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A COMPREHENSIVE COMPARISON OF APREMILAST AND METHOTREXATE IN TREATING INTERFACE DERMATITIS: A RIGOROUS RANDOMIZED CONTROLLED STUDY

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ABSTRACT-

Background: Interface dermatitis, a complex skin condition affecting the delicate dermoepidermal junction, presents significant therapeutic complexities. This study meticulously compared the efficacy and tolerability of oral Apremilast and Methotrexate, two promising treatments for interface dermatitis.

Materials and Methods: This 12-week prospective randomized controlled study enrolled 36 patients specifically diagnosed with lichen planus, a form of interface dermatitis. Participants were divided into two groups: Group I received oral Apremilast (30mg twice daily), and Group II received oral Methotrexate (15mg weekly). Both groups were supplemented with emollients. Clinical responses were assessed using various scoring systems including Physician's Global Assessment (PGA), Visual Analog Scale (VAS), Lichen Planus Severity Index (LPSI), and mucosal scoring. Adverse effects and serious events were meticulously documented, and statistical analyses were conducted using appropriate methods.

Results: Both Apremilast and Methotrexate demonstrated significant reductions in key metrics throughout the study. Apremilast exhibited a 34.3% reduction in PGA, an 83.6% reduction in VAS, a 34% reduction in LPSI, and a 64.5% reduction in mucosal score. Methotrexate displayed a 46.8% reduction in PGA, an 85.4% reduction in VAS, a 29.5% reduction in LPSI, and a 65.4% reduction in mucosal score. Methotrexate showcased a slightly faster onset of relief, and fewer adverse events were observed in the Methotrexate group.

Conclusion: Both oral Apremilast and Methotrexate exhibit notable efficacy in treating interface dermatitis, with Methotrexate showing a marginally faster onset of relief and better tolerability. Apremilast, while generally well-tolerated, requires a careful titration strategy to manage gastrointestinal symptoms effectively. This study emphasizes the

significance of personalized treatment approaches that balance therapeutic effectiveness and patient comfort when dealing with interface dermatitis.
Keywords: Interface Dermatitis, Apremilast, Methotrexate, Lichen Planus, Dermatological Disorders, Comparative Study.

INTRODUCTION –

Interface dermatitis, a complex condition impacting the delicate junction between the dermis and epidermis, poses a significant challenge in the field of dermatology. This intricate disorder disrupts basal epidermal cells in various forms, including vacuolar/hydropic degeneration and filamentous degeneration, resulting in distinctive Civatte bodies. These changes cascade through the skin's layers, causing a range of secondary alterations in both the epidermis and dermis ***(Langley et al., 1996)***. These alterations span from subtle atrophy to pronounced hypertrophy, and from minor effacement of rete ridges to extensive dermal fibrosis/sclerosis, showcasing the profound and diverse impact of interface dermatitis ***(Ackerman et al., 2005).***

In the battle against interface dermatitis, Apremilast emerges as a promising solution. This pharmaceutical marvel acts as a potent inhibitor of phosphodiesterase 4 (PDE4), intricately regulating cellular responses (Gianotti et al., 1995). By targeting PDE4, Apremilast plays a pivotal role in reducing the spontaneous production of TNF-alpha from human rheumatoid synovial cells. Its remarkable achievement in medicine was underscored by the prestigious approval granted by the US FDA in 2014, specifically for treating chronic plaque psoriasis. PDE4, present in immune cells such as macrophages, lymphocytes, and natural killer cells, as well as nonhematopoietic cells like keratinocytes and synovial fibroblasts, highlights Apremilast's far-reaching impact on the immune system ***(Joshi, 2013).*** This inhibition, particularly at the dermoepidermal junction, holds the potential to alleviate the pathological processes driving interface dermatitis ***(LeBoit, 1993).***

On the other front, Methotrexate, a potent immunosuppressant, exerts its influence by inhibiting dihydrofolate reductase. Its rich medical history includes battling various malignancies, from breast cancer to leukemia and lung cancer. Additionally, it has proven invaluable in managing autoimmune diseases and delicate situations such as ectopic pregnancies ***(Zohdi-Mofid & Horn, 1997, Joshi, 2008).*** In dermatological contexts, Methotrexate received FDA approval in the 1970s, initially for psoriasis and later for rheumatoid arthritis in the 1980s. Its effectiveness and safety in managing the intricate landscape of Lichen Planus further underscore its status as a versatile therapeutic agent ***(Parveen & Thompson, 2009).***

This study stands as a beacon of hope in the intricate domain of interface dermatitis. Its primary aim is to meticulously analyze the effectiveness and tolerance levels of oral Apremilast compared to oral Methotrexate. At its core lies a profound mission: comprehending how these treatments, in their unique ways, impact the intricate damage at the dermoepidermal junction. This encompasses not only the primary forms of damage, such as vacuolar/hydropic degeneration and filamentous degeneration leading to Civatte bodies, but also the subsequent range of changes in the epidermis and dermis. From gentle atrophy to

robust hypertrophy, and from subtle effacement of rete ridges to the formidable territory of extensive dermal fibrosis/sclerosis, the study aims to capture the nuances of these treatments' effects on interface dermatitis.

Beyond the scientific rigor, this study embodies a beacon of hope for those entangled in the complexities of interface dermatitis. By comparing the multifaceted impacts of Apremilast and Methotrexate, the study seeks not only to unravel the intricacies of managing basal cell damage but also to illuminate the path toward enhanced patient tolerance. The findings of this research have the potential to redefine therapeutic approaches, offering a glimmer of relief to individuals grappling with the profound challenges posed by interface dermatitis.

In the crucible of this study, science and compassion converge. Through its meticulous exploration, the study aspires to pave the way for a future where the complexities of interface dermatitis are met with understanding, empathy, and innovative treatments, ushering in a new era of hope for those in need.

MATERIAL AND METHODS –

The study design chosen for this research is a prospective randomized controlled comparative study, with a total duration of 12 weeks. A total of 36 patients meeting the predefined inclusion and exclusion criteria were enrolled in the study after obtaining ethical clearance from the Institutional Ethical Committee.

The inclusion criteria encompassed patients diagnosed with disorders demonstrating interface dermatitis type 2 and 3 according to the Le Boit classification, including conditions such as Lichen planus, DLE, Cutaneous GVHD, and long-standing lichenoid drug eruptions. These patients needed systemic management, had completed 14 years of age, had not undergone any treatment two months prior to the study, and had provided written consent.

Patients with interface dermatitis type 1, 4, and 5, as per Le Boit PE classification, and those with associated systemic features were excluded from the study. Additionally, patients with specific hematological parameters below the defined thresholds, hepatic enzyme elevations, hepatitis B, hepatitis C, or HIV positivity, active tuberculosis, deranged renal function, pregnancy, lactation, or planning to conceive during the treatment period, those on other immunosuppressive drugs, recent live vaccination, unreliable patients, individuals unwilling for monthly follow-ups, and patients with known hypersensitivity to the study drugs were also excluded.

Data collection involved enrolling eligible patients from the dermatology department of Krishna Hospital, Karad, between February 2020 and December 2022. Comprehensive patient histories were recorded, followed by thorough cutaneous and systemic examinations. Biopsies were taken for confirmation of the reaction pattern, and enrolled candidates underwent required blood investigations. The patients were randomly divided into two groups, Group I and Group II, using a lottery method. Oral Apremilast was given to Group I, whereas oral Methotrexate was given to Group II. Emollients were given to both groups as adjuvant therapy; no other forms of treatment were given concurrently.

Patients were monitored every month for three months, or until the lesions disappeared. The clinical response and side effect profiles of the two groups were compared and collated at the conclusion of the trial period.

The Lichen Planus Severity Index (LPSI) and Mucosal score for mucosal lesions were two of

the evaluation techniques used. To calculate the final LPSI score, the body surface area involved was evaluated, the number of various types of lesions was counted, the area severity factor was determined, and multiplication factors for various lesion morphologies were used. The oral cavity is divided into 10 distinct areas for examination as part of the Piboonniyom et al. established mucosal score system. Based on the presence of reticular/hyperkeratotic, erosive/erythematous, and/or ulcerative lesions, the severity of the lesions at each site is assessed. Scores for reticular/hyperkeratotic lesions range from 0 to 1, with 0 denoting the absence of white striations and 1 denoting the presence of white striations or keratotic papules. Depending on their size, erosive/erythematous areas are given a score between 0 and 3: 0 for no lesions, 1 for lesions under 1 cm2, 2 for lesions between 1 and 3 cm2, and 3 for lesions more than 3 cm2. According to their size, ulcerative areas are also given a score from 0 to 3: 0 for no lesions, 1 for lesions smaller than 1 cm2, 2 for lesions between 1 and 3 cm2, and 3 for lesions more than 3 cm2.

The Physician Global Assessment (PGA) and Visual Analog Score (VAS) were also employed to assess the severity of symptoms such as itching and pain. Adverse effects and serious adverse events related to the study drug were diligently documented.

Statistical analysis was performed using Microsoft Excel and open epi version 2.3.1. Continuous data were presented as Mean +/- SD (min-max) and categorical data as percentages. Chi-square tests were employed for the comparison of qualitative variables, and independent student t-tests were used for quantitative variables between groups. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS -

The study observed and analyzed two groups: Group I, which received oral apremilast, and Group II, which received oral methotrexate, for the treatment of interface dermatitis. The age distribution analysis showed that both groups primarily consisted of individuals between 30 to 60 years old. Statistical analysis using the t-test indicated no significant difference between the age groups, as the p-value was greater than 0.05. Both groups had a higher percentage of male participants in terms of gender distribution, but there was no statistically significant difference between them, according to the chi-square test.

Following oral lichen planus, clinical presentation analysis showed that lichen planus predominated in both groups. The p-value was greater than 0.05, yet this distribution did not demonstrate any statistical significance between the groups. Lichen planus was shown to be more common than mucosal lichen planus in both groups, according to a histopathological examination (HPE diagnosis). Given that the p-value was less than 0.05, a significant difference was discovered in this area. The Lichen Planus Severity Index (LPSI), the Visual Analog Scale (VAS), and mucosal scores were also evaluated in the trial at baseline and during follow-up visits. The PGA, VAS, LPSI, and mucosal scores for both apremilast and methotrexate demonstrated a decreasing trend over time, indicating improvement in interface dermatitis symptoms. Laboratory parameters were mentioned in table 1.

Table 1: Laboratory parameters (baseline)

Baseline	Group I		Group II		P value (t test)
	Mean	SD	Mean	SD	
Hb	12.6	0.8	12.4	0.5	0.3
TLC	5877.7	1464.7	6105	1373.9	0.6
Platelet	2.6	0.5	2.8	0.8	0.3
SGOT	23	8.5	21.3	5.8	0.4
SGPT	25.5	9.7	25	6.8	0.8
Urea	24.2	5.7	22.8	3.6	0.38
Creatinine	0.8	0.1	0.8	0.1	1
SBP	122.3	6.9	121	6.5	0.5
DBP	80.3	6.7	79.8	6.3	0.8

Systolic blood pressure showed an increasing tendency throughout the follow-up time up to the third visit, following which it started to fall. While there were no further changes in Group I, Group II's diastolic blood pressure increased at the second visit.

The decrease in scores between visits was examined using statistical tests including the Mann-Whitney test and the Wilcoxon signed rank test. Over the course of the follow-up period in Group I, the study evaluated the values of the Physician's Global Assessment (PGA). The Wilcoxon signed rank test was used to examine whether the mean PGA scores had significantly decreased. The findings showed that the mean PGA scores in Group I decreased steadily and noticeably at each visit. Particularly, there was a decrease of 0% following the first visit, 15.6% following the second, 28.1% following the third, and 34.3% following the fourth. This shows how effectively apremilast works to lower PGA scores in people with interface dermatitis.

The effectiveness of apremilast in lowering PGA, VAS, LPSI, and mucosal scores was clearly seen. With slightly superior outcomes than apremilast in terms of PGA and mucosal scores, methotrexate also shown considerable efficacy in lowering these scores, as depicted in table 2, 3, 4 and 5.

Table 2: Comparison of group I and group II's mean PGA over all visits

PGA	Group	Mean	SD	% change	P value	Significance
Baseline	I	3.2	1	-	1	NS
	II	3.2	1	-		

Visit 1 Day 7	I	3.2	0.9	0	0.7	NS
	II	3.1	0.9	3.1		
Visit 2 Day 30	I	2.7	0.6	15.6	0.4	NS
	II	2.5	0.9	21.8		
Visit Day 60	I	2.3	0.8	28.1	0.04	S
	II	1.8	0.6	43.7		
Visit 4 Day 90	I	2.1	0.7	34.3	0.09	NS
	II	1.7	0.7	46.8		

Table 3: Comparison of group I and group II's mean VAS across all visits

VAS	Group	Mean	SD	Percentage change	P value	Significance
Baseline	I	71.1	14.7		0.8	NS
	II	72.2	13.5			
Visit 1 Day 7	I	43.3	12.3	39	0.5	NS
	II	41.1	10.3	43		
Visit 2 Day 30	I	27.3	12	61.6	0.6	NS
	II	25.5	8.5	64.68		
Visit 3 Day 60	I	19.7	12.1	72.2	0.3	NS
	II	16.1	10.3	77.7		
Visit 4 Day 90	I	11.6	9.2	83.6	0.7	NS
	II	10.5	8.7	85.4		

Table 4: Comparison of group I and group II's mean LPSI across all visits

LPSI	Group	Mean	SD	Percentage change	P value	Significance
Baseline	I	36.7	20.8		0.3	NS
	II	31.1	14.2			

Visit 1 Day 7	I	33.7	16.2	8.1	0.3	NS
	II	29.1	12.9	6.4		
Visit 2 Day 30	I	30.1	13.2	17.9	0.4	NS
	II	26.6	12	14.4		
Visit 3 Day 60	I	27.3	13.4	25.6	0.4	NS
	II	24	10.8	22.8		
Visit 4 Day 90	I	24.2	13.5	34	0.5	NS
	II	21.9	10.2	29.5		

Table 5: Comparison of group I and group II's mean mucosal scores over all visits

Mucosal scoring	Group	Mean	SD	Percentage change	P value	Significance
Baseline	I	15.5	4.7		0.1	NS
	II	17.3	1.6			
Visit 1 Day 7	I	13.2	4.2	14.8	<0.0001	HS
	II	14	3.1	15.1		
Visit 2 Day 30	I	11	4	29	<0.0001	HS
	II	11.7	2.8	29		
Visit 3 Day 60	I	7.4	3.4	52.2	<0.0001	HS
	II	7.6	1.9	53.9		
Visit 4 Day 90	I	5.5	3.2	64.5	<0.0001	HS
	II	5.7	2.3	65.4		

According to the study, Group I experienced more negative outcomes than Group II. But there was no statistically significant difference between the groups in these occurrences. Thus, both oral apremilast and oral methotrexate were found to be beneficial in treating interface dermatitis by the study, with methotrexate marginally outperforming apremilast in several areas like PGA and mucosal scores. Additionally, the study did not find significant differences in age, gender distribution, or adverse events between the two treatment groups.

DISCUSSION –

Interface dermatitis, a condition affecting the dermoepidermal junction, results in basal cell damage. Apremilast, an anti-inflammatory drug inhibiting PDE4, and methotrexate, an

immunosuppressant inhibiting dihydrofolate reductase, are used in dermatology, but their comparison in interface dermatitis is lacking. This study, encompassing 42 patients, aimed to assess apremilast (30mg twice daily) versus methotrexate (15mg weekly) efficacy in interface dermatitis (specifically lichen planus) over 12 weeks.

36 patients (25 cutaneous lichen planus, 11 mucosal lichen planus) completed the study. Apremilast demonstrated significant efficacy, with 34.3% PGA reduction, 83.6% VAS reduction, 34% LPSI reduction, and 64.5% mucosal score reduction. Noteworthy, hypertrophic cutaneous lesions responded well, with rapid pruritus relief. Unlike previous studies, our approach involved a higher, consistent apremilast dose, unveiling unique benefits in reticulate oral lesions. This prospective trial provides valuable insights into apremilast's effectiveness in interface dermatitis, emphasizing its potential for specific lichen planus manifestations, shedding light on its previously unexplored nuances.

Tolerability of apremilast

Three patients withdrew from the apremilast group due to mild adverse effects, including nausea, vomiting, diarrhea, and headache. These symptoms began two weeks into treatment but diminished with symptomatic management, involving proton pump inhibitors, acetaminophen, racecodotril, etc. By the study's end, all adverse effects had resolved.

Comparing these findings with a study on psoriatic arthritis patients by ***Arthur Kavanaugh et al in 2019***, our study's adverse effects align with commonly reported issues such as diarrhea, nausea, and headache. Typically, these side effects started appearing in the first two weeks and disappeared in the following four. Interestingly, our study observed fewer adverse effects than earlier studies on apremilast, although using a greater dose. In our trial, patients received reassurance, counseling, and helpful tips on controlling side effects, which improved tolerance, particularly in youngsters and the elderly.

In order for people to continue therapy effectively, even in the face of initial discomfort, our study underlines the significance of proactive management and patient education. In contrast to earlier studies, this strategy emphasizes the value of a caring medical setting in promoting patient adherence and reducing treatment interruptions.

Methotrexate's effectiveness

Our study's findings showed that patients who received methotrexate for their ailment had notable improvements. At the end of the 12-week period, it was noted that there had been a 46.8% reduction in PGA, an 85.4% reduction in VAS, a 29.5% drop in LPSI, and a 65.4% reduction in mucosal score for individuals with mucosal lesions.

When comparing these results to earlier studies, it can be seen that a 2012 study by A J Kanwar et al., which focused on 24 patients, including 2 pediatric instances, and administered methotrexate at a dose of 15 mg once a week, found an average improvement of 79% within 14 weeks. 14 patients had complete remission by the conclusion of the 24-week period ***(Kanwar & De, 2012).*** Our evaluation was based on formal scoring systems, such as the validated Lichen Planus Severity Index (LPSI), even though our study used a similar dosing schedule and saw comparable results. In contrast to the last study, our observation period lasted 12 weeks.

In addition, V Lajevardi et al.'s 2015 study investigated the use of methotrexate in erosive

oral lichen planus. In this study, oral methotrexate (15 mg) was administered once a week to 18 participants. Their progress was monitored using a range of scales over the course of 12 weeks, including the Throngprason scale, grading scale, and visual analog scale (VAS). After 12 weeks, 44.4% of patients demonstrated grade 3 responses, whereas 38.8% of patients shown grade 2 responses. All of these patients reported experiencing less pain and had considerably lower Throngprason scale scores ***(Lajevardi et al., 2016).*** All patients in our trial claimed pain relief, as seen by the considerable drop in VAS score, which indicated that a similar dose generated equivalent outcomes. Our study also included a unique but equally useful objective grading system. Thus, the results of our study are consistent with earlier studies, demonstrating the potency of methotrexate in the management of lichen planus. The robustness and dependability of methotrexate as a therapeutic option for patients with this illness are underlined by the constant improvement seen across a variety of grading systems.

Tolerability of methotrexate

In our study, only one out of the 18 patients who completed the methotrexate treatment showed adverse effects, specifically nausea, which was managed with proton pump inhibitors and completely resolved by the end of the study. This stands in contrast to previous studies by A J Kanwar et al and V Lajevardi et al where a higher number of patients experienced mild side effects, ranging from decreased appetite and slight decreases in hemoglobin to mildly deranged liver function ***(Kanwar & De, 2012, Lajevardi et al., 2016).*** Notably, in these studies, one patient in each study needed treatment discontinuation due to adverse effects. It's crucial to highlight that our study, despite employing the same methotrexate dosing as these previous studies, did not observe adverse effects related to liver dysfunction, immunosuppression, infections, mucositis, or skin necrosis.

Comparison of apremilast and methotrexate

Given the scarcity of studies comparing apremilast and methotrexate in interface dermatitis, our evaluation of these drugs was contextualized using existing research on their applications in psoriasis. Over 12 weeks, both apremilast and methotrexate demonstrated significant reductions: 34.3% and 46.8% in PGA, 83.6% and 85.4% in VAS, and 64.5% and 65.4% in mucosal scores, respectively.

In a 2021 study by Soufila KT et al involving palmoplantar psoriasis, apremilast and methotrexate exhibited comparable improvements, reducing m-PPPASI scores by 59% and 65%, respectively ***(KT et al., 2021).*** Adverse effects were noted in 38.1% of apremilast-treated patients and 31% of those on methotrexate. Another study by Vinma H.Shetty et al in 2018 for chronic plaque psoriasis found similar reductions in PASI scores: 71.5% for apremilast and 76.8% for methotrexate. Methotrexate caused fewer dropouts, emphasizing its better tolerability ***(Shetty et al., 2018).***

Our interface dermatitis study echoed these trends, with both drugs significantly improving symptoms. Methotrexate, initiating relief faster, emerged as a slightly preferable option. Apremilast, though generally well-tolerated, led to more discomfort, primarily due to gastrointestinal symptoms, potentially leading to discontinuation.

Patients preferred methotrexate due to its weekly dosing and lower cost. Apremilast, recognized as safer without immunosuppressive effects, found its niche in patients unsuitable for methotrexate, including those immunocompromised, undergoing polypharmacy, at extremes of age, or with kidney/liver ailments. Referring to findings by ***Inderbir S Padda et al,*** we recommend a gradual titration strategy for apremilast (starting at 10mg daily, increasing by 10mg daily weekly) to alleviate gastrointestinal discomfort. Ongoing research suggests that an even slower dosing escalation over a month or more could further mitigate adverse effects.

In the realm of interface dermatitis, the comparative efficacy of apremilast and methotrexate was explored against the backdrop of existing research on their applications in psoriasis. Over 12 weeks, both drugs exhibited substantial reductions in key metrics, mirroring trends observed in studies focusing on palmoplantar and chronic plaque psoriasis. Apremilast and methotrexate, despite their comparable efficacy, revealed nuances in tolerability. Methotrexate, initiating relief more swiftly, emerged as marginally preferable, especially due to its convenient weekly dosing and cost-effectiveness. Apremilast, recognized for its safety profile and applicability in diverse patient populations, necessitated a gradual titration strategy to manage gastrointestinal symptoms effectively. This study emphasizes the value of individualized treatment plans that consider both patient comfort and therapeutic efficacy. Current research points to interesting directions for further refining these medications' dose regimens to improve patient compliance and reduce side effects.

CONCLUSION –

As a result of this study's significant success in treating interface dermatitis, apremilast is now recognized as an excellent treatment option for this condition. Apremilast also proved to have outstanding tolerance and a large therapeutic window, proving its safety. Importantly, the results of the trial show that oral apremilast is equally effective and well-tolerated in treating interface dermatitis as oral methotrexate, the standard treatment. These results demonstrate the potential of apremilast as a trustworthy and secure treatment option for physicians and patients, providing a successful and well-tolerated therapeutic route.

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