ORIGINAL ARTICLE

Efficacy and safety of Apremilast in the treatment of patients with moderate to severe plaque psoriasis

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ABSTRACT

Introduction: Psoriasis is a chronic disorder with significant morbidity with the need for continual control of disease activity. However, potentially serious toxicity can limit their long term use. The potential toxic effects of long term use of the classic anti-psoriatics, long continuous therapy, higher cost and low socio-economic conditions of patients justify a clinical trial with Apremilast and methotrexate in Bangladesh.

Objective: To determine the efficacy and safety of oral administration of Apremilast in the treatment of patients with moderate to severe plaque psoriasis.

Materials and Methods: A prospective, controlled clinical trial was conducted in patients with psoriasis attending in outpatient department (OPD) of Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh in the year 2018. A total number of 60 patients were selected and they were divided into two groups randomly by lottery method into group-A and group-B. The group A patient received oral methotrexate 15 mg/week in a three 12-hourly divided doses for upto 16 weeks. The group B, patients were given apremilast 30 mg twice daily for upto 16 weeks.

Results: Out of all patients, mean (±SD) age was 45.72 (± 15.0) and 37.28 (±16.94) years, and there were 80% and 60% males in Methotrexate and Apremilast group respectively. Study showed that the base line PASI in Methotrexate and Apremilast were 6.96±4.8 and 11.9±2.8 respectively. In 1st follow up, PASI in Methotrexate and Apremilast were 4.96±3.48 and 8.02±1.94 and in last follow up PASI in Methotrexate and Apremilast were 0.76±0.43 and 7.88±3.38 respectively. Significant improvements were observed in Methotrexate group both in baseline to 1st follow up and 2nd follow up ($p<0.05$). Regarding the percent of improvement at baseline to 1st follow up, in Methotrexate and Apremilast were 29.85 ± 8.95 and 31.93 ± 11.55 respectively. At baseline to 2nd follow up percent of improvement in Methotrexate and Apremilast were 85.86 ± 7.33 and 28.48 ± 39.32 respectively. Regarding adverse effects observed in the both study group, nausea, vomiting and vertigo were more in Apremilast treated group than in Methotrexate group.

Conclusion: On the basis of the study results, Apremilast was found to be less effective, and had poor safety profile than Methotrexate in the treatment of moderate to severe plaque psoriasis.

KEY WORDS: Apremilast, Methotrexate, plaque psoriasis

INTRODUCTION

Psoriasis is a common, chronic, disfiguring, inflammatory and proliferative condition of the skin, in which both genetic and environmental influences have a critical role. The most characteristic lesions consist of red, scaly, sharply demarcated, indurated plaques, present particularly over extensor surfaces and scalp.[1,2] Psoriasis is universal in occurrence. Epidemiological studies from around the world have estimated the prevalence of psoriasis to be anywhere from 0.6 to 4.8%.[3,4] These disfiguring skin lesions are often

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associated with numerous comorbidities, ranging from cardiovascular disease, autoimmune disease, and cancer to psychiatric/psychological disorders.[5-7] Patients with psoriasis experience diminished health-related quality of life (QOL) resulting in physical and mental disability comparable to that seen in patients with other chronic diseases (e.g., diabetes, depression, heart disease).[8,9]

Psoriasis is a chronic skin disease that may require lifelong intermittent treatment. It is assumed that about 30 % of patients have at least moderate disease, often requiring systemic treatment in addition to topical treatment. Patients with moderate to severe disease generally require phototherapy (e.g. narrowband ultraviolet B radiation), photo chemotherapy (oral psoralen plus ultraviolet A radiation) or systemic agents (e.g. Cyclosporine, methotrexate, oral retinoids, fumaric acid esters) to control their disease adequately.[10] However, potentially serious toxicities can limit their long-term use. There is no standard therapeutic approach for patients with moderate to severe psoriasis.[11] National Psoriasis Foundation (USA) Benchmark Survey found that systemic therapies widely used for psoriasis before 2003 have not fully met most patients' needs and less than 40 percent of psoriatic patients are fully satisfied with any of the current therapies eg., acitretin, cyclosporine, methotrexate or PUVA.[12,13]

In March 2014, the Food and Drug Administration (FDA) approved apremilast (Otezla, Celgene Corporation), the first selective inhibitor of phosphodiesterase 4 (PDE4) indicated for adults with active PsA.[14,15] Subsequently, Celgene received FDA approval in September 2014 to further market the drug for the treatment of moderate-to-severe plaque psoriasis in patients for whom phototherapy or systemic therapy is appropriate.[15] By inhibiting PDE4, apremilast prevents the degradation of cyclic adenosine monophosphate (cAMP). The subsequent increased level of cAMP results in an antagonistic effect on the production of proinflammatory cytokines such as TNF-α, IL-23, and interferon (IFN)-γ.[16,17] Since the mid 1950s, methotrexate has become the gold standard by which other systemic psoriasis medications are measured.[18,19] In this respect apremilast compared with methotrexate which has a potential for producing irreversible hepatic damage. With the desire to establish Apremilast as an alternative to traditional first line therapy, this study was carried out to explore the efficacy and safety of this drug in the treatment of psoriasis.

MATERIALS AND METHODS

A prospective, controlled clinical trial was conducted at the Department of Dermatology and Venereology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh in the year 2018. Patients with psoriasis attending outpatient department (OPD) of Dermatology and Venereology, BSMMU, Dhaka were enrolled in this study. Consecuitive type of non-probability sampling. technique was followed. Males or females, ≥ 18 years of age, diagnosis of chronic, moderate to severe plaque psoriasis for at least 12 months prior to Screening, and PASI>10, had an inadequate response, intolerance, or contraindication to at least one conventional systemic agent for the treatment of psoriasis, no prior exposure to biologics for treatment of psoriasis and hemogram level, hepatic and renal function test of the patient within normal limits were selected for the study. On the other hand, psoriasis patients with history of any clinically significant

and uncontrolled systemic diseases; any condition, including the presence of laboratory abnormalities, pregnant or breast feeding women, patients have failed more than 3 systemic agents, patients have a history of, or ongoing chronic or recurrent infectious disease, patients having received, or expected to receive any live virus or bacterial vaccination within 3 months before first administration of IP, or through Week 20 during the study, had a Bacillus Calmette-Guérin (BCG) vaccination within 1 year prior to screening, history of positive human immunodeficiency virus (HIV), or have congenital or acquired immunodeficiency (eg, common variable immunodeficiency disease), active substance abuse or a history of substance abuse within 6 months prior to screening, malignancy or history of malignancy, psoriasis flare or rebound within 4 weeks prior to screening, topical therapy within 2 weeks of randomization or systemic therapy for psoriasis within 4 weeks prior to randomization, use of phototherapy within 4 weeks prior to randomization or prolonged sun exposure or use of tanning booths or other ultraviolet (UV) light sources, prior treatment with apremilast or etanercept and patient unwilling to participate in this study were excluded from the study. Prior to the commencement of this study, approval from Institutional Review Board (IRB) was taken and the informed written consent were taken from each of the patient. Statistical analysis of the results was obtained by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-20) (SPSS Inc, Chicago, IL, USA). The mean and SD values were calculated for continuous variables. Chi square test were done to analyze the categorical variables and Unpaired t-test was done for continuous variables. Statistical significance was set at 0.05 level and confidence interval at 95% level.

PROCEDURE OF DATA COLLECTION

A total number of 60 patients were selected and they were divided into two groups randomly by lottery method into group-A and group-B. Complete history, general physical and dermatological examinations were done for all enrolled patients. For women of reproductive age reproductive history, menstrual history, lactation and pregnancy plan were carefully judged. Data were collected by face to face interview and history and physical findings were recorded in a structured questionnaire. Baseline investigations including complete blood count (total count, differential count), platelet count, Hb%, ESR, urine analysis, random blood sugar(RBS), serum creatinine and liver function test (SGPT) were done. Finally those patients, who matched the inclusion and exclusion criteria according to history, physical examination and laboratory reports and agreed freely to give their informed consent, were selected for the study. Erythema, induration and scaling were recorded in terms of PASI (Psoriasis Area Severity Index) at baseline, after 8 weeks and 16 weeks therapy as the tool of main outcome measure. Adverse effects of the drugs among all patients in both the groups were recorded.

INTERVENTION

The group A patient received oral methotrexate 15 mg/week in a three 12-hourly divided doses for upto 16 weeks (Folic acid supplimentation was also given to the patients of this group). The group B patient were giving apremilast 30 mg twice daily without regard to meals. To re-

duce gastrointestinal side effects associated with the start of therapy, a five-day titration was followed. The initial dose on day 1 was 10 mg in the morning; this was increased to 10 mg in the morning and evening on day 2. The evening dose was further increased by 10 mg (to 20 mg) on day 3. On day 4, the morning dose was increased to 20 mg, so that 20 mg taken twice daily, and on day 5 the evening dose was increased to 30 mg. The maintenance dose of 30 mg twice daily begin on day 6 to upto 16 weeks. Patients were monitored for laboratory investigations at 4 weeks initially, then after 8 weeks. Therapy was continued if the lab parameters remained within normal limits. None of the patient was allowed concurrent use of anti-psoriatic drugs known to interfere with psoriasis or any other systemic treatments. Topical emollients were advised to all patients, while those in group A were allowed folic acid (5 mg/day, 5 days in a week) and anti-emetic when needed. Advice of strict contraceptive measure was given to all married patients of reproductive age. The study period comprised of 16 weeks of treatments in both groups. Patients were followed up for clinical improvement and side-effects of therapy after 8 weeks and then after 16 weeks of drug therapy. Follow-up laboratory investigations were CBC (Complete Blood Count), Random Blood Sugar(RBS), ALT (SGPT), Serum Creatinine and Urine R/M/E.

Improvement were defined as follows:

Cleared ≥75% reduction of PASI score

Marked improvement ≥ 50 – 75% reduction of PASI score

Moderate improvement ≥ 25 – 50% reduction of PASI score

Mild or Inadequate improvement ≤ 25% reduction of PASI score

RESULTS

Table 1 Distribution of patients in both groups by age

Age (in years)	Methotrexate (n=25)	Apremilast (n=25)	p value*
<30	5(20.0)	15 (60.0)	
45-60	15 (60.0)	8 (32.0)	
>60	5 (20.0)	2 (8.0)	
Total	25 (100.0)	25 (100.0)	
Mean (± SD)	45.72 (±15.0)	37.28 (±16.94)	0.068

*t test was done to measure the level of significance.

Figure within parentheses indicates in percentage.

Table 1 shows the age distribution of the patients of both groups. Out of all patients of Methotrexate group, 20.0% patients had age up to 30 years, 60.0% belonged to 45 to 60 years and 20.0% above 60 years. In Apremilast group maximum patients belonged to up to 30 years age group, followed by 32.0% within 45 to 60 years and 8.0% more than 60 years age group. Mean (±SD) age was 45.72 (± 15.0) and 37.28 (±16.94) years in both Methotrexate and Apremilast group respectively.

Table 2 Distribution of patients in both the groups by sex

Sex	Group		p value*
	Methotrexate n(%)	Apremilast n(%)	
	(n=25)	(n=25)	
Male	20(80.0)	15 (60.0)	0.157
Female	5(20.0)	10 (40.0)	
Total	25 (100.0)	25 (100.0)	

*Chi-square test was done to measure the level of significance.

Table 2 shows the sex distribution of the patients. In Methotrexate group 80.0% were male and in Apremilast group 60.0% were male. No statistically significant difference was observed between groups in term of sex.

Table 3 Distribution of improvement scale after 8 weeks

Group			
Improvement scale	Methotrexate n(%)	Apremilast n(%)	p value
Scaling			
Mild improvement	2 (8.0)	3 (12.0)	0.081
Moderate improvement	13 (52.0)	19 (76)	
Marked improvement	10 (40.0)	3 (12.0)	
Erythema			
Mild improvement	2 (8.0)	2 (8.0)	0.999
Moderate improvement	8(38.1)	7 (28.0)	
Marked improvement	15 (42.9)	16 (64.0)	
Plaque			
Mild improvement	3 (12.0)	5 (20.0)	0.014
Moderate improvement	22 (88.0)	20 (80.0)	

*Chi-square test was done to measure the level of significance.

After 8 weeks of treatment, improvement of scaling was more in Methotrexate group (p=0.081), erythema was improved significantly in both group (p=0.999), plaque was improved significantly more in Methotrexate group (p=0.014).

Table 4 Distribution of improvement scale after 16 weeks

Group			
Improvement scale	Methotrexate n(%)	Apremilast n(%)	p value
Scaling			
Moderate improvement	5 (20.0)	8 (32.0)	0.027
Marked improvement	7 (28.0)	10 (40.0)	
Cleared	13 (52.0)	7 (28.0)	
Erythema			
Moderate	2 (8.0)	4(12.0)	0.999
Marked improvement	7 (28.0)	9(36.0)	
Cleared	16 (64.0)	12 (48.0)	
Plaque			
Moderate improvement	5 (20.0)	10 (40.0)	0.001
Marked improvement	16 (64.0)	13 (52.0)	
Cleared	4(12.0)	2 (8.0)	

*Chi-square test was done to measure the level of significance.

After 16 weeks of treatment, improvement of scaling, erythema and plaque was significantly better in Methotrexate group than in Apremilast group ($p<0.05$).

Table 5 Distribution of the patients by PASI

PASI	Group		p value
	Methotrexate (n=25)	Apremilast (n=25)	
Base line	6.96±4.8	11.9±2.	0.001
1st follow up	4.96±3.48	8 8.02±1.94	0.001
Last follow up	0.76±0.43	7.88±3.38	0.001

*Fisher's Exact test was done to measure the level of significance.

Table 5 shows that the base line PASI in Methotrexate and Apremilast were 6.96±4.8 and 11.9±2.8 respectively. At 1st follow up, PASI in Methotrexate and Apremilast were 4.96±3.48 and 8.02±1.94 respectively and at last follow up PASI in Methotrexate and Apremilast were 0.76±0.43 and 7.88±3.38 respectively. Significant improvements were observed in Methotrexate group both in baseline to 1st follow up and 2nd follow up ($p<0.05$).

Table 6 Distribution of percent of improvement based on PASI

Group			
Percent of improvement	Methotrexate **(n=25)**	Apremilast **(n=25)**	**p value***
Baseline to 1st follow up	29.85 ± 8.95	31.93 ±11.55	0.482
Baseline to 2nd follow up	85.86 ± 7.33	28.48 ± 39.32	0.001

*t test was done to measure the level of significance, Data was shown as Mean ± SD.

Table 6 shows that the percent of improvement in baseline to 1st follow in Methotrexate and Apremilast were 29.85 ± 8.95 and 31.93 ± 11.55 respectively. And baseline to 2nd follow up percent of improvement in Methotrexate and Apremilast were 85.86 ± 7.33 and 28.48 ± 39.32 respectively and in 1st follow up to 2nd follow up the percent of improvement in Methotrexate and Apremilast were 78.22 ± 14.98 and -16.21 ± 88.90 respectively.

Table 7 Distribution of the groups by Adverse effects

Side effects	Methotrexate **(n=25)**	Apremilast **(n=25)**
Nausea	1(4%)	3(12%)
Vomiting	1(4%)	2(8%)
Vertigo	0(0.0)	1(4%)
Headache	4%(1)	4%(1)
RTI	0(0.0)	00%(0)
Diarrhoea	0(0.0)	00%(0)

Table 7 shows that in the both study group, nausea was 4% and 12% and vomiting was 4% and 8%, vertigo was 0% and 4% in Methotrexate and Apremilast treated group respectively.

DISCUSSION

Our study findings have similarity with Stein Gold et al, Strober et al, Papadavid et al, Ighani A et al.[20-23] Stein Gold et al conducted a study in patients with moderate plaque psoriasis (BSA 5%-10%; static Physician's Global Assessment [sPGA] score of 3 [moderate]) and naive to systemic therapies for psoriasis. The patients were randomized (2:1) to receive apremilast 30 mg twice daily or placebo for 16 weeks. A total of 136 patients completed the 52-week analysis period (placebo/apremilast, n=50/64; apremilast/apremilast, n=86/121). At week 52, improvements in all efficacy end points observed at week 16 were maintained in the apremilast/apremilast group (mean percentage change from baseline in PGAxBSA: -55.5%; PGAxBSA-75: 42.1%; sPGA response: 33.1%; mean change from baseline in DLQI score: -4.4); similar improvements emerged in the placebo/apremilast group after switching to apremilast. The most common adverse events (≥5% of patients) through week 52 were diarrhea (28.0%), nausea (19.0%), headache (15.2%), nasopharyngitis (10.4%), upper respiratory tract infection (7.1%), vomiting (5.7%), and decreased appetite (5.2%). They concluded that Apremilast was effective in systemic-naive patients with moderate plaque psoriasis with BSA 5%-10%; efficacy was sustained through week 52.[20]

Strober et al conducted a study with patients with psoriasis with body surface area (BSA) 5% to 10% and static Physician's Global Assessment (sPGA) score of 3 (moderate) without prior exposure to systemics were randomized (2:1) to apremilast 30 mg twice daily or placebo for 16 weeks. The primary efficacy endpoint was mean percentage change in the product of sPGA and

BSA scores (PGAxBSA). Of 221 patients (placebo, n=73; apremilast, n=148), >80% had received prior topical therapy. At week 16, apremilast yielded a significantly greater percentage change from baseline in PGAxBSA (-48.1%) vs placebo (-10.2^; P less than 0.0001). Dermatology Life Quality Index scores were significantly improved with apremilast (-4.8) vs placebo (-2.4; P=0.0008). Mean improvements in the Treatment Satisfaction Questionnaire for Medication, version II, were greater with apremilast vs placebo for global satisfaction (63.2 vs 48.7; P less than 0.0001) and treatment effectiveness (57.3 vs 38.8; P less than 0.0001). Most adverse events were mild or moderate; most common were diarrhea, headache, nausea, upper respiratory tract infection, decreased appetite, and vomiting. Researcher concluded that Apremilast was effective and well tolerated, significantly improved quality of life, and was associated with high patient satisfaction in systemic-naive, post-topical patients with moderate plaque psoriasis.[21]

Papadavid et al conducted a study to evaluate efficacy and safety of apremilast in the first 51 patients with psoriasis that had undergone treatment with this novel small molecule in their outpatient clinic. Their primary endpoint was the evaluation of clinical response to apremilast according to the percentage of Psoriasis Area Severity Index (PASI) reduction (ΔPASI) at 16 weeks after treatment initiation. Secondary endpoints were the evaluation at week 16 of (i) PASI; (ii) Dermatology Life Quality Index (DLQI); (iii) Physician Global Assessment (PGA); (iv) Psoriasis Scalp Severity Index (PSSI); and (v) the percentage of patients who achieved ΔPASI50, ΔPASI75, ΔPASI90 and ΔPASI100; (vi) adverse events (AE); (vii) reasons for drug discontinuation; and (viii) drug survival. About 59.3% of the patients who remained on apremilast achieved at least ΔPASI75 at week 16, while 11.1% achieved combined 50% ≤ PASI < 75% and DLQI ≤ 5 (satisfactory response) adequate enough to maintain treatment. Five patients (18.5%) also achieved ΔPASI100. Patients discontinued apremilast (28%), mostly during the first 4 weeks due to adverse events (12%), with gastrointestinal symptoms being the most common, and later due to lack of efficacy (16%). A statistically significant improvement of PASI, DLQI, PGA and PSSI scores was observed after 4 and 16 weeks of treatment relative to pretreatment measurements. They concluded that Apremilast is a safe and efficacious treatment for psoriasis patients as it produces ΔPASI75 and ΔPASI50 responses combined with DLQI ≤ 5 in 16 weeks in 70.4% of the patients.[22]

Ighani A et al assessed the efficacy and safety of apremilast monotherapy in real-world practice. A retrospective chart review was conducted in 2 academic dermatology practices. Efficacy was measured as the proportion of patients achieving a ≥75% reduction from baseline Psoriasis Area and Severity Index score (PASI-75) or a Psoriasis Global Assessment (PGA) score of 0 (clear) or 1 (almost clear) at 16 weeks. Safety was measured as the proportion of patients reporting ≥1 AE at 16 weeks. Thirty-four patients were included. Efficacy: 19 patients (55.9%) achieved PASI-75 or PGA 0/1; Safety: 23 patients (67.6%) experienced ≥1 AEs. Five patients (14.7%) withdrew treatment prior to week 16 due to AEs. One patient withdrew treatment due to mood lability and depression. Common AEs included headache (32.4%), nausea (20.6%), diarrhoea (14.7%), weight loss (8.8%), and loose

stool (8.8%). Their study supported the apremilast monotherapy clinical trial findings, suggesting that it had an acceptable safety profile and significantly reduces the severity of moderate to severe plaque psoriasis.[23]

The primary efficacy endpoint was the percentage of participants who achieved a 75% improvement (reduction) from baseline in the PASI score (PASI-75) at week 16.[17,18] The PASI is a measure of psoriatic disease severity that accounts for lesion characteristics (erythema, thickness, and scaling) and degree of skin surface area involvement on defined anatomical regions. Scores range from 0 to 72, with higher scores reflecting greater disease severity. Though, numerous additional efficacy endpoints were assessed, the key secondary outcome measure was the percentage of participants who achieved a score of 0 (indicating clear) or 1 (almost clear) on the sPGA at week 16, with at least a 2-point reduction from baseline.[24,25] The sPGA is an assessment of the severity of the three primary signs of the disease: erythema, scaling, and plaque elevation, with scores ranging from 0 (clear) to 4 (severe).[18]

While the long-term extension studies and post-marketing reports ultimately shed more light on the overall safety of apremilast, the data from the phase 3 clinical studies in patients with PsA and psoriasis suggest that apremilast is generally well tolerated. The gastrointestinal side effects associated with the agent largely occurred within the first month of treatment and subsequently subsided. Based on the mechanism of action of apremilast, known PDE4 class effects, comorbidities of PsA, and other factors, several adverse drug reactions of special interest were also assessed in the clinical studies. These included, but were not limited to, the risk of serious infections (e.g., tuberculosis), malignancies, major adverse cardiovascular events, and vasculitis. Importantly, no imbalances were observed between apremilast and placebo for any of these AEs, suggesting that apremilast does not increase their risk.[14]

In a multicentre, randomised, placebo-controlled, dose-ranging study, patients (aged ≥18 years) with moderate to severe psoriasis were randomly assigned (in a 1:1:1:1 ratio) to receive oral placebo or apremilast 10, 20, or 30 mg twice daily at 35 US and Canadian sites between Sept 24, 2008, and Oct 21, 2009. At week 16, patients in the placebo group were assigned apremilast 20 or 30 mg twice daily until week 24. 89 patients were randomly assigned apremilast 10 mg, 87 apremilast 20 mg, and 88 apremilast 30 mg twice daily; 88 were assigned placebo. At week 16, PASI-75 was achieved in five patients (6%) assigned placebo, ten (11%) assigned apremilast 10 mg, 25 (29%) assigned 20 mg, and 36 (41%) assigned 30 mg. Apremilast 10 mg did not differ significantly from placebo in achievement of the endpoint (odds ratio 2·10; 95% CI 0·69-6·42); for both apremilast 20 mg (6·69; 2·43-18·5; p<0·0001) and apremilast 30 mg (11·5; 4·24-31·2; p<0·0001), the differences from placebo were significant. Most adverse events (96%) were mild or moderate; at least 5% of patients had nausea, upper respiratory tract infection, diarrhoea, nasopharyngitis, headache, arthralgia (placebo), gastroenteritis, or dyspepsia. Eight serious adverse events occurred (three each, placebo and apremilast 20 mg; two, apremilast 30 mg); none were judged to be related to apremilast. Apremilast had no apparent effect on the results of haematological, urinalysis, immunological or inflammation, serum chemistry, or electrocardiographic tests.[5]

CONCLUSION

On the basis of the study result, Apremilast is found to be less effective with poor safety profile than Methotrexate in the treatment of moderate to severe plaque psoriasis. A prospective multi-centre evaluation with a large sample size and a long study period with long term follow-up are recommended.

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