Filgotinib for Crohn’s disease—expanding treatment options

For decades since the disease’s first description in 1932, there have been few effective options available to treat Crohn’s disease other than corticosteroids, aminosalicylates, thiopurines, and methotrexate. However, the past two decades have witnessed the approval of six different agents in the USA and Europe—three tumour necrosis factor antagonists, two anti-integrins, and an anti-interleukin 12/23 antibody. However, despite these treatment options, unmet need remains with as many as one-quarter of patients failing to achieve even an initial response to each therapeutic class, and a substantial proportion of responders experiencing loss of response subsequently.

In The Lancet, Séverine Vermeire and colleagues report the results of a phase 2 multicentre randomised controlled trial examining the efficacy of filgotinib, a selective janus kinase (JAK1) inhibitor, in Crohn’s disease. Previous phase 2 studies of the non-selective JAK inhibitor, tofacitinib, suggested efficacy in ulcerative colitis but only a modest biochemical response and no statistically significant improvement in clinical remission or response rates in Crohn’s disease. In the present trial, 174 patients with moderate-to-severe Crohn’s disease confirmed by centrally read endoscopy were randomised across 52 centres in Europe to placebo or filgotinib 200 mg daily for 10 weeks. An exploratory arm of the study randomly assigned patients to placebo, filgotinib 100 mg daily, or filgotinib 200 mg daily for a further 10 weeks. The primary outcome was clinical remission at 10 weeks. Secondary outcomes including endoscopic and histological response, and the impact on biomarkers of inflammation and patient-reported outcomes were examined. In an intention-to-treat analysis, 60 (47%) of 128 patients randomly assigned to active treatment achieved clinical remission compared with ten (23%) of 44 patients in the placebo group (difference 24 percentage points [95% CI 9–39], p=0.0077). The difference in rates of remission was more striking for anti-TNF naïve patients (34 [60%] of 57 patients in the filgotinib group vs two [13%] of 16 patients in the placebo group) than anti-TNF experienced patients (26 [37%] of 71 patients in the filgotinib group vs eight [29%] of 28 patients in the placebo group). Endoscopic response and remission rates overall were, not surprisingly, modest in the 10 week trial; few achieved full mucosal healing or deep remission across all groups. There are several strengths in this well designed trial. The use of a number of clinical, endoscopic, and biochemical endpoints ensures robustness of benefit of treatment and provides support for further investigation of this therapeutic mechanism. The requirement for endoscopically active disease at randomisation and use of central readers to adjudicate eligibility and efficacy increased the clarity in the efficacy signal and reduced the potential of bias.

If phase 3 clinical trials were to confirm the efficacy of filgotinib in Crohn’s disease, what will be the potential position of this therapeutic class in our armamentarium? Oral administration makes this an attractive option for many patients over intravenous or injectable routes. Additionally, small molecules might not experience the loss of response due to immunogenicity that plagues uses of biologicals. In this trial, there was little drop in efficacy between weeks 10 and 20 in those subsequently randomised to placebo. Whether using filgotinib in combination with a conventional immunomodulator would yield greater benefits is unknown as concomitant therapy was not permitted in this trial.

One major knowledge gap with filgotinib in this trial, as has been noted with vedolizumab, is that the rates of response and incremental benefit are lower in anti-TNF exposed patients compared with those naive to biologicals. Thus, whereas new treatment options with distinct mechanisms of action are a welcome addition to our armamentarium, they might not be sufficient to meet the needs of the growing proportion of patients refractory to anti-TNF therapies, a population that merits further study particularly as this therapeutic class continues to be the one most commonly used for moderate-to-severe Crohn’s disease. In patients naive to biologicals, the absence of comparative effectiveness trials makes it a continuing challenge for patients and physicians to make an informed decision about selecting a therapeutic class for initial trial. Genetic, tissue, or serum biomarkers to predict response are a much needed important first step towards an informed, personalised, and tailored treatment, and a rigorous attempt at developing such markers should be encouraged for all ongoing clinical trials to define such predictors. In the not too distant future, one can hope that each additional
therapeutic class will expand the Venn diagram of overlapping circles to cover the entire canvas of needs of patients with inflammatory bowel diseases.

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