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IBD

Could oral Janus kinase inhibitor be a new drug treatment for active ulcerative colitis?

The findings of a double-blind placebo-controlled, phase II trial indicate that tofacitinib—an oral inhibitor of the Janus kinase (JAK) family of kinases—has potential as a new treatment option for moderately to severely active ulcerative colitis.

At present, the treatment options for ulcerative colitis are limited to 5-aminosalicylates, steroids, immunosuppressive agents and anti-TNF agents. "Drugs with novel mechanisms of action are needed because many patients do not respond to these medications," explains lead author William Sandborn. "Also, infliximab is administered intravenously, and orally administered medications would be appealing."

> "...tofacitinib [induced] clinical response, clinical remission and mucosal healing..."

The role of JAKs in the pathogenesis of ulcerative colitis has not been elucidated, but their blockade by tofacitinib affects multiple cytokines (interleukins 2, 4, 7, 9, 15 and 21) key to the activation, function and proliferation of lymphocytes; such blockade is expected to result in T-cell and B-cell suppression and maintenance of regulatory T-cell function. Also, tofacitinib has shown efficacy for the treatment of rheumatoid arthritis and psoriasis and for preventing rejection of renal transplants. With this in mind, the authors decided to test the efficacy of tofacitinib in patients with ulcerative colitis and determine the appropriate drug dose to use.

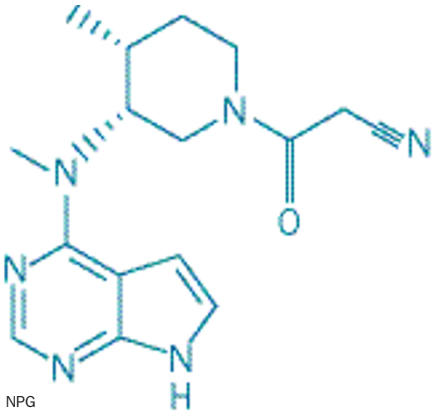
The international, multicentre study, sponsored by Pfizer, was performed over an 8-week period, with a 4-week follow-up period. Eligible participants were adults who had been diagnosed with ulcerative colitis at least 3 months earlier, had a Mayo score of 6–12 and endoscopic evidence of moderately or severely active disease. Concomitant use of oral mesalamine or oral glucocorticoids was allowed at a stable dose of 30 mg or less per day, but azathioprine, 6-mercaptopurine and methotrexate had to be discontinued immediately before starting therapy. Anti-TNF therapy had to be discontinued at least 8 weeks prior to study entry.

194 of 195 patients randomly assigned to receive a study drug were included in the final analysis (the excluded patient was in the placebo group and never received the study drug). 31, 33, 33 and 49 patients received 0.5 mg, 3 mg, 10 mg and 15 mg of tofacitinib twice daily, respectively, and 48 patients received placebo.

At 8 weeks, a clinical response was achieved by 42% of the placebo group and by 32% (P=0.39), 48% (P=0.55), 61% (P=0.10) and 78% (P<0.001) of patients receiving tofacitinib 0.5 mg, 3 mg, 10 mg and 15 mg, respectively. Clinical remission, endoscopic response and endoscopic remission were achieved most notably by patients receiving one of the two highest doses of tofacitinib. The team also measured the effect of tofacitinib on the concentrations of C-reactive protein and fecal calprotectin; it reduced levels of both the marker of inflammation and the marker of IBD.

"The most significant findings were that tofacitinib 10 and 15 mg twice daily were effective for inducing clinical response, clinical remission and mucosal healing, and in reducing levels of the biomarker fecal calprotectin," summarizes Sandborn.

A range of adverse events were reported by patients receiving the study drug or placebo, from abdominal pain to dizziness and headache. The most common infection-related adverse events were influenza and nasopharyngitis; two serious adverse events related to infection were reported in the tofacitinib 10 mg group. Adverse events led to drug discontinuation in 8% of patients in the placebo group and ~3.5% of patients receiving tofacitinib



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(2, 0, 1 and 2 patients in the 0.5 mg, 3 mg, 10 mg and 15 mg groups, respectively). At 8 weeks, tofacitinib increased LDL and HDL cholesterol levels in a dose-dependent manner, but this effect was reversed after the drug was discontinued. Reductions in absolute neutrophil count to <1500 cells per cubic millimetre were observed during the study period in three patients receiving tofacitinib.

"Until now we have been targeting one cytokine at a time. This study shows that multiple anti-cytokine therapy is a promising strategy," says Silvio Danese, Head of the IBD Center at Instituto Clinico Humanitas in Milan. "Obviously, we need to see long-term efficacy and safety data. LDL and HDL cholesterol levels rose in patients with rheumatoid arthritis taking tofacitinib, but, unlike these patients, patients with ulcerative colitis do not have increased mortality from atherothrombotic events."

So, what are the next steps for the team? "Large phase III induction and maintenance trials with tofacitinib are now underway," clarifies Sandborn.

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