ORIGINAL ARTICLE

INTESTINAL RESEARCH

pISSN 1598-9100 • eISSN 2288-1956
https://doi.org/10.5217/ir.2024.00148
Intest Res 2025;23(4):464-474

Propensity score-matched real-world comparative treatment outcomes of Janus kinase inhibitors for ulcerative colitis in patients with and without prior exposure to anti-tumor necrosis factor α antibody

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Background/Aims: Tofacitinib (TFB), filgotinib (FIL), and upadacitinib (UPA) are Janus kinase (JAK) inhibitors approved for moderate-to-severe ulcerative colitis (UC). The appropriate positioning of each JAK inhibitor in the treatment algorithm, however, is unclear. Furthermore, real-world efficacy of JAK inhibitors for patients with UC and prior anti-tumor necrosis factor α antibody (aTNF) treatment are not fully investigated. We compared the efficacy and safety of 3 JAK inhibitors in patients with UC, considering their prior aTNF exposure. **Methods:** A retrospective study was conducted in patients with UC who started TFB, FIL, or UPA at 2 academic centers. This propensity score-matched cohort study assessed the effectiveness of the 3 JAK inhibitors for UC in patients with and without prior aTNF exposure, comparing steroid-free clinical remission and response rates after 8 weeks. **Results:** Among 274 patients who met the inclusion criteria, 145 experienced aTNF exposure (TFB: 59.2%, 100/169; FIL: 34.5%, 20/58; UPA: 53.2%, 25/47). Based on propensity score-matching, UPA led to a higher steroid-free clinical remission rates than TFB (adjusted odds ratio [aOR], 5.57; 95% confidence interval [CI], 1.42–21.90) or FIL (aOR, 9.00; 95% CI, 1.42–57.10) in patients exposed to aTNF. Steroid-free clinical remission and clinical response rates did not differ significantly between each group in patients non-exposed to aTNF. The incidence of adverse events was slightly higher with UPA than TFB or FIL. **Conclusions:** UPA may be more effective for UC than TFB or FIL, especially in patients with previous aTNF exposure, although consideration should be given to adverse events. **(Intest Res 2025;23:464-474)**

Key Words: Ulcerative colitis; Janus kinase; Upadacitinib; Filgotinib; Tofacitinib

INTRODUCTION

Ulcerative colitis (UC) leads to chronic relapsing and refractory inflammation of the entire colon. Medical treatment of UC has markedly advanced since the introduction of anti-tumor necrosis factor α antibody (aTNF) in the early 2000s and now includes a variety of drugs with different mechanisms of action, such as aTNF, anti-interleukin-12/23 antibodies, anti-α4β7 integrin antibody, and Janus kinase (JAK) inhibitors. Although these drugs have broadened the treatment options for patients, their therapeutic efficacy is limited,[1-8] thereby complicating the selection of the appropriate drug in real-world clinical practice.

JAK inhibitors are orally administered small molecule compounds used to treat various immunological diseases, such as

Received September 22, 2024. **Revised** November 18, 2024.
Accepted November 20, 2024.
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https://doi.org/10.5217/ir.2024.00148 • Intest Res 2025;23(4):464-474

rheumatoid arthritis and psoriasis.[9,10] For UC, tofacitinib (TFB) entered clinical use in 2018, followed by filgotinib (FIL) and upadacitinib (UPA), all of which demonstrated significant clinical improvement compared with placebo in phase III trials.[6-8] Each drug has a slightly different selectivity for JAK1 and JAK3.[11] Direct comparisons of their efficacy and safety in real-world clinical practice are available,[12-14] but a detailed analysis of the 3 JAK inhibitors, including FIL, has not yet been fully explored. In addition, the real-world efficacy of JAK inhibitors for patients with/without prior aTNF exposure is unclear. Patients failing first-line aTNF treatment are at increased risk for treatment failure to second-line biologics.[15,16] Direct real-world comparisons of the efficacy of second-line JAK inhibitors, however, have not yet been reported. This study compared the efficacy and safety of 3 JAK inhibitors in a real-world setting using propensity score (PS) matching, focusing on patients with UC and considering their prior exposure to aTNF.

METHODS

1. Ethical Considerations

This study was approved by the Hyogo Medical University Institutional Ethics Review Board (approval number: 4263) and ethical approval was also obtained from Kitasato University Kitasato Institute Hospital. The study was conducted according to the tenets of the Declaration of Helsinki. Because of the retrospective nature of the study, the requirement for written informed consent was waived and the use of an opt-out consent approach was approved by the ethics review board.

2. Study Design and Participant Selection

This study was a retrospective observational study of adult patients with moderate-to-severe UC treated with TFB, FIL, or UPA between May 2018 (TFB approval date) and February 2024 at 2 territory specialist centers in Japan that included both university and non-university hospitals. Inclusion criteria for this study were patients ≥18 years of age with a confirmed diagnosis of UC based on clinical assessments, endoscopy, and histology,[17] UC disease activity at the start of treatment (partial Mayo score [PMS] ≥3),[18] and 8-week follow-up after the start of treatment. Patients previously treated with other JAK inhibitors, poor treatment compliance, and taking immunosuppressive drugs other than prednisolone and immunomodulator were excluded. Patients treated with TFB received 10 mg twice a day, patients treated with FIL received 200 mg/day, and those treated with UPA received 45 mg/day for 8 weeks of remission induction.

3. Data Collection

At inclusion, the following characteristics were collected from each participant for daily clinical practice records: age, sex, disease duration, disease location, disease activity, laboratory data (serum C-reactive protein [CRP], white blood cell count, serum albumin), concomitant use of steroid, and previous treatment with biologics (infliximab, adalimumab, golimumab, ustekinumab, mirikizumab, vedolizumab). All adverse events were collected and categorized using terms from the U.S. Food and Drug Administration.[19] Worsening of UC was not included as an adverse event.

4. Outcomes and Definition

The primary outcome was the rates of steroid-free clinical remission and clinical response after 8 weeks (±2 weeks) of treatment with JAK inhibitors (TFB, FIL, or UPA) in patients with UC and a history of aTNF exposure. Secondary outcomes included steroid-free clinical remission and clinical response rates after 8 weeks of treatment with JAK inhibitors in all participants and steroid-free clinical remission and clinical response rates after 8 weeks of treatment with JAK inhibitors in patients with UC and no history of aTNF exposure. The steroid-free clinical remission and clinical response rates after 8 weeks of treatment with a JAK inhibitor in older UC patients (≥65 years) and the adverse events of each drug were also evaluated. Clinical remission was defined as PMS ≤2 and a rectal bleeding subscore of 0. Clinical response was defined as a decrease of ≥3 points or ≥30% from the baseline PMS at the start of treatment, and a decreased rectal bleeding subscore of ≥1 point or a score of 0 or 1.[2,20] A primary non-response to aTNF was defined as an inadequate response and failure to achieve clinical improvement, while a secondary non-response to aTNF was defined as initial clinical improvement but failure to maintain clinical improvement during the course of treatment.

5. Statistical Analysis

Categorical variables are expressed as proportions and were compared using Fisher exact test or the chi-square test. Ordinal variables were compared using the Kruskal-Wallis test. Mean values were compared by one-way analysis of variance analysis in the case of a normal distribution and the Kruskal-Wallis test in the case of a non-normal distribution. The steroid-free clinical remission and clinical improvement rates after 8 weeks of treatment with TFB, FIL, or UPA were com-

Table 1. Characteristics of Study Population

Characteristic	Tofacitinib (n = 169)	Filgotinib (n = 58)	Upadacitinib (n = 47)	*P*-value
Male sex	108 (63.9)	35 (60.3)	33 (70.2)	0.571
Age (yr)	40 ± 15	42 ± 15	40 ± 16	0.603
Disease duration (yr)	6.7 ± 7.5	8.0 ± 8.0	7.0 ± 7.6	0.554
Disease location				0.591
Proctitis	2 (1.2)	3 (5.2)	1 (2.1)	
Left-sided colitis	35 (20.7)	6 (10.3)	7 (14.9)	
Extensive colitis/pancolitis	132 (78.1)	49 (84.5)	39 (83.0)	
Response to 5-ASA/steroid				
5-ASA intolerance	37 (21.9)	4 (6.9)	8 (17.0)	0.036
Steroid refractory	69 (40.8)	9 (15.5)	23 (48.9)	< 0.001
Steroid dependent	82 (48.5)	22 (37.9)	18 (38.3)	
Baseline corticosteroid use	35 (20.7)	9 (15.5)	8 (17.0)	0.571
No. of previous biologic agents				0.417
0	61 (36.1)	27 (46.6)	13 (27.7)	
1	66 (39.1)	12 (20.7)	19 (40.4)	
≥ 2	42 (24.9)	19 (32.8)	15 (31.9)	
Previous aTNF treatment	100 (59.2)	20 (34.5)	25 (53.2)	0.005
No. of aTNF treatment				0.024
1	76 (45.0)	17 (29.3)	22 (46.8)	
≥ 2	24 (14.2)	3 (5.2)	3 (6.4)	
Disease activity				
PMS	5.8 ± 1.7	4.9 ± 1.8	6.3 ± 1.6	< 0.001
Albumin (g/L)	4.0 ± 2.2	4.0 ± 0.5	3.6 ± 0.7	0.422
CRP (mg/L)	10.1 ± 15.5	5.0 ± 7.6	23.0 ± 36.2	< 0.001

Values are presented as number (%) or mean ± standard deviation.
5-ASA, 5-amion salicylic acid; aTNF, anti-tumor necrosis factor α antibody; PMS, partial Mayo score; CRP, C-reactive protein.

pared between the 2 groups using logistic regression analysis, respectively. We used 1:1 PS matching to adjust for baseline confounders of treatment in each treatment group with a caliper of 0.2 standard deviations of the logit of the PS. PS were generated using multivariate logistic regression with covariates for the variables potentially affecting treatment: sex, age, disease duration, baseline corticosteroid use, serum albumin, serum CRP, and PMS. PS analyses were performed in 2 groups each. After matching, adjusted odds ratios (aOR) and 95% confidence intervals (CI) were calculated for steroid-free clinical remission and clinical response rates after 8 weeks of treatment in each of the 2 groups. EZR (version 1.67, Saitama Medical Center, Jichi Medical University, Saitama, Japan) was used for all analyses and a two-sided *P*-value < 0.05 was considered to indicate a significant difference.

RESULTS

1. Participants

The baseline characteristics of the participants are shown in Table 1. We enrolled 381 patients with moderate-to-severe UC who received JAK inhibitors (196 patients in the TFB group, 94 in the FIL group, and 91 in the UPA group) (Fig. 1). Among the 381 patients, (1) 14 were < 18 years of age, (2) 33 had disease activity not meeting the criteria at the start of treatment, (3) 2 were unable to be followed for the 8-week treatment course (1 transfer, 1 self-interruption), (4) 1 demonstrated poor compliance with oral medication, (5) 3 had missing laboratory data, (6) 54 were previously treated with other JAK inhibitors. Finally, a total of 274 patients comprising 169 patients in the TFB group, 58 patients in the FIL group, and 47 patients in the UPA group were included in the present study (Fig. 1).

https://doi.org/10.5217/ir.2024.00148 • Intest Res 2025;23(4):464-474

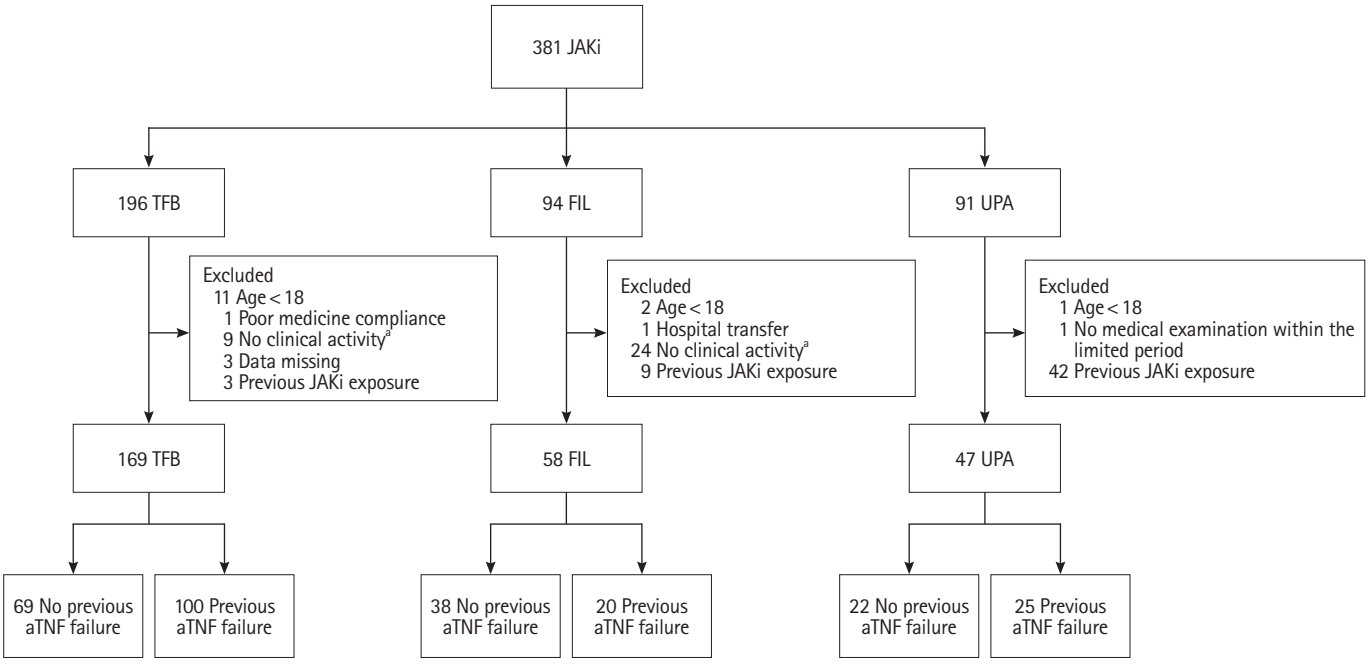

Fig. 1. Flowchart of group identification of patients treated with tofacitinib (TFB), filgotinib (FIL), and upadacitinib (UPA). [a]No clinical activity was defined as a partial Mayo score ≤2. JAKi, Janus kinase inhibitors; aTNF, anti-tumor necrosis factor α antibody.

The number of patients previously treated with aTNF was 100 in the TFB group, 20 in the FIL group, and 25 in the UPA group. The 3 groups did not differ significantly in terms of age, sex, duration of disease, extent of disease, rates of concomitant steroid use at the start of treatment, or number of previous biologic agents. The proportion of patients treated with aTNF was significantly lower in the FIL group (34.5%, 20/58) than in the TFB group (59.2%, 100/169) or the UPA group (53.2%, 25/47, $P=0.005$). PMS was significantly lower in the FIL group than in the other 2 groups (TFB vs. FIL vs. UPA: 5.8±1.7 vs. 4.9±1.8 vs. 6.3±1.6, $P<0.001$). The serum CRP level was also lower in the FIL group than in the other 2 groups (TFB vs. FIL vs. UPA: 10.1±15.5 mg/L vs. 5.0±7.6 mg/L vs. 23.0±36.2 mg/L, $P<0.001$) (Table 1).

2. Overall Effectiveness Outcomes

The overall steroid-free clinical remission rates after 8 weeks of treatment did not differ significantly between the 2 groups (TFB vs. FIL vs. UPA: 44.4% vs. 41.4% vs. 55.3%) (Fig. 2). Similarly, the overall clinical response rates did not differ significantly between the 2 groups after 8 weeks of treatment (TFB vs. FIL vs. UPA: 66.3% vs. 60.3% vs. 70.2%) (Fig. 2). The 2 groups were then compared after PS matching using sex, age, disease duration, baseline corticosteroid use, serum albumin, serum CRP, and PMS as covariates to adjust for baseline confounding

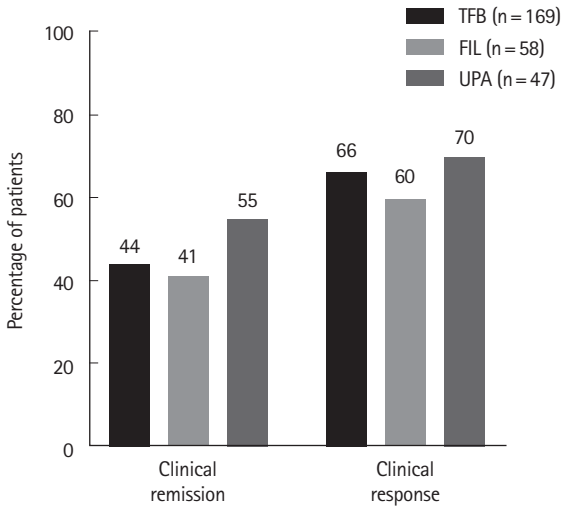

Fig. 2. Steroid-free clinical remission and clinical response rates at week 8 in patients with ulcerative colitis treated with tofacitinib (TFB), filgotinib (FIL), and upadacitinib (UPA). Clinical remission was defined as partial Mayo score (PMS) ≤2 and a rectal bleeding subscore of 0. Clinical response was defined as a decrease ≥3 points or ≥30% from the baseline PMS at the start of treatment.

factors. No difference was detected between the FIL and TFB groups or between the UPA and TFB groups in terms of steroid-free clinical remission or clinical response (Fig. 3, Supplementary Tables 1 and 2). The UPA group had higher steroid-

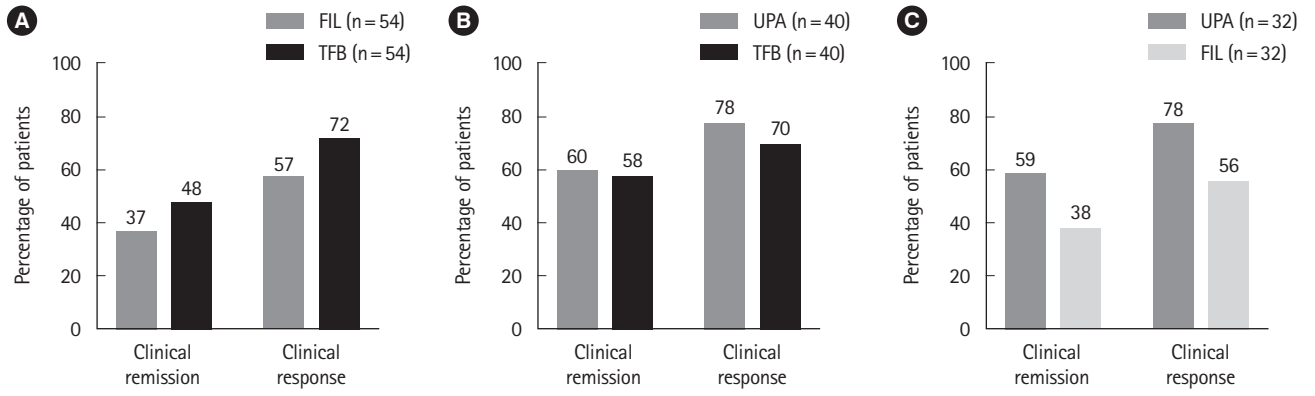

Fig. 3. Steroid-free clinical remission rates and clinical response rats after 8 weeks of treatment with tofacitinib (TFB), filgotinib (FIL), and upadacitinib (UPA) between 2 groups, respectively in total population after propensity score analysis. (A) FIL and TFB. (B) UPA and TFB. (C) IPA and FIL.

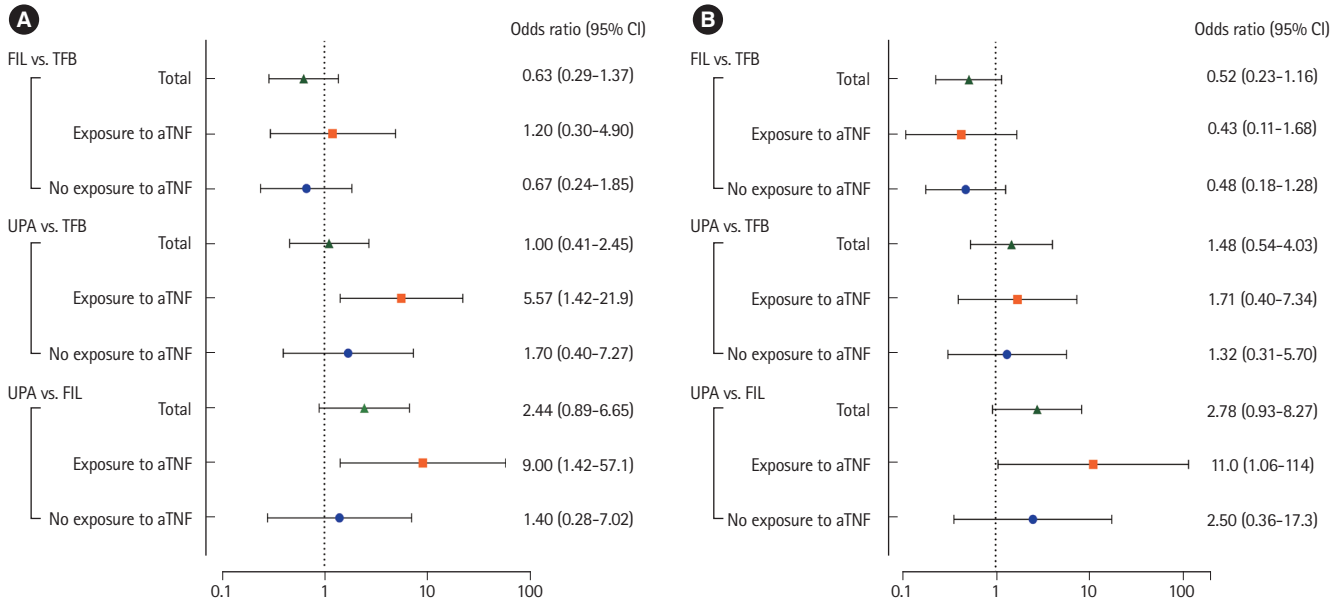

Fig. 4. Forest plot depicting effectiveness. (A) Steroid-free clinical remission and (B) clinical response in TFB, FIL, and UPA groups (total, exposure to aTNF, no exposure to aTNF) at week 8 expressed adjusted odds ratio with 95% confidence interval (CI) after one-to-one propensity score matching. TFB, tofacitinib; FIL, filgotinib; UPA, upadacitinib; aTNF, anti-tumor necrosis factor α antibody.

free clinical remission and response rates than the FIL group (Fig. 3, Supplementary Table 3).

In older patients with UC, the overall steroid-free clinical remission rates after 8 weeks of treatment did not significantly differ between the 2 groups (TFB vs. FIL vs. UPA: 42.8% [6/14] vs. 50.0% [3/6] vs. 83.3% [5/6]) (Supplementary Fig. 1).

3. Effectiveness in Patients with/without a History of aTNF Exposure

We next compared the steroid-free clinical remission and response rates after 8 weeks of treatment in each of the 2 groups, using PS matching as described above, according to whether the patients had prior aTNF exposure. When the rates of the 2 groups were compared with respect to previous aTNF exposure, no differences were detected (Fig. 4). After 8 weeks of treatment in patients with a history of aTNF exposure, the primary outcome of the study, the UPA group had a significantly higher steroid-free clinical remission rates than the TFB group (UPA vs. TFB, 65.0% vs. 25.0%: aOR, 5.57; 95% CI, 1.42–21.90; $P=0.01$), and the FIL group (UPA vs. FIL, 75.0% vs. 25.0%: aOR, 9.00; 95% CI, 1.42–57.10; $P=0.02$) (Figs. 4 and 5). Steroid-free clinical remission and response rates did not differ significant-

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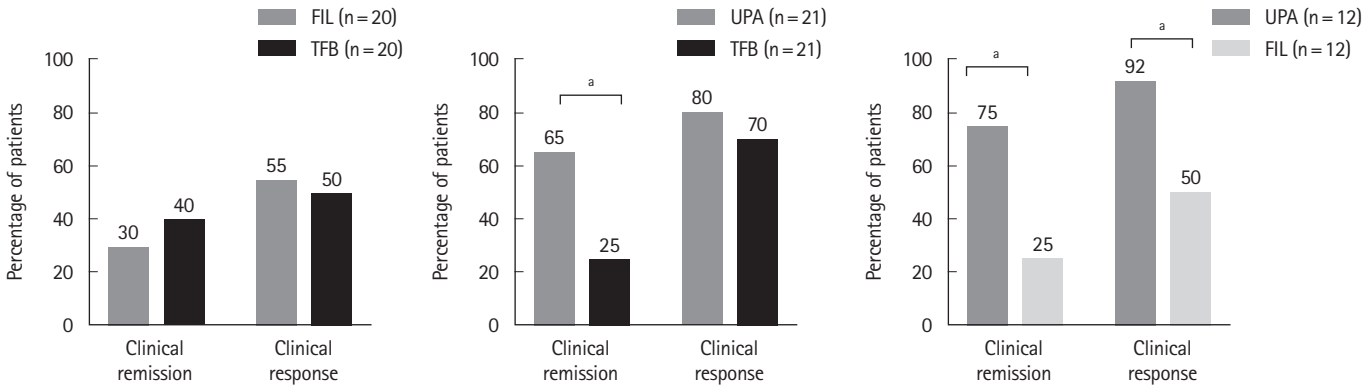

Fig. 5. Comparison of steroid-free clinical remission and clinical response rates at week 8 between each pair of drugs among 3 Janus kinase inhibitor groups with exposure to anti-tumor necrosis factor α antibody after one-to-one propensity score matching. [a]$P<0.05$. TFB, tofacitinib; FIL, filgotinib; UPA, upadacitinib.

Table 2. Safety Data of Tofacitinib, Filgotinib, and Upadacitinib in Total Ulcerative Colitis Patients

Variable	Tofacitinib (n = 169)	Filgotinib (n = 58)	Upadacitinib (n = 47)
Adverse event	27 (16.0)	8 (14.0)	17 (36.0)
Pyrexia	8 (4.7)	0	4 (8.5)
Opportunistic infection	10 (5.9)	2 (3.4)	5 (10.6)
Nasopharyngitis	8 (4.7)	0	3 (6.4)
COVID-19 infection	1 (0.6)	2 (3.4)	1 (2.2)
Pneumonia	1 (0.6)	0	0
Catheter infection	0	0	1 (2.2)
Serious infection	0	0	0
HZ	1 (0.6)	2 (3.4)	0
DVT/PE	0	0	0
Pericarditis	0	0	1 (2.2)
Cold sore	1 (0.6)	0	1 (2.2)
Acne	2 (1.1)	0	2 (4.2)
Stomatitis	1 (0.6)	0	1 (2.2)
Headache	3 (1.8)	0	1 (2.2)
Leukopenia (< 3,000/μL)	2 (1.2)	1 (1.7)	2 (4.2)
Elevated liver enzymes	0	1 (1.7)	0
Serious adverse event	0	0	0
Adverse event leading to discontinuation	8 (4.7)	3 (5.2)	5 (10.6)

Values are presented as number (%).
COVID-19, coronavirus disease 2019; HZ, herpes zoster; DVT, venous thromboembolism; PE, pulmonary embolism.

ly between the TFB and FIL groups (Figs. 4 and 5). Among patients with aTNF failure status, the effectiveness of the 3 JAK inhibitors was slightly higher in the secondary non-response group than in the primary non-response group (Supplementary Fig. 2).

4. Adverse Events

Safety data were collected in patients with UC treated with TFB, FIL, or UPA during the first 8 weeks of treatment. Table 2 shows the overall adverse events for each drug. Overall adverse events were 16%, 14%, and 36% in the TFB, FIL, and UPA groups, respectively. Treatment was discontinued due to ad-

verse events in 5% of patients in the TFB group, 5% in the FIL group, and 11% in the UPA group, with suspected pyrexia being the main cause of discontinuation other than UC disease progression (Table 2). In the TFB group, 21.4% of older patients (n = 14) experienced adverse events. There were no adverse events in the FIL (n = 6) or UPA (n = 6) groups.

DISCUSSION

Three JAK inhibitors, TFB, FIL, and UPA, are commercially available for moderate-to-severe UC in 2024. This study is the first to compare the outcomes of the 3 JAK inhibitors by PS matching according to prior aTNF exposure. Our findings revealed that UPA had a higher steroid-free clinical remission rates than TFB and FIL in the population with previous aTNF exposure and was more effective than FIL in the total population. The incidence of adverse events was also slightly higher for UPA compared with TFB and FIL.

TFB mainly inhibits JAK1 and JAK3, while FIL and UPA mainly inhibit JAK1.[11] Although there are some real-world reports for each drug, no direct comparisons of the outcomes of these 3 drugs have been published. In many countries, the use of JAK inhibitors is approved only for patients with prior exposure to aTNF; therefore, JAK inhibitors are used mostly in patients previously treated with aTNF. In recent years, however, the range of available advanced therapies has expanded and JAK inhibitors are increasingly being introduced in patients without prior aTNF exposure.

The number of reports on the effectiveness of treatment with a new JAK inhibitor in patients previously treated with other JAK inhibitors is limited. Friedberg et al.[21] reported that all patients previously treated with TFB achieved clinical remission with UPA after 8 weeks and Boneschansker et al.[12] reported that UPA led to a high clinical response in patients previously treated with TFB. For comparing the outcomes of the 3 JAK inhibitors in the present study, patients previously treated with a JAK inhibitor were excluded from this study, given the possibility that earlier treatment with other JAK inhibitors might affect the outcome of the new JAK inhibitor.

We demonstrated that the UPA group had a significantly higher steroid-free clinical remission rates than the FIL group in the overall patient population after PS matching. The UPA group also tended to have a higher steroid-free clinical remission rates than the TFB group, but the difference was not statistically significant. In the U-ACHIEVE induction trial, 26.0% and 72.6% of patients receiving UPA achieved clinical remission and clinical response, respectively, at 8 weeks.[8] In the SELECTION trial, 18.2% and 59.1% of the patients receiving FIL achieved clinical remission and clinical response, respectively, at 10 weeks,[7] and in the OCTAVE Induction 1 trial, 18.5% and 59.9% of the patients receiving TFB achieved clinical remission and clinical response, respectively, at 8 weeks.[6] Interestingly, a few studies have reported that UPA is more effective than TFB in the treatment of patients with UC.[13,14] Although above trials differed respect to patient background, observation period, and definition of clinical remission and response, UPA tended to show slightly higher treatment effectiveness than TFB and FIL. Of note, in the present study we excluded the patients who had a history of prior treatment with JAK inhibitors, resulting in more precise comparison of efficacy among JAK inhibitors in the treatment of UC. Moreover, we exactly assessed pre-treatment disease activity and outcome by using PMS, bringing reliable data to compare the efficacy of JAK inhibitors in the treatment of UC. Therefore, our obtained data that UPA tends to be effective than TFB or FIL, which is compatible with previous studies,[13,14,22] may be reliable.

We also revealed that the UPA group had a significantly higher steroid-free clinical remission rates than the TFB and FIL groups in patients with UC and prior aTNF exposure but not in patients with UC and no prior aTNF exposure. Burr et al.[23] examined the relative efficacy of biologic therapies and small molecules in network analysis and showed that UPA ranked first for clinical remission both in patients naïve to aTNF and in those previously exposed to aTNF. In patients previously exposed to aTNF, TFB had the second highest rates of clinical remission compared with placebo,[24] while FIL showed no significant difference compared with placebo.[7] Lu et al.[24] reported that FIL had a similar effect on efficacy as TFB among both biologic-naïve and biologic-experienced cohorts, similar to our result. Traves et al.[11] indicated that UPA (30 mg once daily) had a significantly greater inhibitory effect on the JAK1-dependent pathway than FIL (200 mg once daily). These results suggest that UPA potentially achieves higher clinical effectiveness, especially in an aTNF-exposed cohort. In the United States, JAK inhibitors are recommended to use for moderate-to-severe UC patients who have had an inadequate response or intolerance to aTNFs,[25] whereas strict strategy have not been determined in the use of JAK inhibitors for the treatment of UC in Asian countries. Our present study should be noteworthy since UPA is suggested to be more effective rather than TFB or FIL in UC patients with previous aTNF exposure in Japan as well as Western countries.

https://doi.org/10.5217/ir.2024.00148 • Intest Res 2025;23(4):464-474

On the other hand, it should be noted that all JAK inhibitors are equally effective in cases without aTNF exposure. Our background data before PS matching showed that FIL was used for patients with relatively mild activity, indicating that FIL is preferably prescribed for patients with milder disease in clinical practice. Akiyama et al.[26] showed from their real-world data that it is preferable to start FIL in cases with milder disease activity after failure of the first biologic therapy. Gros et al.[27] also showed low albumin (<3.6 mg/dL) was associated with lower FIL persistence.

Safety issues should be considered in drug selection. In our study, FIL was likely to have fewer adverse events, such as infections, compared with TFB and FIL. FIL has a higher selectivity for JAK1-dependent signaling pathways compared with TFB and UPA and the lowest inhibitory activity of JAK2-dependent and JAK3-dependent signaling pathways. Traves et al.[11] suggested that these differences in JAK pathway inhibitory effects might provide a mechanistic rationale for their safety profiles.

Saruta et al.[28] assessed the cost-effectiveness of all biologics and small molecule therapies for patients with moderate-to-severe UC in biologic failure and biologic-experienced populations. UPA was considered a cost-effective option based on its lower cost to achieve clinical remission in bio-experienced populations and its ability to achieve a clinical response in both bio-naïve and bio-experienced populations. FIL had a lower cost per clinical remission than TFB and UPA in a bio-naïve population. Although the effectiveness of the 3 drugs did not differ significantly in the bio-naïve population after PS matching, these results indicate that FIL may provide good effectiveness for patients with milder clinical disease activity, UPA may have a stronger effect even for aTNF-experienced patients, and TFB can be used in active patients in a balanced manner.

The prevalence of UC in older patients is increasing in Asia.[29-31] The use of JAK inhibitors might be beneficial in those patients but the safety and efficacy of JAK inhibitors in patients with older age-onset UC remains unclear. JAK inhibitors are primarily metabolized by the liver or kidneys,[32] and the functions of these organs are frequently impaired in older patients. Thus, disturbed metabolization of JAK inhibitors might be more likely in patients with older age-onset UC, which could increase the risk of adverse events in those patients. In addition, JAK inhibitors increase the risk of various infections, including herpes zoster,[33-35] suggesting that older patients with suppressed immunity taking JAK inhibitors could be at higher risk of infection. Moreover, JAK inhibitors, compared with aTNF, are associated with a higher risk of major cardiac events and venous thromboembolism in older patients.[36] Together, these findings emphasize the importance of caution regarding treatment with JAK inhibitors, as sufficient safety data are lacking and the efficacy of JAK inhibitors in older patients with UC is unclear. In this context, the present study demonstrated that treatment outcomes with each JAK inhibitor were similar between patients ≥65 years of age and those <65 years of age; severe adverse events were not observed in older patients. Thus, careful administration of JAK inhibitors in older patients with UC may be permissible when other effective treatment options are lacking.

The strength of the present study is that it directly compared the outcomes of treatment with 3 JAK inhibitors under conditions that reduced differences in the patient background by using PS matching. Differences in efficacy according to the presence or absence of prior aTNF exposure were also demonstrated using PS matching. This study has some limitations. First, this study was a retrospective design involving a relatively small number of patients, especially FIL and UPA, because these were approved for the treatment of UC in Japan within the last 2 years. Furthermore, in order to compare the effectiveness among JAK inhibitors more precisely, we excluded the patients who had a history of prior treatment with JAK inhibitors and moreover, conducted PS matching to adjust for baseline confounders. Although biases based on the study design cannot be eliminated, we believe that definite enrolment was advantageous to obtain more reliable data. Second, this study lacked the data of endoscopic examination and biomarkers before and after treatment. Third, long-term outcomes were not investigated because of the short period of time since FIL and UPA were approved.

In conclusion, UPA may be the most effective JAK inhibitor, especially for patients with UC and prior aTNF exposure, but the potential for adverse events must be considered.

ADDITIONAL INFORMATION

Funding Source

The authors received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest

Shinzaki S has received advisor fees from Abbvie GK, Janssen Pharmaceutical, Takeda Pharmaceutical, and honoraria from

Abbvie GK, Alfressa Pharma, Astra Zeneka, EA Pharma, Eisai, Gilead Sciences, Kissei Pharmaceutical, Kyorin Pharmaceutical, Janssen Pharmaceutical, JIMRO, Mitsubishi-Tanabe Pharma, Mochida Pharmaceutical, Nippon Kayaku, Pfizer, Sekisui Medical, Takeda Pharmaceutical, Zeria Pharmaceutical. Kobayashi T has received advisor fees from AbbVie, Activaid, Alfresa Pharma, Alimentiv, Bristol Myers Squibb, Celltrion, Covidien, EA Pharma, Eli Lilly Japan K.K., Ferring Pharmaceuticals, Galapagos, Gilead Sciences, Janssen Pharmaceuticals, JIMRO, Kissei Pharmaceutical, Kyorin Pharmaceutical, Mitsubishi-Tanabe Pharma, Mochida Pharmaceutical, Nippon Kayaku, Pfizer, Takeda, and Zeria Pharmaceutical. The other authors have no conflicts of interest to declare.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

Conceptualization: Ikenouchi M, Fukui H, Kobayashi T, Shinzaki S. Data curation: Ikenouchi M, Nogami A. Formal analysis: Ikenouchi M. Methodology: Ikenouchi M, Fukui H, Yagi S, Kaku K, Sato T, Kawai M, Kamikozuru K, Yokoyama Y, Takagawa T, Tomita T, Kobayashi T, Shinzaki S. Project administration: Shinzaki S. Writing – original draft: Ikenouchi M, Fukui H, Shinzaki S. Writing - review & editing: Yagi S, Nogami A, Kaku K, Sato T, Kawai M, Kamikozuru K, Yokoyama Y, Takagawa T, Tomita T, Kobayashi T. Approval of final manuscript: all authors.

Additional Contributions

We thank Dr. Masataka Igeta (Department of Biostatics, Hyogo Medical University, Hyogo, Japan) for providing statistical support.

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Supplementary Material

Supplementary materials are available at the Intestinal Research website (https://www.irjournal.org).

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