Janus kinase inhibitors for inflammatory bowel disease

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NICE recently recommended the janus kinase (JAK) inhibitor tofacitinib (Xeljanz) for second-line treatment of moderately to severely active ulcerative colitis. This article summarises the efficacy for tofacitinib in inflammatory bowel disease (ulcerative colitis and Crohn's disease), and discusses a new JAK inhibitor, filgotinib, that has shown promise in Crohn's disease.

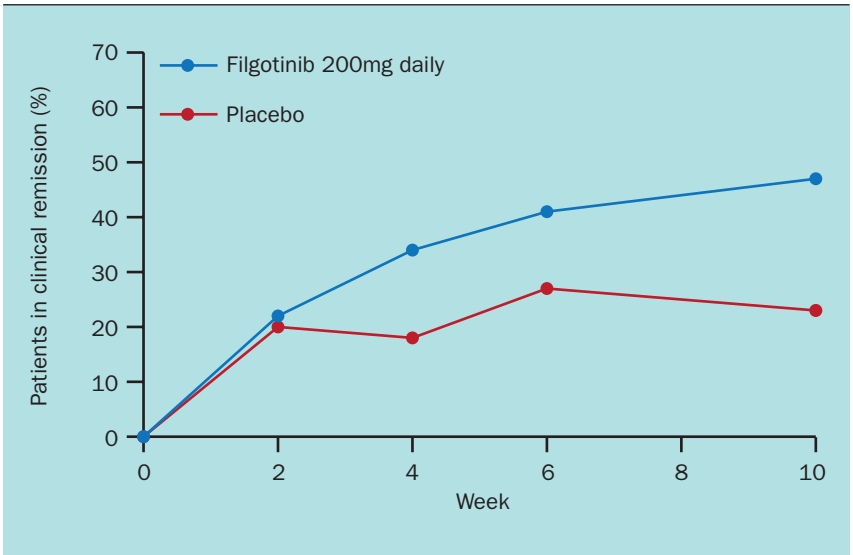

Figure 1. Clinical remission (defined as Crohn's Disease Activity Index <150) over time in response to filgotinib 200mg daily or placebo[10]

The janus kinases JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2) are protein kinases with fundamental roles in cellular immune responses (involving type I cytokines such as IL-2 and related interleukins) and antibody-mediated responses (involving type II cytokines such as the interferons and IL-10-related interleukins).[1] The past 10 years have seen growing interest in the potential of JAK inhibitors in severe inflammatory disorders, such as rheumatoid arthritis, psoriasis and inflammatory bowel disease (ulcerative colitis and Crohn's disease), that are difficult to treat or resistant to conventional treatments.

In 2017, two JAK inhibitors, tofacitinib (Xeljanz) and baricitinib (Olumiant), were introduced in the UK for the treatment of rheumatoid arthritis, and tofacitinib later also received marketing authorisation for psoriatic arthritis and ulcerative colitis. In November 2018, NICE recommended tofacitinib for ulcerative colitis within its marketing authorisation, *ie* the treatment of adults with moderately to severely active ulcerative colitis when conventional therapy or a biological agent cannot be tolerated or the disease has responded inadequately to treatment.[2] The next JAK inhibitor in the pipeline is likely to be filgotinib, which is now undergoing phase 3 trials in patients with ulcerative colitis or Crohn's disease. Other JAK inhibitors in development include itacitinib, peficitinib and upadacitinib.

Inhibition of the individual JAKs is associated with increased risk of specific adverse effects. For example, JAK1 and TYK2 inhibition may increase the risk of bacterial and viral infections; JAK2 inhibition affects haematopoiesis and may lower blood cell count; and JAK3 inhibition may cause lymphopenia.[3] Tofacitinib preferentially inhibits JAK1 and JAK3, baricitinib is selective for JAK1 and JAK2, and filgotinib is selective for JAK1. Clinical trials suggest that the overall tolerability and risk of serious infections with tofacitinib is similar to that of

biological agents,[4,5] but it is presently unclear whether there are differences in the safety of JAK inhibitors when used to treat inflammatory bowel disease. A potential advantage of the JAK inhibitors over biological agents is that they can be administered orally.

Evidence from clinical trials, and the recent NICE approval of tofacitinib for ulcerative colitis, suggests that JAK inhibitors will have an important role in the future management of inflammatory bowel disease. NICE's treatment pathways for inflammatory bowel disease are available online, and the pathway for ulcerative colitis has recently been updated to include tofacitinib as a step 2 therapy option.[6]

Ulcerative colitis

The potential of tofacitinib for inducing remission in patients with ulcerative colitis was convincingly demonstrated in 2012, when a phase 2 trial in 194 adults with moderate to severe active disease reported an eight-week clinical remission rate of 48% with tofacitinib 10mg twice daily compared to 10% with placebo ($p<0.001$).[7] This encouraging start led to the three OCTAVE phase 3 trials of its efficacy and safety as an agent for induction and maintenance.[8]

OCTAVE Induction 1 (n=598) and 2 (n=541) included adults with moderate to severe active ulcerative colitis after failure or intolerance of at least one systemic agent (oral or intravenous corticosteroids, azathioprine, mercaptopurine, infliximab or adalimumab). Treatment with oral aminosalicylates and corticosteroids was permitted. Patients were randomised to receive placebo or treatment with tofacitinib 10mg twice daily for eight weeks. About half had previously been treated with a TNF inhibitor biological therapy, 70–80% with a corticosteroid and 65–75% with an immunosuppressant. Patients who completed OCTAVE Induction 1 or 2 with a clinical response entered the OCTAVE Sustain tofacitinib maintenance trial (n=593).

The main primary and secondary efficacy endpoints in OCTAVE Induction 1 and 2 are summarised in Table 1. At eight weeks, tofacitinib 10mg twice daily was associated with a significantly greater remission rate (the primary endpoint) compared with placebo (16.6–18.5% *vs* 3.6–8.2%), achieving remission in about one in every five or six patients. Improvement in the Mayo score was apparent at the first assessment at two weeks. According to patients' own assessments using the Inflammatory Bowel Disease Questionnaire score, the proportion meeting the criterion for remission at eight weeks was significantly higher with tofacitinib than with placebo (49–52% *vs* 26–38%). Prior treatment with a TNF inhibitor did not significantly alter the differences in eight-week remission rates between tofacitinib and placebo in either trial.

Endpoint (% patients)	OCTAVE Induction 1		OCTAVE Induction 2	
	Tofacitinib	Placebo	Tofacitinib	Placebo
Remission (primary endpoint)*	**18.5%**	**8.2%[a]**	**16.6%**	**3.6%[b]**
Mucosal healing	31.3%	15.6%[b]	28.4%	11.6%[b]
Clinical remission	18.5%	8.2%[a]	16.8%	3.6%[b]
Endoscopic remission	6.7%	1.6%[c]	7.0%	1.8%[c]
Symptomatic remission	11.8%	5.7%[d]	10.7%	2.7%[e]
IBDQ remission	52.5%	37.7%[f]	49.4%	25.9%[b]
IBDQ response	70.0%	54.9%[b]	73.4%	50.0%[b]

*Total Mayo score of ≤2 (range 0–12), calculated from stool pattern, rectal bleeding, endoscopic findings and global physician rating, with no subscore >1 and a rectal bleeding subscore of 0. [a]p=0.007; [b]p<0.001; [c]p=0.04; [d]p=0.06; [e]p=0.009; [f]p=0.004
IBDQ = Inflammatory Bowel Disease Questionnaire; a score of ≥170 is indicative of remission and an increase from baseline of ≥16 points is indicative of treatment response

Table 1. Main efficacy endpoints at eight weeks in the OCTAVE Induction 1 and 2 trials, comparing tofacitinib 10mg twice daily to placebo in the treatment of ulcerative colitis[8]

Most patients entering OCTAVE SUSTAIN had been treated with tofacitinib (88%) and 30% had been in remission. They were re-randomised to treatment with tofacitinib 5mg or 10mg twice daily or placebo. After 52 weeks, remission rates were at least three times greater with tofacitinib (34% and 41% with 5mg and 10mg respectively) compared with placebo (11%). Mucosal healing rates also increased at 52 weeks (37% and 46% *vs* 13% respectively) and, of those in remission at entry to SUSTAIN, 37% achieved a sustained remission (*ie* remission at both 24 and 52 weeks) with 5mg tofacitinib and 47% with 10mg tofacitinib (*vs* 5% with placebo).

Overall adverse event rates were similar for tofacitinib and placebo during the induction (53–60%) and maintenance (72–80%) trials. Serious adverse event rates were slightly higher with placebo. Tofacitinib was associated with higher rates of infection than placebo during induction (18–23% *vs* 15–16%) and maintenance (36–40% *vs* 24%). There were few serious infections but they were more frequent with tofacitinib than placebo in the induction trials. The OCTAVE trials were too short and too small to reliably estimate the risk of cancer and cardiovascular disease.

Crohn's disease

By contrast with the efficacy in treating ulcerative colitis, no significant difference was found between tofacitinib 5mg or 10mg twice daily and placebo in a phase 2 trial in 280 patients with moderate to severe Crohn's disease and a history of inadequate response or intolerance to at least one systemic treatment (corticosteroids, azathioprine, mercaptopu-

rine, methotrexate or a TNF inhibitor).[9] Patients who responded after eight weeks were re-randomised in a 52-week maintenance trial.

After eight weeks of induction therapy, clinical remission rates (Crohn's Disease Activity Index [CDAI] score <150) were not significantly different (37% with placebo *vs* 44% and 43% with tofacitinib 5mg and 10mg twice daily). Remission or response (CDAI score decrease ≥100) rates after 26 weeks of maintenance therapy were also not significantly different at 38%, 40% and 56% respectively. Secondary endpoints and reductions in inflammatory markers suggested improvement but the authors concluded the effect of tofacitinib was minor for both induction and maintenance therapy, in part due to a high placebo response rate.

However, in a smaller phase 2 study (n=174) in patients with moderate to severe Crohn's disease, remission was achieved after 10 weeks in 47% of people treated with filgotinib 200mg daily and 23% assigned to placebo (p=0.0077; see Figure 1).[10] The remission rate was higher with filgotinib treatment among individuals not previously treated with a TNF inhibitor (60% *vs* 37%). Participants in the filgotinib study were slightly younger than the tofacitinib trial population, had a shorter duration of Crohn's disease (about 7–9 years *vs* 11 years), fewer had undergone surgery for Crohn's disease (26–30% *vs* 38–54%) and fewer had prior treatment with a TNF inhibitor (56–64% *vs* 69–79%). These differences, together with the high placebo response in the tofacitinib trial, make it difficult to compare the efficacy of tofacitinib and filgotinib for Crohn's disease.

Summary

The evidence from clinical trials shows that tofacitinib offers the prospect of better outcomes for adults with ulcerative colitis when most current treatment options are unsuitable or have failed, and filgotinib shows similar promise in adults with refractory Crohn's disease. Evidence to date suggests that overall tolerability of JAK inhibitors may match that of the biological agents, and the JAK inhibitors offer a potential advantage in being orally available. However, with no direct comparative trials and a wide range of options for systemic treatment, their place in therapy will not become fully apparent for several years.

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Declaration of interests

None to declare.

Steve Chaplin is a medical writer specialising in therapeutics