



ORIGINAL RESEARCH PAPER

Dermatology

A COMPARATIVE STUDY BETWEEN APREMILAST AND METHOTREXATE BASED ON SAFETY PROFILE AND RESPONSE TO TREATMENT IN CHRONIC PLAQUE PSORIASIS.

KEY WORDS: Apremilast, Methotrexate, Psoriasis

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ABSTRACT

Psoriasis is a chronic, relapsing disorder of the skin that can have a severe psychological and physical impact. The chronic nature of this disease requires a chronic treatment, hence needs use of a safe and equally effective drug. Methotrexate has been a first line drug with a proven efficacy but does not have a high safety profile especially in cases with co-morbidities or cases that need a long treatment. Apremilast, though has a high safety profile and does not need monitoring, has been observed to have lesser efficacy than Methotrexate and has a longer response time. Hence, Apremilast should be considered an option for mild cases of psoriasis and as a switch-over or an additional drug to reduce the total cumulative dose of methotrexate and hence its side-effects. **Background:** Psoriasis is a chronic, relapsing condition associated with psychological impact. Therefore, it is of utmost importance to prescribe a drug which is both effective and has a good safety profile. **Objective:** To prove the efficacy and safety of Apremilast as an additional treatment to methotrexate or as a potential switch over drug. **Methods:** A comparative study of 117 patients with psoriasis over a period of 18 weeks to measure the efficacy of Apremilast as a stand-alone drug and in combination with methotrexate based on improvement of Psoriatic Area Severity Index (PASI) **Results:** Combination of Methotrexate along with Apremilast showed better and faster reduction in PASI score than apremilast when given alone. **Conclusion:** Methotrexate remains the first line of treatment for psoriasis but Apremilast should be considered as an additional therapy and a switch over drug to reduce the cumulative dose of Methotrexate and its side effects.

Introduction

Psoriasis is a chronic, relapsing papulosquamous disorder of skin with genetic and environmental trigger factors. It is associated with many morbidities and psychosocial impact. Due to its chronic relapsing nature and associated mental and physical problem it becomes utmost important to prescribe safe and effective drug to which a patient can adhere for long duration and does not need constant monitoring. Safety of psoriasis treatments is particularly important in view of associated co-morbidities like major depression (16.5%), diabetes mellitus (16.5%), coronary artery disease (8.4%), and myocardial infarction (7.5%).¹ In a hospital based descriptive study done in Tamil Nadu, India between January to March 2019, it was found that 2.6% patients of total number of new cases seen in OPD had psoriasis. Chronic plaque psoriasis was the commonest (63.2%) clinical pattern observed irrespective of age and sex.² The most commonly used drugs in psoriasis (methotrexate, cyclosporine, acitretin) are related to organ toxicity and other side effects, biologics present a problem with cost effectiveness, immunosuppression and inconvenient mode of administration. Therefore, a cost effective drug with lesser side-effects and toxicity, which provides a sufficient response has become the necessity for the management of psoriasis. Apremilast was approved by the US FDA on March 21, 2014, for the management of active rheumatoid arthritis (PsA) in adults. On September 23, 2014, FDA approved apremilast for treating patients of moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy.³

APREMILAST

Apremilast is chemically identified as N-[2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-2,3-dihydro-1,3-dioxo-1H-isindol-4-yl]acetamide, phosphodiesterase-4 inhibitor that prevents conversion of cyclic adenosine monophosphate (cAMP) to adenosine monophosphate.⁴ The

molecular formula and weight of apremilast are C₂₂H₂₄N₂O₇S and 460.5 g/mole, respectively.⁵

Pharmacology: Apremilast is the only orally administered biologic in psoriasis. It is rapidly absorbed, reaching its peak plasma concentration after 2 to 3 hours with 73% bioavailability and 87 L of its mean apparent volume of distribution. Apremilast has a t_{1/2} of 6 to 9 hours.⁶ Metabolism of apremilast occurs through a cytochrome (CYP) 3A4-mediated oxidation. Apremilast is eliminated mainly by the renal route though some of the drug is also excreted through the faeces.⁷

Mechanism of action: While the precise mechanism of action in psoriasis is not clearly defined, many of the cytokine mediators involved in psoriasis are influenced by PDE4. Apremilast does not target any specific cytokine, but restores a balance of pro-inflammatory and anti-inflammatory milieu.⁴ cAMP is a crucial molecule in maintaining homeostasis of the body. The levels of cAMP are determined by enzyme PDE (phosphodiesterase). PDE-4 is specific for cAMP. Therefore, drugs that interact with this enzyme are used for chronic inflammatory disorders.⁸ PDE-4 levels are predominantly concentrated in inflammatory cells, natural killer cells, and keratinocytes.⁹ Apremilast binds to PDE-4 and increases cAMP levels, which successively decreases the levels of pro-inflammatory cytokines like tumor necrosis factor (TNF)- α , interleukin (IL)-23, IL-12, leukotriene B₄ and interferon (IFN)- γ .^{5,9} It increases the levels of anti-inflammatory enzymes like IL-10.¹⁰ Apremilast also binds to toll-like receptor 4 in peripheral blood mononuclear cells further reducing the production of pro-inflammatory cytokines.¹¹ Apremilast also reduces the activity of nitric oxide synthase, an enzyme liable for the synthesis of nitric oxide which is a crucial pro-inflammatory mediator, thereby preventing trafficking of macrophages and myeloid dendritic cells to the dermis and

epidermis in psoriatic skin.¹²

Safety profile: The phase 3 clinical studies suggest that apremilast is usually well tolerated. During a pooled safety analysis of two-phase 3 randomized controlled trials (RCTs, ESTEEM 1 and 2), adverse events resulted in the withdrawal of therapy only in 11.2% of patients.¹³ The associated gastrointestinal side effects (diarrhoea, nausea and headache) largely occurred within the initial months of treatment and subsequently subsided.^{5,9} Other side effects include upper respiratory tract infection, vomiting, nasopharyngitis, upper abdominal pain, hypersensitivity, dyspnea, cough, and skin rash. However, most of these side effects have a mild-to-moderate intensity with a self-limiting nature.⁹ Depression or depressed mood was reported by 1.0% of apremilast-treated patients in the rheumatoid arthritis studies and 1.3% in the psoriasis studies (versus 0.8% and 0.4% with placebo, respectively).⁵ While the general incidence is low, it is recommended that the risks and benefits of apremilast be evaluated carefully prior to initiating therapy in patients with a history of depression and/or suicidal thoughts or behaviour; close monitoring for worsening of such events during therapy is also advised.⁵ 12% of patients in the apremilast group experienced 5% to 10% weight loss versus 5% in the placebo group.⁵ This might happen in association to gastro-intestinal symptoms (nausea and secretory diarrhoea), and hence constant weight monitoring should be done during the therapy.

No significant abnormalities have been found in lab tests.¹⁴ Geriatric population may have more chance of developing gastrointestinal complications, hence apremilast should be given cautiously.¹⁵ The safety and efficacy of apremilast in children has not been studied. However, usage of adult dose of apremilast (30mg BD) in a 14 year old boy with chronic plaque psoriasis not responding to topical therapy, showed successful results without gastrointestinal or other side effects.¹⁶ Apremilast is contraindicated in pregnant and lactating women due to lack of human studies.¹⁷ Dose modifications are needed in patients with severe renal impairment. During the initial dose titration, evening dose is skipped and after 1 week it is continued at 30 mg once daily dose.⁵ No dose adjustment is required for hepatic impairment. Apremilast was used successfully in a psoriatic patient infected with HIV and hepatitis C.¹⁸

Dosage: The recommended dose of apremilast in adults for psoriasis is 30mg taken orally twice a day. The treatment is started with 10mg morning dose with a daily increment of 10mg until day 6 when the recommended dose is reached and continued at an equivalent dose thereafter. This slow increment minimizes gastrointestinal side effects.¹⁸ If a dose is missed, subsequent dose should be taken at the regular time without increasing the dose. In case of overdose, immediate help should be sought and therefore the patient should be managed symptomatically with supportive care.

Laboratory monitoring: Extensive laboratory evaluation and monitoring before initiating or while on apremilast treatment is not needed as laboratory variables did not show any significant changes in the trials of apremilast.¹³ However, it is recommended to test for renal function in patients with severe renal impairment for dose adjustment. It is recommended for evaluation of liver enzymes at baseline only since there is no long-term experience on the use of apremilast in people with hepatic impairment.¹⁹

Drug interactions: Strong CYP450 inducers like rifampicin, phenobarbitone, carbamazepine, and phenytoin should not be simultaneously given with apremilast as they could significantly reduce the amount of apremilast in the body. Methotrexate (Mtx) and apremilast are often administered together, as both drugs lack pharmacokinetic interactions.²⁰

MATERIALS AND METHODS:

Study Design

This was a single-center, comparative study conducted in skin out patient department over a period of two years between November 2018 and October 2020 to assess the safety and efficacy of apremilast without and in combination with methotrexate in patients of chronic plaque psoriasis (including palmo-plantar psoriasis with Psoriasis Area Severity Index (PASI) score less than 5). A total of 117 patients with a PASI score between 5 and 30 on their first visit were included. Disease with lower PASI score was managed with topical treatment with satisfactory results, and disease with PASI score higher than 30 was managed with conventional treatments (Methotrexate, cyclosporine etc.) keeping in mind the necessity of urgent treatment. PASI score was calculated and recorded by the same observer during all visits. The exclusion criteria were pregnancy, lactation, age less than 14 or more than 80, PASI score more than 30 or erythroderma, patient under polypharmacy, immunosuppression (renal or hepatic transplant) and history of any acute or chronic hepatic or renal disease. These exclusion criteria were largely supported by lack of in-depth studies of apremilast and due to contraindications of methotrexate.

Statistical Analysis

Two-tailed t-tests were used to compare means, and Pearson chi-squared test was used to compare proportions between the combination therapy (Apremilast + Methotrexate) and monotherapy (Apremilast) cohorts. Statistically significant difference between cohorts, as defined by P value is less than 0.05 (P < 0.05).

RESULTS

Out of 117 patients, 78 were males and 39 were females. 7 patients dropped out of the study due to unknown reasons and were lost to follow up. All the patients were given the starter pack with incremental dosing for 1 week. Patients who were below 18 years of age (N=7) were given this pack over 2 weeks. All the patients were prescribed capsule pantoprazole with domperidone for 2 weeks, to be taken once daily empty stomach. The patients were followed up every 6 weeks and PASI score was re-evaluated. This study includes patient follow up till 18 weeks (4 visits). Apremilast was well tolerated in 73.6% (81) patients. 12.7% (14) patients experienced mild symptoms like diarrhoea, nausea, headache and fatigue. These resolved completely by the end of second week. The dose was reduced to 30mg once daily at the end of 4 weeks for some patients (N=5, 4.54%) who had mild but persistent symptoms. The patients who continued having any symptoms at the first follow up (6 weeks) were switched to Methotrexate 15mg weekly (N=11, 10%) with folic acid on the other 6 days of the week. Only one patient had symptoms of depression at 4 weeks. Apremilast was stopped for these patients. Reduction of PASI score by more than 25% was considered significant for all visits. Patients who tolerated apremilast well but showed PASI score reduction less than 25% were given methotrexate 15mg weekly along with folic acid on the other 6 days of the week (N=57, 51.8%). Methotrexate was started with prior baseline investigations of complete blood count, renal and liver function tests, Mantoux test and chest X-ray. No monitoring was done for the patients who were on apremilast. Patients who were given Mtx were re-investigated every 3 months. [Table 1]

Table 1: Population demographics and baseline characteristics of patients with clinical response at 0, 6, 12 & 18 weeks of treatment

Variable	Monotherapy (Apremilast) n=42	Combination (Apremilast + Methotrexate) therapy n=57	Replacement therapy n=11	All patients, N=117
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Male, n (%)	30 (71.43)	35 (61.40)	8 (72.72)	78 (66.67)
Mean age, years (SD)	49.52 (19.22)	50.14 (16.71)	48.91 (15.86)	49.56 (17.43)
Baseline PASI 0 wk, mean (SD)	10.39 (5.35)	14.87 (7.11)	12.79 (6.38)	12.90 (6.55)
PASI 6wk, mean (SD)	6.45 (3.41)	11.67 (5.52)	11.17 (5.59)	9.22 (5.59)
PASI 12wk, mean (SD)	3.22 (1.90)	5.46 (2.57)	5.62 (3.05)	4.35 (2.76)
PASI 18wk, mean (SD)	1.04 (0.73)	1.39 (0.82)	1.50 (0.88)	1.19 (0.84)

Two-tailed t-tests was used to compare means, and Pearson chi-squared test was used to compare proportions between the combination therapy (Apremilast + Methotrexate) and monotherapy (Apremilast) cohorts. Statistically significant difference between cohorts, as defined by $P < 0.05$. [Table 2]. This indicated a significant role of methotrexate in reducing PASI score in combination treatment than apremilast when given as a monotherapy.

Table 2: Population demographics and baseline characteristics of patients with clinically significant response at 0, 6, 12 & 18 weeks of treatment

Variable	Monotherapy (Apremilast) n=42	Combination therapy (Apremilast + Methotrexate) n=57	P value
Male, n (%)	30 (71.43)	35 (61.40)	0.707
Mean age, years (SD)	49.52 (19.22)	50.14 (16.71)	0.761
Baseline PASI 0 wk, mean (SD)	10.39 (5.35)	14.87 (7.11)	
PASI 6 wk, mean (SD)	6.45 (3.41)	11.67 (5.52)	0.000
PASI 12 wk, mean (SD)	3.22 (1.90)	5.46 (2.57)	0.000
PASI 18 wk, mean (SD)	1.04 (0.73)	1.39 (0.82)	0.031

DISCUSSION

Out of 110 patients who participated in our study till the end of 18 weeks, only 11 (10%) had to be withdrawn from apremilast due to severe or persistent side effects. These results are comparable to safety analysis of two-phase 3 randomized controlled trials (RCTs, ESTEEM 1 and 2) by Crowley et al¹³ that had a withdrawal of 11.2% of the patients. Only 1 patient (0.9%) with no prior history of any mental illness showed signs of depression at the end of three weeks after starting apremilast as compared to 1.3% in a study by Zerilli et al⁵. The gastrointestinal side effects (nausea, diarrhoea and headache) mostly occurred in the first two to three weeks of starting the treatment and subsequently subsided by the end of 4 weeks. No other side effects were seen. Fatigue and weight loss were associated with secretory diarrhoea and were managed by either dose reduction (N=5, 4.5%) or withdrawal of apremilast. In our study, it was noticed that combination of methotrexate along with apremilast showed better and faster reduction in PASI score than apremilast when given alone.

CONCLUSION

Apremilast is a safe drug which requires no monitoring and has a better tolerance with least side effects as compared to the standard treatment of chronic plaque psoriasis. Methotrexate gives faster results as compared to Apremilast but needs constant monitoring and has a lower safety profile. Hence though Methotrexate may still be gold standard treatment for chronic plaque psoriasis, Apremilast should be

considered either an additional treatment when treating initially or should be considered as a switch over drug of choice.

LIMITATIONS: Patients with severe disease (PASI >30), were not included in the study due to the need for urgency of treatment and were straight away put on methotrexate or secukinumab. This study also does not observe the safety of apremilast in patients with chronic renal or hepatic disease. This study did not include patients who were taking Methotrexate for Psoriatic Arthritis (PsA) and neither did it observe effect of apremilast for PsA.

Declaration of patient consent: The authors certify that they have obtained written informed consent from all the patients. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understood that their names and initials will not be published and due efforts will be made to conceal their identity but anonymity cannot be guaranteed.

Financial support and sponsorship - Nil.

Conflicts of interest - There are no conflicts of interest.

REFERENCES

- [1] Cohen BE, Martires KJ, Ho RS. Psoriasis and the risk of depression in the US population: National Health and Nutrition Examination survey 2009-2012. *JAMA Dermatol* 2016;152(1):73-79. 8. Schafer PH, Parton
- [2] Velappan R, Venu S, Ramasamy S, Chellappan L. Current scenario in clinical trends of psoriasis in tertiary care hospital. *Int J Res Dermatol* 2019;5:452-6
- [3] Fala L. Otezla (Apremilast), an oral PDE-4 inhibitor, receives FDA approval for the treatment of patients with active psoriatic arthritis and plaque psoriasis. *Am Health Drug Benefits* 2015;8:105-10
- [4] Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem Pharmacol* 2012;83(12):1583-90.
- [5] Zerilli T, Ocheretyan E. Apremilast (Otezla): A New Oral Treatment for Adults With Psoriasis and Psoriatic Arthritis. *PT* 2015;40(8):495-500.
- [6] Wu A, Rohane P, Ng J, DeGroot B, Colgan B, Laskin OL, et al. Safety/tolerability and pharmacokinetics of multiple oral doses of apremilast in healthy male subjects. *Clin Pharmacol Ther* 2012;91:S26.
- [7] Wu A, Scheffler M. First-time-in-man, safety/tolerability and pharmacokinetics of ascending oral doses of apremilast (APR) in healthy subjects (HS). *J Invest Dermatol* 2011;131:S86.
- [8] Pagès L, Gavalda A, Lehner MD. PDE4 inhibitors: A review of current developments (2005-2009). *Expert Opin Ther Pat* 2009;19:1501-19.
- [9] Bubna AK. Apremilast: A dermatologic perspective. *Indian J Drugs Dermatol* 2016;2:75-82
- [10] Serezani CH, Ballinger MN, Aronoff DM, Peters-Golden M. Cyclic AMP: Master regulator of innate immune cell function. *Am J Respir Cell Mol Biol* 2008;39:127-32.
- [11] Schafer PH, Parton A, Gandhi AK, Capone L, Adams M, Wu L, et al. Apremilast, a cAMP phosphodiesterase 4 inhibitor, demonstrates anti-inflammatory activity in vitro and in a model of psoriasis. *Br J Pharmacol* 2010;159:842-55.
- [12] Gottlieb AB, Strober B, Krueger JG, Rohane P, Zeldis JB, Hu CC, et al. 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
- [13] Crowley J, Thaci D, Joly P, Peris K, Papp KA, Goncalves J, et al. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for >=156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermatol* 2017;77:310-7.e1
- [14] Reich K, Griffiths C, Leonardi C, Papp K, Kircik L, Day R, et al. Long term safety and tolerability of apremilast, an oral phosphodiesterase4 inhibitor, in patients with moderate to severe psoriasis: Results from a phase III, randomized, controlled trial (ESTEEM 1). *J Am Acad Dermatol* 2014;70:AB174.
- [15] Afra TP, Razmi TM, Dogra S. Apremilast in psoriasis and beyond: Big hopes on a small molecule. *Indian Dermatol Online J* 2019;10:1-12.
- [16] Smith RL. Pediatric psoriasis treated with apremilast. *JAAD Case Rep* 2016;2:89-91.
- [17] Gerosa M, Argolini LM, Artusi C, Chighizola CB. The use of biologics and small molecules in pregnant patients with rheumatic diseases. *Expert Rev Clin Pharmacol* 2018;11:987-98.
- [18] Reddy SP, Shah VV, Wu JJ. Apremilast for a psoriasis patient with HIV and hepatitis C. *J Eur Acad Dermatol Venereol* 2017;31:e481-2.
- [19] Nast A, Amelunxen L, Augustin M, Boehncke WH, Dressler C, Gaskins M, et al. S3 Guideline for the treatment of psoriasis vulgaris, update-Short version part 1-Systemic treatment. *J Dtsch Dermatol Ges* 2018;16:645-69
- [20] Poole RM, Ballantyne AD. Apremilast: First global approval. *Drugs* 2014;74:825-37.