Dear Colleagues:

Thank you for your participation in this Ask the Faculty Q&A for the program The ***JAK-STAT Pathway in Inflammatory Bowel Disease—Expert Insights and Discussion of the Latest Research***. We are responding here to 2 questions that participants submitted. We are pleased to share this information with you, and hope you find it a clinically useful addition to the program.

1. What do you consider to be the place of JAK-STAT inhibitors in the treatment pathway for patients with IBD?

JAK inhibitors have a potential place in treating patients with moderate-to-severe IBD who have not been previously treated with biologic agents, who relapse, or, as salvage therapy for patients who fail biologic therapy.[1-2] JAK-STAT inhibitors also have potential as agents in combination regimens, or as substitutes for corticosteroids in the first-line setting. Many of the participants in the induction and maintenance OCTAVE trials for tofacitinib were treatment refractory and had failed either anti-tumor necrosis factor (TNF) or conventional therapy, and approximately half of the OCTAVE study participants were receiving corticosteroids at the time of treatment with tofacititib. Although results for tofacitinib have been conflicting in patients with moderate-to-severe Crohn's disease, filgotinib has shown efficacy in these patients.[2] Patients 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, but filgotinib could also be effective in patients who are both naïve and previously exposed to anti-TNF. JAK inhibition has other advantages. Oral therapies may be preferable for many patients vs injectable agents. These small molecules also have a short half-life and rapid drug elimination, which could be beneficial in situations such as adverse events, surgery, or pregnancy. The issue of immunogenicity is also much less with an oral agent. Evidence of mucosal healing in some patients in the clinical trials suggests that these agents fulfill many of the treatment goals in IBD patients. [3-4] However, JAK-STAT inhibitors may be unsuitable for patients with hyperlipidemia and multiple cardiac risk factors. We still need additional research to identify which patients should be treated with JAK inhibitors, including biomarker studies, and what the optimal doses are for patients with UC and Crohn's disease.

2. What strategies should I use to monitor patients being treated with these newer medications?

Neither tofacitib nor filgotinib has yet been approved for treating patients with ulcerative colitis or Crohn's disease, but clinical trial results reveal clues about potential monitoring parameters. Induction and maintenance of clinical remission are treatment goals for patients with IBD. Efficacy in clinical trials for filgotinib in Crohn's disease was measured via clinical response rates and clinical remission rates defined as Crohn's Disease Activity Index (CDAI) scoring of less than 150 at week 10.[2] Laboratory data for monitoring filgotinib included vital signs, ECG, and biomarker evaluation (C-reactive protein and fecal calprotectin). A colonoscopy was done and biopsies taken for histopathological analysis during screening and at week 10. In clinical practice, endoscopy, cross-sectional imaging, or biomarkers, may be feasible monitoring options for patients being treated with JAK inhibitors to monitor progress toward treatment goals. In addition to monitoring patients for treatment response, clinicians will also need to offer patients counsel on how to recognize and when to report signs and symptoms associated with treatment-related adverse events, including, for filgotinib, urinary tract infections, nasopharyngitis, and worsening of underlying disease. Clinical trial monitoring parameters for tofacitinib were similar to those associated with filgotinib, with the addition of lipid profiles to assess patients for the development of dose-dependent hyperlipidemia, and close monitoring for signs of infection. The average

concentration of tofacitinib was similar between patients who were in remission and those who were not, at the end of induction and maintenance trials. So, unlike monoclonal antibodies, therapeutic drug monitoring will likely be less necessary in patients treated with tofacitinib.

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2. 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

3. Danese S, Grisham M, Hodge J, Telliez JB. JAK inhibition using tofacitinib for inflammatory bowel disease treatment: a hub for multiple inflammatory cytokines. *Am J Physiol Gastrointest Liver Physiol.* 2016;310:G155-62

4. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): Determining therapeutic goals for treat-to-target. *Am J Gastroenterol.* 2015;110(9):1324-1338.

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