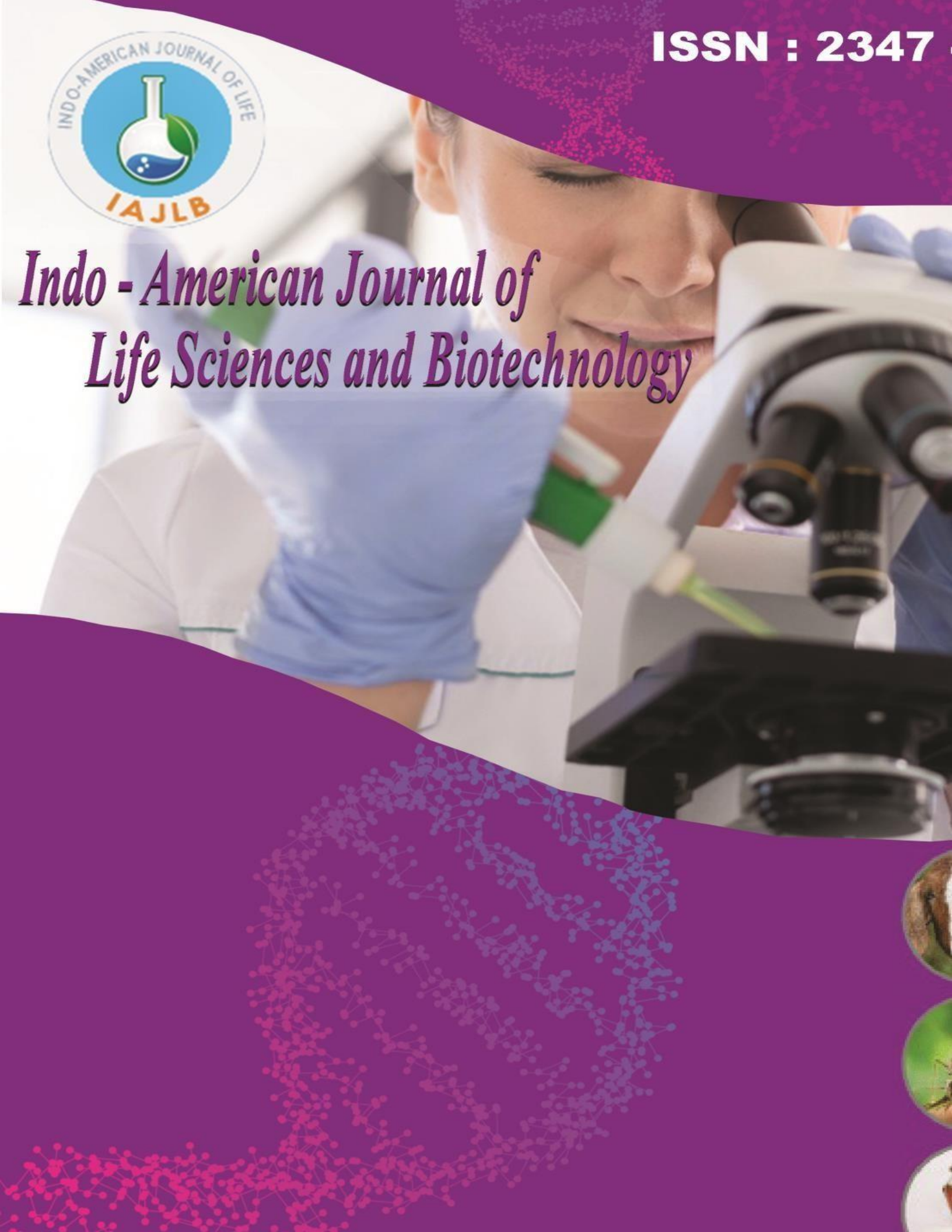




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A randomized, parallel, open-label clinical study comparing the effectiveness and safety of apremilast with methotrexate in individuals with moderate to severe palm plantar psoriasis.

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Abstract:

Various studies have revealed varying outcomes regarding the safety and effectiveness of apremilast in comparison to methotrexate. Therefore, more research into the function of A prenilast in palmo plantar psoriasis is required. Patients with moderate to severe palmoplantar psoriasis were the subjects of a randomized, prospective, parallel-group, open-label trial. For 16 weeks, they were randomly assigned to either the methotrexate group (n = 19) or the apremilast group (n = 22). Reduced scores on the modified palmoplantar psoriasis severity index (mPPPASI) from week 0 to week 16 served as the primary effectiveness metric. Additional metrics included the percentage of patients who achieved a Static Physician Global Assessment score of 0 (clear) or 1 (almost clear), the percentage of patients who achieved mPPPASI75 (75% reduction in mPPPASI score) by the end of 16 weeks, and the proportion of patients who demonstrated a dermatology life quality index decline of at least 5àpoints from the beginning. At 16 weeks, there was no statistically significant difference between the two groups in terms of m-PPPASI score drop, however there was a significant decline from week 0 to week 16 within the group. The secondary efficacy measures had identical outcomes. Out of the twenty-four adverse events documented in the methotrexate group, three individuals had abnormal liver function tests. Out of the 19 adverse events documented in the apremilast group, 2 patients had an infection of the upper respiratory tract. In the treatment of moderate to severe palmoplantar psoriasis, apremilast is just as effective as methotrexate, but it is more tolerable. Static Physician Global Assessment, Dermatology Life Quality Index, Palmoplantar Psoriasis, Palmoplantar Psoriasis Area and Severity Index, Apremilast

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It is more likely for psoriasis to appear before the age of 30. The high expense of therapy and the significant psychological and social effects of psoriasis have a negative effect on sufferers' quality of life (QOL).[2]

Scalp, face, intertriginous, genital, palmoplantar, and nail psoriasis are the many types of psoriasis that may be found. Patients with palmoplantar psoriasis have more limited mobility and fewer self-care options, and they also have varying responses to medicines. The third topical treatment is the first line of defense against palmoplantar psoriasis. When a patient's skin doesn't react to a topical treatment, the next step is phototherapy, which is followed by systemic therapy. Methotrexate and cyclosporine are the systemic medications that are first-lined for palmoplantar psoriasis. Apremilast and biologicals like ustekinumab and infliximab are second-line systemic medicines.[4] There is still a need for innovative, safe, and effective psoriasis medications, even if there are current therapy options the third Apremilast is an oral medication that inhibits the phosphodiesterase-4 (PDE-4) enzyme. The responses of immune cells are influenced by PDE-4 because it controls the amounts of cyclic adenosine monophosphate. The US Food and Drug Administration (USFDA) gave its approval in September 2014, and the Drug Controller General of India (DCGI) gave its approval in October 2017 for the treatment of moderate to severe plaque psoriasis. After a long wait, the Food and Drug Administration has finally authorized an oral medicine to treat psoriasis.[5]

Diarrhea, headache, nausea, nasopharyngitis, and upper respiratory tract infections were among the most common side events in the Apremilast group, although they ranged in severity from mild to severe. There was no evidence of cumulative or organ-specific toxicity with Apremilast.[6]

Psoriasis, especially severe types of psoriasis that need long-term maintenance, may be treated with methotrexate.[7] Comparing Apremilast's effectiveness and safety against those of standard systemic treatment for palmoplantar psoriasis is an area where research is sparse. Methotrexate was shown to be more efficacious and safer than Apremilast in a prior study comparing the two in patients with palmoplantar psoriasis.[8]

For individuals with persistent plaque psoriasis, several trials evaluated the safety and effectiveness of oral methotrexate with Apremilast. Methotrexate had superior effectiveness and tolerability in one research, whereas both medications had similar efficacy in the other.

Although several trials have demonstrated Apremilast's safety and effectiveness in comparison to methotrexate, further data is needed to confirm Apremilast's significance in psoriasis. Therefore, this research was designed to assess the effectiveness and safety of Apremilast compared to methotrexate in treating moderate to severe palmoplantar psoriasis.

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

A tertiary care teaching hospital's dermatological outpatient department (OPD) served as the site of the investigation. Individuals diagnosed with moderate-to-severe palmoplantar psoriasis who meet any of the following criteria and are between the ages of 18 and 65, regardless of gender: The research included participants with a score of 12 or higher on the modified palmoplantar psoriasis area severity index (mPPASI), a percentage of palmoplantar surface area involvement more than 10%, or a score of 3 or 4 on the Static Physician Global Assessment scale (sPGA). 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 >10,000/ μ L, and platelet counts <150,000/ μ 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.

Research technique

Patients for the study were chosen after discussing the matter with the dermatologist. They were provided with patient records document written in a common language. Written, informed permission was obtained from everyone who want to participate. In addition to taking a thorough medical history, doing a physical exam, and measuring blood glucose levels, we also ran tests to check the kidney and liver functions (ALT and serum creatinine), as well as a complete blood count (CBC). Patients were given one of the following drugs at random using random number tables:

For the first seven days, members of Group 1 took 10 mg of Apremilast once in the morning. Then, on days two and three, they took 10 mg in the morning and 20 mg in the evening. On day four, they took 20 mg twice daily. On day five, they took 20 mg in the morning and 30 mg in the evening. On days six and seven, they took 30 mg twice daily. The recommended dosage after finishing the starting pack was 30 mg taken orally twice day for a total of 16 weeks.

The second group took methotrexate tablets, with a starting dosage of 5 mg. A maintenance dosage ranging from 7.5 to 30 mg/week was achieved by a gradual increase in doses of 2.5 to 5 mg/week. The dosage was either taken once weekly or split into

thirds and given 12 hours apart based on the patient's tolerance. Administered after a meal. On non-working days, a 1 mg tablet of folic acid was administered.

For the purposes of this research, topical corticosteroids (betamethasone dipropionate 0.05%) and non-medicated moisturisers were acceptable treatments. Four check-ins were scheduled at 4, 8, 12, and 16 weeks after the first assessment.

Evaluate the effectiveness

The main measure of effectiveness was the decrease in mPPPASI score from the beginning to the end of the 16-week period. To evaluate the severity of palmoplantar psoriasis, the mPPPASI score is a modification of the psoriasis area and severity index (PASI). An overall mPPPASI score might be anywhere from zero (indicating no psoriasis symptoms) to seventy-two (indicating severe symptoms). One such metric was the percentage of patients who, after 16 weeks, had achieved a sPGA score of 0 (clear) or 1 (nearly clear). A subject's psoriasis's induration, scaling, and erythema severity may be evaluated using the sPGA score. (ii) Achieving mPPPASI 75 at the end of 16 weeks (75% reduction in mPPPASI score) and mPPPASI 90 at the conclusion of the trial (90% decline in mPPPASI score) is also recorded. (iii) The percentage of patients whose Dermatology Life Quality Index (DLQI) scores have decreased by at least five points compared to their initial baseline.

Evaluation of discomfort

Patients were encouraged to report any adverse effects to the outpatient department (OPD) and were asked about the incidence of any such occurrences at each visit. The

occurrence and severity of adverse events were documented. Lab tests including complete blood count and serum glutamic-pyruvic acid During each subsequent appointment, transaminase (serum ALT) tests were conducted. The dermatologist ensured that any adverse events reported throughout the research were adequately treated. The dermatologist decided whether to continue or change the management when the trial was over.

Data analysis using statistics

According to previous research, we know that there should be at least a 6-point difference in mPPPASI scores between the two groups. We used a standard deviation of 7.1, an alpha of 0.05%, and a power of 80% to determine the sample size. The "PS for sample size" software (version 3.1.2), created by W. D. Dupont and W. D. Plummer and published in August 2014, was used to calculate the sample size based on these data. There were a total of 23 participants in the study. The final tally for each group was 25 after accounting for a 10% dropout.

The demographic parameters were analyzed using the Fisher exact test for categorical variables, such as gender. The age, length of illness, and numerical continuous variables were all tested using an unpaired t-test. Post hoc Friedman test To compare the group's mPPPASI and DLQI scores at several follow-up visits, Dunn's test was used. The mPPPASI and DLQI scores were compared between the two groups using the Mann-Whitney U-test. The chi-square test was used to compare the two groups' rates of patients achieving mPPPASI 75 or higher and sPGA scores of 0 or 1 at 16 weeks.

The statistical analysis was conducted using GraphPad Prism version 8.0.2. A statistically significant result was defined as $P < 0.05$.

Final Product

Out of 72 individuals that were assessed for the trial, 22 were deemed ineligible and were subsequently excluded. Fifty patients were divided into two groups and given different treatments; 41 of those patients completed the trial as instructed and received appropriate follow-up. The methotrexate group had six dropouts,

whereas the apremilast group had three. Data were examined in accordance with the analytical methodology. Patients' demographics and clinical data were similar across the two therapy groups at baseline, as shown in Table 1. The decrease in m-PPPASI scores from 0 to 16 weeks in the methotrexate and Apremilast groups is shown in Figure 1. There was no statistically significant difference in the decline of m-PPPASI scores between the two groups, but there was a decline beginning in week

Table 1: Baseline demographic and clinical characteristics of study patients

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-PPPASI score* ^β	20.34±9.13	21.72±8.6	0.36
Baseline sPGA score* ^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
Duration of disease (years)* ^α	7.95±5.95	6.51±7.37	0.24
Family history of psoriasis, n(%)** ⁰		2(9)	0.49
Comorbidities, n(%)**	4(21)	5(22.7)	0.89
Diabetes mellitus	2	2	
Hypertension	1	2	
Hypothyroidism	1	1	
Chronic kidney disease	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 Physician Global Assessment, SD=Standard deviation

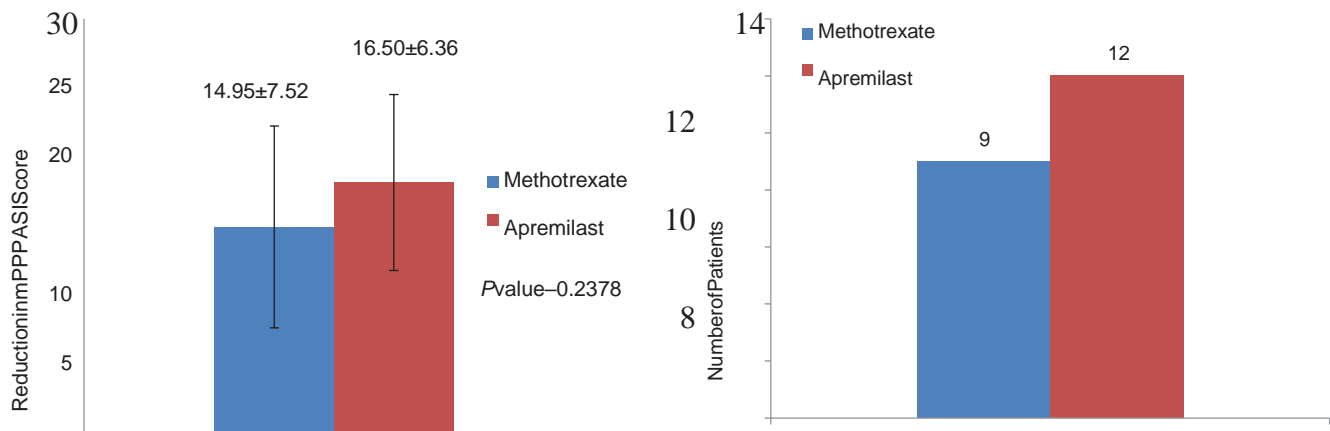


Figure 1: Reduction in modified palmoplantar psoriasis area and severity index score from 0 week to 16 weeks in the two treatment groups. Data analyzed by the Mann-Whitney *U*-test. mPPPASI: Modified palmoplantar psoriasis area and severity index

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 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

Table 2: Adverse events reported in the two study

groups

Adverse events	Number of patients	
	Methotrexate (n=19), n (%)	Apremilast (n=22), n (%)
Diarrhea	7(36.8)	8(36.36)
Nausea and vomiting	6(31.5)	5(22.7)
Headache	4(21)	4(18.18)
Upper respiratory tract infection	0	2(9.1)
Abdominal pain	4(21)	0
Abnormal LFT	3(15.7)	0
Total	24	19

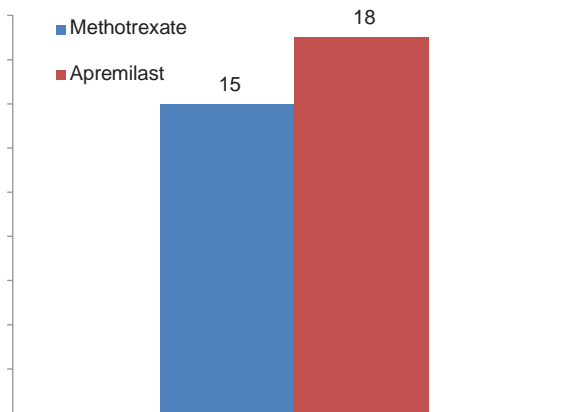


Figure 3: Number of patients showing at least 5-point reduction in dermatology life quality index from baseline. Data analyzed by Fisher's exact test. DLQI: Dermatology life quality index

Percentages are denoted by numbers in parenthesis. LF: The role of the liver ground level. Many published research have found the same thing. After 16 weeks of therapy with apremilast, people with palmoplantar psoriasis showed a statistically significant reduction in mPPPASI scores, sPGA scores, and/or DLQI scores, according to several placebo-controlled trials. referenced as [6,8,12, 13] The severity index score and area of palmoplantar pustulosis were significantly reduced in the apremilast group compared to the placebo group at week 16 in a prior study including

patients with palmoplantar psoriasis (P = 0.016).[14] While the majority of previous trials either included one arm or used placebos, our investigation evaluated apremilast's effectiveness to that of an active comparator. Since this immunosuppressive drug has shown a considerable clinical improvement in individuals with palmoplantar psoriasis, methotrexate is often used as a systemic agent for treatment.[15] Consequently, methotrexate was used as the active comparator in this evaluation.

Until yet, we have only found one published trial on palmoplantar psoriasis that compared apremilast to methotrexate, an active comparator. The research found that apremilast was just as effective as methotrexate in treating palmoplantar psoriasis.[8] So, to compare our trial findings with other published data, we need to know how effective apremilast is compared to other active comparators. From 8 to 16 weeks, our research found that mPPPASI values in both groups decreased steadily. In a research comparing methotrexate with apremilast for palmoplantar psoriasis, it was shown that the apremilast group had a significant drop in m-PPPASI scores in the first eight weeks, but then they started to plateau between weeks eight and sixteen. In contrast, the methotrexate group showed a linear trend in the lowering of m-PPPASI values.[8]

A least 75% improvement in plaque psoriasis severity index (PASI75) has been proposed as the definition of "clinically significant success" in this disease.[16] Studies have also employed mPPPASI75 and mPPPASI90 to evaluate clinical improvement in palmoplantar psoriasis patients.(8, 12) At week 16, the numbers of patients in both groups who achieved

mPPPASI75 and mPPPASI90 were similar ($P = 0.57$ and $P = 0.92$, respectively). Another head-to-head comparison study determined that the numbers of patients who achieved mPPPASI75 and mPPPASI90 were similar in the methotrexate and apremilast groups ($P = 0.49$ and $P = 0.27$, respectively). However, our study found that the percentage of patients who achieved these parameters was lower in both groups compared to the others (33.3% vs. 40.5% attained mPPPASI75 and 14.3% vs. 23.8% attained mPPPASI90).[8] In contrast to our research (14.3%), a single-arm study found a lower percentage of patients reaching mPPPASI75.[12]

One major issue with PASI is that it is not widely utilized by professionals, which means that both patients and clinicians have trouble understanding it. The same holds true with mPPPASI. However, these scales are often used in research investigations, but they are not frequently employed in clinical practice. The mPPPASI results were evaluated by the head of the school.

investigator. Conversely, global evaluations developed by physicians see extensive use in patient care. These are quite simple to recognize and evaluate. Medical professionals use these scales in their daily work.[16] Disease has no impact on quality of life for patients whose sPGA scores are 0 or 1. Results showed no significant difference between the two groups in terms of the percentage of patients who achieved a 0 or 1 sPGA score at week 16 ($P = 0.87$). While not a single research on apremilast in palmoplantar psoriasis has used the sPGA as an evaluation tool, several studies have done so using the palmoplantar physicians global assessment (PPPGA). A pooled analysis revealed that there were significantly more

patients in the apremilast group who achieved a PPPGA score of 0 or 1 at week 16, compared to the placebo group, in a placebo-controlled study of palmoplantar psoriasis ($P = 0.34$) [14]. Among patients with palmoplantar psoriasis, 34.7% managed to achieve a PPPGA score of 0/1 at 16 weeks in a apremilast single-arm trial. The DLQI is the gold standard for evaluating quality of life in psoriasis studies [13]. Lesion severity scores, like mPPPASI and sPGA, work in tandem with the DLQI score. Quality of life (QOL) metrics may confirm that clinically relevant improvements have occurred in clinical trials when there is a statistically significant improvement in the mean change in lesion severity ratings. Many therapeutic studies employ a five-point decrease in DLQI scores as an evaluation metric. Both groups had similar rates of patients attaining a 5-point drop in DLQI at week 16 in this trial [16]. Another research found similar outcomes in individuals with palmoplantar psoriasis; both the methotrexate and apremilast groups showed similar changes in DLQI ratings from week 0 to week 16.[8]

Due to not being able to be followed up with, six patients in the methotrexate group and three in the apremilast group discontinued participation in the trial. Their reasons for dropping out could not be determined since they could not be reached, even after many phone efforts.

Due to the length of time required to cure psoriasis, side effects are typical. The methotrexate group had 24 adverse events compared to the apremilast group's 19 (19). All of the published studies have reported the same thing: that the study medicines had known harmful effects. pages 18–21

Limitations

One issue is that the trial was open-label, which increases the likelihood of bias, especially when subjective criteria are employed to determine effectiveness. Two, there was a very limited sample size when

Our research limits the applicability of our findings to a broader demographic. Thirdly, the evaluation of long-term effectiveness maintenance or adverse events, which is essential in this chronic condition, cannot be done within the confines of the trial, even with the short follow-up period.

summary

It is not possible to generalize the outcomes of this research due to its limited sample size, even though we found that apremilast and methotrexate are equally effective in palmoplantar psoriasis. One other thing that prevents people from using apremilast is how expensive it is. Therefore, apremilast may be worth considering as a therapy option for a subset of palmoplantar psoriasis patients who have not responded to or are unable to take currently available medications. Nevertheless, even this requires confirmation via larger-scale investigations.

References:

1. Psoriasis. *The New England Journal of Medicine* 2009;361:496-509. Nestle FO, Kaplan DH, Barker J.
2. PB Nayak, BS Girisha, and TM Noronha. A research conducted in South India examined the relationship between the severity of psoriasis, family income, and quality of life. *Journal of Indian Dermatology Online*, 2018;9:165–9.

3. The authors of the study are Papp K, Reich K, Leonardi CL, Kircik L, Chimenti S, Langley RG, and colleagues. Results of a phase III randomized controlled study evaluating the effects of apremilast in psoriasis (ESTEEM 1) in patients with moderate to severe plaque psoriasis using the oral phosphodiesterase 4 (PDE4) inhibitor. The citation for the article is *J Am Acad Dermatol* 2015;73:3749.

4. Miceli A, and Schmieder GJ; 4. Psoriasis around the palms and soles of the feet. Published by StatPearls in 2021, Treasure Island (FL) is a jeweler's paradise. You may access it at this link: <https://www.ncbi.nlm.nih.gov/books/NBK448142/>. [As of August 22, 2021].

5. Morrell DS, Sewell MJ, Burkhart CN. *Dermatological pharmacology*, Chapter 70. That instance, in Goodman and Gilman's *The Pharmacological Basis of the Rapetics*. McGraw-Hill Education, 13th edition, page 1288.

6. The current authors include Bissonnette, Haydey, Rosoph, Lynde, Bukhalo, Fowler, and others. Apremilast as a therapy for moderate to severe palmoplantar psoriasis: Findings from a randomized, double-blind trial. *J Eur Acad The dermatologist* published the article in 2018 with the DOI number 32: 403-10.

7. Psoriasis (Chapter 18), by Gudjonsson JE and Elder JT. Included in: Fitzpatrick's *Dermatology in General Medicine*. Book by McGraw-Hill Education. Pages 197–229.

8. S. Kt, V. Thakur, T. Narang, S. Dogra, and S. Handa 7. A randomized controlled study comparing the safety and effectiveness of methotrexate with apremilast in the

treatment of palmoplantar psoriasis. *Am J Clin Clin Clinical dermatology* 2021;22:415–23.

9. Shetty VH, Goel S, Babu AM, Eram H. Researchers compared the safety and effectiveness of oral methotrexate with that of oral apremilast in treating moderate to severe chronic plaque psoriasis.

10. Solaram M, Thomason D, Signorovitch JE, Betts KA, Armstrong AW. Efficacy and incremental cost per responder of methotrexate compared to apremilast for psoriasis patients who had never used methotrexate. "Journal of the American Academy of Dermatology" published in 2016 with the DOI 75:740–7406.

11. Brownasso AM, Salvini C, and Massone C. 11. An open-label pilot study with five patients evaluating efalizumab for severe palmo-plantar psoriasis. *Journal of the European Academy of Dermatology and Venereology* 2009;23:415–9.

12. The group consisting of Willismann-Theis, Kromer, Gerdes, Linker, Magnolo, Sabat, and others. Aplatilost in palmoplantar pustulosis: an open-label research including many centers (APLANTUS). The citation for this article is *J Eur Acad Dermatol Venereol* 2021;35:204550.

13. Apremilast — A medication that helps with palmoplantar psoriasis, according to Parasramani SG and Pillai J. *Ancient Egypt Journal of the American Academy of Dermatology and Venereology*, 2021;41:103.

14. Bissonnette R, Pariser DM, Wasel NR, Goncalves J, Day RM, Chen R, and others. Results of a combined analysis from the phase II PSOR-005 and phase III ESTEEM clinical trials in patients with moderate to severe psoriasis regarding the use of

apremilast, an oral phosphodiesterase-4 inhibitor, for the treatment of palmoplantar psoriasis. *Journal of the American Academy of Dermatology* 2016;75:99-105.

15. orses t. Diabetic palmoplantar eczema pustulosis: Existing therapies and potential outcomes in the future. I work The citation for the article is *J Clin Dermatol* 2016;17:349–58.

16. Krueger GG and Feldman SR.. Clinical studies use psoriasis evaluation instruments. *Annals of Rheumatology* 2005;64 Suppl 2:i65–8.

17. Authors: Viswanathan HN, Chau D, Milmont CE, Yang W, Erondur N, Revicki DA, and others. When individuals with moderate to severe psoriasis achieve total skin clearance, their health-related quality of life improves and the intensity of their symptoms is decreased. *Journal of the American Academy of Dermatology*, Volume 26, Issue 9, 2015, pages 235-09.

18. REDITREXTM (Methotrexate), a drug approved by the FDA. This document may be accessed at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/210737s0001bl. **Last access**: August 12, 2022.

19. Maxtrex 10 mg Capsules. The Electronics Medicines Compendium. You may get this information at: <https://www.medicines.org.uk/emc/product/1377/smpc>. **Last access**: August 12, 2022.

20. OTEZLA (Apremilast), a drug approved by the FDA. This document may be accessed at this URL: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/205437s0061blPDF. **Last access**: August 12, 2022.

21. Otezla Film Coated Tablets, 30 mg.
Electronics Medicines Compendium,

22. This information may be accessed at:
<https://www.medicines.org.uk/emc/product/3648/smpc>. **Last access**: August 12,
2022.