

JAK1 inhibition and inflammatory bowel disease

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Abstract

Primary non-response and secondary loss of response remain a significant issue with the currently available treatment options for a significant proportion of patients with inflammatory bowel disease (IBD). There are multiple unmet needs in the IBD treatment algorithm and new treatment options are required. As our understanding of the pathogenesis of IBD evolves, new therapeutic targets are being identified. The JAK-STAT pathway has been extensively studied. Tofacitinib, a JAK1 inhibitor, is now licensed for use in the induction and maintenance of ulcerative colitis and there are a large number of molecules currently under investigation. These new small molecule drugs (SMDs) will challenge current treatment pathways at a time when clinical therapeutic outcomes are rapidly evolving and becoming more ambitious. This is a review of the current JAK1 inhibitors in IBD including the current evidence from clinical trials.

Key words: inflammatory bowel disease, ulcerative colitis, Crohn's disease, JAK1 inhibitors

Rheumatology key messages

- Lack of efficacy is a significant problem in IBD patients treated with biological medicines.
- SMDs offer an attractive set of characteristics and provide an unmet need in IBD management.
- Robust real-world data is now required to support the use of JAK1 inhibitors in IBD.

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract with the two main forms being Crohn's disease (CD) and ulcerative colitis (UC) [1, 2]. They exhibit a relapsing and remitting course and patients often require long-term medical treatment to remain in remission. Therapeutic options for the management of IBD have largely followed those in rheumatology with corticosteroids, aminosaliculates and immunomodulators being the mainstay of medical management for many years [3]. The introduction of targeted biological therapies significantly changed the management of IBD. These drugs markedly improved outcomes for these patients, as well as those with other immune-mediated inflammatory conditions. Infliximab (a tumour necrosis factor- α receptor blocker) was the first monoclonal antibody licensed for use in the treatment of IBD in 1998 [4]. Since then, three more anti-TNF molecules (adalimumab, golimumab and certolizumab)

have been licensed for use in IBD. More recently, other pathways have been targeted including the IL12/23 axis with ustekinumab and lymphocyte tracking pathways with vedolizumab.

Monoclonal antibodies are not without their limitations. The PANTS study was a real-world efficacy study of infliximab and adalimumab that suggested primary non-response rates at week 14 of 23.8% and non-remission rates of 63.1% at week 52 [5]. Over a period of a year, 10–20% of patients will lose response during treatment (secondary loss of response) or have an adverse event necessitating discontinuation of treatment [6, 7]. Immunogenicity is being better understood as a major mechanism of treatment failure. The current literature supports the use of combination therapy with immunomodulators to reduce the risk of antibody formation. However, this approach has its own risks including increased risk of infection and malignancy [5].

More recently, two different pathways have been targeted with monoclonal antibodies to increase therapeutic options in IBD; the IL12/23 antagonist ustekinumab and the $\alpha 4\beta 7$ anti-integrin vedolizumab. The IM-UNITI trial showed 53% of CD patients receiving ustekinumab every eight weeks were in remission at week 44 [8]. Clinical remission rates for vedolizumab from the GEMINI trials were 42% and 39%, for UC and CD

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respectively, at 52 weeks [9, 10]. It would appear that these newer biologics have similar limitations to anti-TNFs with primary non-response and secondary loss of response, although the mechanisms for this are less clear currently. The development of biosimilar anti-TNFs has reduced drug acquisition costs and possibly increased access to biologics for IBD patients. However, parenteral administration (infliximab) and associated costs of dispensing and monitoring all biologics remains a burden on both healthcare systems and patients.

Given the limitations of the currently available biologics in the management of IBD, there is clearly a need for additional therapeutic options for IBD patients. As our understanding of the mechanisms involved in the pathogenesis of IBD have evolved, there has been increasing interest in new small molecules. Small molecule drugs (SMDs) are organic compounds that have a low molecular weight of <900 daltons. They rapidly diffuse across cell membranes and are absorbed into the systemic circulation [11].

SMDs have advantages over larger molecule biologics. Firstly, they can be orally administered. Small molecules also have a rapid onset of action, are more stable in terms of their structure and have a short half-life. This is particularly useful when rapid drug elimination is required such as pre-surgery or with concurrent infection. These drugs also have more predictable pharmacokinetics and immunogenicity is not an issue. In addition, these drugs are much simpler and less expensive to manufacture.

Compliance and long-term adherence with oral medication is a well-known challenge in chronic disease management [12]. Patients will often express a preference for using oral medication over intravenous and subcutaneous administration; however, this should not be assumed [13, 14]. Other disadvantages of SMDs include hypersensitivity and allergic reactions, drug–drug interactions and off-target toxicity [15].

The JAK-STAT signalling pathway has been studied extensively and has led to the exploration of the use of Janus kinase (JAK) inhibitors in IBD. There are four intracellular tyrosine kinases in the JAK family (JAK1, JAK2, JAK3 and TYK2) and seven intracellular transcription factors [signal transducers and activators of transcription (STAT)]. These combine to activate the JAK-STAT pathway and exert their effects on different cytokine receptors. Blocking JAK-mediated inflammatory pathways can change the innate and adaptive immune responses involved in IBD and therefore reduce chronic gastrointestinal inflammation [16]. IL-6 is an important driver of inflammation in IBD in addition to IL-12 and IL-23 [17, 18]. These cytokines all mediate their effects via the JAK-STAT pathway: IL-6 via JAK1, JAK2 and TYK2, which activate STAT3; and IL-12 and IL-23 via JAK2 and TYK2, which activate STAT3 and STAT4, respectively [19, 20]. Pre-clinical murine models have shown the importance of these cytokines in the pathogenesis of colitis and support the use of JAK in the treatment of gastrointestinal inflammation [21–24].

There are currently several JAK inhibitors in large regulatory registration programmes in IBD (Table 1). Some are selective, blocking a combination of JAK molecules, while others block all JAK molecules (pan-JAK inhibitors). Combination JAK inhibition may offer an advantage by blocking multiple inflammatory pathways. However, this could increase the risk of adverse events. Selective JAK inhibition could provide an opportunity to use lower doses and thus fewer side effects to achieve efficacy. This is especially true of JAK1, which is thought to dominate the JAK-STAT pathway [25]. This review evaluates the use of JAK1 inhibitors in the treatment of inflammatory bowel disease.

Tofacitinib

Tofacitinib is a JAK1, JAK3 and, to a lesser extent, JAK2 inhibitor [26]. It was the first JAK inhibitor licensed and approved for use in moderately to severely active UC with previous inadequate response to conventional therapy [27]. It was approved by both the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in 2018 [28, 29]. Tofacitinib is administered orally and is rapidly absorbed with a time to peak concentration of 30 min. It therefore has a quick onset of action compared with other drugs used in IBD and lends itself to early assessment of efficacy and thus timely reduction to a maintenance dose. It has a short half-life of approximately three h and therefore requires twice-daily dosing. Tofacitinib is metabolised by cytochrome CYP3A4 and so may interact with other drugs that induce or inhibit CYP3A4. It also requires dose adjustment in hepatic and renal impairment or if patients become cytopenic.

Initial data for tofacitinib was from a phase II, multi-centre, randomized, placebo-controlled, dose-finding trial in which 194 adult patients with moderate to severe UC received either placebo or four different doses of tofacitinib (0.5 mg, 3 mg, 10 mg or 15 mg twice daily) for eight weeks. Results showed a statistically significant difference in the primary end point (≥ 3 -point reduction in Mayo activity score) for those in the 15 mg group compared with placebo (78% vs 42%, $P < 0.001$). Clinical remission and endoscopic remission (secondary endpoints) were also higher in the 3 mg, 10 mg and 15 mg groups vs placebo [30].

The phase III programme OCTAVE went on to assess tofacitinib as induction therapy (OCTAVE Induction 1 and 2) as well as maintenance therapy (OCTAVE Sustain). The induction trials showed that those in the active treatment arm achieved the primary end point (remission at eight weeks) more frequently than the placebo arm (18.5% vs 8.2%, $P = 0.007$). Again, mucosal healing was greater in the tofacitinib 10 mg group compared with placebo. A sub-group analysis showed there was no significant difference in those who were anti-TNF experienced compared with those who were naïve in terms of both primary and secondary endpoints. However, this should be interpreted cautiously due to

TABLE 1 Summary of the current JAK1 inhibitors in IBD

JAK inhibitor	Target	Indication	Clinical trials and results
Tofacitinib	JAK1, JAK3 JAK2 (lesser extent)	UC ASUC CD	Licensed for use in UC Case series only Phase II: primary end point not achieved
Filgotinib	Highly selective JAK1	UC CD	Phase IIb/III: in progress; preliminary results suggest all primary endpoints met. Published, peer-reviewed data awaited. Phase IIb/III: phase IIb primary end point achieved, phase III in progress
Upadacitinib	JAK1	UC CD	Phase IIb/III: phase IIb primary end point achieved, phase III in progress Phase II: co-primary endpoints not met Phase IIb: primary end point not achieved
Peficitinib	JAK1, JAK3 JAK 2 (lesser extent)	UC	Phase II: in progress Phase IIb: primary end point not achieved
Brepocitinib	Tyk2, JAK1	UC CD	Phase II: in progress Phase II: in progress
TD-1473	Pan-JAK	UC CD	Phase IIb/III: in progress Phase II: in progress

ASUC: acute severe ulcerative colitis; CD: Crohn's disease; UC: ulcerative colitis.

the reduced sample size. OCTAVE Sustain showed higher remission rates at week 52 for those on 5 mg and 10 mg twice daily compared with placebo (34.3% and 40.6% vs 11.1%, $P < 0.01$) [31].

There were no major safety concerns regarding the use of tofacitinib in the IBD trials. Overall, it is well tolerated and appears to have a similar safety profile to conventional therapies [32]. However, an increase in the incidence of venous thromboembolic events (VTE) in patients over the age of 50 with rheumatoid arthritis and at least one other cardiovascular risk factor receiving 10 mg twice a day of tofacitinib was noted in a safety trial (NCT02092467). Following this, a *post-hoc* analysis of UC patients with tofacitinib exposure (2404 patient-years exposure) showed that one patient had a deep vein thrombosis and four had pulmonary emboli with VTE risk factors. This analysis was limited by small sample size and so must be interpreted with caution [33]. However, in the already pro-thrombotic state of active UC, this does raise significant concerns. Pending further data, our pragmatic approach is to conduct a timely assessment of response to the 10 mg twice daily dose and reduce to maintenance dosing as soon as possible or change therapy in the case of non-response.

Given its rapid onset of action and efficacy, tofacitinib may have a role in the management of acute severe ulcerative colitis (ASUC). Berinstein *et al.* conducted a retrospective survey of four patients with ASUC and showed that high dose tofacitinib (10 mg three times daily for three days) was safe and effective and reduced the risk of urgent colectomy [34]. Similarly, Kotwani *et al.* described their experience with four patients who were all treated with 10 mg twice daily effectively. They were all discharge by day 21 with no requirement for

urgent colectomy within 90 days [35]. Honap *et al.* describe a series of seven anti-TNF refractory patients treated with tofacitinib in a hospital setting. Five patients, of which three had ASUC, had a rapid clinical and biochemical response and were discharged within one week of admission. Of those, three remained in remission. However, four of the seven patients did eventually require colectomy (two during their index admission and two following re-admission) [36]. Randomized controlled trials with larger numbers are now required to validate these findings and determine the best place for tofacitinib in the ASUC treatment algorithm.

Clinical trials have also looked at the use of tofacitinib in CD. In a randomized, double-blind, placebo-controlled phase II study of 139 patients with moderate to severe CD on different doses of tofacitinib (1 mg, 5 mg or 15 mg twice daily) vs placebo for four weeks, there was no difference between the groups in terms of response or remission rates [37]. Given the short duration of the trial, a further phase IIb randomized, multicentre trial evaluated the efficacy of tofacitinib in active CD over an eight-week period. A total of 180 patients received either 5 mg, 10 mg or placebo twice daily. Again, there was no significant difference in the primary end point with a high placebo response. However, *post-hoc* analysis of the data showed efficacy of tofacitinib vs placebo in CD when objective markers of disease activity were used together with CDAI scoring [38]. This suggests that further carefully designed trials are required to explore the role for tofacitinib in the management of CD. It also highlights the need for objective evidence of inflammation prior to commencing treatment in IBD or recruitment into interventional studies [5].

Filgotinib

Filgotinib is a highly selective JAK1 inhibitor with 30 times selectivity for JAK1 over JAK2 and 50 times selectivity for JAK1 over JAK3 [39]. Filgotinib is administered orally once daily and is rapidly absorbed and eliminated with a half-life of approximately 6 h. This JAK1 inhibitor is currently an investigational product and has not been approved by the FDA, EMA or any other regulatory bodies for the management of IBD.

Filgotinib was first evaluated in a phase IIb study for active CD involving 174 patients who were randomized to either filgotinib 200 mg or placebo for an initial ten-week period. They were then reassigned based on their CDAI clinical responder status to either filgotinib 200 mg, 100 mg or placebo for a further ten weeks. At week ten, 47% in the treatment arm compared with 23% in the placebo arm achieved the primary end point (clinical remission with CDAI <150) with a *P*-value of 0.008. Importantly, data from this study supported the use of filgotinib in both biologic experienced and naïve patients [40]. A phase III trial is currently in progress to validate these findings (NCT02914561).

In embryofetal development studies, filgotinib caused embryolethality and teratogenicity in rats and rabbits. This was observed at doses similar to human exposure (200 mg once daily). There was no impact on female fertility but male fertility was impaired, which could be temporary or permanent. The MANTA study is currently evaluating the testicular safety of filgotinib in adult males with moderately to severely active IBD to assess this risk further (NCT 03201445). There were no other significant safety concerns.

A further phase IIb/III study is also underway to evaluate the efficacy of filgotinib in the induction and maintenance of remission in patients with moderately to severely active UC (NCT02914522). Preliminary results released earlier this year suggest that filgotinib 200 mg achieved all primary endpoints including clinical remission at week ten and maintenance of remission at week 58 compared with placebo [41]. More detailed analysis of the study is awaited.

Upadacitinib

Upadacitinib is an orally administered selective JAK1 inhibitor currently in phase II trials for the treatment of CD and UC. It has a half-life of 6–16 h. *In-vivo* assays have shown up to 60-fold selectivity for JAK1 over JAK2 and over 100-fold selectivity for JAK1 over JAK3 [42].

A phase II, multicentre, randomized, double-blind study evaluated the efficacy and safety of multiple dosing regimens of upadacitinib in adult patients with moderate to severely active Crohn's disease with previous inadequate response or intolerance to immunosuppressants or anti-TNF agents. It involved a 16-week dose-ranging induction phase and a 36-week extension. In total, 220 patients were randomized to upadacitinib 3 mg, 6 mg, 12 mg, 24 mg twice a day, 24 mg once a

day or placebo. The co-primary endpoints were clinical remission (defined as average daily stool frequency ≤ 1.5 and abdominal pain score ≤ 1.0) at week 16 and endoscopic remission (defined as Simple Endoscopic Score for CD ≤ 4 and ≥ 2 -point reduction from baseline, with no sub-score >1) at week 12/16. Clinical remission was achieved by 13%, 27% ($P \leq 0.1$), 11% 22% and 14% of patients receiving 3 mg, 6 mg, 12 mg, 24 mg twice daily and 24 mg daily respectively compared with 11% of patients on placebo. Of the 220 patients, endoscopic remission was achieved in 10% ($P < 0.1$ vs placebo), 8%, 8% ($P < 0.1$ vs placebo), 22% ($P < 0.01$ vs placebo) and 14% ($P < 0.05$ vs placebo) in the respective treatment arms compared with none in the placebo arm. The maintenance phase was associated with continued responses and reduction in inflammatory markers in those who were responders after the initial 16-week induction phase [43]. The study showed that endoscopic remission increased with dose but not clinical remission and so the co-primary endpoints were not met.

The U-ACHIEVE programme is set to evaluate the safety and efficacy of upadacitinib in UC and consists of three trials: a phase IIb dose-ranging induction study, a phase III dose confirming induction study and a phase III maintenance study. In the first study, 250 adults with moderately to severely active UC were randomized to receive placebo or four different doses of extended release upadacitinib (7.5 mg, 15 mg, 30 mg or 45 mg) once daily for eight weeks. Results showed that 8.5%, 14.3%, 13.5% and 19.6% of patients receiving the four consecutive doses achieved clinical remission (according to the adapted Mayo activity score) compared with none of those in the placebo arm ($P = 0.052$, $P = 0.013$, $P = 0.011$ and $P = 0.002$, respectively) [44]. The dosing and maintenance studies are ongoing, but the data so far suggests that further development of upadacitinib in both CD and UC is justified.

Other molecules

There are three other molecules that exhibit a degree of JAK1 inhibition currently under investigation in IBD trials. Peficitinib is more selective for JAK1 and JAK3 over JAK2. It has already shown efficacy in the treatment of rheumatoid arthritis [45]. Peficitinib is similar to tofacitinib in terms of potency for JAK1 and JAK3 but less so for JAK2 and may therefore demonstrate a more favourable safety profile [46]. Sands *et al.* conducted a phase IIb, dose-ranging trial on 219 adult patients with moderate to severe UC who received 25 mg, 75 mg, 150 mg once daily, 75 mg twice daily or placebo. The primary end point was dose-response at week eight assessed by changes in Mayo score from baseline. There was no significant dose-response demonstrated but a greater proportion of patients in the treatment arms receiving ≥ 75 mg once daily achieved a clinical response suggesting some level of efficacy. There were no safety signals identified [47]. Further work will need to focus on higher daily doses or split dosing.

Brepocitinib is a Tyk2/JAK1 inhibitor which is currently being investigated in phase II trials for both CD and UC (NCT03395184, NCT02958865).

TD-1473 is an orally administered gut-selective pan-JAK inhibitor that has been designed to act locally at the site of inflammation with minimal systemic exposure. A phase Ib, multicentre, double-blind, placebo-controlled trial evaluated the safety, tolerability and pharmacokinetics of TD-1473 in 40 subjects with moderately to severely active UC. Subjects were randomized to receive 20 mg, 80 mg, 270 mg or placebo for four weeks. TD-1473 yielded high intestinal (*vs* plasma) drug concentrations and showed trends towards reduced levels of clinical, endoscopic and histological disease activity [48]. A further phase IIb/III set of studies are underway to evaluate the use of TD-1473 in the induction and maintenance of subjects with UC (NCT03758443). A phase II study to evaluate the efficacy, safety and tolerability of TD-1473 in subjects with moderately to severely active CD is also in recruitment phase (NCT03635112).

The position of JAK inhibitors in IBD management

When a new class of treatment emerges, existing treatment algorithms are challenged and it is necessary for clinical teams to gain knowledge and confidence to use these new treatments. There is always a pressing need for real-world evidence given the differences in patients exposed to new treatments in large clinical trial programmes (to demonstrate efficacy and provide initial safety data for regulatory purposes) to those patients treated in every day clinical practice (effectiveness). This becomes ever more challenging as the number of different modes of action and options within these categories further increases. The available evidence suggests that a patient's previous biologics history may not influence the efficacy of JAK inhibitors, unlike biologics, which will be an important consideration. Factors that will dictate the decision on where to position JAK inhibitors will include relative cost (particularly with respect to the availability of competitively priced biosimilar molecules), safety, patient characteristics (including co-morbidities and age), speed of onset and patient preference, which is arguably the most important factor to ensure compliance with an oral medication. Safety concerns around VTE and fertility need further exploration. Finally, it is important to ensure that these new treatment options should not be used to delay surgery if this would be the most appropriate next step for the patient.

Currently, tofacitinib is the only licensed JAK inhibitor for use exclusively in UC. In a UK context, the National Institute for Health and Care Excellence (NICE) concluded that tofacitinib can be used in the same position in the treatment pathway as biological therapies, which is as a second- or third-line treatment. They recommend tofacitinib as an option for treating moderately to

severely active ulcerative colitis when conventional therapy or a biological agent cannot be tolerated or there has been an inadequate or loss of response to treatment. This recommendation has been based on the current evidence as well as comparisons with current conventional therapies in terms of cost and health-related benefits. They also conclude that tofacitinib has major benefits in being orally administered and also in terms of it having a reduced risk of immunogenicity and is therefore an important new treatment option for patients with UC [49].

The role and position of JAK inhibitors in the treatment of extra-intestinal manifestations (EIM) of IBD is yet to be determined. The main areas classically affected are the joints, skin, eyes, liver and biliary tract. The JAK-STAT pathway has been implicated in several EIMs. A *post-hoc* analysis of the OCTAVE programme showed that low patient numbers did not allow any meaningful conclusion to be drawn regarding the use of tofacitinib in EIMs [50]. JAK inhibitors have a clear role in rheumatology and dermatology, but extrapolating the results from these immune-mediated inflammatory diseases to the treatment of EIMs is not straightforward and further evidence for their role in this scenario is required [51].

Conclusion

The emerging data on JAK1 inhibitors is encouraging and shows they have the potential to meet some of the therapeutic gap that exists with current treatments. It opens up new options to both physicians and patients by targeting a different part of the inflammatory cascade. This is particularly true for those who are non-responders to current therapies. The significance of the targeting of specific combinations of JAK molecules may be important and further work is needed to determine this.

There is now a need for comprehensive real-world observational data to support their use and provide more information about tolerability, hospitalization rates, requirements for surgery and safety. Head-to-head trials with biologics with carefully considered study designs will help to inform treatment pathways as will the discovery and development of specific biomarkers for efficacy and toxicity.

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Data availability statement

Data are available upon reasonable request by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and Statistical Analysis Plan (SAP) and execution of a Data Sharing Agreement (DSA). All data relevant to the study are included in the article.

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