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Topical application of Apremilast in the treatment of mild to moderate psoriasis

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ABSTRACT

Mild to moderate psoriasis is highly prevalent in about 80% of the global psoriatic population. Current available treatment options for mild to moderate psoriasis are topical dosage forms and are associated variety of setbacks. To address these setbacks, Apremilast topical gels, 2% & 4%, w/w were developed, and a clinical proof of concept study (POC) was performed to establish efficacy and safety. A single centre randomized, double-blind, placebo-controlled study was conducted with apremilast topical gels 2% & 4% w/w in adult mild to moderate psoriatic patients for 12 weeks. The efficacy of the gels was evaluated by comparing the PASI scores before and after treatment of 12 weeks. Both gels exhibited a significant reduction in PASI values when compared with baseline PASI scores. An average percentage inhibition of PASI with test products, i.e. 2% and 4% w/w Apremilast topical gels, are about 46.8% and 34.6%, respectively, after 12 weeks of treatment. The results confirm that the apremilast topical gels are a good option for the treatment of mild to moderate psoriasis and have to be explored further.

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INTRODUCTION

Psoriasis is a common, chronic, inflammatory dermatosis seen in practice. It is characterised by erythematous, well-demarcated plaques and rounded scales which look like silvery mica [1]. The etiology of psoriasis understood very poorly as on today and is considering as results of a complex relationship between genetics, Immunity, environment, skin barrier disruption, etc. [2–4].

There is no complete cure for psoriasis. Psoriasis is associated with a high degree of morbidity, and the current medications have a high degree of side effects and are can use for a limited period of time. Psoriatic patients quality of life will be impacted by many means such as decreases levels of employment and income, etc. [5, 6]. As there is no complete cure of the disease, the patients have to undergo continuous treatment to manage the disease. The costs of long-term therapy and social costs of the disease have a major impact on health care systems and on society.

Based on the severity of the disease, the disease is classified as mild (< 3% BSA), Moderate (4-10% BSA) and severe (>10% BSA) and the treatment options also depends on the severity of the disease [7]. The prevalence of mild to moderate psoriasis is around 70-80% of global psoriatic patients

Table 1: Baseline demographic and disposition of the patients.

Characteristic	Treatment with 2% gel	Treatment with 4% gel	Treatment with placebo
Baseline demographic information			
Enrolled (N)	12	12	12
Age (Years)			
Mean	39.75	37.67	48.00
Range	28-57	24-58	24-57
Sex (%)			
Male	75	50	50
Female	25	50	50
Baseline PASI (%)			
Mild	50	62	13
Moderate	50	38	87
Disposition of patients			
Drop out	2	3	3
12 weeks of treatment	10	9	8
Withdrawn	0	0	1
Follow up period (28 days)	10	9	8
Adverse event	0	0	0
Death	0	0	0
Other	0	0	0

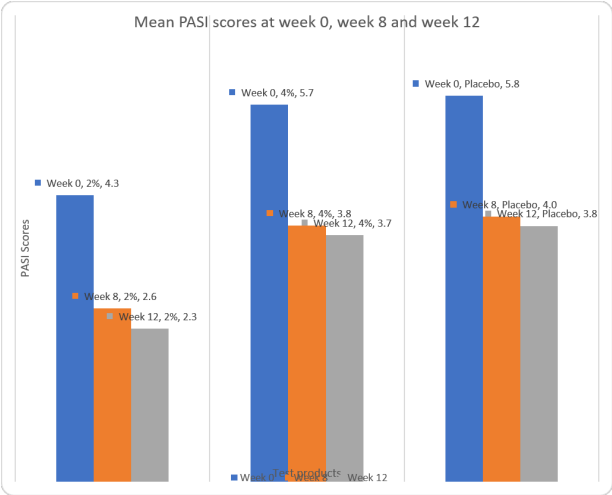

Figure 1: Mean PASI scores of 2%, 4% and Placebo gels at week 0, week 8 and week 12

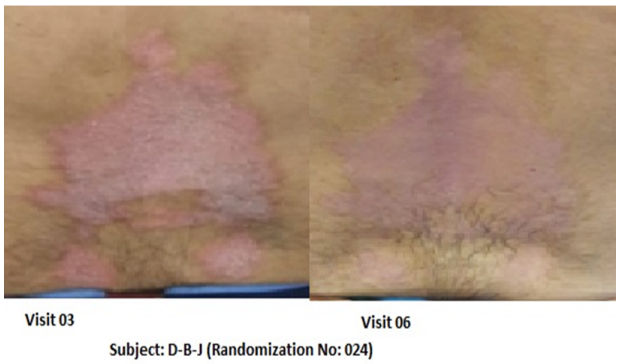

Figure 2: Variation of severity in different visits (week 0 & 8)

(2-3%) [8]. For mild to moderate disease, first-line treatment involves topical therapies, including corticosteroids, vitamin D3 analogues, and combination products. [9] These topical treatments are efficacious and can be safely initiated and prescribed by primary care physicians. Patients with more severe and refractory symptoms might require further evaluation by a dermatologist for systemic therapy. Despite their efficacy, these are associated with limitations in their use as a result of application site reactions and safety concerns with long-term use. Hence novel topical therapies that may potentially improve up on the risk-benefit profile of current treatment options are needed.

Recently, Apremilast tablets, PDE4 inhibitor, was approved for the treatment of moderate to severe psoriasis and psoriatic arthritis [10], but it requires dose titration to avoid gastrointestinal side effects (nausea and diarrhoea). To address these side effects of the oral apremilast tablets and to target the major pool of psoriatic patients, an attempt has been made and developed Apremilast, PDE4 inhibitor,

Table 2: Activities performed during the study period

Visit No	1	2	3	4	5	7	8	9	10
Activity/ Week	Screening	Washout period	Baseline / Randomization	Week 2	Week 4	Week 8	Week 12 (End of the treatment)	Week 16	Week 20 (End of the study)
Days	2 weeks	Day -14 to Day -1	0	14+2 days Window period	28+2 days Window period	56+2 days	84+2 days	112+2 days	140+2 days
Obtain informed consent	X	-	-	-	-	-	-	-	-
Investigator's confirmation of Psoriasis	X	-	-	-	-	-	-	-	-
Assessment of Inclusion/Exclusion criteria	X	-	X	-	-	-	-	-	-
Medical and Treatment history	X	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-
Physical examination	X	X	X	X	X	X	X	X	X
PASI Score	X	X	X	X	X	X	X	X	X
Randomization	-	-	X	-	-	-	-	-	-
Dispensing of Topical moisturizer	X	-	-	-	-	-	-	-	-
Topical moisturizer withdrawal	-	-	X	-	-	-	-	-	-
Dispense study medication	-	-	X	X	X	X	X	X	-
Safety monitoring	X	-	X	X	X	X	X	X	X
Collect previous visit medication	-	X	X	X	X	X	X	X	X

topical gels, 2% and 4% w/w to treat the mild to moderate psoriasis. A prototype proof of concept study was performed to evaluate the efficacy and safety of apremilast 2% and 4% gel in patients aged more than 18 years with mild to moderate psoriasis.

MATERIALS AND METHODS

The efficacy and safety of Apremilast Topical Gels, 2%, 4% w/w against placebo, was studied in patients with mild to moderate psoriasis. The study was a randomised, double-blind, placebo-controlled, three-arm parallel study and is studied for 12-week in 36 volunteers at Gandhi Medical College, Secunderabad, India. During the study period, safety and efficacy was studied by recording the PASI scores and adverse effects before and after the treatment. The patient disposition details are presented in Table 1, and the different activities performed during the study are presented in Table 2. After explaining the purpose of the trial to the patient, written consent was obtained from each patient for participating in the study. The ethical approval number is IEC/GMC/2018/12, dt. 30.03.2018.

On the day of randomization, the base line area (psoriasis affected area) was determined by taking the photographs, and PASI scores were recorded under the supervision of the principal investigator. Patients were asked to apply a layer of gel on psoriasis affected area twice daily throughout 12 week study period and also instructed to apply test drug as needed to newly identified psoriatic lesions that appeared after day 1. Also instructed to visit bi-weekly or monthly (Week 2, 4, 8 and 12) for reviewing the efficacy and safety.

Evaluation

Efficacy

The efficacy end point of the study is to assess the change in PASI from baseline and at Week 12. The % recovery was calculated by measuring the change in the PASI scores with 2% and 4% gels after 12 weeks of treatment. Signs of psoriasis were measured throughout the treatment period. The secondary efficacy end points are checking the safety and tolerability of the gels throughout the study period.

Safety

The safety was evaluated by monitoring adverse events (AEs and SAEs) during the study period. Adverse events were categorized based on the severity and relationship to the study drug. Adverse Events that occurred post-treatment (events that occurred after the first dose of medication and up to 14 days post-treatment) was also recorded.

RESULTS AND DISCUSSION

A total of 52 volunteers were scrutinized, 36 of whom were recruited and were randomized into three groups, 2%, 4% and placebo groups, at a ratio of 12: 12: 12. 16 volunteers did not meet the inclusion criteria and were excluded. 2, 3 and 4 volunteers are dropped from 2%, 4% and placebo groups, respectively.

A significant reduction in PASI scores was observed with test products after 12 weeks of treatment when compared with the baseline PASI scores. The mean % recovery with 2% and 4% gels are 46.8% and 34.6% respectively. The change in PASI scores and intensity of the affected area before and after treatment is presented in Figures 1 and 2 respectively.

None of the test product, including placebo, have shown any side effects like irritation, redness, itching or swelling throughout the study period. No adverse events reported with topical apremilast gel, including the gastro intestinal adverse events observed with oral apremilast tablets.

Based on the mean % change in PASI, AEs and SAEs, it was concluded that both test products, 2% and 4% gels were effective in the treatment of mild to moderate psoriasis. These efficacy and safety profiles of the novel topical formulation of apremilast gel allows localised therapy at the site of inflammation and reducing the risk of systemic side effects observed with oral apremilast and other PDE4 inhibitors.

CONCLUSION

Apremilast topical gel decreased disease severity by subsiding the signs and symptoms of psoriasis. Also demonstrated a favourable safety profile in which none of the patients have reported any adverse events. No patients have stopped the medication due to serious adverse effects.

Apremilast topical gel represents a promising new option for patients with mild to moderate psoriasis based on the favourable safety and efficacy profiles. Further studies need to explore to confirm the potential of topical apremilast gel.

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Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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