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Original Research Article

Comparative evaluation of liver function test in refractive psoriasis patients treated with tofacitinib and apremilast

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ABSTRACT

Background: Psoriasis is a chronic inflammatory skin disease that requires long-term management, often necessitating systemic treatments for moderate to severe cases. Tofacitinib, a Janus kinase (JAK) inhibitor, and apremilast, a phosphodiesterase 4 (PDE4) inhibitor, are increasingly used in refractory cases. Monitoring liver function is crucial due to potential hepatotoxicity. This study compared the impact of tofacitinib and apremilast on liver function tests (LFTs) over 12 months in patients with refractory psoriasis.

Methods: A retrospective cohort study was conducted at D. Y. Patil Hospital, Kolhapur, involving 150 patients treated between January 2019 and December 2021. Patients received either tofacitinib (5 mg twice daily) or apremilast (30 mg twice daily) for at least 12 months. Exclusion criteria included a history of liver disease, significant alcohol consumption, and incomplete medical records. Baseline and follow-up LFTs at 3, 6, and 12 months were analyzed using paired t-tests and independent t-tests.

Results: Among 150 patients, 75 were treated with tofacitinib and 75 with apremilast. Baseline characteristics, including LFTs, were similar between groups. The tofacitinib group exhibited significant increases in ALT and AST levels at all follow-up points compared to the apremilast group ($p<0.01$). Mean ALT rose from 25.6 U/l to 42.3 U/l in the tofacitinib group, while in the apremilast group, it increased from 24.9 U/l to 28.9 U/l. ALP and bilirubin levels remained stable.

Conclusions: Tofacitinib is associated with higher incidence of liver enzyme elevations than apremilast. Regular liver function monitoring is recommended for patients on tofacitinib.

Keywords: Apremilast, Hepatotoxicity, Liver function tests, Psoriasis, Tofacitinib

INTRODUCTION

Psoriasis is a chronic, immune-mediated skin disorder marked by red, scaly plaques that predominantly affect areas such as the scalp, elbows, knees, and lower back. It is a multifaceted condition with a global prevalence of approximately 2-3%, significantly impacting patients' quality of life due to its persistent and recurring nature.[1,2] Additionally, psoriasis can present as psoriatic arthritis, leading to considerable joint-related morbidity.[3]

A thorough understanding of psoriasis pathophysiology is crucial, as its development involves a complex interplay of genetic factors, environmental triggers, and immune dysregulation. Central to the disease is the abnormal proliferation and differentiation of keratinocytes,

influenced by various immune cells, including dendritic and T cells, along with cytokines like tumor necrosis factor-alpha (TNF-α), interleukin (IL)-17, and IL-23.[4,5] These cytokines are key players in the inflammatory processes that define psoriasis.[6]

Management strategies for psoriasis focus on alleviating inflammation and normalizing keratinocyte behavior. Treatment options range from topical therapies for mild cases to systemic interventions for more severe forms.[7] Traditional systemic agents, including methotrexate, cyclosporine, and acitretin, can be effective but are often associated with significant adverse effects, including hepatotoxicity, necessitating vigilant liver function monitoring during treatment. Recently, biological therapies targeting specific immune pathways have transformed the treatment landscape for moderate to severe psoriasis. However, these therapies tend to be costly and require injection, which limits their accessibility.[8] As a result, there is an increasing interest in effective oral alternatives.[9]

Tofacitinib, an oral Janus kinase (JAK) inhibitor, works by modulating the JAK-STAT signalling pathway implicated in psoriasis pathogenesis.[10] By inhibiting this pathway, tofacitinib decreases the activity of several pro-inflammatory cytokines, leading to improvements in psoriasis symptoms.[11] Clinical trials have established its effectiveness in reducing psoriasis severity and enhancing quality of life for patients.[12] However, its immunomodulatory effects raise concerns regarding potential adverse events, particularly infections and liver toxicity, highlighting the need for regular liver function assessments during treatment.

On the other hand, apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor that elevates intracellular cyclic adenosine monophosphate (cAMP) levels, which in turn suppresses the production of pro-inflammatory mediators involved in psoriasis development.[13] Apremilast has demonstrated efficacy in mitigating both psoriasis and psoriatic arthritis, boasting a favourable safety profile, with gastrointestinal side effects such as nausea and diarrhoea being the most common.[11,12] Unlike tofacitinib, apremilast is not significantly linked to hepatotoxicity, making it a compelling choice for long-term psoriasis management.

Liver function tests (LFTs) are essential for monitoring safety in patients receiving systemic therapies for psoriasis. These tests measure enzymes like alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin levels. Elevated enzyme levels may indicate liver injury, potentially requiring modifications to or discontinuation of the offending treatment. Given the chronic nature of psoriasis and the necessity for long-term systemic therapy, it is vital to comprehend the hepatic safety profiles of treatments such as tofacitinib and apremilast to ensure optimal patient outcomes.[14]

This study aimed to compare the effects of tofacitinib and apremilast on liver function tests in patients with refractory psoriasis over a 12-month duration. The specific objectives were to: i) assess changes in liver enzyme levels (ALT, AST, ALP, and bilirubin) from baseline at 3-, 6-, and 12-months post-treatment initiation. ii) Determine the incidence and severity of liver enzyme elevations in patients treated with tofacitinib compared to those receiving apremilast. iii) Offer recommendations for liver function monitoring in patients on these treatments based on the findings of the study.

METHODS

This study was a retrospective cohort analysis conducted at D. Y. Patil Hospital, Kolhapur, focusing on patients with refractory psoriasis treated with either tofacitinib or apremilast. The study period extended from January 2022 to March 2024. Ethical approval was obtained from the institutional review board, and informed consent for the use of medical records for research purposes was secured from all patients.

Inclusion criteria

Age: adults aged 18 years or older. Diagnosis: confirmed diagnosis of moderate to severe plaque psoriasis by a dermatologist. Refractory status: patients refractory to at least one conventional systemic therapy. Treatment: patients treated with either tofacitinib (5 mg twice daily) or apremilast (30 mg twice daily) for a minimum of 12 months. Medical records: complete medical records available for the entire study period.

Exclusion criteria

Liver disease: history of liver disease or significant alcohol consumption (defined as >21 units per week for men and >14 units per week for women). Concomitant medications: use of other hepatotoxic medications during the study period. Pregnancy/breastfeeding: patients who were pregnant or breastfeeding at any time during the treatment period. Incomplete records: patients with incomplete medical records or missing key liver function test data.

Data collection

Data extracted from electronic medical records (EMRs) by trained research staff using a standardized data collection form. The following data points collected:

Demographic characteristics

Age: age at the start of the study period. Gender: male or female. Body mass index (BMI): calculated from height and weight. Duration of psoriasis: time since diagnosis. Previous treatments: list of previous systemic treatments for psoriasis. Comorbid conditions: presence of any

comorbid conditions, such as diabetes or cardiovascular disease.

Liver function tests

Baseline LFTs: initial measurements of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin levels before starting treatment. Follow-up LFTs: measurements at 3 months, 6 months, and 12 months after initiating treatment with either tofacitinib or apremilast.

Adverse events

Liver enzyme elevations

Incidence of liver enzyme elevations, defined as ALT or AST levels exceeding twice the upper limit of normal (ULN).

Treatment modifications

Any dose adjustments or discontinuations of the drug due to liver-related adverse events.

Other adverse events

Other adverse events related to liver function, such as jaundice or clinical symptoms indicative of liver dysfunction.

Comparison of liver function tests

Within-group comparisons

Changes in liver function tests (ALT, AST, ALP, bilirubin) from baseline to follow-up points (3, 6, and 12 months) were analyzed using paired t-tests.

Between-group comparisons

Differences between the two treatment groups (tofacitinib and apremilast) at each follow-up point were analyzed using independent t-tests for continuous variables and chi-square tests for categorical variables.

Statistical Software SPSS

All statistical analyses were conducted using SPSS software (version XX). A p value of <0.05 was considered statistically significant for all tests.

Ethical considerations

The study approved by the institutional ethical committee of D. Y. Patil Hospital Kolhapur. All patient data were anonymized to protect confidentiality. Informed consent was obtained from all patients for the use of their medical records for research purposes.

RESULTS

Demographic characteristics

A total of 150 patients with refractory psoriasis were included in the study, with 75 patients in the tofacitinib group and 75 in the apremilast group. The baseline characteristics of the study population are summarized in Table 1.

Table 1: Baseline characteristics of study population.

Characteristics	Tofacitinib group	Apremilast group	P value
Age (years)	46.2±12.3	44.7±11.8	0.374
Gender (male)	41 (54.7%)	38 (52%)	0.733
BMI	27.8±4.1	27.3±3.9	0.458
Duration of psoriasis (years)	12.5±5.8	11.9±6.0	0.560
Previous systemic treatments	3.2±1.1	3.1±1.0	0.689
Comorbid conditions	29 (38.7%)	28 (37.3%)	0.855

Table 2: Baseline liver function tests (LFTs) were comparable between the two groups.

Parameters	Tofacitinib group	Apremilas group	P value
ALT (U/l)	26.2±7.5	25.7±7.3	0.663
AST (U/l)	22.8±6.9	22.4±6.6	0.727
ALP (U/l)	80.1±20.3	78.7±19.8	0.653
Bilirubin (mg/dl)	0.7±0.2	0.7±0.2	0.804

Baseline liver function tests (LFTs) were comparable between the two groups is shown in Table 2.

Changes in liver function tests over time

The changes in liver function tests from baseline to 3 months, 6 months, and 12 months is shown in Table 3.

Incidence of liver enzyme elevations

The incidence of liver enzyme elevations (ALT or AST levels exceeding twice the upper limit of normal) was higher in the tofacitinib group compared to the apremilast group, as shown in Table 4.

Treatment modifications due to liver-related adverse events

Two patients in the tofacitinib group required dose adjustments due to elevated liver enzymes. These adjustments were successful in managing the elevations, and no patients required discontinuation of tofacitinib. In contrast, no patients in the apremilast group required dose adjustments or discontinuation due to liver-related adverse events.

Table 3: The changes in liver function tests from baseline to 3 months, 6 months, and 12 months.

Parameters	Time point	Tofacitinib group	Apremilast group	P value
ALT(U/l)	Baseline	26.2±7.5	25.7±7.3	0.663
	3 months	34.5±9.8	27.1±7.5	<0.001
	6 months	37.6±10.1	27.8±7.6	<0.001
	12 months	42.3±11.3	28.9±7.7	<0.001
ALP(U/l)	Baseline	80.1±20.3	78.7±19.8	0.653
	3 months	82.5±21.0	79.5±20.2	0.489
	6 months	83.7±21.5	80.2±20.3	0.399
	12 months	85.4±22.0	81.0±20.4	0.300
AST(U/l)	Baseline	22.8±6.9	22.4±6.6	0.727
	3 months	29.3±8.4	23.0±6.7	<0.001
	6 months	31.7±8.9	23.5±6.8	<0.001
	12 months	35.6±9.7	24.4±7.0	<0.001
Bilirubin (mg/dl)	Baseline	0.7±0.2	0.7±0.2	0.804
	3 months	0.8±0.2	0.7±0.2	0.157
	6 months	0.8±0.2	0.7±0.2	0.123
	12 months	0.8±0.2	0.7±0.2	0.109

Table 4.: The incidence of liver enzyme elevations.

Parameters	Tofacitinib group	Apremilas group	P value
ALT>2XULN	18	5	0.004
AST>2XULN	15	4	0.009

Multivariate analysis

Multivariate logistic regression analysis identified treatment with tofacitinib as a significant predictor of liver enzyme elevations, even after adjusting for potential confounders (age, gender, BMI, duration of psoriasis).

Key findings

Demographic and clinical characteristics

Baseline characteristics were well-matched between the tofacitinib and apremilast groups.

Liver function tests

Significant increases in ALT and AST levels were observed in the tofacitinib group at all follow-up points compared to baseline and to the apremilast group.

Incidence of liver enzyme elevations

The tofacitinib group had a significantly higher incidence of liver enzyme elevations compared to the apremilast group.

Treatment modifications

Two patients in the tofacitinib group required dose adjustments due to elevated liver enzymes, whereas no such adjustments were needed in the apremilast group.

Predictors of liver enzyme elevations

Treatment with tofacitinib was identified as a significant predictor of liver enzyme elevations in the multivariate analysis.

These findings highlight the need for careful liver function monitoring in patients treated with tofacitinib and suggest that apremilast may have a more favorable hepatic safety profile in the treatment of refractory psoriasis.

DISCUSSION

This study aimed to evaluate the hepatic safety profiles of tofacitinib and apremilast in patients with refractory psoriasis over a 12-month treatment period. Our findings indicate that tofacitinib is associated with significant elevations in liver enzymes (ALT and AST) compared to apremilast, which did not exhibit similar changes. The incidence of liver enzyme elevations was notably higher in the tofacitinib group, and multivariate analysis confirmed that treatment with tofacitinib is a significant predictor of these elevations.

Tofacitinib, a Janus kinase (JAK) inhibitor, interferes with the JAK-STAT signalling pathway, which plays a crucial role in inflammatory and immune responses. While effective in alleviating psoriasis symptoms, our results raise concerns about its potential hepatotoxicity. The significant increases in ALT and AST levels observed at 3, 6, and 12 months suggest that tofacitinib may have hepatotoxic effects in some patients. Specifically, the higher incidence of liver enzyme elevations in the tofacitinib group (24% for ALT and 20% for AST) emphasizes the need for regular liver function monitoring in these patients.

Conversely, apremilast, a phosphodiesterase 4 (PDE4) inhibitor, increases intracellular cyclic adenosine monophosphate (cAMP) levels, leading to a reduction in pro-inflammatory cytokine production. Our study found no significant changes in liver enzyme levels among patients treated with apremilast, with a low incidence of liver enzyme elevations (6.7% for ALT and 5.3% for AST). This finding aligns with the favorable safety profile of apremilast, suggesting it may be a safer long-term treatment option for refractory psoriasis.

Our results are consistent with previous research highlighting elevated liver enzymes in patients treated with tofacitinib. For instance, in a phase II study by Papp et al, the safety and efficacy of apremilast in patients with moderate to severe plaque psoriasis were investigated. The study reported no significant liver enzyme elevations, supporting the notion of apremilast as a safe option for the long-term management of psoriasis, consistent with our findings.[15]

Another study done by Álvaro-Gracia et at reviewed the safety profile of tofacitinib and noted that while effective for treating rheumatoid arthritis, there were significant elevations in liver enzymes reported in various clinical settings, highlighting the need for monitoring similar to our findings in psoriasis patients.[16]

Crowley et al conducted a pooled safety analysis from two phase 3 trials. They found that apremilast maintained a favorable safety profile over 156 weeks, with no significant increases in liver enzymes, reinforcing its role as a safer alternative to tofacitinib.[17]

Sandborn et al found that tofacitinib administration in ulcerative colitis patients also led to liver enzyme elevations, which necessitates monitoring during treatment. This aligns with our findings of hepatotoxicity associated with tofacitinib.[18]

My emphasis on regular monitoring of liver function tests for patients on tofacitinib aligns with recommendations made in clinical guidelines. The FDA has noted that monitoring is critical for those on tofacitinib due to its hepatotoxic risks, particularly in patients with pre-existing liver conditions. My study suggestion to consider apremilast as a viable alternative reflects current clinical practices that prioritize patient safety and drug tolerability.[19]

The hepatic effects of tofacitinib necessitate vigilant monitoring of liver function tests (LFTs) during treatment. Clinicians should obtain baseline LFTs before initiating tofacitinib and perform periodic assessments thereafter. Patients with pre-existing liver conditions or those concurrently using other hepatotoxic medications may require more frequent monitoring and potentially alternative therapies. Given apremilast's favorable hepatic safety profile, it presents an attractive option for patients concerned about liver toxicity. Its oral administration and lack of significant hepatotoxicity make it particularly suitable for the long-term management of refractory psoriasis, especially in patients with a history of liver dysfunction.

CONCLUSION

This study provides a comparative evaluation of liver function in patients with refractory psoriasis treated with tofacitinib and apremilast over 12 months. Our findings indicate that tofacitinib is associated with significant elevations in liver enzymes, highlighting the need for regular monitoring of liver function tests. In contrast, apremilast demonstrates a favorable hepatic safety profile, with minimal changes in liver enzymes and a low incidence of hepatotoxicity. These results support the careful consideration of hepatic safety when selecting systemic treatments for psoriasis, particularly in patients with pre-existing liver conditions. Future research should aim to further elucidate the long-term hepatic effects of these treatments and explore strategies to mitigate potential adverse effects.

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Ethical approval: The study was approved by the Institutional Ethics Committee of D. Y. Patil Medical College, Kolhapur, India

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