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Editorial

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JAK or GUT Selectivity: Tipping the Balance for Efficacy and Safety in Ulcerative Colitis

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We read with great interest the article by Sandborn *et al*. in the recent issue of the *Journal of Crohn's and Colitis*[1] regarding TD-1473, a new gut-selective JAnus Kinase [JAK] inhibitor for the treatment of ulcerative colitis [UC]. TD-1473 is an orally administered small molecule that acts on the JAK/STAT pathway, inhibiting key mechanisms of the innate and adaptive immune response.[2] There are four isoforms of JAK [JAK1, JAK2, JAK3, and TYK2].[2] JAK3 is expressed mainly in haematopoietic cells [myeloid and lymphoid cells], and the others are ubiquitously expressed.[2]

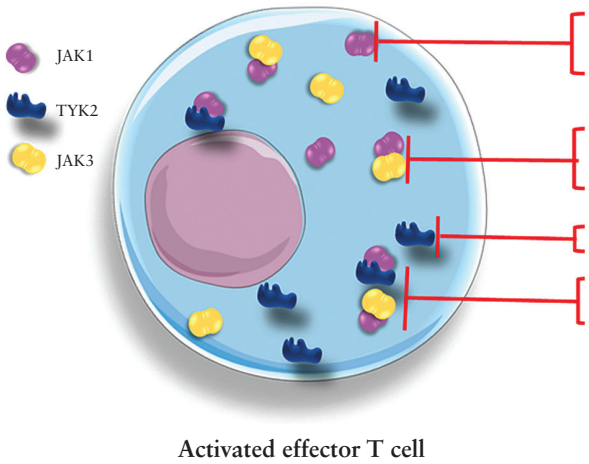
In 2018, tofacitinib was the first pan-JAK inhibitor to be approved for the treatment of patients with moderately to severely active UC.[3] Despite the proven efficacy of tofacitinib, several adverse events [AEs] have been reported, including an increase in low-density lipoprotein [LDL] cholesterol values, numerical reduction of leukocytes with consequent increased risk of severe infections, malignancies, and pulmonary embolisms.[4,5]

Similarly to tofacitinib, TD-1473 inhibits all JAK isoforms, but the inhibition is restricted only to the gut, suggesting an equivalent efficacy and a theoretically reduced percentage of AEs.[6] Sandborn *et al*.[1] analysed TD-1473 preclinical data and TD-1473 safety results from phase 1a and 1b trial on healthy volunteers and UC patients, respectively. In in vitro models, TD-1473 had tofacitinib-like potency in targeting JAK and was effective in reducing experimental colitis in murine models.[1] In addition, high colon drug concentrations and low serum plasma levels were found.[1] In healthy volunteers, the drug was safe as a single dose [up to 1000 mg] and as a daily dose [up to 300 mg per day] for 14 consecutive days.[1] In UC patients, the advantageous TD-1473 pharmacokinetic profile was confirmed, with high drug tissue values and low plasma concentrations.[1] After 28 days, there were no significant differences between patients treated with three different doses [20, 80, or 270 mg] of TD-1473 and placebo in terms of AEs.[1] An increase in LDL values was found in only one patient treated with 80 mg TD-1473.[1] Furthermore, although the study was not powered to assess drug efficacy, the clinical, biochemical [C-reactive protein and faecal calprotectin], endoscopic, and histological outcomes had a positive efficacy trend in the TD-1473 groups compared with placebo.[1] The promising pharmacokinetic characteristics of TD-1473 and its apparently reassuring safety profile were likely related to its selectivity. TD-1473 belongs to the 'second-generation' of small molecules which, unlike the 'first-generation' [e.g. tofacitinib], are selective towards specific targets. In recent years, several second-generation small molecules have been developed and are still being tested [Figure 1].

Filgotinib and upadacitinib are selective JAK1 inhibitors, PF-06700841 and PF-06651600 selectively block JAK1/TYK2 and JAK3, respectively, and BMS-986165 targets TYK2.[7] TD-1473 is the only molecule that simultaneously inhibits all JAK isoforms with a selective gut mechanism.[7] However, it is important to underline that JAK selectivity is related to drug concentration, and dosage increase results in loss of selectivity.[7] The major TD-1473 advantages are the rapid action mechanism and the oral administration; the main concerns about its use are related to the drug class safety profile.[1] Importantly, the JAK signalling blockage interferes with several mechanisms, including haematopoiesis in the case of JAK2 and proinflammatory cytokines in the case of JAK1, TYK2, and JAK3.[7] For this reason, systemic inhibition of JAK2 could lead to impaired haematopoiesis, causing a reduction in blood cell counts, and the blockage of the other kinases could determine an increased rate of infections.[7]

Interestingly, no alteration in red blood cells, white blood cells, or platelet count was reported after treatment with TD-1473 and no opportunistic or serious infections were recorded.[1] These results could be justified by the selective TD-1473 action mechanism and confirmed by its pharmacokinetics, which demonstrates a high drug tissue concentration and a low concentration in plasma.[1] Indeed, the favourable ratio between serum and histological drug levels could allow TD-1473 to act mainly in inflamed tissues and reduce systemic exposure.[8]

The gut selectivity story started with vedolizumab, which was shown to block only the gut α4β7 integrin and to have an excellent safety profile.[9] Despite the undoubted benefits, the main limitation of gut selectivity was the lack of control of extra-intestinal



Compound	Intracellular target	Gut selectivity?	Disease	Status
Filgotinib	JAK1	NO	CD	Phase III
			UC	Phase III
Upadacitinib	JAK1	NO	CD	Phase III
			UC	Phase III
Tofacitinib	Pan-JAK	NO	UC	Approved
TD-1473	Pan-JAK	**YES**	CD	Phase II
			UC	Phase III
BMS-986165	TYK2	NO	CD	Phase II
PF-06700841/ PF-06651600	JAK1/JAK3/ TYK2	NO	CD	Phase II
			UC	Phase II

Figure 1. JAK inhibitors approved or being tested for the treatment of chronic inflammatory bowel diseases.

manifestations related to intestinal inflammation.[10] This could also apply to TD-1473, but further investigations are needed. In a recent systematic review with meta-analysis[11] of randomised clinical trials, tofacitinib, filgotinib, peficitinib, upadacitinib, and TD-1473 showed to be effective in determining clinical response in patients with Crohn's disease [CD] and clinical and endoscopic response in UC subjects. An increased risk of infections was detected in patients treated with JAK inhibitors, and the onset of herpes zoster [HZ] infections was recognised as a likely drug class adverse event.[11]

Another systematic review and meta-analysis[12] confirmed the high risk of HZ infections after treatment with small molecules [tofacitinib, upadacitinib, filgotinib, and baricitinib], but no association was found with other AEs, including infections, severe infections, malignancies, thromboembolic events, and cardiovascular risk. Based on these data, utmost attention should be paid and HZ vaccination should be recommended for all patients before starting treatment with JAK inhibitors.[13]

The small molecules' development is implementing the treatment armamentarium of patients with inflammatory bowel diseases [IBD]. On the other hand it is creating new dilemmas regarding drug choice, management, and follow-up of patients, and the prospect of personalised treatments based on the characteristics of each individual patient. In this context of progressive expansion of the available therapeutic options, the drug benefit-risk ratio should be a key factor when choosing first-line treatment. The ongoing phase 2/3 study [NCT03758443] will provide essential data to confirm the safety and to assess the efficacy of TD-1473 in UC. Additional information on TD-1473 safety will be obtained from the recruiting phase 2 study in CD [NCT03635112].[14] Finally, head-to-head trials between the JAK inhibitors and between JAK inhibitors and biologics are necessary to clarify the role of JAK selectivity in the efficacy and safety of small molecules, to correctly position these drugs in a therapeutic algorithm, and to evaluate the feasibility of any combination therapies.

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Conflict of Interest

FD'A declares no conflict of interest. LP-B has served as a speaker, consultant, and advisory board member for Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC- Pharma, Index Pharmaceuticals, Amgen, Sandoz, For- ward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, Theravance. SD has served as a speaker, consultant, and advisory board member for Schering-Plough, AbbVie, Actelion, Alphawasserman, AstraZeneca, Cellerix, Cosmo Pharmaceuticals, Ferring, Genentech, Grunenthal, Johnson and Johnson, Millenium Takeda, MSD, Nikkiso Europe GmbH, Novo Nordisk, Nycomed, Pfizer, Pharmacosmos, UCB Pharma, and Vifor.

Author Contributions

FD wrote the article. LPB critically reviewed the content of the paper and supervised the project. SD conceived of and critically revised the manuscript. The manuscript was approved by all authors.

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