Best Practice & Research Clinical Gastroenterology 38-39 (2019) 101606

Contents lists available at ScienceDirect

Best Practice & Research Clinical Gastroenterology

journal homepage: https://ees.elsevier.com/ybega/default.asp

Pharmacology, efficacy and safety of JAK inhibitors in Crohn's disease

Christopher Ma [a, b], Vipul Jairath [b, c, d], Niels Vande Casteele [b, e, *]

[a] Division of Gastroenterology and Hepatology, University of Calgary, 3280 Hospital Drive NW, Calgary, Alberta, T2N 4Z6, Canada
[b] Robarts Clinical Trials, Inc, #200, 100 Dundas Street, London, Ontario, N6A 5B6, Canada
[c] Department of Medicine, Division of Gastroenterology, Western University, London, Ontario, Canada
[d] Department of Epidemiology and Biostatistics, Western University, London, Ontario, Canada
[e] Department of Medicine, University of California San Diego, 9500 Gilman Drive, #0956, La Jolla, CA, 92093, United States

ARTICLE INFO

Article history:
Received 27 February 2019
Accepted 4 March 2019

Keywords:
Inflammatory bowel disease
Crohn's disease
Janus kinase
Tyrosine kinase
JAK-STAT

ABSTRACT

Orally bioavailable inhibitors of the tyrosine kinases (TYKs), also referred to as Janus kinases (JAKs), are being evaluated for the treatment of patients with Crohn's disease (CD), ulcerative colitis (UC), and other chronic inflammatory disorders. To date, three JAK inhibitors have been tested in patients with moderate-to-severe CD: tofacitinib (pan-JAK inhibitor), filgotinib (JAK1 inhibitor) and upadacitinib (JAK1 inhibitor). Clinical development of tofacitinib was discontinued in CD because the primary endpoint of clinical remission in the phase II induction and maintenance trials was not met, although outcomes may have been influenced by trial design flaws and a high placebo rate was noted. In contrast, filgotinib did meet its primary endpoint of clinical remission at week 10 in the phase II FITZROY trial, in addition to several other clinically important secondary outcomes, spurring a subsequent larger phase III trial. Following promising results for upadacitinib in its phase II trial, larger phase III trials were also initiated to corroborate the efficacy results. Although JAK inhibitors appear to have an acceptable safety profile, higher rates of infections compared to placebo were noted. Overall, JAK inhibitors constitute a new promising class of drugs, given the efficacy signals observed in pivotal clinical trials in several chronic inflammatory diseases. Here we review the existing evidence on the pharmacology, safety and efficacy of JAK-STAT inhibitors that are currently under investigation for the treatment of patients with CD.

Introduction

Orally bioavailable inhibitors of the tyrosine kinases (TYKs), also referred to as Janus kinases (JAKs), are being evaluated for the treatment of patients with Crohn's disease (CD), ulcerative colitis (UC), and other chronic inflammatory disorders. Four JAKs are known: JAK1, JAK2, JAK3 and TYK2, of which each protein, in different combinations, can be associated with the intracellular domain of cell surface receptors of cytokines or growth factors [1]. Upon binding of the receptor ligand, JAKs can phosphorylate the signal transducers and activators of transcription (STATs) in the cell's cytoplasm, that in turn modulate expression of differential genes in the nucleus via binding to specific STAT-binding sequences in the DNA [2]. There has been an increasing interest in this pathway as JAK1 and JAK3 are associated with many T cell-derived cytokines that have been linked to inflammatory bowel disease [3,4]. JAK-STAT inhibitors constitute a new promising class of drugs, given the efficacy signals observed in pivotal clinical trials in several chronic inflammatory diseases. Here we review the existing evidence on the pharmacology, safety and efficacy of JAK-STAT inhibitors that are currently under investigation for the treatment of patients with Crohn's disease.

Tofacitinib

Tofacitinib (Pfizer Inc., New York, United States) is a potent inhibitor of JAK1 and JAK3. The half-maximal inhibitory concentration (IC_{50}) of tofacitinib for JAK1 was found to be 74 nM with a 10-fold selectivity for JAK1 over JAK2 [5]. Tofacitinib has a linear and dose-proportional pharmacokinetic (PK) profile with a functional half-life of ~3 h [6]. The clearance is mediated primarily by hepatic metabolism (70%) and renal elimination (30%). Cytochrome P450 (CYP) 3A4 is the primary hepatic enzyme responsible for metabolization and CYP2C19 the secondary, with circulating metabolites <10% [7].

* Corresponding author. University of California San Diego Department of Medicine, 9500 Gilman Drive, #0956, La Jolla, CA, 92093, United States.
E-mail address: nvandecasteele@ucsd.edu (N. Vande Casteele).

https://doi.org/10.1016/j.bpg.2019.03.002
1521-6918/

The first phase IIa induction trial of tofacitinib in patients with CD was conducted by the Study A3921043 Investigators and reported by Sandborn et al. in 2014 [8]. In this 4-week induction trial, 139 patients with moderate-to-severe CD were randomized to either placebo, tofacitinib 1 mg, 5 mg, or 15 mg twice daily (BID). No significant differences in clinical response or remission were observed between treatment with tofacitinib and placebo, although reductions in C-reactive protein (CRP) and fecal calprotectin (FCP) were observed in patients receiving tofacitinib 15 mg BID. Inadequate dosing and short trial duration were hypothesized as potential reasons for the negative trial results and so subsequently, the efficacy of tofacitinib as an induction and maintenance agent for CD was investigated in two larger sequential, integrated, placebo-controlled parallel-group multicenter randomized phase IIb trials (NCT013932626 and NCT01393899) [9]. In the induction study, adult patients with moderate-to-severe CD (defined by a Crohn's Disease Activity Index (CDAI) $\geq$220 and $\leq$ 450), endoscopic ulcerations (as determined by the site investigators), and inadequate response or intolerance to corticosteroids, azathioprine/6-mercaptopurine, methotrexate, or tumor necrosis factor (TNF) antagonists were randomized 3:2:2:4 to receive placebo or tofacitinib 5, 10, or 15 mg BID for 8 weeks. A protocol amendment dropped the 15 mg group and patients were subsequently randomized 1:1:1 to placebo or tofacitinib 5 or 10 mg BID. Patients receiving TNF antagonists underwent a washout period of 8 weeks prior to randomization. In the maintenance study, patients achieving a CDAI decrease from baseline $\geq$100 points or clinical remission (CDAI <150) at week 8 were re-randomized 1:1:1 to receive placebo or tofacitinib 5 or 10 mg BID for 26 weeks. A mandatory corticosteroid tapering algorithm was applied, with decreasing doses by 5 mg prednisolone-equivalent per week until 20 mg/day, and then by 2.5 mg/week until 10 mg/day.

The primary efficacy outcome in the induction study was clinical remission, defined by CDAI <150 at week 8; clinical response defined by decreases in CDAI $\geq$70 (CR70) and $\geq$100 (CR100) from baseline were secondary endpoints. In post-hoc analysis, Panes et al. evaluated the proportion of patients achieving patient-reported outcome remission (PRO2 <75, calculated as the sum of stool frequency (SF) and abdominal pain (AP) scores; and PRO3 <80, calculated as the sum of SF, AP, and general well-being scores). The primary endpoint in the maintenance study was clinical remission or CR100 at week 26; assessment of the change in CRP and FCP over time were secondary endpoints.

A total of 280 patients were randomized in the induction study, with 92 assigned to placebo and 86 to each of the 5 mg and 10 mg BID tofacitinib arms; 76.9% (70/91) of patients randomized to placebo and 77.9% (134/172) of patients randomized to tofacitinib had previously been exposed to a TNF antagonist and approximately one third were using concomitant corticosteroids at study entry. At week 8, there were no significant differences in clinical remission between patients treated with placebo (36.7%) or either dose of tofacitinib (43.5% and 43.0% for 5 mg BID and 10 mg BID, respectively), even after stratification by previous TNF antagonist exposure. Patients in the 5 mg BID tofacitinib treatment arm had significantly higher rates of CR100 (70.6% vs. 54.4%, $p < 0.05$), CR70 (76.5% vs. 62.2%, $p < 0.05$), PRO2-75 (58.8% vs. 40.0%, $p < 0.05$), PRO3-80 (38.8% vs. 24.4%, $p < 0.05$), and change in CDAI (-149.7 versus -117.4); however, only changes in PRO2-75 and baseline CDAI were significant amongst patients treated with tofacitinib 10 mg BID compared to placebo. Patients treated with either dose of tofacitinib had greater mean decreases in baseline CRP compared to placebo ($p < 0.001$) although mean changes in FCP were not significant at week 8.

In the maintenance study, a total of 180 patients were re-randomized, 59 to placebo, 60 to tofacitinib 5 mg BID, and 61 to tofacitinib 10 mg BID. At week 26, the proportion of patients achieving CR100 or remission was not significantly different in the placebo group (38.1%) compared to patients receiving either dose of tofacitinib (39.5% in the 5 mg BID group and 55.8% in the 10 mg BID group). There was also no difference in the proportion of patients achieving clinical remission or sustained remission at weeks 20 and 26, or differences in mean CDAI from baseline comparing placebo to either tofacitinib dose. However, patients receiving 10 mg BID tofacitinib did have significantly lower CRP and FCP compared to patients receiving placebo after 26 weeks of therapy.

With respect to safety outcomes, treatment-emergent AEs were reported in 60.4%, 58.1%, and 60.5% of patients receiving placebo, tofacitinib 5 mg and 10 mg BID groups, respectively, after induction therapy. In the maintenance study, treatment-emergent AEs were reported in 74.6%, 83.3%, and 78.7% of patients, respectively. Nominally, serious AEs were more commonly reported in the maintenance study than in the induction study (10.0–13.1% vs. 3.3–11.6%), and more commonly amongst patients receiving tofacitinib 10 mg BID (11.6% in induction, 13.1% in maintenance) compared to tofacitinib 5 mg BID (3.5% in induction, 10.0% in maintenance) or placebo (3.3% in induction, 11.9% in maintenance). In both induction and maintenance, gastrointestinal side effects, namely nausea and CD worsening, and infections were the most commonly reported AEs. In the maintenance study, three patients treated with tofacitinib 5 mg BID experienced serious infections (*Clostridium difficile* colitis, *C. difficile* infection and septic shock, two perianal abscesses) and two patients treated with tofacitinib 10 mg BID experienced serious infections (perianal abscess, pneumonia influenza), but no cases of opportunistic infections were confirmed by adjudication. Two cases of non-serious herpes zoster were reported in patients treated with tofacitinib 10 mg BID. Treatment with tofacitinib was associated with 8.4% and 11.5% increases from baseline in total cholesterol for patients treated with tofacitinib 5 mg and 10 mg BID, respectively, at week 8. At week 26, mean change from baseline in total cholesterol was 3.3% and 0.2% for patients treated with tofacitinib 5 mg and 10 mg BID, respectively. No cases of cardiovascular events were reported in either induction or maintenance.

Overall, the findings of this induction and maintenance trial suggest some biological treatment effect with tofacitinib in CD. However, the study failed to meet its primary endpoints likely due to an excessively high placebo response and remission rate. The authors have speculated on several trial design factors that may have contributed to this high placebo response, including the use of site-investigator rather than blinded central reading for study enrolment, absence of defined FCP or CRP enrolment criteria, high proportion of patients receiving corticosteroids, slow prolonged corticosteroid taper during maintenance, and use of the CDAI as the primary endpoint rather than endoscopic or patient-reported outcomes. Indeed, in post-hoc analysis restricted to patients with a Simple Endoscopic Score (SES-CD) >11 at baseline, treatment with tofacitinib was associated with significantly greater rates of clinical remission (48.9% with tofacitinib 10 mg BID vs. 23.4% with placebo, $p < 0.05$) and composite remission defined by CDAI<150 and $\geq$ 50% decrease in CRP or FCP (25.5% with tofacitinib 10 mg BID vs. 6.4% with placebo, $p < 0.05$) [10]. Similarly, placebo response and remission rate were substantially decreased when the analysis was restricted to patients with baseline CRP $\geq$5 mg/L or FCP $\geq$250 mg/kg. Irrespectively, tofacitinib drug development in phase III trials for CD were not continued.

Filgotinib

Filgotinib (GLPG0634, GS-6034, Galápagos NV, Mechelen, Belgium) is an oral JAK1 selective inhibitor with and IC_{50} for JAK1 of

629 nM and a 28-fold selectivity for JAK1 over JAK2 [5]. Extensive metabolization of the parent compound is occurring by carboxylesterases, leading to an active metabolite with and IC_{50} for JAK1 of 11.9 μM and 8-fold selectivity for JAK1 over JAK2 [11]. Filgotinib has a dose-proportional PK profile, characterized by a rapid absorption and biphasic elimination, with an apparent mean terminal elimination half-life of ~6 h for the parent compound and ~23 h for the active metabolite. This leads to a substantially higher exposure (~16–20-fold) of the active metabolite over parent filgotinib, which may compensate for the lesser potency of the former in contributing to the PD effect [12].

The efficacy of filgotinib as an induction agent in CD was investigated in the European multicenter phase II FITZROY study [13]. Compared to the phase II trials of tofacitinib, the FITZROY study used more strict inclusion criteria: eligible adult CD patients were required to have active inflammation and ulceration at screening defined by a centrally read ulceration score of ≥1 in at least one ileocolonic segment and total SES-CD ≥7, in addition to CDAI 220–450. Washout periods of 8 weeks for TNF antagonists and 25 days for immunosuppressants were required, although stable dose concurrent oral corticosteroids (≤30 mg prednisolone equivalent or budesonide ≤9 mg per day) were permitted. The study consisted of two 10-week components: patients were initially randomized 3:1 to filgotinib 200 mg daily or placebo, stratified by TNF antagonist exposure, baseline CRP, and oral corticosteroid use. After 10 weeks, patients not responding to placebo were switched to filgotinib 100 mg daily for 10 weeks whereas patients responding to filgotinib were re-randomized 2:2:1 to filgotinib 200 mg daily, 100 mg daily, or placebo. Patients not responding to filgotinib during part 1 were re-randomized 3:1 to filgotinib 200 mg daily or placebo. The intention-to-treat analysis comprised of all patients who received either a single dose of filgotinib or placebo.

The primary outcome was clinical remission defined by CDAI<150 at week 10. Clinical remission and response by CDAI and PRO2, endoscopic response (SES-CD reduction ≥50%), endoscopic remission (SES-CD ≤4 and ulcerated surface subscore ≤1 in all five ileocolonic segments), mucosal healing (SES-CD = 0), deep remission (CDAI<150 and SES-CD≤4 and ulcerated surface subscore ≤1 in all five segments), and changes in CRP and FCP were assessed as secondary outcomes. All endoscopic endpoints were adjudicated by a blinded central reader. A total of 174 patients were randomized; 44 patients were assigned to placebo and 130 patients to filgotinib 200 mg daily. 64% (28/44) and 56% (73/130) of patients receiving placebo or filgotinib, respectively, had previously experienced primary or secondary loss of response or intolerance to TNF antagonists. 52% (23/44) and 50% (65/130) of patients receiving placebo or filgotinib, respectively, were receiving concomitant oral corticosteroids.

Clinical remission was achieved by 47% (60/128) of patients treated with filgotinib compared to 23% (10/44) patients receiving placebo (p = 0.0077); this effect was more pronounced amongst patients naïve to TNF antagonist therapy (60% vs. 13%). Furthermore, CR100 was achieved by 59% (76/128) of patients treated with filgotinib compared to 41% (18/44) of patients receiving placebo at week 10 (p = 0.0453). Patients receiving filgotinib were significantly more likely to achieve PRO2 remission (50%, 64/128) compared to placebo (30%, 13/44) (p = 0.0277). At week 10, numerically although not statistically higher rates of SES-CD 50% response (25% vs. 14%, p = 0.16), endoscopic remission (14% vs. 7%, p = 0.31), mucosal healing (4% vs. 2%, p = 0.82), and deep remission (8% vs. 2%, p = 0.31) were observed comparing patients treated with filgotinib to placebo. A significant reduction in mean baseline total D'Haens histopathology score (difference −3.8 [95% CI: −7.4, −0.3], p = 0.0359) was observed with filgotinib therapy compared to placebo. Similarly, patients treated with filgotinib were more likely to normalize their CRP and FCP. Finally, patients treated with filgotinib experienced a greater mean increase in baseline Inflammatory Bowel Disease Questionnaire (IBDQ) health-related quality of life score (+33.8 [standard error (SE) 3.0] vs. +17.6 [SE 5.1] for placebo, p = 0.0046). The second observational component of the FITZROY study demonstrated that 50% (15/30) and 71% (10/14) of initial filgotinib responders randomized to filgotinib 200 mg or 100 mg daily, respectively, were in clinical remission at week 20. Among initial placebo non-responders, 59% (13/22) achieved CR100 at week 20 and 32% (7/22) achieved clinical remission.

A pooled safety analysis of both part 1 and 2 was performed, comprising all periods of placebo or filgotinib exposure. The proportion of patients experiencing treatment-emergent AEs were similar between those receiving filgotinib (75%, 114/152) and placebo (67%, 45/67). A nominally higher rate of serious AEs occurred in patients receiving filgotinib compared to placebo (9%, 14/152 vs. 4%, 3/67). Importantly, serious infections were reported in four patients receiving filgotinib and none in the placebo group. These findings corroborate a relatively high rate of serious and opportunistic infections with tofacitinib therapy in ulcerative colitis (up to 5% in the OCTAVE trials) [14] and in pooled safety data from rheumatoid arthritis [15]. Specifically, the risk of herpes zoster infection appears to be elevated and may relate to class effects from JAK inhibition rather than drug-specific AEs. Treatment with filgotinib was also associated with an 11% increase in mean HDL and 12% increase in mean LDL at week 20.

Several important conclusions from the FITZROY study are likely to inform the design of clinical trials of JAK inhibitors moving forwards. First, the FITZROY study used central reading of endoscopy to define both enrolment criteria and outcomes; correspondingly, there was a high rate of screening failure (44%) from inadequate endoscopic disease burden. However, the enrolment of an appropriate population of patients with active inflammation at baseline was associated with reduced clinical and endoscopic placebo response rates in this study compared to phase II trials of tofacitinib. Although treatment with filgotinib did not meet the prespecified endoscopic outcomes, it should be considered that assessment of endoscopic ulcer resolution at 10 weeks may be too early of a time point for assessment and an SES-CD score ≤4 is a highly stringent endpoint to achieve. Taken together, the consistently positive effects of treatment on clinical, patient-reported, endoscopic, histologic, and biomarker endpoints in the FITZROY study has fuelled interest that filgotinib may be a promising oral therapy for CD. Hence, a large combined phase III induction and maintenance trial evaluating filgotinib in moderate-to-severe CD is currently enrolling (Diversity1, NCT02914561). Additionally, a phase II trial evaluating the efficacy of filgotinib for achieving a primary fistula endpoint at week 24 is enrolling (Divergence2, NCT03077412); this would be the first placebo-controlled trial assessing a primary CD fistula outcome since the landmark ACCENT II trial of infliximab [16]. Finally, a phase II trial evaluating the efficacy of filgotinib for small bowel CD, measuring disease activity both by PROs and magnetic resonance imaging is currently recruiting (NCT03046056).

Upadacitinib

Upadacitinib (ABT-494, AbbVie, Chicago, United States) is an oral JAK1 selective inhibitor with a 74-fold selectivity for JAK1 over JAK2 [17]. Upadacitinib is characterized by a bi-exponential and dose-proportional PK profile with a functional half-life of ~4 h [18]. Elimination of upadacitinib occurs through hepatic metabolization [CYP3A4 & CYP2D6] (80%) and urinary elimination (20%).

The efficacy of upadacitinib as an induction and maintenance therapy in CD has been evaluated in a phase II 16-week induction and 36-week blinded extension study (CELEST); data from this trial has been presented in abstract form [19–22]. Patients with moderate-to-severe CD (defined by CDAI 220–450, average daily liquid/soft SF score ≥2.5 or daily AP score ≥2.0, and total SES-CD ≥6 or ≥4 for isolated ileal disease) were randomized to placebo or one of five upadacitinib doses (3, 6, 12, 24 mg BID or 24 mg daily) for 16 weeks, followed by a 36-week blinded extension treatment period. Patients enrolled in the CELEST trial had almost exclusively failed or were intolerant to TNF antagonists (96%). The co-primary endpoints were clinical remission (defined by SF ≤ 1.5 and AP ≤1, both not worse than baseline) and endoscopic remission (SES-CD ≤4 and ≥2-point reduction from baseline with no subscore >1). A modified clinical remission definition of SF ≤ 2.8 and AP ≤1.0, both not worse than baseline in patients with SF ≥ 4 or AP ≥2.0 at baseline was also used. Other secondary endpoints included clinical response (defined by ≥ 30% reduction in AP or SF) and endoscopic response (defined by ≥ 25% reduction in baseline SES-CD).

A total of 220 patients were randomized (37 to placebo, 39 to 3 mg BID, 37 to 6 mg BID, 36 to 12 mg BID, 36 to 24 mg BID, and 35 to 24 mg upadacitinib daily). A clear dose response relationship for clinical remission was not observed, although at week 16, a higher proportion of patients treated with upadacitinib 6 mg BID (27%, 10/37) achieved PRO-defined clinical remission compared to placebo (11%, 4/37) ($p < 0.10$). Amongst patients receiving corticosteroids at baseline, treatment with upadacitinib 24 mg BID was associated with significantly higher rates of clinical remission (33.3%, 5/15) compared to placebo (0%, $p < 0.05$) [21]. A clearer dose response relationship for endoscopic remission was observed: no patients treated with placebo achieved endoscopic remission whereas 14% (5/35) of patients receiving upadacitinib 24 mg daily and 22% (8/36) of patients receiving upadacitinib 24 mg BID achieved endoscopic remission ($p < 0.05$ and $p < 0.01$, respectively). Higher proportions of patients treated with upadacitinib 6 mg BID, 12 mg BID, 24 mg BID, and 24 mg daily achieved ≥25% and >50% reductions in SES-CD from baseline compared to placebo (14% and 3%, respectively) ($p < 0.05$ for all comparisons). Patients treated with the highest upadacitinib dose (24 mg BID) also had significantly greater reductions in high sensitivity CRP compared to placebo (−14.8 vs. −0.1 mg/L, $p < 0.01$).

The pooled proportion of patients experiencing any treatment-emergent AE in the induction study were 73% (27/37) in the placebo group and 82% (150/183) in the upadacitinib arms. Serious adverse events occurred in 5% (2/37) of patients receiving placebo and 15% (27/183) of patients receiving upadacitinib. Eight patients receiving upadacitinib experienced a serious infectious event, including *Eschericia coli* bacteremia, subcutaneous abscess, anorectal abscess, two severe urinary tract infections, and four cases of sepsis. Two patients experienced a myocardial infarction and two small bowel perforations occurred (all amongst patients receiving upadacitinib).

Patients completing 16-week induction were then randomized 1:1:1 to double-blind upadacitinib 3 mg BID, 12 mg BID, or 24 mg daily for 36 weeks; a subsequent protocol amendment dropped the 24 mg daily dose in favor of an intermediate 6 mg BID treatment arm. A total of 180 patients were re-randomized and results were stratified by clinical and endoscopic response at week 16. Amongst clinical responders at week 16, clinical remission was achieved in 25% (8/32), 28.6% (4/14), 41.4% (12/29), and 31.6% (6/19) of patients receiving upadacitinib 3 mg BID, 6 mg BID, 12 mg BID, and 24 mg daily, respectively, at week 52. Amongst clinical and endoscopic responders at week 16, 25% (5/20), 25% (2/8), 37.5% (6/16), and 10% (1/10) of patients receiving upadacitinib 3 mg BID, 6 mg BID, 12 mg BID, and 24 mg BID, respectively, achieved week 52 endoscopic remission. No new safety signals were identified in the maintenance study: among 178 patients included in the safety analysis, AEs were reported in 70% (125/178), serious AEs in 15% (26/178), and infections in 34% (60/178) of patients receiving upadacitinib.

Based on promising clinical and endoscopic efficacy in the CELEST trial, particularly in a difficult-to-treat patient CD population failing biologic therapy, two large phase III trials enrolling patients failing either biologic (NCT03345836) or conventional non-biologic (NCT03345849) therapies are now enrolling.

Summary

JAK inhibitors are an attractive therapeutic option given that these are orally bioavailable molecules with an acceptable safety profile that have demonstrated efficacy in patients with CD, both naïve and with prior exposure to TNF antagonists. Head-to-head trials are needed to determine positioning of JAK inhibitors for the treatment of moderate-to-severe active CD alongside TNF antagonists, ustekinumab and vedolizumab. Network meta-analyses, based on indirect comparisons, have indicated that in patients with moderate-to-severe UC, the efficacy of JAK inhibitors was comparable to the aforementioned biologics [23] and that in patients with prior exposure to TNF antagonists, JAK inhibitors were ranked highest as a second-line treatment [24]. Similar results are to be expected in patients with CD, but network meta-analyses are currently not available.

As more JAK inhibitors are being evaluated, it is clear that study design of clinical trials for this class of therapy is key. Ensuring enrolment criteria include patients with active inflammation and using central reading of endoscopy for enrolment and endpoint adjudication can reduce clinical and endoscopic placebo response rates as shown for filgotinib in comparison to tofacitinib trials. Furthermore, assessment of endoscopic ulcer resolution before 10 weeks may be too early for achieving the stringent endpoint of SES-CD score ≤4. Most compounds undergo extensive hepatic metabolization, whereby the PK profile may be impacted by other compounds that are either inducers, inhibitors, or substrates of CYP enzymes. Although well described for the systemic circulation, the PK profile of JAK inhibitors at site of action, in the gut tissue, remains to be elucidated. From a PD perspective, further translational research needs to unravel the specific mechanism of action of JAK inhibitors, the importance of JAK selectivity and/or locally acting JAK inhibitors. This could help identify predictors of response to JAK inhibitors and may guide patients to the most effective treatment more efficiently.

Practice points

- JAK inhibitors have the potential to become an attractive treatment option for patients with active moderate-to-severe CD.

Research points

- Head-to-head trials are needed to determine positioning of JAK inhibitors for the treatment of patients with moderate-to-severe active CD.
- Determining the exposure-response relationship of JAK inhibitors at site of action, in the gut tissue, may help with drug development of more targeted therapies with less systemic exposure.
- Identifying predictors and biomarkers of efficacy to JAK inhibitors may help to guide patients to the most effective therapy more efficiently.

- Real-world evidence studies are needed to evaluate the safety (e.g. risk of infections) of treatment with JAK inhibitors in patients with moderate-to-severe CD.

Conflict of interest statement

CM has no conflict of interest to declare. VJ reports consulting fees from AbbVie, Eli Lilly, GlaxoSmithKline, Arena pharmaceuticals, Genentech, Pendopharm, Sandoz, Merck, Takeda, Janssen, Robarts Clinical Trials, Topivert, Celltrion, and speaker's fees from Takeda, Janssen, Shire, Ferring, Abbvie, Pfizer. NVC reports research support from R-Biopharm and Takeda and consulting fees from Boehringer Ingelheim, Janssen, Pfizer, Progenity, Prometheus and Takeda, outside of the submitted work.

Acknowledgement

Dr. Christopher Ma is supported by a Clinician Fellowship from the Canadian Institutes of Health Research and the Canadian Association of Gastroenterology. Dr. Niels Vande Casteele is supported by a Research Scholar Award from the American Gastroenterological Association.

References

[1] Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. Immunol Rev 2009;228:273–87.
[2] Shuai K, Liu B. Regulation of JAK-STAT signalling in the immune system. Nat Rev Immunol 2003;3:900–11.
[3] Lovato P, Brender C, Agnholt J, Kelsen J, Kaltoft K, Svejgaard A, et al. Constitutive STAT3 activation in intestinal T cells from patients with Crohn's disease. J Biol Chem 2003;278:16777–81.
[4] Schreiber S, Rosenstiel P, Hampe J, Nikolaus S, Groessner B, Schottelius A, et al. Activation of signal transducer and activator of transcription (STAT) 1 in human chronic inflammatory bowel disease. Gut 2002;51:379–85.
[5] Van Rompaey L, Galien R, van der Aar EM, Clement-Lacroix P, Nelles L, Smets B, et al. Preclinical characterization of GLPG0634, a selective inhibitor of JAK1, for the treatment of inflammatory diseases. J Immunol 2013;191:3568–77.
[6] Mukherjee A, Hazra A, Smith MK, Martin SW, Mould DR, Su C, et al. Exposure-response characterization of tofacitinib efficacy in moderate to severe ulcerative colitis: results from a dose-ranging phase 2 trial. Br J Clin Pharmacol 2018;84:1136–45.
[7] Dowty ME, Lin J, Ryder TF, Wang W, Walker GS, Vaz A, et al. The pharmacokinetics, metabolism, and clearance mechanisms of tofacitinib, a janus kinase inhibitor, in humans. Drug Metab Dispos 2014;42:759–73.
[8] Sandborn WJ, Ghosh S, Panes J, Vranic I, Wang W, Niezychowski W, et al. A phase 2 study of tofacitinib, an oral Janus kinase inhibitor, in patients with Crohn's disease. Clin Gastroenterol Hepatol 2014;12:1485–14893 e2.
[9] Panes J, Sandborn WJ, Schreiber S, Sands BE, Vermeire S, D'Haens G, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. Gut 2017;66:1049–59.
[10] Sands BE, Panés J, Higgins PDR, Moscariello M, Chan G, Su C, et al. Post-hoc analysis of tofacitinib crohn's disease phase 2 induction efficacy in subgroups with baseline endoscopic or biomarker evidence of inflammation. Inflamm Bowel Dis 2018;24:S56–7.
[11] Galien R, Vayssiere B, De Vos S, Auberval M, Vandeghinste N, Dupont S, et al. Analysis of the JAK1 selectivity of GLPG0634 and its main metabolite in different species, healthy volunteers and rheumatoid arthritis patients. Arthritis Rheum 2013;65. Abstract 478.
[12] Namour F, Diderichsen PM, Cox E, Vayssiere B, Van der Aa A, Tasset C, et al. Pharmacokinetics and pharmacokinetic/pharmacodynamic modeling of filgotinib (GLPG0634), a selective JAK1 inhibitor, in support of phase IIB dose selection. Clin Pharmacokinet 2015;54:859–74.
[13] Vermeire S, Schreiber S, Petryka R, Kuehbacher T, Hebuterne X, Roblin X, et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial. Lancet 2017;389:266–75.
[14] Sandborn WJ, Su C, Sands BE, D'Haens GR, Vermeire S, Schreiber S, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med 2017;376:1723–36.
[15] Cohen S, Radominski SC, Gomez-Reino JJ, Wang L, Krishnaswami S, Wood SP, et al. Analysis of infections and all-cause mortality in phase II, phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. Arthritis Rheum 2014;66:2924–37.
[16] Sands BE, Anderson FH, Bernstein CN, Chey WY, Feagan BG, Fedorak RN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. N Engl J Med 2004;350:876–85.
[17] Voss J, Graff C, Schwartz A, Hyland D, Argiriadi M, Camp H, et al. THU0127 Pharmacodynamics of A Novel JAK1 selective inhibitor in rat arthritis and anemia models and in healthy human subjects. Ann Rheum Dis 2014;73:222.
[18] Mohamed MF, Camp HS, Jiang P, Padley RJ, Asatryan A, Othman AA. Pharmacokinetics, safety and tolerability of ABT-494, a novel selective JAK 1 inhibitor, in healthy volunteers and subjects with rheumatoid arthritis. Clin Pharmacokinet 2016;55:1547–58.
[19] Sandborn WJ, Feagan BG, Panes J, D'Haens GR, Colombel JF, Zhou Q, et al. Safety and efficacy of ABT-494 (upadacitinib), an oral Jak1 inhibitor, as induction therapy in patients with crohn's disease: results from celest. Gastroenterology 2017;152:S1308–9.
[20] Panes J, Sandborn WJ, Loftus EV, Van Assche GA, Ghosh S, Zhou Q, et al. Efficacy and safety of upadacitinib maintenance treatment for moderate to severe crohn's disease: results from the celest study. Gastroenterology 2018;154. S-178-S-9.
[21] Panaccione R, Atreya R, Ferrante M, Dubinsky M, Sands BE, Abreu MT, et al. Upadacitinib improves steroid-free clinical and endoscopic endpoints in patients with crohn's disease: data from the celest study. Gastroenterology 2018;154. S-384.
[22] Peyrin-Biroulet L, Louis E, Loftus EV, Lee WJ, Cataldi F, Lacerda AP, et al. Improvement in patient-reported outcomes with upadacitinib in patients with moderately to severely active crohn's disease: 52-week data from the celest study. United European Gastroenterol J. 2018;6.
[23] Bonovas S, Lytras T, Nikolopoulos G, Peyrin-Biroulet L, Danese S. Systematic review with network meta-analysis: comparative assessment of tofacitinib and biological therapies for moderate-to-severe ulcerative colitis. Aliment Pharmacol Ther 2018;47:454–65.
[24] Singh S, Fumery M, Sandborn WJ, Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. Aliment Pharmacol Ther 2018;47:162–75.