Ulcerative Colitis – Curtain Raiser Provides a Promising Glimpse

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Just two months after the US Food and Drug Administration's (FDA's) approval, the European Commission has approved Pfizer's Xeljanz® (tofacitinib) for the treatment of moderately to severely active ulcerative colitis (UC) in adults who have failed to respond adequately to or are intolerant of conventional therapy or a biologic agent; this makes the drug the first-in-class oral Janus kinase (JAK) inhibitor. It is also expected to receive approval in Japan soon, the clinical and cost-effectiveness evaluation is in progress in UK as well.

Before Xeljanz®, there was no oral treatment available for moderately to severely active UC that could both induce and maintain steroid-free remission. According to the president of the European Crohn's and Colitis Organization's (ECCO's) governing board, "this approval of Xeljanz®, the first JAK inhibitor to be approved for this condition, offers the ulcerative colitis community an additional treatment option."

Demand for safe and efficacious oral therapies for UC treatment has been constant, as the available treatment options – tumor necrosis factor (TNF) blockers and the alpha 4 integrin inhibitor (Entyvio®) – can be administered only via parenteral routes. Remicade® (infliximab) was the first TNF blocker approved for moderately to severely active UC in 2005, followed by Humira® (adalimumab) and Simponi® (golimumab). Evidence suggests that these parenterally administered treatment options are associated with major limitations such as

- Parenteral administration that necessitates regular visits to infusion centers for intravenous administration or specific storage needs for subcutaneously administered drugs
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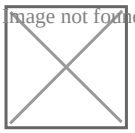
Infusion or injection site reactions observed in 20% of Remicade®-treated patients compared with 10% of placebo; 20% of Humira®-treated patients compared to 14% in the placebo; 3.4% of Simponi®-treated patients compared with 1.5% in control-treated patient and 4% of Entyvio®-treated patients compared with 3% of placebo.

Given that UC is a chronic and lifelong debilitating condition, it has a profound impact on a patient's quality of life and takes a significant toll psychologically. Oral therapies with ease of administration could, therefore, be a treatment options that overcomes the above mentioned shortcomings of parenteral treatment options.

Xeljanz® approval is potentially the start of an exciting new era of oral therapeutic options for UC treatment. Acuity Knowledge Partners estimates 45 therapies under development for UC treatment, of which 11 would be available to treat patients with moderately to severely active UC by 2024, with four of these 11 therapies are expected to offer oral administration.



A little further down the pipeline, other JAK inhibitors are being developed, including AbbVie's upadacitinib and Gilead/Galapagos' filgotinib. Both companies' JAK inhibitors, currently in phase III development, are more selective for JAK1 than Xeljanz® (JAK1/JAK2/JAK3). The clinical meaningfulness of selectivity toward the JAK enzyme is likely to emerge in the ongoing phase III trials.

Other promising oral therapies are the sphingosine-1-phosphate receptor (S1PR) modulators that could influence the treatment landscape significantly. Celgene is developing ozanimod, a highly selective S1PR modulator; long-term treatment with the drug has shown durable efficacy, safety and tolerability at the two-year follow-up of the Touchstone extension trial. Ozanimod's moderate onset of action could be balanced with a long-term effect. "The time to effect may be a little slower, but the long-term effect seems to be as good as or better than other mechanisms of action", said Stephen Hanauer, MD, medical director at Northwestern University, Chicago.
Another S1PR modulator, etrasimod by Arena Pharmaceuticals, met both primary and secondary outcomes with statistical significance for patients given a higher dose (2mg) of the drug for 12 weeks in the phase II OASIS trial. Arena Pharmaceuticals intends to initiate the phase III program for etrasimod soon.

The primary end points of phase II trials of both S1PR modulators were different, and cross-trial comparison is complex. Phase III trial results of the two drugs could provide a better understanding of their clinical profiles and associated advantages. At present, Celgene appears to be ahead in the clinical development program for the novel oral drug ozanimod, as

the company is already recruiting for the phase III trial.

It will likely be a couple of years before we see whether these oral therapies offer a significant clinical benefit in addition to the dosage advantage or whether they should be prescribed to a limited patient pool facing challenges in receiving parenteral therapies.

The Life Sciences Team at Acuity Knowledge Partners has supported large and mid-tier pharma and healthcare firms in assessing the competitive landscape and formulating new product development strategies. We have experience in multiple therapeutic areas, including gastrointestinal disorders and oncology and cardiovascular diseases. We endeavor to provide our clients with robust and actionable insights, to distinguish their products and maximize their market potential.

Bibliography

1. Prescribing information;
Remicade®,
Simponi®, Humira® and Entyvio®

2. Tofacitinib Advisory Committee Briefing Materials, Pfizer 2018

3. Press Releases, tofacitinib updates; US FDA, NICE UK and MHLW Japan

4. Mocci G et al, Dermatological adverse reactions during anti-TNF treatments: Focus on inflammatory bowel disease, Journal of Crohn's and colitis, 2013

5. Company website (Company reports 2017 and press releases);
AbbVie,
Gilead,
Galapagos,
Pfizer,
Arena Pharmaceuticals and
Celgene

6. Kling J, et al. Ozanimod has lasting effect on ulcerative colitis, GI Hepatology News, 2016

7. Clinical trials;
NCT02447302,
NCT01647516,
NCT01465763,
NCT01458951

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