New drugs in Inflammatory bowel disease

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Inflammatory bowel disease (IBD) is an immune mediated condition with a progressive or relapsing and remitting disease course. IBD can be categorized broadly into Crohn`s Disease (CD) and Ulcerative Colitis (UC). Though these conditions primarily affect the gastrointestinal tract, extra-intestinal manifestation have been reported to occur in up to 55% of CD and 35% UC patients [1,2]. Furthermore, CD can also lead to intestinal strictures, abscesses and fistulas. Uncontrolled inflammation can also lead to an increased risk of malignancy. The pathogenesis of IBD is multifactorial with various factors postulated to affect the disease course. The better understanding of these pathologies has led to new therapeutic modalities.

Nowadays, our routine daily therapeutic arsenal, apart from aminosalicylates includes a variety of biologicals and small molecules: thiopurines, methotrexate (CD only), monoclonal antibody against tumor necrosis factor α [TNF-α]), an IgG1 antibody which blocks the α4β7 integrin which is gut selective (vedoluzimab), an IgG monoclonal antibody which binds to the p40 subunit of interleukins 12 and 23 (ustekinumab) and a Janus kinase (JAK) inhibitor (tofacitinib) for patients with UC.

Over time, some of these drugs also obtain new indications. Recent studies have shown that vedoluzimab has showed promising results in the treatment of resistant pouchitis [3].

However, though we have these drugs available, we still have a subset of patients who either fail to enter remission or develop loss of response to the available drugs. These cases are known as primary or secondary non-responders. Up to a third of patients may have primary non-response to biologicals and up to 50% of patients develop either a secondary loss of response or a serious adverse event necessitating the discontinuation of medications [4].

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This has led to the analysis of pathway mechanisms involved and thus the development of new drugs. The following medications offer hope both for the physician and even more for the patient. These drugs are summarised in Table 1.

Table 1.

Drug	Mechanism of Action
Upadacitinib	JAK-1 inhibitor
Filgotinib	JAK-1 inhibitor
Risankizumab	Monoclonal antibody directed against the p19 subunit of IL-23
Mirikizumab	Monoclonal antibody directed against the p19 subunit of IL-23
Brazikumab	Monoclonal antibody directed against the p19 subunit of IL-23
Guselkumab	Monoclonal antibody directed against the p19 subunit of IL-23
Etrasimod.	Sphingosine 1 phosphate receptor modulators
Ozanimod	Sphingosine 1 phosphate receptor modulators
Ontamalimab	Anti- mucosal addressin cell adhesion molecule-1 Monoclonal Antibody

JAK: Janus kinase; IL: interleukin

JAK Inhibitors

Tofacitinib, which is a JAK1 and JAK 3 inhibitor, is licensed for patients with UC. Upadacitinib (UPA) is a JAK1 selective inhibitor which is being studied for use in IBD.

UPAs action is associated with the down regulation of various proinflammatory cytokines which include the following interleukins: IL-2, 4, 6, 7, 9, 15, 21, and

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interferon gamma (IFN-γ) which are implicated in the pathogenesis of IBD.

Viral reactivations and infections such as herpes simplex are documented as potential adverse effects of all JAK inhibitors. Tofacitinib is associated with an increased risk of thrombosis and further studies are needed to assess this risk with UPA [5].

Data from rheumatoid arthritis demonstrated that the risk of infection was higher with tofacitinib when administered at 10 mg, twice daily (RR: 2.75; 95% CI, 1.72 to 4.41) compared to upadacitinib, 15 mg, daily (RR: 1.35; 95% CI, 1.14 to 1.60) [6].

UPA may play a role in patients who have failed to respond to conventional IBD treatment.

UPA was evaluated in a phase 3, multicentre, randomised, double-blind, placebo-controlled clinical programme which consisted of two replicate induction studies (U-ACHIEVE induction [UC1] and U-ACCOMPLISH [UC2]) and a single maintenance study (U-ACHIEVE maintenance [UC3] in UC patients.

Statistically significantly more patients achieved clinical remission with upadacitinib 45 mg (26% of patients in UC1; 34% of patients in UC2) than in the placebo group (5% of patients in UC1 and 4% of patients; p<0.0001).

In the maintenance study, clinical remission was achieved by statistically significantly more patients receiving upadacitinib [15 mg (42%); 30 mg (52%)] than those receiving placebo (12%; p<0·0001). The most commonly reported adverse events in UC1 were nasopharyngitis (5% of patients in the upadacitinib 45 mg group vs 4% of patients in the placebo group), creatine phosphokinase elevation (4% vs 2%), and acne (5% vs 1%). In UC2, the most frequently reported adverse event was acne (27% of patients in the upadacitinib 45 mg group vs 2% in the placebo group). In UC3, the most frequently reported adverse events (≥5%) were worsening of UC (13% of patients in the upadacitinib 15 mg group vs 7% of patients in the upadacitinib 30 mg group vs 30% of patients in the placebo group), nasopharyngitis (12% vs 14% vs 10%), creatine phosphokinase elevation (6% vs 8% vs 2%), arthralgia (6% vs 3% vs 10%), and upper respiratory tract infection (5% vs 6% vs 4%) [7].

UPA treatment is also effective in resolving extraintestinal manifestations (EIMs) in UC patients. Results from the UPA Phase 3 programme demonstrated a higher number of EIM symptom resolution compared to placebo following induction treatment with UPA 45 mg and after maintenance treatment with UPA 15 or 30 mg. However only the 30 mg dose provided a statistically significant improvement when compared to placebo (p<0.001) [8].

In the CELEST phase 2 study, patients were randomly assigned to either receive UPA or placebo, no comparison was made to other conventional treatment for CD. UPA was shown to induce clinical (p<0.10) and endoscopic remission (p<0.01) at week 16 in CD patients compared to placebo [5].

The JAK1 inhibitor filgotinib was found to have a higher fistula response (47.1% vs placebo 25%) and remission rates (47.1% vs placebo 16.7%) after 24 weeks of 200mg once daily dosing [9]. Filgotinib at a once daily dose was also found to be effective in inducing (26.1% vs placebo 15.2%) and maintaining remission at week 58 (23.8% vs placebo 13.5%) in patients with moderate to severe UC [10].

IL-23 inhibitors

Though, ustekinumab is licensed for the treatment of IBD, further studies are being performed on other interleukin (IL-) inhibitors. One such selective IL-23 inhibitor is Risankizumab (RZB) which binds to the p19 subunit.

In both ADVANCE and MOTIVATE induction studies, patients were assigned to either risankizumab 600 mg, risankizumab 1200 mg or placebo. The primary analysis population comprised 850 participants in ADVANCE and 569 participants in MOTIVATE. All coprimary endpoints at week 12 were met in both trials with both doses of risankizumab (p ≤0.0001).

In ADVANCE, CDAI clinical remission rate was 45% (adjusted difference 21%, 95% CI 12-29; 152/336) with risankizumab 600 mg and 42% (17%, 8-25; 141/339) with risankizumab 1200 mg versus 25% (43/175) with placebo; endoscopic response rate was 40% (28%, 21-35; 135/336) with risankizumab 600 mg and 32% (20%, 14-27; 109/339) with risankizumab 1200 mg versus 12% (21/175) with placebo.

In MOTIVATE, CDAI clinical remission rate was 42% (22%, 13-31; 80/191) with risankizumab 600 mg and 40% (21%, 12-29; 77/191) with risankizumab 1200 mg versus 20% (37/187) with placebo; and endoscopic response rate was 29% (18%, 10-25; 55/191) with risankizumab 600 mg and 34% (23%, 15-31; 65/191) with risankizumab 1200 mg versus 11% (21/187) with placebo.

The overall incidence of treatment-emergent adverse events was similar among treatment groups in both trials. Three deaths occurred during induction (two in the placebo group [ADVANCE] and one in the risanki-

zumab 1200 mg group [MOTIVATE]). The death in the risankizumab-treated patient was deemed unrelated to the study drug [11].

In the FORTIFY maintenance study, patients were randomly assigned to either the risankizumab 180 mg, risankizumab 360 mg group or the placebo group.

Greater clinical remission and endoscopic response rates were reached with 360 mg risankizumab versus placebo (CDAI clinical remission: 52% vs 41%; endoscopic response: 47% vs 22%). Higher rates of CDAI clinical remission (55%) and endoscopic response (47%) were achieved with the 180mg dose [12]. There are currently ongoing trials to assess its use in UC.

Mirikizumab (MIRI) is a humanized, IgG4 monoclonal antibody directed against the p19 subunit of IL-23 [13]. The Phase 3 LUCENT-1 study assessed the efficacy and safety of mirikizumab as induction therapy in patients with moderately to severely active UC. A significantly greater proportion of patients treated with MIRI achieved clinical remission at Week 12 (MIRI: 24.2% vs placebo: 13.3%; p=0.00006) with an improvement in other secondary endpoints (p<0.00001) [14, 15].

In a study with CD patients, Mirikizumab effectively induced endoscopic response after 12 weeks in patients with moderate-to-severe CD and demonstrated durable efficacy to Week 52.

At Week 12, endoscopic response was significantly higher for all mirikizumab groups (200, 600, or 1000 mg) compared with placebo (200 mg: 25.8%, p=0.079; 600 mg: 37.5%, p= 0.003; 1000 mg: 43.8%, p<0.001; placebo: 10.9 %). Endoscopic response at Week 52 was 58.5% in the intravenous group and 58.7% in the subcutaneous SC group [16].

Brazikumab (MEDI2070) is another monoclonal antibody targeting IL-23. In a phase 2 trial brazikumab was shown to achieve clinical remission at week 8 in 49.2% of patients with severely active CD compared to placebo (p=0.01), with a greater response being noted at week 12 [17].

Guselkumab (GUS), is an IL-23 p19 subunit antagonist. In the QUASAR Induction Study (phase 2b randomized, double-blind, placebo-controlled) its efficacy and safety were evaluated in patients with moderately to severely active UC who had an inadequate response or intolerance to conventional (thiopurines or corticosteroids) or advanced therapy (TNFα antagonists, vedolizumab, or tofacitinib).

At Week 12, a significantly greater proportion of patients treated with GUS 200 mg and 400 mg achieved clinical response compared with placebo (61.4% and 60.7% vs 27.6%, respectively, both p<0.001). The proportion of patients reporting adverse events, serious adverse events and adverse events leading to discontinuation in the GUS groups were not greater compared with placebo with no serious infections, malignancy and death being reported for GUS [18].

The phase 2 GALAXI 1 study assessed the clinical efficacy and safety of GUS maintenance therapy, using different dosages in patients with moderately to severely active CD through week 48.

The proportion of patients achieving clinical remission at week 48 ranged from 57.4-73.0% among GUS dose groups, with the vast majority of patients in clinical remission being also in corticosteroid-free remission at week 48 (55.7-71.4%). Key safety event rates were similar among GUS dose groups with no opportunistic infections, tuberculosis, or deaths being reported in any group [19].

Sphingosine 1 phosphate receptor modulators

A drug which is targeting a different pathway is etrasimod. This drug is a selective sphingosine 1 phosphate receptor (S1P) modulator which is administered as an oral preparation. S1P is expressed on lymphocytes and plays a vital role in lymphocyte trafficking.

The administration of etrasimod in patients with moderate to severe UC and at a dose of 2mg daily showed significant clinical improvement (p=0.009) and endoscopic improvement (p=0.003) compared to placebo.

An open-label extension study evaluated safety and efficacy of etrasimod for up to 52 weeks. At the end of the study clinical response was met in 64% of patients, 33% of patients were in clinical remission, and 43% demonstrated endoscopic improvement. In those patients who at week 12 had clinical response, clinical remission, or endoscopic improvement, these effects were maintained to end of treatment in 85%, 60%, or 69% of patients [20].

The use of etrasimod is advantageous as it is a once daily oral dose. Given that it is a small molecule, no immunogenicity is anticipated. Overall treatment with etrasimod was well tolerated, with fewer than 10% of patients discontinuing the drug. Treatment emergent adverse effects reported were mild to moderate in severity. The most commonly reported included nasopharyngitis, upper respiratory tract infections and anaemia [21].

Ozanimod is another selective sphingosine-1-phosphate receptor modulator, administered as an oral formulation. In a randomized, double-blind, placebo-controlled trial of ozanimod as induction and maintenance therapy in patients with moderately to severely active UC, clinical remission was significantly higher among patients who received ozanimod than among those who received placebo during both induction (18.4% vs. 6.0%, p<0.001) and maintenance (37.0% vs. 18.5% [among patients with a response at week 10], p<0.001).

The incidence of clinical response was also significantly higher with ozanimod than with placebo during induction (47.8% vs. 25.9%, P<0.001) and maintenance (60.0% vs. 41.0%, p<0.001). The incidence of any infection with ozanimod was similar to that with placebo during induction but higher than that with placebo during maintenance. Serious infection occurred in less than 2% of the patients and elevated liver aminotransferase levels were more common with ozanimod [22].

STEPSTONE was a phase 2, uncontrolled, multicentre trial in adults with moderately to severely active CD. At week 12, a reduction from baseline in Crohn's Disease Activity Index (CDAI) score was observed (mean change -130.4 [SD 103.9]) in 39.1%, of patients and response (CDAI decrease from baseline ≥100) in 56.5% of patients. Currently there are Phase 3 placebo-controlled trials [23].

Anti-MAdCAM-1 (mucosal addressin cell adhesion molecule-1) Monoclonal Antibody

Ontamalimab (SHP647), is a fully human immunoglobulin G2 monoclonal antibody against mucosal addressin cell adhesion molecule-1. OPERA II, is a multicenter, open-label, phase 2 extension study, assessing the long-term safety and efficacy of ontamalimab in patients with moderate-to-severe CD. The most common adverse event leading to study discontinuation was CD flare (19.8%). Two patients died and these incidents were not considered to be drug related. The inflammatory biomarker concentrations decreased. Remission rates (Harvey-Bradshaw Index [HBI] ≤ 5; baseline, 48.1%; week 72, 37.3%) and response rates (baseline [decrease in CDAI ≥ 70 points], 63.1%; week 72 [decrease in HBI ≥ 3], 42.5%) gradually decreased [24].

In Opera the use of this drug did not demonstrate any efficacy at any clinical endpoint compared with placebo [25].

TURANDOT II was a phase 2, multicentre, open-label study in patients with moderate-to-severe UC. The primary objective was safety. Mucosal healing was also assessed. Overall, 36.1% experienced drug-related adverse events, 5.5% of patients had serious infections, the most common being gastroenteritis (0.9%). One death and 4 cancers occurred and were considered to be unrelated to ontamalimab. Mucosal healing increased from 20.3% at baseline to 28.5% at week 16 and was maintained until week 144 of follow-up [26].

Unfortunately, currently no cure is available for IBD. Choosing the most appropriate drug can also be challenging for the physician especially when one has to even consider the economic burden, side-effect profile and response rate. Though having various drugs enables both the physician and the patient to have more medical options, choosing the right drug at the right time for a particular patient is challenging. The next step that is required is advancing personalised medicine – obtaining the scientific knowledge and biomarkers in order to choose the right drug for the right patient. However, in the meantime, knowing that new drugs may become available offers much needed hope for all patients and more particularly for those with severe IBD and perianal fistulating disease.

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