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Editorial

# Revolutionary Therapies in Patients with Moderate-to-Severe IBD in 2018

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## Editorial

There has been great progress towards the development of new agents for the treatment of Inflammatory Bowel Disease (IBD). New therapeutic avenues have become possible, including the development of agents that target specific genetic pathways found to be relevant in patients with IBD. Moderate-to-severe IBD patients have required an infusion or subcutaneous injection therapies in the past, but there is an influx of new oral medications in development and a promising one is already approved by the FDA, tofacitinib. We will summarize this progress in this editorial.

IBD is a chronic and progressive immune mediated condition of the Gastrointestinal (GI) tract influenced by both genetic and environmental factors. IBD is comprised of Chronic Ulcerative Colitis (CUC) and Crohn's Disease (CD). While both autoimmune disorders affect the GI tract, CUC is limited to the colon and rectum, whereas CD may affect any part of the GI tract. Patients with these conditions require lifelong medical therapy, or sometime surgery, depending on their disease severity and complications. It is recommended that moderate-to-severe IBD patients be treated with a combination of anti-TNF agents' with immunomodulatory therapy to increase the likelihood of a steroid-free induction and mucosal healing with long-term remission [1]. Since 1997, where the first randomized controlled trial showed the effectiveness of infliximab, there has been a significant improvement in IBD patients' management. This has led to the introduction of many other anti-TNF biological agents such as adalimumab, certolizumab and golimumab. Anti-TNFs induce approximately 30% clinical remission and 50% clinical response in patients with moderate-to-severe CD. Moreover, the secondary loss of response may vary between 10 to 50% depending on the maintenance treatment follow-up period. According to our own experience and general census, the treat-to target strategy with anti-TNFs is a crucial approach to changing the natural history of moderate-to-severe IBD patients. Earlier intervention with a top-down therapy may be future direction in the selected patients with a close therapeutic drug concentration monitoring as needed [1-6].

Although therapies with anti-TNFs have reduced relapse rates, allowed mucosal healing and, as a result, improved long-term outcomes in substantial portions of moderate-to-severe IBD patients, there is a need for new agents. Therefore, the gut-selective humanized monoclonal antibody against alfa-4-beta-7 integrin (Vedolizumab) is now FDA approved as another effective and safe treatment option for both moderate-to-severe CUC and CD patients either before or after anti-TNFs refractory patients' management [7,8].

Another biologic agent, ustekinumab (Stelara), an anti-IL 12/23, became FDA approved in September 2016 for patients with moderate-to-severe Crohn's disease. This fully human IgG1k monoclonal antibody binds the p40 subunit of IL-12 and IL-23. In addition to initial promising studies with ustekinumab, current evidence shows very encouraging results with ustekinumab in moderate-to-severe CD patients refractory to anti-TNFs, with significantly increased rates of clinical response and remission compared to placebo [9,10]. In addition, both ustekinumab and vedolizumab are attractive options with a relatively low immunogenicity, a favorable safety profile, relatively lesser risks of infections and malignancies [7-10].

Tofacitinib is a Janus Kinases (JAK) 1-3 inhibitor that results in suppression of B and T cells as an important target in IBD. This oral agent has been studied in various autoimmune conditions, including rheumatoid arthritis and psoriasis with good overall efficacy and an acceptable safety profile. Also, tofacitinib is most recently approved by the FDA to be used in moderate-to-severe CUC patients with significant clinical remission and response rates compared to placebo [11]. However, tofacitinib did not exhibit better results than placebo in patients with CD [12] by the doses used in the research trials. The reported adverse events were nasopharyngitis, opportunistic infections, lymphopenia, hyperlipidemia, transient serum transaminase and creatinine elevations [11,12].

Biosimilars have been produced to closely resemble the anti-TNFs whose patent have expired and are manufactured with the same amino acid sequences as a reference anti-TNF. While they may reduce cost (possibly around 40%), biosimilars are not identical to anti-TNFs.

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Although the FDA required PK/PD profiles, safety, switch and immunogenicity data with these "econosimilars", more than 20 biosimilars have been used in European and various other countries since 2005 in moderate-to-severe IBD patients [13,14]. Table 1 depicts five biosimilars are already approved by the FDA for patients with moderate-to-severe IBD.

| **Anti-TNF Agents:** |
|---|
| Infliximab [Remicade] |
| Adalimumab [Humira] |
| Certolizumab [Cimzia] |
| Golimumab [Simponi] |
| **Integrin Inhibitor Agents:** |
| Natalizumab [Tysabri] |
| Vedolizumab [Entyvio] |
| **Anti-IL-12/23 Agent:** |
| Ustekinumab [Stelara] |
| **JAK -3 Inhibitors:** |
| Tofacitinib [Xeljanz] |
| **Biosimilars (BSs):** |
| As Infliximab BSs |
| Inflectra |
| Renflexis |
| Ixifi |
| As Adalimumab BSs |
| Amjevita |
| Cyltezo |

**Table 1:** FDA approved agents in 2018.

All FDA approved and commercially available agents for moderate-to-severe CUC and CD patients are shown in table 1. Despite the tremendous progress, there are a significant number of IBD patients who are still refractory to these available agents. The future looks promising as several new target specific treatment options have been identified [15-17] and research trials are underway to determine the efficacy and safety of these agents as shown in table 2.

| | | |
|---|---|---|
| Etrolizumab | Anti-beta-7 | GI spec. integrin antagonist |
| Tocilizumab | Anti-IL-6 | Humanized MCA |
| Brazikumab and others | Anti-IL-23 | Humanized MCA |
| Filgotinib and others* | Anti-JAK 1 | Immunomodulator |
| Ozanimod and others* | Sphingosine 1P1R | Lymph. receptor agonist |
| AJM300* | Anti-alfa-4 | Integrin antagonist |
| Apremilast* | Phosphodiesterase 4 | Lysis of cAMP |
| Laquinimod* | Quinolone-3-carboxidw | Promoting regulatory T-cells |
| PPC* | GI mucus | Phosphatidylcholine |
| *PO agents | | |
| Modified from ref. # 15 | | |

**Table 2:** New agents in development for the treatment of IBD.

Etrolizumab is an anti-beta-7 GI specific integrin antagonist, and available research trial results are quite similar to vedolizumab as an effective and safe promising biologic agent for moderate to severe CUC patients. There is not enough convincing data with this agent in patients with CD at this time [15-17].

IL-6 is a proinflammatory cytokine activating immune cells. Limited studies with humanized monoclonal IL-6 antibody, Tocilizumab, showed a higher clinical response in moderate to severe CD patients compared to placebo. However, clinical remission rates and endoscopic improvement were not significantly different in tocilizumab treated patients compared to placebo [16]. No further studies with this agent are planned at this time [15-17].

Several new IL-23 specific monoclonal antibodies are in clinical trial development including brazikumab, risankizumab, tildrakizumab and guselkumab. Latest phase II trial has promising results of risankizumab and brazikumab in CD patients with limited adverse events [16,18].

There is a great need for effective, tolerable, safe and economical PO agents for treatment of moderate-to-severe IBD patients [15,16-20]. As shown in table 2, the last six are promising orally delivered small molecule target-focused agents.

Filgotinib is an oral JAK-1 inhibitor. A recent post-hoc-analysis showed clinical remission with this immunomodulatory januskinase inhibitor better than placebo regardless of disease location and duration in patients with moderate-to-severe CD [19,20]. This agent has quite similar adverse events as seen with tofacitinib, and its testicular toxicity is under investigation. Currently phase III trials are underway in moderate-to-severe CUC and CD patients. Another oral JAK-1 inhibitor, upadacitinib, showed promising results in moderate-to-severe CD patients. A number other of JAK-1 inhibitors, such as peficitinib, are currently in the development phase.

Sphingosine receptor modulators are also in the clinical trial phase for IBD therapy. Ozanimod, an oral sphingosine receptor agonist, is under investigation for treatment of moderate-to-severe CUC and CD patients [15,16,21]. It stimulates S1P1 on lymphocytes resulting in receptor internalization and a functional antagonism that causes sequestration of lymphocytes in a peripheral lymphoid organs and reduction in circulating lymphocytes. It has been shown in phase II clinical trials that Ozanimod was significantly superior to placebo at inducing mucosal healing and clinical remission in moderate-to-severe CUC and CD patients [20]. Minor adverse events were noted with this promising agent. In this group, other lymphocyte receptor agonists such as etrasimod and amiselimod are currently in the development phase.

AJM300 is a small molecule oral alpha-4-integrin antagonist that acts by inhibiting the binding of lymphocyte on inflamed intestinal epithelium as an anti trafficking agent. Phase II clinical trials in patients with moderately active CUC showed much better results with AJM300 compared to the placebo group. Mucosal healing rates were also better with AJM300 compared to the placebo. No PML cases were observed during this study, but a phase III study is pending with this promising agent that has shown to be well tolerated with minimal adverse events [15-17,22].

Apremilast is an oral small molecule inhibitor of Phosphodiesterase-4 (PDE-4) modulating pro-and anti-inflammatory mediator. The PDE-4 is an enzyme responsible for lysis of cAMP. Significant numbers of patients with CUC were in clinical remission when compare to placebo in a short-term initial study and further research trials are pending to observe for the long-term outcome [15-17,23].

Laquinimod is an oral quinolone-3-carboxide that may decrease pro-inflammatory immune cells and activates anti-inflammatory genes. Preliminary studies showed better clinical response in CD patients compared to placebo with adverse events similar to placebo. Phase IIb/III trials are currently awaited [24].

Phosphatidylcholine (PPC) is a GI mucus and key component of mucosal barrier. Initial European studies showed a statistically significant improvement in patients with mesalazine-refractory CUC and no detectable adverse events. To date, limited available data on PPC are very promising and this agent may have a role in management of mild-to-moderate CUC in a near future [25].

While there has been the movement to develop new therapies for IBD, long term data will show true efficacy in the management for patients with moderate-to-severe CUC and CD. For now there is great progress on providing our patients with new and innovative therapies for their long term medical management, including oral therapies, which have not been available until now. With finding different mechanisms to target, we could be able to help those patients who are refractory to commercially available agents. It is important to note that extensive and costly research trials are pending with all above mentioned new biologic and immunomodulator agents in our Center and around the world. These agents may have huge implications and hopefully less costly. We really have to wait to see their final outcome for effectiveness and safety within the next 5-10 years. This will likely have huge implications not only for IBD patients and clinicians, but for society as a whole.

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## Conflicts of Interest

The authors are involved in clinical research with AbbVie, Janssen, Pfizer, Celgene, UCB, Takeda, F. Hoffman-La Roche and Bristol-Myers Squibb. The research income stays in the Division for various other research and educational activities. There is no financial interest such as honoraria, participation in speakers' bureaus, membership, employment, consultancies, stock ownership, or other equity interests.

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