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Filgotinib in Crohn's Disease: JAK Is Back

Vermeire S, Schreiber S, Petryka R, 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;389:266–275.

Crohn's disease (CD) is a chronic destructive and disabling condition. Monoclonal antibodies (anti-tumor necrosis factor [TNF], vedolizumab, and ustekinumab), have revolutionized the management of IBD patients, significantly improving patients' quality of life and allowing intestinal healing. However, more than one-third of patients do not respond to these drugs and 10% to 20% of primary responders will lose response every year, leading to repeat hospitalizations and surgeries. Therefore, there remains a high unmet need for CD patients.

Small molecules represent the next generation of selective drugs in inflammatory bowel disease (IBD), including CD. One of the main advantages of small molecules over biologics is the potential of oral administration that can dramatically improve patient satisfaction compared with the parenteral administration required for monoclonal antibodies. Moreover, the short half-life of small molecules may constitute an advantage especially in situations where rapid drug elimination is desired, such as adverse events, surgery, or pregnancy (Gut 2017;66:199–209). Janus kinases (JAKs) are intracellular cytoplasmic tyrosine kinases transducing cytokine-mediated activation of membrane receptors, by the phosphorylation of signal transducers and activators of transcription (STATs; Am J Physiol Gastrointest Liver Physiol 2016;310:G155–162; Pharmacol Res 2013;76:1–8). Four JAK subtypes (JAK1, JAK2, JAK3, and TYK2) are currently known, as implicated in the pathogenesis of immune-mediated disease (Pharmacol Res 2016;111:784–803) and, in particular, of IBD. Therefore, JAK inhibitors may be a valid alternative for the treatment of IBD in the near future. Recent data from clinical trials on the efficacy and safety of tofacitinib, a JAK inhibitor that blocks mainly JAK-1 and JAK-3, but also JAK-2 to a lesser extent, show interesting results in the induction and maintenance of clinical remission in moderate-to-severe ulcerative colitis patients (N Engl J Med 2017;376:1723-1736), whereas data on CD did not show significant differences in terms of clinical remission toward placebo (Gut 2017;66:1049-1059). In this context, the results of the FITZROY trial were eagerly awaited.

Vermeire et al investigated efficacy and safety of a novel selective JAK inhibitor, filgotinib (GLPG0634, GS-6034) in patients with moderately to severely active CD (Lancet 2017;389:266–275). Filgotinib is 30 times more selective for JAK1 over JAK2, and 50 times more selective for JAK1 over JAK3 (Lancet 2017;389:266–275). This phase II study (the FITZROY study) was conducted in 52 centers in 9 different countries across Europe. More than 311 patients were screened, and 174 patients were randomized 3:1 to receive filgotinib 200 mg once a day or placebo for 10 weeks. Patients who responded at week 10 were re-randomized to receive either filgotinib 200 mg once a day, filgotinib 100 mg once a day, or placebo for an additional 10-week period. Patients were stratified according to C-reactive protein (CRP) levels at baseline ($\leq$10 or $>$10 mg/L), concomitant use of oral steroids, and previous exposure to anti-TNF agents.

The primary endpoint was clinical remission, defined as a Crohn's Disease Activity Index (CDAI) score of $<$150 at week 10. Of all randomized patients, data from 128 patients treated with filgotinib and 44 treated with placebo study were analyzed, as the intention-to-treat population. At week 10, clinical response was achieved in 59% of patients receiving filgotinib and in 41% of those who received placebo ($P = .0453$). Among patients who were naïve to anti-TNF, clinical response was achieved in 67% of patients treated filgotinib compared with 44% in the placebo group, whereas 54% and 39% of patients previously exposed to anti-TNF were clinical responders at week 10. Clinical remission was achieved in 47% of patients receiving filgotinib compared with 23% receiving placebo ($P = .0077$). Moreover, a greater proportion of patients treated with filgotinib achieved PRO2 remission, a composite index based on daily stool frequency and self-reported abdominal pain, compared with placebo (50% vs 30%; $P = .0277$). Histologic improvement according to the D'Haens score (Inflamm Bowel Dis 2014;20:2092–2103; Gastroenterology 1998;114:262–267) and improved quality of life was more frequent in patients treated with filgotinib compared with

placebo ($P = .03$ for the global D'Haens score, $P = .02$ for the activity D'Haens subscore, and $P = .004$ for the Inflammatory Bowel Disease Questionnaire). No differences were observed in all endoscopic outcomes (endoscopic response, defined as a decrease of the Simple Endoscopic Score for Crohn's Disease (SES-CD) score by $\geq$50% compared with baseline, endoscopic remission, defined as a SES-CD $\leq$ 4, and ulcerated surface subscore $\leq$ 1 in all 5 segments, mucosal healing, defined as a SES-CD of 0, and deep remission, defined as a combination of endoscopic remission and CDAI $\leq$ 150, as assessed by a single central reader (all $P > .05$), although serologic and fecal markers of inflammation (CRP and calprotectin) had a significant reduction ($\geq$ 50%) in 27% of patients receiving filgotinib compared with 4% in the placebo group ($P = .02$).

At week 20, between 50% and 71% of initial filgotinib 200 mg responders showed clinical remission according to the re-randomization to filgotinib or placebo, and between 67% and 79% showed clinical response. Among patients who did not respond to placebo at week 10, 59% of patients achieved clinical response at week 20 after being switched to filgotinib 100 mg, and 32% showed clinical remission.

The safety analysis did not reveal any difference in terms of rates of adverse events, serious adverse events, serious infections, or adverse events leading to discontinuation.

Comment. Pharmacologic JAK inhibition has been shown to be effective in patients with ulcerative colitis (N Engl J Med 2012;367:616–624), but contrasting data have emerged in CD patients. Tofacitinib, a nonselective JAK inhibitor showed no clear efficacy over placebo in 2 phase II randomized, controlled trials for induction and maintenance of remission in moderately to severely active CD patients (Gut 2017;PMID: 28209624). This recent trial conducted >280 patients in the induction phase, and 180 in the maintenance phase, did not show superiority of tofacitinib 5 or 10 mg twice daily over placebo in terms of clinical remission. However, a significant reduction in CRP levels ($P < .001$ for both doses of tofacitinib), but not in fecal calprotectin levels was observed. The lack of defined thresholds for biomarkers, the lack of endoscopic data, and the slow tapering of prolonged corticosteroid therapy may have resulted in higher placebo response rates, and the consequent no difference toward the active study drug groups. This explanation may be supported by the significant reduction observed in PRO2-75 and PRO3-80 from patients treated with both dosages of tofacitinib compared with placebo.

The FITZROY study has several strengths. First, the clinical efficacy of pharmacologic inhibition of JAK1-mediated pathway results significantly higher than placebo in several outcomes, such as clinical response, clinical remission, quality of life, biomarkers, and histologic improvement. All these rates are in line with current approved molecules for CD. Second, this is the first trial exploring and showing efficacy over PRO2 as a clinical outcome, as recently requested by the European Medicine Agency and the Food and Drug Administration. However, after 2 decades of trials on biologics using CDAI as a primary endpoint, PRO2 are not fully validated and the optimal cutoff defining response and remission is yet to be determined.

Although filgotinib was effective in inducing clinical and biological remission, endoscopic response and mucosal healing rates were not different from placebo. As discussed by the authors, one explanation of this limitation may be the short time for the assessment of endoscopic outcomes as the optimal timing for assessing mucosal healing with JAK inhibitors in CD is unknown. In contrast with endoscopic data, inflammatory biomarkers, such as CRP and calprotectin levels, resulted significantly decreased of $\geq$50% since baseline in 27% of patients compared with only 4% of patients, confirming the biological effects of JAK inhibition and their potential relevance to inflammation in CD.

Filgotinib seemed to be generally safe and well-tolerated. Compared with placebo, there were no signals suggesting an increased risk of opportunistic infections or other relevant side effects. The most common adverse events were nasopharyngitis and urinary tract infections, which also occurred in similar rates in patients treated with placebo, whereas only 1 case of pneumonia, 1 case of herpes zoster reactivation, and 4 cases of oral candidiasis over none reported in the placebo group were observed. The good safety and tolerability profile of filgotinib was in line with the previous data on >700 patients with rheumatoid arthritis enrolled in the DARWIN trials (Ann Rheum Dis 2016;Epub ahead of print Ann Rheum Dis 2016;Epub ahead of print). However, because phase II trials are underpowered to establish the safety profile of a drug and have a very limited follow-up time, further larger prospective long-term data are needed to confirm the preliminary observations in IBD.

In contrast with tofacitinib, patients treated with filgotinib responded in a different way according to previous exposure to anti-TNF. Those who were naïve to anti-TNFs had a 2-fold increased response rate compared with those who experienced at least 1 anti-TNF in the past, similar to data obtained with monoclonal antibodies (anti-TNF agents, vedolizumab, ustekinumab). However, the overall efficacy data suggest that filgotinib could be effective in both naïve and previously exposed to anti-TNF patients.

In conclusion, the results of this study open again new perspectives on the role of small molecules, and, in particular, on the role of selective JAK1 inhibition in CD in a near future, both on the clinical and the translational point of view. The next phase III of the clinical development of filgotinib will hopefully confirm these encouraging results for this new generation of molecules in IBD.

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Conflicts of interest
The authors have made the following disclosures: Gionata Fiorino served as a consultant and Advisory Board Member for MSD, AbbVie, Takeda, Janssen, Mundipharma, Celltrion, Alfa Wassermann, Sandoz, Pfizer; Silvio Danese has served as a speaker, consultant, and advisory board member for Schering-Plough, Abbott Laboratories, Merck, UCB-pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Danone, Alpha Wasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor, and Johnson & Johnson. LPB: Honoraria from Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boerhinger-Ingelheim, Lilly, HAC-Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis.

A Penetrating Look at Eosinophilic Esophagitis Pathogenesis: Direct Antigen Exposure in the Esophagus?

Marietta EV, Geno DM, Smyrk TC, et al. Presence of intra-epithelial food antigen in patients with active eosinophilic oesophagitis. Aliment Pharmacol Ther 2017;45:427–433.

Eosinophilic esophagitis (EoE) is a chronic Th-2–mediated inflammatory condition that is most likely caused by exposure to food antigens (Gastroenterology 2015;148:1143–1157). Dietary elimination therapy is effective for many patients with EoE, and is considered a first-line management option (Curr Gastroenterol Rep 2015;17:464). How the immune system is activated by food antigens in EoE remains a mystery, especially because food passage to the stomach is relatively rapid (within approximately 10 seconds), and the esophageal mucosa is a stratified squamous epithelium (and thus relatively impenetrable and lacking in antigen-presenting cells; Pharmacol Ther 2014;146:12–22). Therefore, the 'smoking gun' whereby food antigens are shown to elicit the characteristic eosinophil rich infiltrate on contact with esophageal mucosa remains elusive.

The study by Marietta et al aims to answer part of the question, "Do food antigens contact the esophageal mucosa and cause EoE?" by assessing if gliadin, a protein component of gluten, may penetrate the esophageal mucosa (Aliment Pharmacol Ther 2017;45:427–433). A secondary endpoint was the quantification of dilation of intracellular spaces and comparison with esophageal eosinophil count, using light microscopy. Ten patients with active EoE off treatment, 10 patients with inactive EoE after budesonide treatment, 5 patients with EoE on a gluten-free diet, and 6 healthy controls were included. Esophageal biopsies were performed on all patients and processed in a standardized fashion, a rabbit polyclonal IgG antibody to gliadin being applied to the frozen section. In an attempt to determine the time dependence of gliadin penetration, a gliadin-rich soy solution was sprayed onto the distal esophageal lumen (during gastroscopy) in patients with EoE (active or inactive) before obtaining a second set of biopsies.

There are several findings of note. First, gliadin was found to penetrate the esophageal mucosa, and could be visualized within the cytoplasm as well as the intracellular spaces. Second, gliadin was found in the esophageal mucosa at greater concentrations in those with active EoE, compared with inactive EoE, and was not found in healthy controls. Third, infusion of gliadin rich soy sauce 5 minutes before repeat biopsy did not influence the intensity of gliadin staining. Taken together, the results of this novel study support the plausibility of direct immune activation by contact of food antigens with the esophageal mucosa, although several caveats are raised, and the process does not seem to occur within minutes.

Comment. This study is novel and addresses a perplexing question in EoE pathogenesis, specifically whether antigens are present within the esophageal epithelium. Although EoE is considered to be an antigen-mediated disorder, it is neither clear how food antigens initially trigger the disease process in an individual patient, nor where these food antigens may be absorbed and presented in the gastrointestinal tract. This latter point is of interest; until recently, the esophagus was considered to be a transport organ, rather than an absorptive or immunologically active one. Additionally, owing to the very short transit time in the esophagus, it is unknown how long an antigen must contact the mucosa to be able to be absorbed. There have been conflicting results in the literature related to barrier function defects and antigen absorption. Katzka et al initially suggested that small bowel permeability could be compromised, but Warners et al recently contradicted these findings by demonstrating an impairment in esophageal, but not duodenal barrier integrity (Gut 2015;64:538–543; Am J Gastroenterol 2017 Apr 18 Epub ahead of print). The results of the Marietta study showing that gliadin itself is present in the esophageal mucosa in patients with active EoE, less notable in posttreatment EoE patients with inactive disease, and not found in controls presents a proof of principle that a large antigen, such as gliadin, can be present in the esophageal epithelium (Aliment Pharmacol Ther 2017;45:427–433). Moreover, the correlation between increased gliadin staining and more severe dilated intercellular spaces, could suggest a possible mechanism.

The results, however, should be interpreted with caution, and potential limitations are discussed by the authors. One issue is the absence of a control group with gastroesophageal reflux disease. When considering the premise that binding of antigliadin antibodies is indicative of in vivo antigen penetration (and presumably later antigen presentation and immune activation), it is worth raising the alternative possibility that inflammation per se makes the sampled tissue more friable and likely to bind the anti-gliadin antibodies, as opposed to representing an antigen/antibody interaction per se. Indeed, although the use of DAPI (4',6-diamidino-2-phenylindole) nuclear counterstain