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An open-label, randomised, parallel clinical research evaluating the safety and efficacy of methotrexate and apremilast in patients with moderate to severe palm plantar psoriasis.

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Abstract:

Comparing apremilast to methotrexate, many studies have produced conflicting results on its efficacy and safety. Therefore, additional study is needed to determine how Apremilast works in palmoplantar psoriasis.A randomised, prospective, parallel-group, open-label study was conducted on patients with moderate to severe palmoplantar psoriasis. They were randomised to either the apremilast group (n = 22) or the methotrexate group (n = 19) for a duration of 16 weeks. The main efficacy parameter was decreased scores on the modified palmoplantar psoriasis severity index (mPPPASI) between weeks 0 and 16. The proportion of patients who showed a dermatology life quality index decline of at least 5àpoints from the start, the percentage of patients who achieved mPPPASI75 (75% reduction in mPPPASI score), and the percentage of patients who obtained a Static Physician Global Assessment score of 0 (clear) or 1 (almost clear) were additional metrics.Although there was a substantial reduction from week 0 to week 16 within the group, there was no statistically significant difference in the drop in m-PPPASI scores between the two groups at 16 weeks. The results of the secondary efficacy measures were the same. Three people had abnormal liver function tests out of the twenty-four adverse events reported in the methotrexate group. Two individuals had an upper respiratory tract infection out of the 19 adverse events reported in the apremilast group.Apremilast is more tolerated than methotrexate when used to treat moderate to severe palmoplantar psoriasis. Static Physician Global Assessment, Dermatology Life Quality Index, Palmoplantar Psoriasis, Palmoplantar Psoriasis Area and Severity Index, Apremilast.

Introduction

Psoriasis is more likely to manifest before the age of thirty. The quality of life (QOL) of psoriasis patients is negatively impacted by the high cost of treatment as well as the serious psychological and social consequences of the condition.[2] There are several forms of psoriasis, including genital, palmoplantar, nail, intertrigonous, scalp, and facial psoriasis. In addition to having fewer choices for self-care and more restricted mobility, patients with palmoplantar psoriasis often react differently to medications. The initial line of therapy for palmoplantar psoriasis is the third topical medication. Phototherapy and systemic therapy are the following steps when a patient's skin does not respond to a topical treatment. The first-line systemic treatments for palmoplantar psoriasis include methotrexate and cyclosporine. Second-line systemic medications include biologics and apiculists such as infliximab and ustekinumab.[4] Even if there are already available treatment alternatives for psoriasis, there is always a demand for novel, secure, and efficient treatments. The thirdThe phosphodiesterase-4 (PDE-4) enzyme is inhibited by the oral drug apremilast. PDE-4 regulates the levels of cyclic adenosine monophosphate, which affects immune cell responses. The treatment of moderate to severe plaque psoriasis was approved by the US Food and Drug Administration (USFDA) in September 2014 and the Drug Controller General of India (DCGI) in October 2017. The Food and Drug Administration has finally approved an oral medication to treat psoriasis after a protracted delay.[5]

Although they varied in severity from moderate to severe, the most frequent adverse effects in the Apremilast group were upper respiratory tract infections, nasopharyngitis, headache, nausea, and diarrhoea. Apremilast showed no signs of cumulative or organ-specific harm.[6] Methotrexate may be used to treat psoriasis, particularly severe forms that need long-term care.[7] There is little evidence comparing the safety and efficacy of apremilast to those of conventional systemic therapy for palmoplantar psoriasis. A previous research comparing Apremilast with Methotrexate in patients with palmoplantar psoriasis found that the former was safer and more effective than the latter.[8] Several studies assessed the efficacy and safety of oral methotrexate combined with Apremilast for people with chronic plaque psoriasis. While both drugs were equally effective in one study, methotrexate was more efficacious and more tolerable in the other. Even though a number of studies have shown that Apremilast is safer and more effective than methotrexate, further research is required to determine its importance in treating psoriasis. Thus, the purpose of this study was to evaluate the safety and efficacy of Apremilast in treating moderate to severe palmoplantar psoriasis in comparison to methotrexate.

Technical Approach

A random, prospective, parallel-group, open-label trial was conducted. For this research, the institutional ethics committee gave its permission. All procedures followed the standards of Good Clinical Practice and adhered to the ethical norms laid forth in the

Declaration of Helsinki. The Clinical Trial Registry of India received the study registration (CTRI/2020/05/025198).

Patients' selection

The experiment was conducted in the dermatological outpatient department (OPD) of a teaching hospital that provides tertiary care. People between the ages of 18 and 65, regardless of gender, who have been diagnosed with moderate-to-severe palmoplantar psoriasis and who fit any of the following criteria: Participants in the study had to have a modified palmoplantar psoriasis area severity index (mPPPASI) score of 12 or higher, a Static Physician Global Assessment scale (sPGA) score of 3 or 4, or a proportion of palmoplantar surface area involvement more than 10%. Patients receiving systemic therapy (conventional or biologics) within 12 weeks before randomization, pregnant and lactating women and women of reproductive age group who did not practice contraception or had a history of practicing unreliable method of contraception such as withdrawal method, calendar method, or use of vaginal spermicides, and patients with psoriatic arthritis, pustular psoriasis, or any other dermatological disease or with impaired renal function (glomerular filtration rate <60 mL/ min, serum creatinine >1.4 mg/dL, and blood urea nitrogen >20 mg/dL), impaired hepatic function (alanine transaminase [ALT, normal value: 7–55 U/L], aspartate aminotransferase [normal value: 10–40 U/L], more than two times of the upper limit of normal range), or abnormal complete blood count (CBC) (Hemoglobin % <11 g/dL in females and <14 gm/dL in males, white blood cell counts <4000 or >L, and platelet countsμ10,000/ <L), patients receiving beta blockers, aspirin, chloroquine, and lithium; patients suffering from any other chronic/systemic disorder except diabetes mellitus, hypertension, hypothyroidism, and chronic kidney disease were excluded from the study.μ150,000/

Research technique

Following a discussion with the dermatologist, research participants were selected. A document including patient records in a common language was given to them. Every participant gave their written, informed consent to participate. A comprehensive medical history, physical examination, blood glucose measurement, and tests for liver and kidney function (ALT and serum creatinine) as well as a complete blood count (CBC) were performed. Using random number tables, patients were randomly assigned to receive one of the following medications:

Group 1 participants got 10 mg of Apremilast once daily for the first seven days. They then took 10 mg in the morning and 20 mg in the evening on days two and three. They took 20 mg twice a day on day four. They took 20 mg in the morning and 30 mg in the evening on day five. 30 mg twice a day was what they took on days six and seven. Following completion of the initial pack, 30 mg given orally twice daily for 16 weeks was the suggested dose.

The initial dose for the second group's methotrexate pills was 5 mg. The dosages were gradually increased from 2.5 to 5 mg/week to a maintenance dosage that ranged from 7.5 to 30 mg/week. Depending on the patient's tolerance, the dose was either taken once a week or divided into thirds and spaced out by 12 hours. given after a meal. A 1 mg folic acid pill was given on non-working days.

Topical corticosteroids (betamethasone dipropionate 0.05%) and over-the-counter moisturisers were considered appropriate therapy for this study. Four check-ins were planned for four, eight, twelve, and sixteen weeks after the first evaluation.

Evaluate the effectiveness

The reduction in mPPPASI score from the start to the end of the 16-week period served as the primary indicator of efficacy. The mPPPASI score is a variation of the psoriasis area and severity index (PASI) used to assess the severity of palmoplantar psoriasis. The range of an overall mPPPASI score is zero, which means there are no psoriasis symptoms, to seventy-two, which means there are severe symptoms. The proportion of patients who had a sPGA score of 0 (clear) or 1 (almost clear) after 16 weeks was one such statistic. The sPGA score may be used to assess the degree of erythema, scaling, and induration associated with a subject's psoriasis. (ii) It is also noted that mPPPASI 90 at the end of the experiment (90% fall in mPPPASI score) and mPPPASI 75 at the end of 16 weeks (75% reduction in mPPPASI score) were attained. (iii) The proportion of patients whose scores on the Dermatology Life Quality Index (DLQI) had dropped by at least five points from their starting position.

Evaluation of discomfort

At every appointment, patients were questioned about the frequency of any negative effects and urged to report them to the outpatient department (OPD). Adverse event frequency and severity were recorded. Laboratory tests such as serum glutamic-pyruvic acid and full blood count Transaminase (serum ALT) assays were performed at each follow-up visit. The dermatologist made sure that any negative side effects that were identified throughout the study were appropriately addressed. After the study ended, the dermatologist made a decision about whether to continue or alter the care.

Data analysis using statistics

We know that the two groups' mPPPASI scores should vary by at least 6 points based on prior experiments. To calculate the sample size, we utilised a power of 80%, an alpha of 0.05%, and a standard deviation of 7.1. Based on these statistics, the sample size was determined using the "PS for sample size" program (version 3.1.2), developed by W. D. Dupont and W. D. Plummer and released in August 2014. The research had 23 individuals in total. After deducting a 10% dropout rate, the final total for each group was 25. The Fisher exact test for categorical data, such gender, was used to examine the demographic factors. An unpaired t-test was used to examine numerical continuous variables, age, and duration of sickness. Friedman post hoc test Dunn's test was used to compare the group's mPPPASI and DLQI scores at many follow-up visits. The Mann-Whitney U-test was used to compare the two groups' mPPPASI and DLQI values. The frequencies of patients in the two groups who achieved mPPPASI75 or higher and sPGA scores of 0 or 1 at 16 weeks were compared using the chi-square test. GraphPad Prism 8.0.2 was used to perform the statistical analysis. A result was considered statistically significant if $P < 0.05$.

Final Product

22 of the 72 participants that were evaluated for the experiment were found to be ineligible and were later removed. Forty-one of the fifty patients who were split into two groups and given various therapies finished the experiment as directed and were given the proper follow-up. There were six dropouts in the methotrexate group and three in the apremilast group. The data were analysed using the analytical approach.At baseline, the two treatment groups' patient demographics and clinical information were comparable, as Table 1 illustrates.Figure 1 illustrates the decline in m-PPPASI scores in the methotrexate and apremilast groups from 0 to 16 weeks. The drop in m-PPPASI scores started in week one, although there was no statistically significant difference between the two groups.

Table1:Baselinedemographicandclinicalcharacteristicsofstudypatients

Characteristics	Methotrexate(*n*=19)	Apremilast(*n*=22)	*P*
Age(years)*α	45.58±12.32	40.95±10.08	0.20
Gender**			
Men	12	15	0.73
Women	7	7	
Baseline m-PPPASIscore*β	20.34±9.13	21.72±8.6	0.36
Baseline sPGAscore*β	3.37±0.49	3.45±0.50	0.75
Baseline DLQI score*β	7.47±3.15	7.50±2.66	0.95
Durationofdisease(years)*α	7.95±5.95	6.51±7.37	0.24
Familyhistoryofpsoriasis,*n*(%)**	0	2(9)	0.49
Comorbidities,*n*(%)**	4(21)	5(22.7)	0.89
Diabetesmellitus	2	2	
Hypertension	1	2	
Hypothyroidism	1	1	
Chronickidneydisease	0	1	

Values are expressed as mean±SD

**Data analyzed by Fisher's exact test, αData analyzed by unpaired *t*-test, Data analyzed by the Mann–Whitney *U*-test.Numbers in parentheses indicate percentages. m-PPPASI=Modified palmoplantar psoriasis area and severity index, DLQI=Dermatology life quality index,sPGA=Static PhysicianGlobalAssessment,SD=Standarddeviation

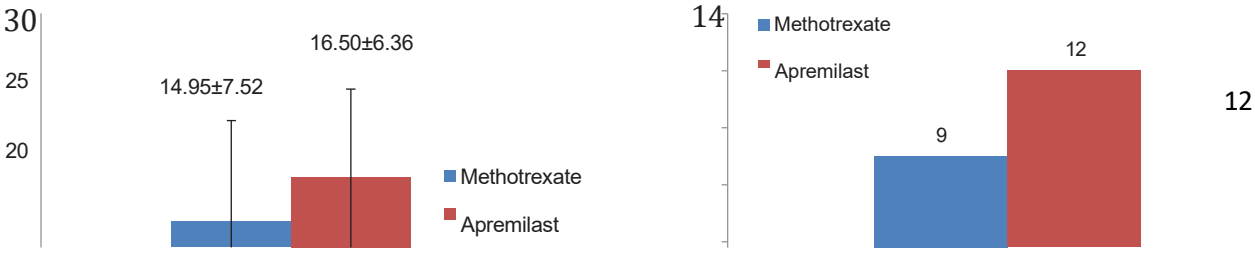




Figure1: Reductioninmodifiedpalmoplantarpsoriasisareaandseverityindexscorefrom0weekto16weeksinthetwotreatmentgroups.DataanalyzedbytheMann–Whitney*U*-test.mPPPASI:Modifiedpalmoplantarpsoriasisareaandseverityindex

Statistical significance was seen in both groups from 0 to 16 weeks.This data was examined using the Mann-Whitney U-test.At week 16, Table 2 displays the number of patients that achieved m-PPPASI75 and m-PPPASI90. Fifteen individuals in the methotrexate group and nineteen in the apremilast group achieved m-PPPASI75. Seven patients in the methotrexate group and eight individuals in the apremilast group achieved m-PPPASI90. There was no statistically significant difference between the two groups in terms of the number of patients who achieved m-PPPASI75 and m-PPPASI90.Patients who had a sPGA score of 3 or 4 at baseline were able to achieve a score of 0 or 1 (Figure 2). Both groups had similar numbers of individuals who achieved a 0 or 1 sPGA score (P = 0.64). The number of patients in both groups who achieve a DLQI decrease of at least 5 points is similar (P = 0.81), as shown in Figure 3.

The two treatment groups were compared for common adverse events in Table 3. Most of the negative side effects were mild to moderate in severity.

Subject for debate

For several studies, the mPPPASI score has been the gold standard for measuring progress. It enables the quantification of the severity of palmoplantar pustulosis and palmoplantar plaque psoriasis, two clinical variations of the same condition.the eleventh The original PPPASI was solely meant for pustular-PPP, however the m-PPPASI score is somewhat different. At 8 weeks into therapy, both medications significantly reduced the mPPPASI score compared to

Table2:Adverseeventsreportedinthetwostudy

groups		
Adverseevents	**Numberofpatients**	
	Methotrexate (*n*=19),*n* (%)	**Apremilast (*n*=22),*n* (%)**
Diarrhea	7(36.8)	8(36.36)
Nauseaandvomiting	6(31.5)	5(22.7)
Headache	4(21)	4(18.18)
Upperrespiratorytractinfection	0	2(9.1)
Abdominalpain	4(21)	0
AbnormalLF	3(15.7)	0
Total	24	19

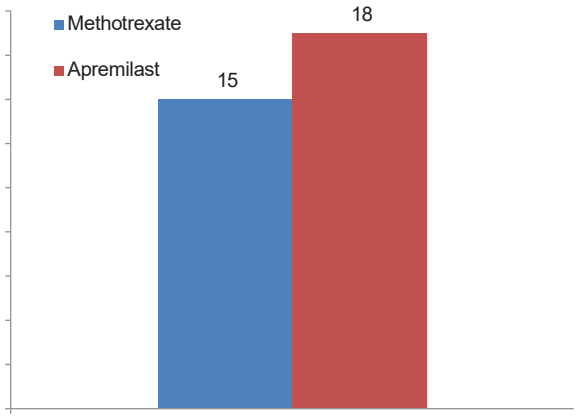


Figure3: Numberofpatientsshowingatleast5-pointreductionindermatologylifequalityindexfrombaseline.Dataanalyzedby Fisher'sexacttest.DLQI:Dermatologylifequalityindex

Numbers in parentheses indicate percentages. LF: The liver's function at the ground level.The same conclusion has been reached by several published studies. According to several placebo-controlled studies, individuals with palmoplantar psoriasis had a statistically significant decrease in mPPPASI scores, sPGA scores, and/or DLQI scores after 16 weeks of apremilast medication.cited in [6, 8, 12, 13] In a previous research with patients with palmoplantar psoriasis, the apremilast group had a substantially lower severity index score and area of palmoplantar pustulosis at week 16 when compared to the placebo group (P = 0.016).[14] Our study compared the efficacy of apremilast to that of an active comparator, while most prior studies either utilised placebos or just one arm. Methotrexate is often used as a systemic therapy for palmoplantar psoriasis since it is an immunosuppressive medication that has shown a significant clinical improvement in patients with this condition.[15] As a result, the active comparator in this assessment was methotrexate.

As of right now, we are only aware of one published study that compared the active comparator methotrexate to apremilast for palmoplantar psoriasis. According to the study, apremilast and methotrexate were equally efficient in treating palmoplantar psoriasis.[8]

Therefore, we need to know how effective apremilast is in comparison to other active comparators in order to compare the results of our experiment with other published data. Our study revealed that both groups' mPPPASI levels gradually declined between 8 and 16 weeks. According to a study comparing apremilast and methotrexate for palmoplantar psoriasis, the apremilast group's m-PPPASI scores significantly decreased over the first eight weeks of treatment, but subsequently began to plateau between weeks eight and sixteen. On the other hand, the m-PPPASI levels decreased linearly in the methotrexate group.[8]

It has been suggested that "clinically significant success" in treating this condition is defined as an improvement of at least 75% in the plaque psoriasis severity index (PASI75).[16] mPPPASI75 and mPPPASI90 have also been used in studies to assess clinical improvement in individuals with palmoplantar psoriasis.(8, 12) Patients in both groups reached mPPPASI75 and mPPPASI90 at almost the same rates at week 16 (P = 0.57 and P = 0.92, respectively). The number of patients who attained mPPPASI75 and mPPPASI90 was comparable in the methotrexate and apremilast groups, according to another head-to-head comparative study (P = 0.49 and P = 0.27, respectively). The proportion of patients who matched these criteria, however, was lower in both groups than in the others, according to our research (mPPPASI75 was accomplished by 33.3% vs. 40.5%, and mPPPASI90 by 14.3% vs. 23.8%).[8] A single-arm trial reported a smaller proportion of individuals achieving mPPPASI75 compared to our findings (14.3%).[12]

One of the main problems with PASI is that experts do not use it often, which makes it difficult for patients and doctors to grasp. This also applies to mPPPASI. Though they are not often used in clinical practice, these scales are widely utilised in research studies. The head of the school investigator assessed the mPPPASI findings. On the other hand, global assessments created by doctors are widely used in patient treatment. These are quite easy to identify and assess. These scales are used by medical practitioners on a regular basis.[16] For patients with sPGA scores of 0 or 1, disease has no effect on quality of life.The proportion of patients who obtained a 0 or 1 sPGA score at week 16 did not significantly vary between the two groups, according to the results (P = 0.87). The palmoplantar physicians global assessment (PPPGA) has been utilised in a number of trials on apremilast in palmoplantar psoriasis, however the sPGA has not been employed as an evaluation instrument in any of them. In a placebo-controlled trial of palmoplantar psoriasis, a pooled analysis showed that a substantially higher number of patients in the apremilast group compared to the placebo group attained a PPPGA score of 0 or 1 at week 16 (P = 0.34) [14].In a apremilast single-arm experiment, 34.7% of patients with palmoplantar psoriasis were able to attain a PPPGA score of 0/1 at 16 weeks.When assessing quality of life in psoriasis research, the DLQI is the gold standard [13]. The DLQI score complements lesion severity measures such as mPPPASI and sPGA. When there is a statistically significant improvement in the mean change in lesion severity assessments, quality of life (QOL) measurements may verify that clinically meaningful changes have taken place in clinical trials. A five-point drop in DLQI scores is a common assessment

statistic used in treatment research.In this experiment, the percentage of patients in both groups who achieved a 5-point decline in DLQI at week 16 was comparable [16]. Similar results were seen in another study including people with palmoplantar psoriasis; from week 0 to week 16, the DLQI scores of the methotrexate and apremilast groups changed similarly.[8]

Three patients in the apremilast group and six in the methotrexate group stopped taking the study because they could not be followed up with. Even after many phone attempts, they were unreachable, therefore it was impossible to ascertain the reasons behind their dropout.

Side effects are common since psoriasis takes a long time to heal. The apremilast group had 19 adverse events, whereas the methotrexate group experienced 24 (19). The findings of every published research have been consistent: the study medications had known negative side effects.pages 18–21

Limitations

One problem is that the experiment was open-label, which raises the possibility of bias, particularly when subjective standards are used to assess efficacy. Two, the sample size was quite small when

Our study restricts the generalisability of our results to a larger population. Thirdly, even with the short follow-up period, the trial's limitations exclude the assessment of long-term efficacy maintenance or adverse events, which is crucial in this chronic illness.

summary

Despite our finding that apremilast and methotrexate are equally efficient in treating palmoplantar psoriasis, the small sample size of this study makes it impossible to generalise the results. The cost of apremilast is another factor that keeps people from utilising it. Therefore, for a subgroup of patients with palmoplantar psoriasis who have not reacted to or are unable to use presently available drugs, apremilast may be worth exploring as a therapeutic option. However, even this has to be verified by more extensive research.

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