DOI: https://doi.org/10.70749/ijbr.v3i6.2927

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://ijbr.com.pk
ISSN: 2960-2793/ 2960-2807

Role of JAK Inhibitors in Steroid-dependent IBD

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ARTICLE INFO

Keywords: Inflammatory bowel disease; steroid-dependent IBD; JAK inhibitors; tofacitinib; upadacitinib; steroid-free remission

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Declaration
Authors' Contribution: All authors equally contributed to the study and approved the final manuscript.

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History
Received: 17-03-2025 Revised: 12-06-2025
Accepted: 16-06-2025 Published: 30-06-2025

ABSTRACT

Background: Long-term corticosteroid-related complications result in steroid dependence in inflammatory bowel disease (IBD), which continues to be a significant challenge in its treatment. JAK inhibitors have also become a useful oral targeted agent in moderate-to-severe IBD providing quick onset of activity and may have steroid-sparing effects. **Objective:** To evaluate the efficacy and safety of JAK inhibitors in achieving steroid-free remission among patients with steroid-dependent IBD. **Methods:** This is a prospective observational cohort study that was carried out at Faisalabad Teaching Hospital, Faisalabad Medical University, between March 2024 and August 2024. A total of 86 adult patients with steroid-dependent ulcerative colitis or Crohn disease were included. Patients received standard-dose tofacitinib or upadacitinib and were followed at 8 and 24 weeks. The primary outcome was steroid-free clinical remission at 24 weeks. Mainly, steroid-free clinical remission was attained at 24 weeks. The secondary outcomes were clinical response, inflammatory markers reduction, steroid discontinuation rate, and safety profile. The SPSS version 26 was used to analyze the data, and $p \leq 0.05$ was considered significant. **Results:** At 24 weeks, JAK inhibitor therapy was associated with significant improvement in clinical and laboratory outcomes. Steroid-free remission and complete steroid discontinuation were achieved in a substantial proportion of patients, with parallel reductions in CRP and fecal calprotectin levels. Adverse events were mostly mild and manageable, and treatment discontinuation due to adverse events was uncommon. **Conclusion:** Tofacitinib and upadacitinib appear to be effective and reasonably safe steroid-sparing options in patients with steroid-dependent IBD. They demonstrated favorable remission outcomes with acceptable tolerability over 24 weeks.

INTRODUCTION

IBD, which includes ulcerative colitis and Crohn disease, is a relapsing and remitting chronic inflammatory gastrointestinal tract disease with immune-mediated pathogenesis. Although there are innovations in biologic treatment, corticosteroids are still popular in the induction of remission in moderate-severe disease. Nevertheless, there are several negative effects related to steroid therapy in the long-term perspective such as osteoporosis, metabolic imbalances, high blood pressure, diabetes, risk of infections, and adrenal suppression. Thus, steroid dependence, which is the inability to reduce corticosteroids without the recurrence of the disease, is a serious clinical issue in the treatment of IBD [1-3].

Therapeutic approaches in IBD have changed over the last ten years to steroid-sparing approaches. Biologic anti-tumor necrosis factor (TNF), integrin and interleukin pathway agents have enhanced the outcome but there are still limitations associated with primary non-response, secondary loss of response, immunogenicity, high cost and parenteral administration. Inhibitors of JAK are a new type of small-molecule or oral agents which regulate intracellular cytokine signaling pathways in the intestinal inflammation. These agents suppress the action of several pro-inflammatory cytokines by inhibiting JAK-STAT signaling and provide fast clinical response [4-6].

Recent studies have demonstrated the effectiveness of tofacitinib and upadacitinib in moderate-to-severe ulcerative colitis and selected patients with Crohn disease. But practical evidence to assess their particular contribution to steroid-dependent IBD, especially in the South Asian population, is scarce. Besides, scarce information about steroid-free remission rates and safety outcomes in local tertiary care settings are available [7-9]. Therefore, this study aimed to evaluate the efficacy and safety of tofacitinib and upadacitinib in achieving steroid-free remission among patients with steroid-dependent IBD at a tertiary care hospital in Faisalabad.

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METHODOLOGY

This is a prospective observational cohort study that was carried out at Faisalabad Teaching Hospital, Faisalabad Medical University (FMU), Faisalabad, and throughout six months between March 2024 and August 2024. The research was conducted with permission of Institutional Ethical Review Committee of Faisalabad Medical University. Informed consent was obtained in writing and informed consent was obtained by all participants before enrollment and the study followed the principles of the Declaration of Helsinki.

The sample size consisted of 86 patients who were diagnosed of steroid-dependent inflammatory bowel disease (IBD) by consecutive non-probability sampling. The dependence on steroids was characterized as the inability to taper corticosteroids under 10 mg/day prednisolone in three months of the treatment or recidivation of steroids in three months of discontinuation. The inclusion criteria included patients who have the confirmed cases of ulcerative colitis or Crohn disease aged between 18 and 65 years using both clinical, endoscopic, and histopathological methods. Patients in the active severe infections, any malignancy, thromboembolic disorder history, pregnant, uncontrolled cardiovascular disease, or intolerance to Janus kinase (JAK) inhibitors were excluded.

The baseline demographic data such as age, gender, duration, and type and extent of IBD, prior biologic exposure, and length of steroid use were collected. The Mayo score of ulcerative colitis and the Crohn's Disease Activity Index (CDAI) were the measures of disease activity. At baseline, laboratory parameters, such as C-reactive protein (CRP), fecal calprotectin, liver functions tests, and lipid profile were also received.

All eligible patients received JAK inhibitor therapy in the form of tofacitinib or upadacitinib according to routine clinical practice and the discretion of the treating gastroenterologist. The follow-up of patients was done at 8 weeks and 24 weeks. Tapering of steroids was done progressively and under clinical response. The main result was that the steroid-free clinical remission was achieved at the 24-week point. Secondary outcomes were clinical response, decreased inflammatory markers, mucosal healing, time to steroid withdrawal, and adverse events.

Data were entered and analyzed using SPSS version 26. Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Paired t-test was used to compare pre- and post-treatment laboratory parameters, and chi-square test was applied for comparison of categorical outcomes. A p-value ≤ 0.05 was considered statistically significant.

RESULTS

A total of 86 patients with steroid-dependent inflammatory bowel disease (IBD) were included in the study. The mean age of the patients was 38.6 ± 11.4 years. Ulcerative colitis was more frequent than Crohn's disease. Most patients presented with moderate-to-severe baseline disease activity, and more than half had previous biologic exposure, reflecting a relatively treatment-refractory population.

Table 1

Baseline Demographic and Disease Characteristics (n = 86)

Variable		Value
Mean Age (years)		38.6 ± 11.4
Male		47 (54.7%)
Female		39 (45.3%)
Type of IBD	Ulcerative Colitis	55 (64.0%)
	Crohn's Disease	31 (36.0%)
Mean Disease Duration (years)		6.2 ± 3.1
Prior Biologic Exposure		52 (60.5%)
Anti-TNF Failure		37 (43.0%)
Mean Duration of Steroid Use (months)		9.4 ± 2.8

Patients were predominantly diagnosed with ulcerative colitis, with a mean disease duration of 6.2 years. More than half of the patients had prior biologic exposure, reflecting a treatment-refractory population.

Table 2

Baseline Disease Activity and Laboratory Parameters (n=86)

Variable	Mean ± SD / n (%)
Baseline Mayo Score (UC, n = 55)	8.4 ± 1.2
Baseline CDAI (CD, n = 31)	312 ± 48
CRP (mg/L)	18.6 ± 6.3
Fecal Calprotectin (µg/g)	524 ± 118
Endoscopic Severe Disease	53 (61.6%)

Baseline assessment showed that most patients had moderate-to-severe disease activity, with elevated CRP and fecal calprotectin levels. Endoscopic severe disease was present in 61.6% of patients, indicating a high inflammatory burden at study entry.

Table 3

Treatment Characteristics of JAK Inhibitors (n = 86)

Variable	n (%)
Tofacitinib	55 (64.0%)
Upadacitinib	31 (36.0%)
Standard Induction Dose Used	86 (100%)
Concomitant Immunomodulator	29 (33.7%)
Mean Duration of Therapy (weeks)	24 ± 6

The most frequently used JAK inhibitor was tofacitinib, followed by upadacitinib. Standard induction dosing was used in all patients, while one-third received concomitant immunomodulator therapy.

Table 4

Clinical Outcomes and Steroid Withdrawal (n = 86)

Outcome	8 Weeks	24 Weeks	p-value
Clinical Response	68 (79.1%)	74 (86.0%)	0.041
Clinical Remission	45 (52.3%)	63 (73.3%)	0.008
Steroid-Free Remission	39 (45.3%)	58 (67.4%)	0.003
Complete Steroid Discontinuation	—	64 (74.4%)	—
Mean Time to Steroid Withdrawal (weeks)	—	10.2 ± 3.4	—

Clinical outcomes improved significantly over 24 weeks following treatment with JAK inhibitors. Clinical remission increased from 52.3% at 8 weeks to 73.3% at 24 weeks, while steroid-free remission rose from 45.3% to 67.4%. In addition, 74.4% of patients were able to discontinue

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corticosteroids completely by 24 weeks, with a mean withdrawal time of 10.2 ± 3.4 weeks.

Table 5
Laboratory Improvement and Safety Profile (n = 86)
A. *Laboratory Improvement*

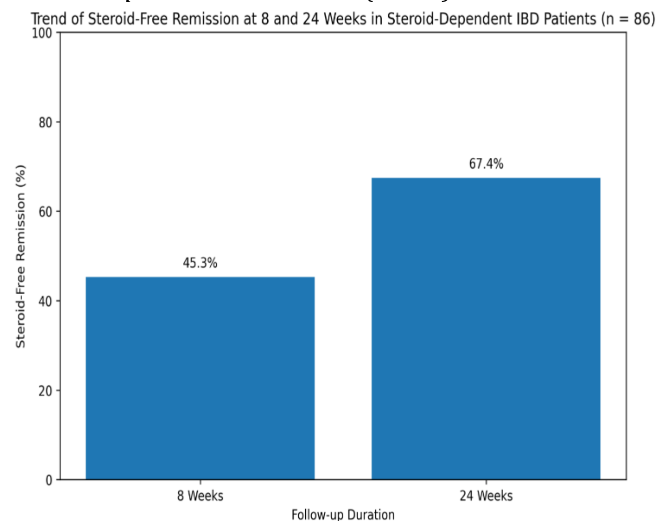
Parameter	Baseline	24 Weeks	p-value
CRP (mg/L)	18.6 ± 6.3	6.9 ± 3.2	<0.001
Fecal Calprotectin (µg/g)	524 ± 118	198 ± 72	<0.001

B. *Adverse Events*

Adverse Event	n (%)
Mild Infections	18 (20.9%)
Herpes Zoster	5 (5.8%)
Elevated Lipids	14 (16.3%)
Liver Enzyme Elevation	7 (8.1%)
Thromboembolic Events	1 (1.2%)
Discontinuation Due to Adverse Events	6 (7.0%)

Inflammatory biomarkers improved significantly by week 24, indicating a strong biochemical response to treatment. Adverse events were generally mild, and serious complications remained infrequent.

Figure 1
Trend of Steroid-Free Remission at 8 and 24 Weeks in Steroid-Dependent IBD Patients (n = 86)



The proportion of patients achieving steroid-free remission increased from 45.3% at 8 weeks **to** 67.4% at 24 weeks.

DISCUSSION

Steroid dependence remains a major therapeutic challenge in inflammatory bowel disease because prolonged corticosteroid exposure is associated with significant metabolic, infectious, and cardiovascular complications. In the present study, we evaluated the role of tofacitinib and upadacitinib in achieving steroid-free remission among patients with steroid-dependent IBD treated at a tertiary care hospital in Faisalabad. The findings indicate that these oral JAK inhibitors were associated with meaningful clinical improvement, successful steroid withdrawal, and acceptable short-term safety [10-12].

In the present cohort, steroid-free remission and complete steroid discontinuation were achieved in a substantial proportion of patients by 24 weeks. These findings are consistent with international evidence demonstrating the efficacy of tofacitinib and upadacitinib in moderate-to-severe IBD, particularly in patients who are refractory to conventional therapy or previously exposed to biologics [13-15]. The favorable outcomes in our study may also reflect careful patient selection, early monitoring, and close follow-up in a specialized tertiary care setting.

A significant reduction in CRP and fecal calprotectin was observed over the follow-up period, supporting the biological effectiveness of JAK inhibition. These agents rapidly suppress inflammatory signaling pathways by modulating intracellular cytokine transmission, which may explain both the early clinical response and the successful steroid taper observed in many patients [16-18]. Their oral route of administration and lack of immunogenicity also offer practical advantages over biologic therapies

The safety profile in the present study was generally acceptable. Most adverse events were mild, with infections and lipid abnormalities being the most commonly observed complications. Herpes zoster occurred in a small proportion of patients, which is in keeping with previously published safety data on JAK inhibitors. Only a few patients discontinued therapy due to adverse events, while serious complications such as thromboembolism were rare [19].

The ability to achieve steroid-free remission is clinically important because chronic steroid exposure is associated with osteoporosis, diabetes, adrenal suppression, hypertension, and increased infection risk. Our findings therefore support the steroid-sparing value of tofacitinib and upadacitinib in routine clinical practice, especially in patients with difficult-to-treat disease and prior biologic exposure. [20].

However, this study has several limitations. It was conducted at a single center and had a relatively small sample size and short follow-up duration of 24 weeks. Long-term remission, endoscopic healing, and long-term safety outcomes could not be fully assessed. In addition, the absence of a comparative biologic arm limits direct comparison of efficacy. Larger multicenter studies with longer follow-up are needed to better define sustained remission, relapse patterns, and long-term cardiovascular and thromboembolic safety.

CONCLUSION

Tofacitinib and upadacitinib demonstrated significant efficacy in achieving steroid-free remission in patients with steroid-dependent inflammatory bowel disease. A substantial proportion of patients were able to discontinue corticosteroids within 24 weeks, accompanied by marked improvement in clinical status and inflammatory biomarkers. The safety profile was acceptable, with predominantly mild adverse events.

These findings support the role of tofacitinib and upadacitinib as effective steroid-sparing therapeutic options in moderate-to-severe IBD, particularly in patients with prior biologic exposure. Further multicenter studies with longer follow-up are recommended to confirm sustained remission and better evaluate long-term safety.

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