Tofacitinib, an oral Janus kinases inhibitor, in active ulcerative colitis.

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Introduction

Ulcerative colitis (UC) is a chronic life long inflammatory disease of the colon, which can affect daily life by impairment of work and leisure activities. Unfortunately, etiology remains unknown and, differently from Crohn's disease, few therapies have been shown to be effective in inducing and maintaining long-term remission. Steroids and mesalazine are widely used to treat UC flares, but steroids cannot be used in the long term, and they are not able to change the natural history of the disease. Evidence on efficacy and safety of thiopurines is weak. Biological therapies, directed against Tumor Necrosis Factor (TNF)-α, are effective in inducing and maintaining remission, heal the colonic mucosa and reducing the risk of colectomy, but, up to now, only infliximab and, very recently, adalimumab have been approved for active moderate-to-severe UC1-3. A consistent number of subjects does not respond, or is intolerant to anti TNFs, and therefore cannot be treated appropriately without frequent courses of steroids. New effective therapies other than steroids are urgently needed in UC patients, with different mechanism of action than anti TNFs.

Sandborn et al. conducted a phase 2 prospective multicenter international randomized controlled trial4 to investigate efficacy and safety of tofacitinib, a selective oral inhibitor of Janus kinases (JAK), which can block several pro-inflammatory gamma chain-containing cytokines, and therefore interfere with lymphocyte activation, function and proliferation. They enrolled 194 adults with moderately to severely active ulcerative colitis. Subjects were randomly assigned to receive tofacitinib at a dose of 0.5 mg, 3 mg, 10 mg, or 15 mg or placebo twice daily for 8 weeks. The primary outcome of this study was a clinical response at week 8, defined as an absolute decrease from baseline in the Mayo Score with objective reduction of rectal bleeding.

Why is this study important?

The Authors found that 78% of subjects receiving the highest dose of tofacitinib (15 mg bid) had clinical response compared to 42% of those receiving placebo ($p<0.001$). Clinical remission was observed in 48% and 41% of subjects receiving 10 and 15 mg bid respectively compared to 10% of placebo ($p<0.001$). The response and remission rates for the lowest doses were not statistically significantly different from placebo. Endoscopic response was found in 78% of subjects receiving 15 mg bid of tofacitinib vs. 46% receiving placebo ($p<0.001$), endoscopic remission was observed in 30% and 27% receiving 10 mg and 15 mg bid respectively compared to 2% of placebo. No differences were found for lower dosages.

The most frequent adverse events were infections and nasopharingitis. Two patients receiving 10 mg had serious adverse events (abscesses). Three patients had neutropenia (< 1500/mm3), and in all patients, receiving tofacitinib, a reversible dose dependant increase in lipid profile was observed (both HDL and LDL levels), which remains unexplained. Generally, adverse event rates were not statistically significantly higher that placebo group.

Conclusion

This study showed the efficacy of tofacitinib at week 8 in inducing clinical and endoscopic response and remission. Such promising results need to be confirmed in large phase 3 trials, but it opens further perspectives on new molecules to be used in ulcerative colitis, other than anti TNF agents. Tofacitinib might be an effective and safe alternative in patients, who do not respond or are intolerant to current biological agents, or even as first line biological therapy after failure of immunosuppressants.

Some remarks rose from the reading of this paper. First one, the increase of lipids should be further investigated. This could be especially concerning in the maintenance phase, with severe adverse events on the long-term (i.e. cardiovascular thrombosis). Secondly, endoscopic response rates in the placebo group are surprisingly high, similarly with recent studies on adalimumab in ulcerative colitis, which can depend on the natural course of UC or the high interobserver variability in terms of endoscopic lesions in UC. Third, the efficacy of tofacitinib might address further investigation on the role of JAK kinases and similar molecules in the pathogenesis of UC.

References

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