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OFFICE perspectives

The JAK-STAT Pathway in Inflammatory Bowel Disease—Expert Insights and Discussion of the Latest Research

Dear Colleague:

Induction and maintenance of remission for patients with inflammatory bowel disease (IBD), remains challenging, and approximately 25% of patients do not respond to treatment. This CME-certified activity reviews emerging agents that target the JAK-STAT pathway in IBD, and, if approved, how they might be used in the clinic to improve outcomes for patients.

3.1 million people over 18 years old have a diagnosis of ulcerative colitis or Crohn's disease.

- People with IBD are often diagnosed later in the progression of this disease, risking a worsening of disease and serious complications.
- ~25% patients fail to achieve response with conventional and biologic therapies.

The pathogenesis of IBD is multifactorial.

- A tightly regulated interaction between microbiota, the gut-associated immune system, and epithelial defense mechanisms, maintains homeostasis within the intestinal mucosa.
- Genetic and environmental pressures can disrupt homeostasis and result in a dysregulated immune and bacterial interaction pathway.
- Treatment typically aims to reduce the overactive and proinflammatory pathways that take place in the inflamed mucosa.

Janus kinases (JAKs) play a role in regulating cellular proliferation, differentiation, and immune cell functioning.

- JAK inhibitors modulate signaling of proinflammatory cytokines that are integral to lymphocyte activation, function and proliferation.

Tofacitinib is a small molecule, oral JAK inhibitor with specificity for JAK kinases 1 and 3.

- A phase 2 trial involving patients with moderate-to-severe active UC showed superior rates of clinical response, clinical remission, and endoscopic remission, with a 78% response rate in the highest dose group (15 mg).
- In a long-term study, tofacitinib demonstrated significantly greater efficacy vs placebo; at week 52, 34.3% of patients on the 5-mg dose and 40.6% of patients on the 10-mg dose reached remission. Efficacy was similar in patients previously treated with antitumor necrosis factor inhibitors (TNFi) and in TNFi-naïve patients.
- Only small treatment effects have been observed for tofacitinib vs placebo in phase 2 Crohn's disease studies; however, the reduction in objective inflammatory biomarker concentrations suggests that tofacitinib might have a biologic effect in CD.
- Tofacitinib has an established safety profile in rheumatoid arthritis; adverse events in UC include anemia, infection risk, and dose-dependent hyperlipidemia.

Filgotinib 100 mg and 200 mg is a selective JAK inhibitor being investigated in IBD.

- In a phase 2 Crohn's disease study, clinical response and remission were higher for filgotinib 200 mg vs placebo (59% vs 41%; 47% vs 23%, respectively).
- Clinical response and remission rates were higher for anti-TNFi-naïve patients.
- The main adverse events were associated with worsening of underlying disease; the lipid profile was favorable, with an increase in high-density lipoprotein cholesterol, but no change in low-density lipoprotein cholesterol.

JAK inhibitors may have a role to play 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.

- Oral therapies may be preferable for many patients vs injectable agents.
- JAK-STAT inhibitors may be unsuitable for patients with hyperlipidemia and multiple cardiac risk factors.

Yours sincerely,

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