



Editorial

JAK Inhibitors: Back to Small Molecules for the Treatment of IBD

Julian Panés^a and Severine Vermeire^b

^aHospital Clínic de Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain ^bDepartment of Gastroenterology, University Hospitals Leuven, Leuven, Belgium

Corresponding author: Severine Vermeire, MD PhD, Department of Gastroenterology, University hospitals Leuven, Departmental Chair CHROMETA (Chronic diseases & Metabolism), KU Leuven, Herestraat 49, 3000 Leuven, Belgium. Tel: +32 16 34 42 25; Fax: +32 16 34 44 19; Email: Severine.Vermeire@uzleuven.be

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Inflammatory bowel disease [IBD] is now known to be a polygenic disorder in which gene-environment interactions play a role, although the aetiology of both Crohn's disease and ulcerative colitis remains poorly understood. Nevertheless, there have been significant advances in understanding various components involved in the pathophysiology of these conditions, and over the past decade the role of several key pro-inflammatory cytokines, such as TNF, IL-12, IL-23, and cell-associated targets, such as $\alpha_4\beta_7$ integrin or S1P receptors, have become evident and constitute the rationale for drug development programmes modulating these targets.¹

Current treatment recommendations for ulcerative colitis and Crohn's disease emphasise the importance of early therapeutic intervention and treat-to-target strategies in which treatment adjustments are determined by measurement of therapeutic response, with the target of remission and mucosal healing.² Even considering a treat-to-target approach, clinical guidelines commonly recommend initiating treatment with conventional synthetic therapies such as mesalazine [in ulcerative colitis], glucocorticoids, and an immunomodulator in case of steroid dependence, followed—in those patients with inadequate response to conventional therapy—by parenterally administered biologic therapy.^{3,4} The introduction two decades ago of monoclonal antibodies targeting TNF revolutionised the long-term outcomes for many patients with IBD, in terms of improved quality of life and reduced disability. But in spite of these advances, many unmet needs remain. For example, among patients started on a biologic, drug remission is only achieved and sustained at 1 year in less than one-third of treated patients.⁵ Furthermore, even in those achieving remission according to clinical or endoscopic scores, symptoms may persist including increased stool frequency, abdominal pain, joint manifestations, and fatigue.⁶ Furthermore, loss of response to biologic drugs, in part as a consequence of the immunogenicity of the administered protein, as well as drug discontinuations due to intolerance or adverse effects, emphasise the ongoing need for a new generation of alternative therapies. Therefore,

further advances remain necessary with a goal of restoring immune homeostasis and more complete symptom control.

In the past two decades, all new therapies approved for the treatment of inflammatory bowel disease by European or American regulatory agencies have been monoclonal antibodies. These are large molecular mass molecules unable to penetrate the cell membrane and are therefore directed against extracellular targets. By contrast, low molecular mass, orally available, small molecules can penetrate the lipid bilayer of the cell membrane and modulate the activity of components of the intracellular inflammatory signalling cascade. Several small molecules are under development as an attractive alternative to biologic therapies for IBD. The most promising among these to date have been inhibitors of the Janus kinase [JAK] enzymes. The JAK family comprises four members: JAK1, JAK2, JAK3, and TYK2.⁷

A number of studies have demonstrated expression of different JAK isoforms and the downstream signal transducer and activator of transcription [STAT] proteins in the inflamed intestine of patients with Crohn's disease and ulcerative colitis. Many pro-inflammatory cytokines implicated in IBD pathogenesis bind to Type I and Type II cytokine receptors that are dependent on the JAK-STAT pathway for signal transduction.⁸ Therefore, JAK inhibitors are capable of modulating various components of the redundant inflammatory cascade, whereas monoclonal antibodies affect in a highly selective manner a single component, each strategy having potential advantages or disadvantages.

As for JAK inhibitors, several molecules with variable degrees of selectivity and specificity for the JAK enzymes are being investigated in IBD but also in other domains of medicine, such as haematology [myelofibrosis, polycythaemia vera]. In immune-mediated diseases such as rheumatoid arthritis, psoriatic arthritis, psoriasis, atopic dermatitis, alopecia areata, lupus erythematosus, the JAK-STAT pathway is significantly implicated in disease biology and is targeted.

It is clear from the successful development programme of tofacitinib, and the promising results of other JAK inhibitors in both ulcerative colitis [UC] and Crohn's disease [CD], that JAK inhibition has a place in the management of IBD. However, long-term safety studies in rheumatological populations, and in patients with ulcerative colitis taking tofacitinib, have reported a higher risk for reactivation of herpes zoster, especially with higher doses.⁹ This increased risk is probably a class effect of all JAK inhibitors, and likely related to inhibition of IFN and IL-15. Besides, there is uncertainty around a potential thrombogenic risk, as demonstrated in rheumatoid arthritis patients.¹⁰ Therefore, more selective JAK-1, JAK-3 or TYK2 inhibitors are expected to result in improved safety, while keeping the same efficacy. They nevertheless remain systemic drugs, and the best way of treating IBD patients would include a gut-selective JAK inhibitor, with high intestinal exposure and target engagement, without systemic effects. Developments in all these areas are ongoing.

Finally, where to position JAK-inhibitors in IBD management? Although results from tofacitinib and other JAK selective inhibitors show efficacy in both TNF-naïve and experienced patients, positioning in the market depends on many more variables including price setting, presence of [competitive but cheaper] biosimilar agents, safety aspects, speed of onset of action, stability of response, efficacy with extra-intestinal symptoms, use during pregnancy, etc. Also, we are starting to see head-to-head studies with biologic agents, of which results will undoubtedly influence clinical practice. Likewise, JAK inhibitors merit head-to-head testing against the currently approved anti-TNFs, vedolizumab and ustekinumab. In the end, patient preference should not be neglected, as we ask our patients to be compliant for many years.

In conclusion, with the introduction of JAK inhibitors in the therapeutic landscape of IBD, more options are offered to patients and clinicians. This can only be applauded. Both the academic and the pharmaceutical community should now invest in large international strategic trials and biomarker discovery, to identify the most appropriate drug class in a given disease subtype and patient subtype.

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