efficacious at this dosage. Usually 4–8 weeks are required for the therapeutic effects of the drug to become evident. It is taken once in a week, orally. Either in a single dose or in three doses taken at an interval of 12-hour over a period of 24 hours. It is started with a test dose of 2.5 mg and then gradually increase dose until a therapeutic level is achieved (average range, 10–15 mg weekly; maximum, 25–30 mg weekly). It is associated with various side effects which includes Hepatotoxicity, chronic use of the drug may lead to hepatic fibrosis, fetal abnormalities or death, myelosuppression therefore drug is contraindicated during pregnancy. Therefore, baseline complete blood count (CBC) and liver function tests (LFT) have to monitored weekly until target dose is achieved, then every 4–8 weeks.

Apremilast is a new drug which is taken orally for treatment of conditions like psoriasis and psoriatic arthritis. This oral drug selectively targets the molecules which are inside the immune cells of the body. It acts by adjusting the complicated processes of inflammation within the cell, thereby correcting the overactive immune response that causes inflammation in people with psoriatic disease, leading to improvement in flaking and scaling as well as joint tenderness and swelling. Apremilast is an oral phosphodiesterase type 4 inhibitor (PDE4) which works intracellularly and helps to regulate various inflammatory mediators, including pathways which are relevant for the pathogenesis of psoriasis. Inhibition of this PDE4 inhibition elevates intracellular cyclic adenosine monophosphate, which in turn down-regulates the inflammatory responses and modulates production of anti-inflammatory cytokines.

Apremilast was approved by the US Food and Drug Administration (FDA) in 2014 and by the European Commission in 2015 for treatment of psoriasis and psoriatic arthritis. It is the first oral drug to receive FDA approval for psoriasis since 1996. It is available as a 30-mg tablet which has to be taken by mouth. Its dosing begins as a five-day medication that is a start pack, where the dosage has to gradually increased until the recommended dose of 30 mg twice daily is reached. This drug is designed to be taken continuously to maintain improvement. In patients with severe renal impairment, the area under the plasma drug concentration-time curve (AUC) of apremilast increased by approximately 88% while clearance diminished by approximately 47%, thereby warranting dosage reductions.

Aim and objectives

- To study the efficacy and safety of oral apremilast vs oral Methotrexate in patients with moderate to severe chronic plaque psoriasis.

- To access clinical improvement based on clinical photographs.

METHODS

This was a hospital based, prospective comparative study conducted at Department of Dermatology of A. J. Institute of Medical Sciences, Mangalore from February 2018 to August 2018. Seventy diagnosed cases of moderate to severe chronic plaque psoriasis who gave written informed consent for the treatment were enrolled into two groups to receive 16 weeks of treatment with either oral Apremilast or oral Methotrexate.

The Inclusion criteria were patients aged 18 years or older; chronic plaque psoriasis patients with any one of the criteria’s A) Psoriasis Area and Severity Index (PASI) score of 12 or higher, B) body surface area involvement 10% or more; patients willing for treatment.

Exclusion criteria were patients with clinically significant or major uncontrolled disease; patients on biologics within the past 12 to 24 weeks; patients on active topical agents for psoriasis within the past 2 weeks; patients with liver or renal impairment; patients with insulin-dependent diabetes mellitus, uncontrolled hypertension; patients with Hepatitis B or HIV infection; pregnant, breast-feeding patients.

The patients were explained regarding the objectives as well as the method of study. A complete history was taken, clinical examination and biopsy was done wherever it was necessary. Patients underwent the necessary investigations monthly until week 16. If relevant abnormality in any of the laboratory values was noted during treatment or during an event of any serious and intolerable side effects the patients were discontinued from the present study and relevant anti-psoriatic treatment was started for the patients.

The patients were divided into two groups of 35 each, A and B. Group A was treated with oral methotrexate and Group B was treated with oral Apremilast and were evaluated every 4 weeks for a period of 16 weeks and the last follow-up was at 24th weeks.

Group -A

Methotrexate was given orally as 15 mg per week (given in three divided doses with a 12-hour interval between doses, according to the schedule of Weinstein and Frost). Tab folic acid was given to the patients on all the other days for a period of 16 weeks. The treatment was continued for 16 weeks and the last follow-up was at 24th weeks. In the event of intolerable and serious adverse effect, patients were discontinued from the treatment.

Drugs known to interfere with psoriasis or with the systemic treatments (or with both) were not allowed.
Group–B

Apremilast was given orally to the patient,

Starter pack -
- Day 1: 10 mg in AM, no evening dose
- Day 2: 10 mg AM and PM
- Day 3: 10 mg AM and 20 mg PM
- Day 4: 20 mg AM and PM
- Day 5: 20 mg AM and 30 mg PM
- Day 6 and 7: 30 mg AM and PM

After the patient completed the starter pack, for maintenance 30 mg tablets was given per orally twice daily for a period of 16 weeks and the last follow-up was at 24th weeks.

Outcome was assessed on the basis of:

1) The score for the psoriasis area-and-severity index (PASI) which is the primary outcome which helps to monitor the response of psoriasis to the therapeutic regimen and it was evaluated at baseline and then every 4 weeks for a period of 16 weeks and the last follow-up was at 24 weeks. 25

2) Psoriasis disability index:

The patients’ quality of life was assessed by using psoriasis disability index (PDI). 26 The PDI is a 15-item scale that specifically addresses self-reported disability in areas of daily activities, employment, personal relationships, leisure and treatment effects. The items are concerned with the practical effects of psoriasis in every day’s life.

The scores are calculated based on the series of 4 answers -
- Not at all - scores 0
- A little - scores 1
- A lot - scores 2
- Very much - scores 3.

If the question remains unanswered score is 0. The PDI is calculated by summing the score of each of the 15 questions resulting in a maximum of 45 and a minimum of 0. The higher the score, the more quality of life is impaired. The license for the PDI score was obtained - © Dermatology Life Quality Index. AY Finlay, GK Khan, April 1992'.

3) Clinical improvement was assessed based on photographic documentation done at baseline and then after 16 weeks.

Statistical analysis

Student’s unpaired t-test was used to test the significance difference in the outcome between two groups. Mean and standard deviation was used for continuous variable and P value of <0.05 was considered significant.

RESULTS

Seventy patients diagnosed for chronic plaque psoriasis were divided into 35 patients in each group and were treated with oral apremilast and oral methotrexate.

Out of these 35 patients in group A– 32 patients continued the medication while 2 patients withdrew the consent and 1 patient was discontinued due to abnormal laboratory values.

In group B out of 35 patients, only 21 patients continued the course while we lost 6 patients to follow-up due to non-compliance, 3 patients withdrew the consent and 5 patients had adverse effects. The baseline data of all these patients are given in Table 1.

Table 1: Demographic data at baseline.

|                      | Methotrexate (n=32) | Apremilast (n=21) |
|----------------------|---------------------|-------------------|
| Age (in years)       | 39.78±2.07          | 39.42±3.15        |
| (mean±sd)            |                     |                   |
| Male: female ratio   | 19:13               | 12:9              |
| Duration of psoriasis | 13±1.68            | 14±2.63           |
| (in years) (mean±sd) |                     |                   |
| (n=total number of patients in each group) |            |                   |

PASI score

The rate of response to the medications was evaluated based on PASI score which was evaluated and tested at the baseline, every 4 weeks for a period of 16 weeks and the last follow-up was at 24 weeks.

The % of improvement was calculated at the end of 16 weeks using the following formula:

\[
\text{#% of improvement in PASI score at 4 months} = \frac{\text{PASI score at baseline} - \text{PASI score at 4 months}}{\text{PASI score at baseline}} \times 100\%
\]

On accessing the results in group-A patients after 16 weeks of treatment, patients showed around 76.8% of improvement which on comparing with patients with oral Apremilast was relatively more. The% of improvement in PASI score in methotrexate group at the end of 16 weeks was statistically significant (p<0.05) as compared to that of group B. The% of improvement in patients at the end of 16 weeks in the other group was 71.5% such that a difference noticed was of around 5%. (Table 2, Figure 1)
On follow-up at 24th week patients in group A showed sustained results as compared to that of patients in group B.

PDI: PDI score was used and was assessed at the baseline and then at the end of 16 weeks and the time of follow-up

### Table 2: PASI score at baseline, at 8 and 16 weeks and % of improvement in PASI score at 16 weeks.

| Drugs             | PASI score (mean±sd) | % OF improvement in PASI score | P value |
|-------------------|----------------------|-------------------------------|---------|
|                   | At baseline          | At 8 weeks                    | At 16 weeks |
| Methotrexate (n=32) | 19.88±2.65           | 9.94±1.90                    | 4.60±1.47 | 76.8% | <0.0001 |
| Apremilast (n=21)  | 19.54±3.15           | 10.01±0.83                   | 5.56±1.05 | 71.5% | <0.0001 |

At the end of treatment that is after 16 weeks, the PDI became 17.90±3.87 in group A which was statistically significant (p<0.05) as compared to patients in group B which was 20.34±2.98 (Table 3). PDI score showed consistency at the time of follow-up in group A patients as compared to that of patients in the other group.

### Clinical improvement based on photographic documentation

On evaluation, patients with oral methotrexate showed more improvement as compared to the patients with oral Apremilast based on clinical photographs (Figure 2–9).
Figure 5: Oral methotrexate - patient 4 (A) before treatment; (B) after treatment at 16th week.

Figure 6: Oral apremilast - patient 1 (A) before treatment; (B) after treatment at 16th week.

Figure 7: Oral apremilast - patient 2 (A) before treatment; (B) after treatment at 16th week.

Figure 8: Oral apremilast - patient 3 (A) before treatment; (B) after treatment at 16th week.

Figure 9: Oral apremilast - patient 4 (A) before treatment; (B) after treatment at 16th week.

Table 4: Side effects and abnormal laboratory findings.

| Side effects                  | Methotrexate n=32 (%) | Apremilast n=21 (%) |
|-------------------------------|-----------------------|---------------------|
| Diarrhoea                     | 2 (6.25)              | 5 (28.8)            |
| Nausea and vomiting           | 4 (12.5)              | 8 (38.09)           |
| Upper respiratory tract       | 1 (3.12)              | 6 (28.5)            |
| Infections                    | 3 (9.37)              | 6 (28.5)            |
| Git intolerance               | 2 (6.25)              | 7 (33.3)            |
| Headache                      | 0                     | 9 (42.8)            |
| Mood disorders                | 0                     | 3 (14.2)            |
| Abdominal pain                | 1 (3.12)              | 0                   |
| Abnormal LFT’s                | 3 (9.37)              | 0                   |

Side effects observed were less in patients treated with methotrexate as compared to that of patients treated with tab Apremilast. The most side effects observed in group A were nausea and vomiting and few patients had abnormal liver function tests. Group B patients complained of headache, nausea, suicidal tendencies and depression was observed in few patients. Some of the patients complained of diarrhea and gastrointestinal intolerance. Therefore, there was non-compliance amongst the patients in group B (Table 4).

DISCUSSION

Psoriasis is defined as chronic inflammatory disorder which is genetically determined and leads to hyper-proliferation of the skin. It is a disfiguring condition in which there is alteration in growth and differentiation of the epidermis. Various factors play a major role in its etiology like hormonal, environmental, genetic, drugs, trauma, sunlight. The most common type of psoriasis is chronic plaque psoriasis which is characterized by well-defined red color plaques which are scaly and indurated involving the extensors aspect of the body and also the scalp.27,28 Psoriasis had a bimodal distribution of age of onset. According to a study done by Lomholt the average age reported was 12 years.29 According to a study done in
large US surveys, average age of onset was reported to be 28 years. While on the studies done in UK said mean age of onset as 33 years such that around 75% patients had psoriasis before 46 years of age. In our study, patients in both the groups were in the mean age group of 39.78±2.07 and 39.42±3.15 respectively and the mean duration of psoriasis in all the patients was around 13-14 years. In one of the German study, early age of onset was 16 years and 22 years and the later age involved was 57-60 years. In our study both males and females were almost equally affected in a ratio of 19:13 in the first group while ratio of 12:9 in group B patients. As per various studies psoriasis affects equally both males and females. One of the studies done in Germany showed the peak age of onset was 22 years in males and 16 years in females. Methotrexate inhibits DNA synthesis by competitive inhibition of dihydrofolate reductase, and may thus exert an antimitotic action on the epidermis. Oral medication can be given once in a week or can be given in divided doses in three parts 12 hours apart over period of 12 hours and dose can be increased by 2.5-5 mg/week. Methotrexate helps in reducing the severity of psoriasis by at least 50% in more than 75% of patients. In our study, the same dosage of methotrexate was started orally for the patients and patients achieved PASI of 4.60±1.47 by the end of 16 weeks reporting an improvement of 76.85% and the psoriasis disability index showed an reduction from 37.81 to 17.90 (mean). According to various studies, patients usually presents with complains of oral ulcers, gastrointestinal discomfort following the intake of tablet due to folic acid deficiency. Only few patients complained of gastrointestinal intolerance as tablet folic acid was prescribed to our patients. One of the retrospective studies have shown if methotrexate is given in low dosage for a longer period of time it has better efficacy and have reduced or minimal side effects. Apremilast is an oral PDE4 inhibitor which mainly acts over the cyclic adenosine monophosphate and helps in signaling of intracellular functions, and reduces the levels of proteins to modulate the immunity and thereby improves the inflammation which is associated with psoriasis. According to data and results of ESTEEM 1, 2 Apremilast has proved to be efficacious and safe for moderate to severe psoriasis and also is efficacious in patients with various comorbidities. According to the four phase studies done on this drug 30 mg twice daily dosage shows PASI response ranging from 29 to 41%. According to our study, patients on Apremilast showed improvement in PASI score of 71.5% at the end of 16 weeks. Side effects observed in our study in the group with oral Apremilast were more than that of patients taking methotrexate. Various trials have reported diarrhea and nausea as one of the major adverse effects and patients don’t need any routine laboratory investigations as no changes have been noticed. In our study patients main side effects observed were nausea, headache, diarrhea. 14.2% had depression and psychiatric problems. The label of the drug also reports warning of depression at around 16 weeks.

CONCLUSION

Apremilast is a new drug recently approved for management of psoriasis but due to its daily dosing, non-compliance was observed amongst the patients and it was associated with various side effects. On comparing the two drugs, methotrexate was comparatively better tolerated and had better efficacy and safety. This study has been done and presented as only few comparative studies of these two drugs have been done till now. Only few studies have been done on use of oral Apremilast in treatment of psoriasis and much data is yet not available. More studies are required to further prove the efficacy of Apremilast in treatment of this disorder.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee

REFERENCES

1. Nestle FO, Kaplan DH, Barker J. Psoriasis. N Engl J Med. 2009;361(5):496–509.
2. Menter A, Gottlieb A, Feldman SR, Van Voorhees AS, Leonardi CL, Gordon KB et al. Guidelines of care for the management of psoriasis and psoriatic arthritis: section 1. Overview of psoriasis and guidelines of care for the treatment of psoriasis with biologics. J Am Acad Dermatol. 2008;58(5):826–50.
3. Chang CA, Gottlieb AB, Lizzul PF. Management of psoriatic arthritis from the view of the dermatologist. Nat Rev Rheumatol. 2011;7(10):588–98.
4. Kurd SK, Gelfand JM. The prevalence of previously diagnosed and undiagnosed psoriasis in US adults: results from NHANES 2003–2004. J Am Acad Dermatol. 2009;60(2):218–24.
5. Augustin M, Reich K, Glaeske G, Schaefer I, Radike M. Co-morbidity and age-related prevalence of psoriasis: analysis of health insurance data in Germany. Acta Derm Venereol. 2010;90(2):147–51.
6. Sterrn RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. J Invest Dermatol Symp Proc. 2004;9(2):136–9.
7. Naldi L. Epidemiology of psoriasis. Curr Drug Targets Inflamm Allergy. 2004;3:121-8.
8. Henseler T, Christophers E. Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. J Am Acad Dermatol. 1985;13:450-6
9. Weinstein GD. Methotrexate for Psoriasis. JAMA. 1973;225(4):412.
10. Tanew A, Radakovic-Fijan S, Schemper M, Höningsmann H. Narrowband UV-B phototherapy vs photochemotherapy in the treatment of chronic...
plaque-type psoriasis: A paired comparison study. Arch Dermatol. 1999;135(5):519–24.
11. Gateva V, Sandling JK, Hom G, Taylor KE, Chung SA, Sun X, et al: A large-scale replication study identifies TNIP1, PRDM1, JAZF1, UHRF1BP1 and IL10 as risk loci for systemic lupus erythematosus. Nat Genet. 2009;41(11):1228–33.
12. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. Biochem Pharmacol. 2012;83:1583-90.
13. Otezla. Summit, NJ: Celgene Corporation; 2014. Available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=3acf6751-827d-11e2-9e96-0800200c9a66. Accessed March 18, 2015.
14. Otezla [summary of product characteristics]. Uxbridge, United Kingdom: Celgene Europe Ltd; 2015. Available at: http://ec.europa.eu/health/documents/community-register/2015/20150115130395/anx_130395_en.pdf. Accessed March 18, 2015
15. Soriatane. Research Triangle Park, NC: Stiefel Laboratories Inc; 2014. Available at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9e4a4f8c-4c8fb915-aeb18cb149be. Accessed March 18, 2015.
16. Neoral. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2013. Available from: http://daily med.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a755f7-11f1-4670-95d4-2965b9538ae3. Accessed March 18, 2015.
17. Methotrexate. Fort Lee, NJ: DAVA Pharmaceuticals Inc; 2009. Available from: http://daily med.nlm.nih.gov/dailymed/drugInfo.cfm?setid=9e4a4f8c-4c8fb915-aeb18cb149be. Accessed March 18, 2015.
18. Oxsoralen-Ultra. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 2015. Available from: http://daily med.nlm.nih.gov/dailymed/drugInfo.cfm?setid=a9f51dc4-9031-43bf-943c-cb236695f123. Accessed March 18, 2015.
19. Available at: https://www.psoriasis.org/about-psoriasis/ treatments/oral-treatments. Accessed March 18, 2015.
20. Otezla (apremilast) prescribing information. Summit, New Jersey: Celgene Corp.; 2014.
21. Food and Drug Administration Center for Drug Evaluation and Research. Nov, 2013. Application number: 205437Orig1s000: clinical pharmacology and biopharmaceutics review, 2013.
22. Weinstein G, Frost P. Methotrexate in psoriasis: a new therapeutic schedule. Arch Dermatol 1971;103:33-8.
23. Roenigk HH Jr, Auerbach R, Mailbach HI, Weinstein GD. Methotrexate in psoriasis: revised guidelines. J Am Acad Dermatol. 1988;19:145-56.
24. Lebwohl M, Ellis C, Gottlieb A. Cyclosporine consensus conference: with emphasis on the treatment of psoriasis. J Am Acad Dermatol. 1998;39:464-75.
25. Fredriksson T, Pettersson U. Severe psoriasis - Oral therapy with a new retinoid. Dermatologica. 1978;157:238-44.
26. Fortune DG, Main CI, O’Sullivan TM, Griffiths CE. Quality of life in patients with psoriasis: the contribution of clinical variables and psoriasis-specific stress. Br J Dermatol. 1997;137:755–60.
27. Rook’s Textbook of Dermatology, 8th edition. Edited by DA Burns, SM Breathnach, NH Cox and CEM Griffth ths. Blackwell Publishing Ltd. 2010.
28. Fry L: An Atlas of Psoriasis. Carnforth, Parthenon Publishing, 1992.
29. Lamholt G. Psoriasis: Prevalence, Spontaneous Course and Genetics. A Census Study on the Prevalence of Skin Diseases on the Faroe Islands. Copenhagen: GEC Gad; 1963: 31–3.
30. Farber EM, Nall ML. The natural history of psoriasis in 5600 patients. Dermatologica 1974;148:1–18.
31. Nevitt GJ, Hutchinson PE. Psoriasis in the community: prevalence, severity and patients’ beliefs and attitudes towards the disease. Br J Dermatol. 1996;135:533–7.
32. Fry L. Psoriasis. Br J Dermatol 1988;119(4):445-61.
33. Nickoloff BJ, Mitra RS, Green J, Zheng XG, Shimizu Y, Thompson C, et al. Accessory cell function of keratinocytes for superantigens. Dependence on lymphocyte function-associated antigen-1/ intercellular adhesion molecule-1 interaction. J Immunol. 1993;150(6):2148-59.
34. Haustein UF, Ryttmer M. Methotrexate in psoriasis: 26 years’ experience with low-dose long-term treatment. J Eur Acad Dermatol Venereol 2000;14:382–8.
35. Gottlieb AB, Strober B, Krueger JG. An open-label, single-arm pilot study in patients with severe plaque-type psoriasis treated with an oral anti-inflammatory agent, apremilast. Curr Med Res Opin. 2008;24:1529-38.
36. Helmick CG, Lee-Han H, Hirsch SC, Baird TL, Bartlett CL. Prevalence of psoriasis among adults in the U.S.: 2003-2006 and 2009-2010 National Health and Nutrition Examination surveys. Am J Prev Med. 2014;47(1):37-45.
37. Paal C, Cather J, Goederham M, Poulin Y, Mrowietz U, Ferrandiz C, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). Br J Dermatol. 2015;173(6):1387-99.
38. Cameron RT, Baillie GS. cAMP-specific phosphodiesterases: modulation, inhibition, and activation. In: Botana LM, Loza M, eds. Therapeutic targets: modulation, inhibition, and activation. 1st ed. Hoboken, NJ: John Wiley & Sons, Inc; 2012: 1-35.

Cite this article as: Shetty VH, Goel S, Babu AM, Eram H. A comparative study of the efficacy and safety of oral apremilast versus oral methotrexate in patients with moderate to severe chronic plaque psoriasis. Int J Res Dermatol 2018;4:563-9.