FDA Approves Tofacitinib For Ulcerative Colitis

Ulcerative colitis (UC) is a chronic non curable inflammatory disease affecting the large intestine (1). This disease manifested by ulceration in the colon, bloody diarrhea and systemic manifestations including anemia seen in the advance stages. Its exact etiology is not fully understood (2). Current therapies for this disease include: anti-inflammatory and immunosuppressant agents in the early stages with more aggressive options such as the anti-tumor necrosis alpha (TNF-α) in the severe stages (3). Many patients may still do not achieve complete response on these medications and still experience episode of relapse (4) thus; additional new treatment options with different mechanism of action are needed to increase the efficacy rate. Janus kinase is a family of tyrosine kinase proteins responsible to regulate the signaling of many immune mediators including interferons that are implicated in the pathogenesis of UC. Recently, FDA approves tofacitinib, an oral tyrosine kinase inhibitor for the management of UC (5).

This approval was based on three randomized, double blinded, placebo controlled multi - center clinical trials (phase 3). These trials were conducted from April 2012 till May 2016. The aim of these studies was to evaluate the effect of tofacitinib in the management of moderate to severe UC. The first two trials (called OCTAVE 1 and OCTAVE 2) aimed to study the effect of tofacitinib for induction of remission, where the third trial (OCTAVE Sustain) that followed the first two studies aimed to evaluate its effect on maintaining the remission. After receiving the international review board (IRB) approval and written informed consent provided to the patients, eligible patients (598 patients, 541patients in OCTAVE1, OCTAVE 2 respectively) were randomly assigned in a 4:1 ratio to receive either tofacitinib 10 mg twice daily or placebo for a total of eight weeks. Patients who achieved clinical response in these two trials were eligible to enroll in OCTAVE Sustain trial. In this trial, 593 patients were randomized in a 1:1:1 ratio to receive either tofacitinib 5 mg twice daily, 10 mg twice daily or placebo for a total of 52 weeks. Inclusion criteria for the three studies were: age>18, confirmed diagnosis of UC for at least 4 months, moderate-severe UC confirmed by Mayo endoscopic score of 6-12 (the score ranges from 0-12, with higher values means more severe UC), Patient have had treatment failure with/ or have had unacceptable side effects from at least one of the following: glucocorticoids, azathioprine, mercaptopurine, infliximab, or adalimumab. Oral aminosalisylates were permitted during the treatment. Exclusion criteria were: Crohn's disease, ulcerative colitis limited to the distal 15 cm of colon, fulminant colitis, toxic megacolon, ischemic colitis. Azathioprine, mercaptopurine, infliximab, or adalimumab, were not allowed to be given concomitantly with tofacitinib. Eligible patients for the third trial were those who attain clinical response in the first two

studies. Clinical response was defined as a reduction in Mayo score by at least 3 points with reduction in rectal bleeding.

For the first two studies, the primary end points were remission (defined as Mayo score of ≤2, rectal bleeding subscore of 0) at week 8. The key secondary end point was mucosal healing at week 8. In the OCTAVE Sustain trial, the primary end point was maintaining the remission after 52 weeks; key secondary end points were mucosal healing and glucocorticoid-free (for at least 4 weeks before the assessment).

The results from the study OCTAVE 1 trial showed that 18.5 % of patients received tofacitinib compared with 8.2% of those received placebo attain remission at week 8 (P value <0.007). In the second study, 16.6% of patients received tofacitinib achieved remission versus 3.6% of those received placebo. (P value < 0.001). In OCTAVE Sustain trial, 34.3% of patients in 5 mg group and 40.6% in 10 mg group compared with 11.1% of the placebo group achieved remission (P value < 0.001). Mucosal healing is statistically significant in patients received tofacitinib compared to placebo in the three trials. The need for steroid therapy was also lower in a statistically significant difference compared with the placebo group (P value< 0.001) (5).

Side effects were reported more frequently in patients receiving tofacitinib (5, 10 mg) compared with the placebo group. Increasing the risk of infections (23% compared with 15.6 % in the placebo group) was the most reported side effect.

Based on the analysis of these three clinical trials, the efficacy and safety of tofacitinib make it an option for patients with moderate to severe UC including those who fail the anti-TNF therapy.

In conclusion, tofacitinib seems to provide a new era in the treatment of moderate to severe ulcerative colitis with its ability to induce and maintain mucosal healing compared with placebo. Further future studies are still needed to evaluate its long term safety and efficacy.

References

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