Introduction:

Tofacitinib, filgotinib, and upadacitinib are Janus Kinase inhibitors (JAKi) effective in inducing and maintaining remission in moderate-to-severe ulcerative colitis (UC). However, limited data exists regarding outcomes in patients on a second JAKi after prior treatment failure. Here we describe the effectiveness of induction with a second JAKi in a cohort of UC patients.

Methods:

In this retrospective cohort study, UC patients from 20 UK hospital treated with a second JAKi were included. Clinical endpoints, as defined in Table 1, were assessed at week 8. Corticosteroid use, prior advanced therapies, and reason for cessation of first JAKi were documented.

Table 1. Clinical, biochemical, and endoscopic parameters used to assess clinical outcomes.

	Response	Remission
Clinical		
SCCAI or pMayo	Reduction ≥3 or sustained <2	<2
Biochemical		
FCal and CRP	FCal or CRP reduction of 50% and no increase in either parameter	FCal <200 µg/g and CRP ≤5 mg/L
Endoscopic		
UCEIS	Reduction ≥2	≤1
MES	Reduction ≥1	≤1

SCCAI: Simple Clinical Colitis Activity Index, pMayo: partial Mayo Score, FCal: Faecal calprotectin, UCEIS: Ulcerative Colitis Endoscopic Index of Severity, MES: Mayo Endoscopic Subscore

Results:

99 patients commenced induction therapy with a second JAKi, 87% of whom had active disease by disease activity index, endoscopy or biomarkers. First JAKi was stopped due to failure or side effects in 86% of cases. Tofacitinib was the most commonly used first JAKi (72%). Second JAKi was upadacitnib in 77% and filgotinib in 23%. There was no significant difference in the SCCAI ($p=0.834$) or pMayo ($p=0.074$) at baseline in those given either drug. Exposure to at least one other advanced therapy in addition to the first JAKi was seen in 78 patients, and 45 patients required steroids during induction. Both the median SCCAI and pMayo scores improved from 7 (SCCAI 5-9, pMayo 5-8) at baseline to 2 (SCCAI 0-3) and 1 (pMayo 0-3) at 8 weeks ($p<0.001$).

Paired endoscopy results were available in 27 patients, showing an overall improvement from a median UCEIS 5 (5-6) and MES 2 (2-3) to 1.5 (0-5) and 1 (1-2.5) respectively (UCEIS $p<0.001$, MES $p=0.019$). Median faecal calprotectin reduced from 650 (331-1500) to 62 (31-173) in 45 patients ($p<0.001$). 56% (15/27) of patients achieved endoscopic remission and a further 19% (5/27) of patients achieved an endoscopic response. Of the 82 patients with paired disease activity index at baseline and 8 weeks, 52% (43/82) achieved clinical remission and further 26%(21/82) achieved a clinical response. Of the patients who achieved clinical remission, 93% (40/43) were in steroid free remission, 64% (9/14) in endoscopic remission and 88% (22/25) in biochemical remission. There was no significant difference in remission rates depending on disease extent, number of previous advanced therapies, choice of first or second JAKi, or reason for cessation of

first JAKi including primary non-response (p=0.99). Serious adverse events were admission for IV steroids, colectomy and VTE (1 each), withdrawal due to adverse event n=1, zoster infections n=3.

Conclusions:

Our results suggest that treatment with filgotinib or upadacitinib following exposure to another JAKi can be effective in inducing clinical remission in UC. Efficacy was similar in our cohort regardless of mechanism of failure of first JAKi or whether upadacitinib or filgotinib was used as a second JAKi. The observed safety profile was as expected especially with considerable risk of zoster infections.