*Abstract* / Povzetek predavanja

# JAK after JAK – nonsense or reality

Jurij Hanžel[1,2]
[1]*Department of Gastroenterology, University Medical Centre Ljubljana, Slovenia*
[2]*Medical Faculty, University of Ljubljana, Slovenia*

Correspondence: jurij.hanzel@kclj.si
Slovenian journal of gastroenterology / Gastroenterolog 2025; supplement 2: 27–28

***Keywords**: filgotinib, tofacitinib, upadacitinib, ulcerative colitis*

Janus kinase (JAK) inhibitors are an attractive oral drug class, which is highly efficacious for the treatment of ulcerative colitis (UC). Three agents, filgotinib, tofacitinib, and upadacitinib are available with variable affinities for different JAK receptor types and arguably different efficacy and safety profiles. Since the days of the tumour necrosis factor antagonist monopoly, clinicians have not faced the dilemma whether to cycle or switch – should loss of response or an adverse event prompt switching to an entirely different drug class or is choosing a different JAK inhibitor equally effective?

Rheumatologists have a longer history of using JAK inhibitors and have meticulously curated registry data. Seventeen national registries were pooled to perform a cohort study of 2000 patients who discontinued a JAK inhibitor (1). Roughly 20% (365/2000) cycled to a different JAK inhibitor, whereas the remainder (1635/2000) switched to a different drug class. In this study, both strategies were similarly effective, with a slightly higher retention rate when cycling JAK inhibitors. When the first JAK inhibitor was discontinued due to an adverse event, it was more likely that the second treatment would also be stopped due to an adverse event among cyclers, but not among switchers. (2, 3)

These data in conjunction with clinical need have prompted similar practices in UC (2–4). The three available cohort studies demonstrated a consistent rate of symptomatic remission after induction of approximately 50% (Table 1). These findings are also corroborated by biochemical and endoscopic outcomes, albeit with a higher percentage of missing data, given the real-world setting of these studies. Numerous interesting observations have emerged from these studies, although they all merit further exploration in prospective studies, as the retrospective non-randomized design potentially undermines the robustness of findings from these cohort studies. Overall, upadacitinib could perhaps be more effective than filgotinib as the second JAK inhibitor (2, 4). Higher symptomatic burden and the use of corticosteroids upon initiation of the second JAK inhibitor were both associated with a lower likelihood of symptomatic remission after induction (2, 4). Primary non-response to a JAK inhibitor was associated with lower persistence in one of the studies (4). Reassuringly, no new or particularly concerning safety signals emerged.

In summary, cycling to a second JAK inhibitor after failure of the first JAK inhibitor appears to be an effective and safe therapeutic option. Future prospective studies will help shape evidence-based sequencing of JAK inhibitors in UC.

*Table 1. An overview of dedicated cohort studies evaluating the effectiveness and safety of a second Janus kinase inhibitor in ulcerative colitis. Results shown using non-responder imputation, survival estimates using the Kaplan-Meier method. Abbreviations: FILGO – filgotinib, TOFA – tofacitinib, UPA – upadacitinib.*

| Study | Population | Main results | Notes |
|---|---|---|---|
| Osty et al. 2025 (2) | 169 (UPA 105, FILGO 54, TOFA 10) | Steroid-free clinical remission at weeks 8-14: 47.9% (81/169)<br>Treatment persistence at 6 months: 64% | Steroids at baseline decreased the likelihood of success.<br>Upadacitinib possibly most effective as second drug (imbalance!) |
| Radia et al. 2025 (3) | 131 (UPA 111, FILGO 20) | Clinical remission at week 8: 48.9% (64/131)<br>Clinical remission at week 24: 31.3% (41/131)<br>Biochemical remission at week 8: 35.9% (47/131)<br>Biochemical remission at week 24: 26.0% (24/131)<br>Treatment persistence at week 24: 84% | No statistically significant differences observed between UPA and FILGO. |
| Innocenti et al. 2025 (4) | 243 (UPA 212, FILGO 24, 7) | Steroid-free clinical remission at week 12: 48% (116/243)<br>Steroid-free clinical remission at week 26: 49% (120/243)<br>Steroid-free clinical remission at week 52: 28% (69/243)<br>Biochemical remission at week 12: 37% (89/243)<br>Endoscopic improvement by week 26: 22% (53/243) | Higher likelihood of treatment failure in patients using baseline steroids and those with higher symptomatic burden.<br>On univariate analysis, primary non-response to the first drug was also associated with a lower likelihood of success.<br>Lower treatment persistence observed with FILGO than with UPA (imbalanced groups!). |

**References:**


1. Pombo-Suarez M, Sanchez-Piedra C, Gomez-Reino J, et al. After JAK inhibitor failure: to cycle or to switch, that is the question - data from the JAK-pot collaboration of registries. Ann Rheum Dis 2023;82(2):175-81.
2. Osty M, Altwegg R, Serrero M, et al. Effectiveness and Safety of a Second JAK Inhibitor in Ulcerative Colitis: The J2J Multicentre Study. Aliment Pharmacol Ther 2025;62(4):430-39.
3. Radia C, Danso Y, Ritchie S, et al. Is 2nd JAKi treatment for UC worth the effort? A retrospective, multi-Centre UK study. J Crohn's Colitis 2025 [Epub ahead of print]
4. Innocenti T, Hanzel J, Truyens M, et al. Sequencing JAK-inhibitors in ulcerative colitis: effectiveness and safety of switching within treatment class. UEG Journal 2025 [Congress abstract]