Emerging treatments for inflammatory bowel disease

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Abstract: Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is characterized by chronic inflammation, a relapsing and remitting clinical course, requirement for lifelong medication and often, significant morbidity. While multiple effective therapeutic options exist for the treatment of IBD, a proportion of patients will either fail to respond or lose response to therapy. Advances in therapeutics, such as the gut-specific anti-integrins, now offer patients an alternative option to systemic immunosuppression. Anti-interleukin 12 (anti-IL-12)/IL-23 agents offer new and effective treatment options for CD, while the oral small molecules now offer an oral alternative for the treatment of moderate-to-severe disease, previously requiring subcutaneous injection or intravenous infusion. Alternatives to pharmacological treatment such as stem-cell transplant and faecal microbiota transplant are also showing some promise in the treatment of both CD and UC.

Keywords: Crohn's disease, inflammatory bowel disease, ulcerative colitis

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Introduction

Inflammatory bowel disease (IBD) comprises two major disorders: Crohn's disease (CD) and ulcerative colitis (UC). Both conditions are characterized by histologic chronic inflammation, periods of clinical relapse and remission, use of medication and risk of surgery, and impaired quality of life.

While a universal, validated definition of 'remission' is lacking for IBD, the concept of 'deep remission', encompassing clinical remission, biochemical remission and mucosal healing, has become established in the literature as the optimum therapeutic target for optimizing quality of life and preventing disease progression. It is to this standard that we must assess all new therapies.

Historically, the mainstay of treatment for UC has been aminosalicylates, with short courses of steroids for severe flares, and escalation to immunomodulators and anti-tumour necrosis factor alpha (anti-TNFα) inhibitors should remission not be maintained. Aminosalicylates appear ineffective in CD, where remission may be induced using enteric-coated budesonide in patients with distal ileal, ileocaecal or right-sided colonic disease, or prednisolone in patients with more severe or extensive disease. Should remission not be maintained, immunomodulators and anti-TNFα inhibitors may be used either in combination or as monotherapy with clinical factors used to predict those who may benefit from a 'top-down' approach with early aggressive therapy.

In spite of the tremendous advances made in recent years in IBD therapeutics, approximately 30% of patients are primarily unresponsive to anti-TNFα and even among responders, up to 10% will lose their response to the drug every year. In addition, current IBD medications are associated with significant infectious and neoplastic side effects. It is therefore clear that the development and implementation of highly effective drugs or drug combinations with favourable side-effect profiles for patients is an important, unmet need. The pathogenesis of IBD remains unclear but is thought to be multifactorial, including genetic and environmental components, and it is

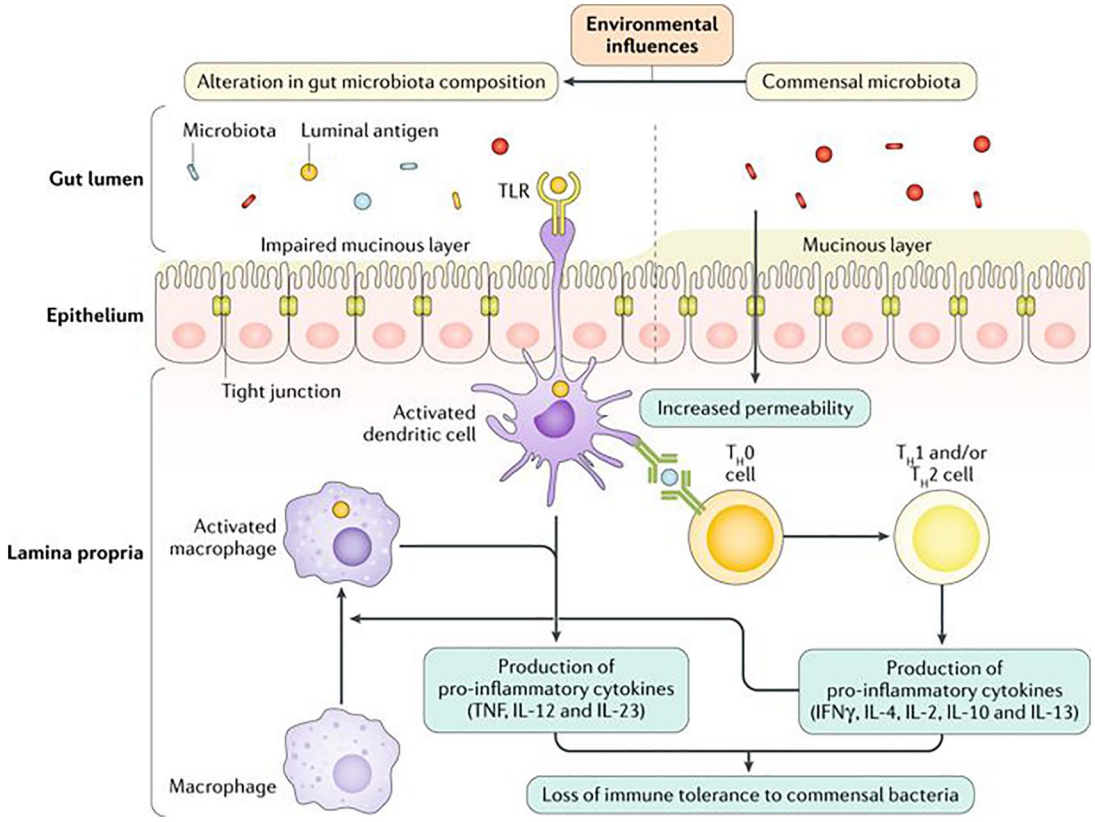

Figure 1. The inflammatory cascade in inflammatory bowel disease.[1]
IFNγ, interferon gamma; IL, interleukin; Th, T-helper cell; TLR, toll-like receptor; TNF, tumour necrosis factor.

in understanding these factors and the inflammatory cascade they induce that therapeutic targets emerge and progress will be made (Figure 1). This review examines a number of newly approved and upcoming therapeutic options for IBD, including newer anti-TNFα agents, S1P-receptor modulators, antiadhesion agents, IL-12/IL-23 inhibitors, transforming growth-factor beta (TGFβ) inhibitors, Janus kinase (JAK)/STAT inhibitors, stem-cell transplant and faecal microbiota transplant (FMT), all of which shall be discussed below.

New anti-TNFs

AVX-470

AVX-470 is an orally administered polyclonal immunoglobulin purified from the colostrum of cows immunized with recombinant human TNF. These large molecules are poorly absorbed from the gastrointestinal tract into the systemic circulation and are therefore suitable for oral delivery. Estimated concentrations of TNF-specific antibodies are shown to be 1000-fold less than levels seen in systemic anti-TNF agents and therefore, the risks of systemic immunosuppression and complications of this are lower. In the study by Harris and colleagues, the greatest effects of AVX-470 were seen in the 3.5 g/day dosing group, with a greater percentage of patients achieving clinical response and both clinical and endoscopic remission when compared with placebo at week 4.[2] While further trials are required, AVX-470 may offer an alternative to both subcutaneous and intravenous infusions of traditional anti-TNFs in UC, with lower immunogenicity and systemic side effects.

Anti-adhesion biologics

The first anti-adhesion biologic to establish an evidence base in IBD was natalizumab, which causes nonspecific inhibition of both α4β7- and α4β1-integrins, and was used as second-line or rescue therapy for the treatment of IBD, mainly

in North America. However, there is a substantial risk of developing progressive multifocal leukoencephalopathy (PML), a devastating and fatal neurological disorder, caused by the reactivation of the JC virus. Studies of natalizumab use in multiple sclerosis showed a PML incidence of 1 per 1000.[3] Because of this, gut-specific anti-integrin therapy is favoured.

α4β7-integrin is an adhesion molecule expressed on the surface of gut-specific lymphocytes and is a target for the drug vedolizumab, discussed below. They bind to mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1), which exists on intestinal vasculature and mediates leukocyte trafficking to the gut.[4] Like vedolizumab, etrolizumab selectively binds the β7 subunit of α4β7, but also αεβ7 integrin heterodimers. This gives a double-headed treatment approach, antagonizing the egress of lymphocytes by blocking the interaction between α4β7 and MAdCAM-1 at the vascular level, and also blocking the interaction between αεβ7 and E-cadherin, potentially avoiding the retention of αεβ7+ cells in the intraepithelial compartment.[5] The concomitant blockade of αεβ7-E-cadherin avoids the adhesion of intraepithelial T cells to the epithelial cells.[6] Around 1–2% of circulating lymphocytes express αεβ7, while it is present in over 90% of intraepithelial lymphocytes and intestinal dendritic cells.[7,8] Etrolizumab may block immunological pathways that trigger and maintain chronic inflammation directly at the mucosal level, with no systemic effects.[9]

A systematic review and meta-analysis by Luthra and coworkers showed that there is no significant increase in either the rate of opportunistic infection or malignancies with non-gut-specific (natalizumab) or gut-specific anti-integrin antibodies (vedolizumab, etrolizumab) compared with placebo.[10]

Vedolizumab

Vedolizumab is an anti-α4β7-integrin monoclonal antibody approved for use in both UC and CD.[11] The GEMINI 1 trial provided significant safety and efficacy data for the use of vedolizumab in UC.[12] The results of this study showed superiority of vedolizumab *versus* placebo in all primary and secondary outcomes. A subsequent Cochrane meta-analysis showed that vedolizumab is superior to placebo in UC for achieving clinical response, clinical remission and endoscopic remission.[13] The 2015 Toronto consensus guidelines for nonhospitalized UC recommend the use of vedolizumab in patients with moderate-to-severe UC who have failed corticosteroid, immunomodulator or anti-TNF therapy,[14] while the European Crohn's and Colitis organization guidelines recommend vedolizumab as either first-line therapy to induce remission or after anti-TNF failure.[15]

The GEMINI 2 and 3 trials examined the use of vedolizumab in CD.[16,17] These studies showed less favourable outcomes with regard to clinical remission at 6 weeks when compared with the UC cohort. No mucosal healing data were collected in GEMINI 3. It was proposed that the mechanism of action of vedolizumab may require a longer duration of treatment in CD when compared with UC in order to induce and maintain remission. At 10 weeks, vedolizumab is superior to placebo in inducing remission.[17] GEMINI 2 showed superiority of vedolizumab to placebo in achieving both clinical- and steroid-free remission at 52 weeks. A further meta-analysis showed that vedolizumab is superior to placebo for inducing and maintaining clinical remission in Crohn's but inferior to adalimumab in maintaining remission.[18] Several retrospective cohorts, however, with long duration of follow up, including those by Shelton, Baumgart and Amiot, have shown that vedolizumab is effective at inducing and maintaining remission at week 14, both in anti-TNFα-naïve and -treated patients.

Vedolizumab appears to have a favourable safety profile. The most common adverse events, all occurring $\leqslant$ 6% are: headache, nasopharyngitis, nausea, arthralgia, upper respiratory tract infection and fatigue.[19] Among all participants of the GEMINI 1, 2 and 3 trials, no cases of PML were observed. Vedolizumab should be considered as primary therapy in those patients with infection-related concerns, most notably, the elderly IBD cohort.[20] There has been conflicting evidence surrounding the perioperative use of vedolizumab and the risk of postoperative infections following intestinal surgery. Lightner and coworkers have shown that 26% of CD patients who received vedolizumab within 12 weeks prior to major abdominal surgery experienced a 30-day postoperative surgical site infection; significantly higher than those receiving neither anti-TNFα or biologic

therapy.[21] A recent study showed that the use of vedolizumab in patients undergoing non-intestinal surgery conferred no increased risk of postoperative infections, readmission or reoperation when compared with control, and therefore, no washout period is required.[22] There is an increased risk for gastroenteritis when compared with placebo with vedolizumab therapy, but serious *Clostridium difficile* infections occur at a rate $\leqslant$ 0.6%.[23] Although drug and anti-drug antibody levels are not yet commercially available for vedolizumab, the GEMINI trials showed a positive correlation between vedolizumab levels and clinical efficacy. Anti-vedolizumab antibodies, are present in 1–4.1% of patients, with no patients having consistently positive results in GEMINI 3.

Data presented at UEGW 2018 from the VISIBLE1 trial showed that subcutaneous vedolizumab, 108 mg administered every 2 weeks, was safe, efficacious and well tolerated as maintenance therapy in UC patients following induction with intravenous (IV) vedolizumab 300 mg. It showed a safety and efficacy profile similar to that of IV vedolizumab. Subcutaneous vedolizumab was significantly superior to placebo in mucosal healing and durable clinical response. Clinical remission was significantly higher in both anti-TNFα-inhibitor-naïve and -failure patients.[24]

Etrolizumab

Etrolizumab represents the next generation of anti-adhesion molecules.[25] Phase I and II trials have been conducted on the safety and efficacy of etrolizumab in UC.[26,27] Etrolizumab may offer an alternative, not only to anti-TNFs, but also vedolizumab in the treatment of UC due to its different mechanism of action, giving an additional blockade and layer in the control of intestinal inflammation when compared with vedolizumab.

Data from phase I and II trials show that etrolizumab is superior to placebo in inducing both clinical remission and endoscopic healing at week 10. Patients taking steroids, not taking immunomodulators and who were anti-TNF naïve, were more likely to reach clinical remission at week 10. There was a greater reduction in those achieving remission at week 10 in addition to a significant increase in the expression of E-cadherin. There was no decrease in aE+ cells in the lamina propria, showing the high selectivity of the molecule at the mucosal level.[8]

Serious adverse events were reported as 12% overall between etrolizumab and placebo.[28] Higher rates of influenza-like illness, arthralgia and rash were observed in those receiving etrolizumab 100 mg when compared with the 300 mg or placebo cohorts. The severity of all events was deemed to be mild or moderate.[7,8] There was no association between antibody formation and pharmacokinetic parameters of the drug.[7]

The phase III BERGAMOT induction trial examined the use of etrolizumab in patients with moderate-to-severe CD who were refractory or intolerant to anti-TNF agents, immunosuppressants or corticosteroids. Patients were assigned 2:2:1 to the 105 mg subcutaneous 4-weekly, 210 mg at week 0, 2, 4, 8 and 12 or placebo groups during a 14-week induction period. Endpoints included clinical remission defined as a Crohn's Disease Activity Index (CDAI) $<$ 150, CDAI-100 and -70 responses, PRO2 remission, symptomatic remission and endoscopic improvement defined as $>$50% reduction from baseline Simple Endoscopic Score for Crohn's Disease (SES-CD) at week 14. A sum of 300 patients were included in the trial, with 73% being anti-TNF exposed. Symptomatic remission was observed in a greater proportion of patients receiving etrolizumab 105 mg and 210 mg compared with placebo at weeks 6, 10 and 14. More patients achieved endoscopic improvement with etrolizumab therapy when compared with placebo at week 14. CDAI remission was greater in the etrolizumab group at week 14 (23.3%, 28.9% and 16.9%, respectively). Enrolment into induction cohorts and maintenance phase is ongoing.[29]

While phase III trials are ongoing, etrolizumab is emerging as a potential therapeutic agent in the treatment of UC and CD. It offers an alternative to anti-TNF therapy in those who have shown primary nonresponse, secondary loss of response or those not suitable for anti-TNF therapy, as mentioned above. It may also offer an alternative to vedolizumab.

Abrilumab

Abrilumab is a monoclonal antibody that selectively blocks α4β7 and can be administered subcutaneously, with high bioavailability and a long half-life.[30,31] A recently published randomized, phase IIb study showed that treatment with abrilumab significantly improved 8-week remission

rates (13.5%) when compared with placebo (4.4%) in patients with moderate-to-severe UC who had failed conventional therapies. Clinical response was seen in almost half of all patients and mucosal healing in one third of patients treated with a dose of either 70 mg or 210 mg, compared with 26% and 16.8% who received placebo, respectively.[32] Induction of response, along with increases in clinical remission and mucosal healing at week 6, show similar results to that of vedolizumab in the GEMINI trials.[11] PML was not observed in trial patients.

PF-00547659

PF-00547659 is a subcutaneously administered monoclonal antibody that inhibits binding of α4β7-integrin to MAdCAM with high affinity and selectivity.[33] Two phase II, randomized, double-blind, placebo-controlled trials have been conducted on this agent. The TURANDOT trial examined safety and efficacy of PF-00547659 in moderate-to-severe UC.[9] At 12 weeks of treatment, 23.6% in the treatment arm compared with 5.5% in the placebo arm were in endoscopic remission, with the highest rates of remission observed in anti-TNF-naïve patients. Although a limited, 12-week study, the safety profile seemed similar to placebo.[9]

The OPERA study looked at the clinical response to PF-00547659 in moderate-to-severe CD.[34] Response was measured using the CDAI score at 8 and 12 weeks. There was no statistically significant reduction in CDAI scores when compared with placebo, with 27% of the highest-dose group of PF-00547659 *versus* 48% of the placebo cohort exhibiting a response, rendering the trial a failure.

IL-12/IL-23 inhibitors

Interleukin 12 (IL-12) is produced by phagocytic and dendritic cells in response to microbial stimulation, driving cell-mediated immunity by inducing lymphokine-activated killer cells and activation of natural killer (NK) cells and T lymphocytes.[35] IL-12 is a key inducer of T-helper 1 (Th1) cells, promoting cell-mediated immunity to intracellular pathogens, delayed-type hypersensitivity and macrophage activation.[36] IL-23 is critical for Th17 differentiation,[37] which produce several pro-inflammatory cytokines, including IL-17A and F, TNFα, IL-22, IL-26 and interferon gamma.[38] By preventing IL-12 and IL-23 from binding to the IL-12Rβ1 receptor chain of IL-12 and IL-23 receptor complexes on the surface of NK and T cells, neutralizing IL-12 and IL-23-mediated responses, these drugs prevent IL-17 and IL-22 cytokine production.[39] Dysregulation of the Th1/Th17 pathways has been strongly linked to CD, rheumatoid arthritis, psoriasis and multiple sclerosis, all of which may be treated with selective interleukin inhibitors.

Ustekinumab

Ustekinumab is a monoclonal antibody to the p40 subunit of IL-12 and IL-23 that has been approved for the treatment of moderate-to-severe CD. Clinical efficacy and safety data were collected *via* the UNITI-1, UNITI-2 and IM-UNITI trials. All studies examined patients who had failed anti-TNF therapy or conventional therapies. Ustekinumab showed benefit over placebo, irrespective of previous exposure to anti-TNF.[40] In UNITI-1, the patient cohort had severe CD of long duration, were primary or secondary nonresponders or had adverse side effects to at least one anti-TNF agent. In UNITI-2, most patients were anti-TNF naïve. At week 8, 20.9% of patients in UNITI-1, receiving 6 mg/kg dosing were in remission when compared with placebo. UNITI-2 showed higher absolute rates of remission against placebo, attributable to the treatment naïve, and less severe nature of disease. Decline and normalization of C-reactive protein (CRP) and faecal calprotectin (FCP) levels were seen with ustekinumab therapy, both at week 8 and week 44. Among all three trials (UNITI-1, -2 and IM-UNITI), the rate of serious adverse event was 9.9%, 12.1% and 15%, respectively. Thirteen patients experienced serious infection.

The UNIFI trial examined the efficacy of ustekinumab as induction and maintenance therapy in patients with UC. The drug was evaluated as 8-week induction and 44-week maintenance therapy in moderate-to-severe UC. A total of 961 patients were randomized to receive an IV induction dose of 130 mg, a weight-based dose of 6 mg/kg, or placebo. Patients with response to induction therapy after 8 weeks of administration were randomized to receive 90 mg of ustekinumab either 8 weekly or 12 weekly. The primary endpoint in the induction and maintenance trials was clinical remission (total Mayo score < 2 and no subscore > 1 on any of the four Mayo

scale components). The percentage of patients achieving clinical remission at week 8 who had received a dose of 130 mg (15.6%) or 6 mg/kg (15.5%) was significantly higher than those who received placebo (5.3%; $p < 0.001$ for both comparisons). The percentage of patients with clinical remission at week 44 was significantly higher among those assigned to 90 mg every 12 weeks (38.4%) or every 8 weeks (43.8%) than those assigned to placebo (24.0%; $p = 0.002$ and $p < 0.001$), respectively. The incidence of serious adverse events with ustekinumab therapy was similar to that with placebo. Ustekinumab was shown to be more effective than placebo for inducing and maintaining remission in patients with moderate-to-severe UC.[41]

Risankizumab

Risankizumab is a humanized monoclonal antibody to the p19 subunit of IL-23.[42] Risankizumab offers a more selective downregulation than ustekinumab, not affecting IL-12-dependent T-cell pathways which are important for infection and cancer immunity.[43] A recent randomized, double-blind, placebo-controlled phase II study examined the efficacy of IV risankizumab for the induction of remission in moderate-to-severe CD, with a primary outcome of clinical remission (CDAI < 150) at week 12.[44] A total of 69% of patients had been exposed to at least two anti-TNFs, indicating a highly treatment-refractory population. At week 12, 31% of patients achieved clinical remission compared with 15% of the placebo group. A total of 20.99% of those treated with the 600 mg dosing regimen achieved clinical remission when compared with placebo. Larger decreases in CRP and FCP were seen at week 12, when compared with placebo. The most common side effect observed was a worsening of underlying CD. The results thus far suggest that specific blockade of IL-23 *via* inhibition of p19 may be a viable therapeutic approach in Crohn's and warrants further investigation.[44]

Small-molecule drugs

Small-molecule drugs (SMDs) have a molecular weight < 1 kDa,[45] and most are organic compounds composed of oxygen, carbon and nitrogen.[46] Their low molecular weight allows SMDs to diffuse readily through cell membranes, when compared with large macromolecules such as the anti-TNFαs,[47] which may weigh up to 144 kDa, as in the case of infliximab. A wide variation in the size and structure of biologics significantly affects the administration route, target site, pharmacokinetics, antigenicity and drug–drug interactions.[48] A significant advantage of SMDs over biologic therapy is the ability to take the medication orally, which may be preferential to the patient; removing the need for hospital attendance, self-injection and repeated cannulation. SMDs tend to have a short serum half-life and may offer an advantage over biologics in cases where rapid elimination of the drug is required.[46] SMDs also offer advantage over biologics due to their lack of immunogenicity. They do, however, require once- or twice-daily dosing, which may affect compliance and therefore, disease control.

JAK inhibitors

Tofacitinib is a recently licensed, oral JAK inhibitor that inhibits JAK1, JAK2, JAK 3 and TYK2.[49] Cytokines activate intracellular JAKs, which causes phosphorylation and activation of STAT proteins, regulating the expression of target genes.[50] The JAK–STAT pathway is shown to be involved in the pathogenesis of IBD, and because JAKs are activated in pairs and in various combinations of cytokine receptors, JAK inhibition has the potential to block several inflammatory pathways concomitantly.[45,51]

The clinical efficacy and safety of tofacitinib for the treatment of moderate-to-severe UC were examined in the OCTAVE trials.[52] The primary endpoint of clinical remission at week 8, was met by a significantly higher number of patients in the tofacitinib group in both trials when compared with placebo (18.5% *versus* 8.2%). Mucosal healing, with a Mayo subscore ⩽ 1, was more common in the tofacitinib group. Both anti-TNF-naïve and previously exposed patients had equal benefit when treated with tofacitinib in induction studies; however, OCTAVE Sustain data showed less stable remission in TNF-failure patients where 10 mg twice-daily dosing seems to be more important than in TNF-naïve patients. Data for the use of tofacitinib in CD have not been promising to date.[53]

In the OCTAVE trials, tofacitinib was well tolerated but there was an increased risk for herpes zoster infection, anal abscess, cellulitis, *C. difficile* infection, pneumonia and venous thromboembolism.[54] An increased risk of lung cancer, breast cancer, lymphoma (and gastric cancer in Japan

only) was observed when compared with placebo in rheumatoid arthritis studies.[55]

Sphingosine-1-phosphate receptor modulators

Sphingosine-1-phosphate (S1P) binds specifically to five widely expressed subtypes of the G-protein-coupled receptor $S1P_{1–5}$.[56] The S1P receptors have been shown to mediate angiogenesis, vascular tone and permeability, and the trafficking of lymphocytes, both to the lymphoid organs and their migration into the circulation.[57] S1P modulators bind to the S1P receptor and induce its internalization and degradation, trapping lymphocytes within lymphoid tissue.[58] This results in a reduction in the levels of circulating effector T cells and causes selective immunosuppression, without downregulating overall immune function.[59]

Ozanimod is an orally administered S1P receptor modulator; selectively modulating $S1P_1$ and $S1P_5$ receptors. It is currently under investigation in the treatment of IBD as part of the phase II clinical trial: the TOUCHSTONE study evaluated the efficacy of ozanimod in the induction and maintenance therapy in patients with moderate-to-severe UC.[60] Significant differences were seen at week 32 with respect to clinical remission, clinical response and mucosal healing, with slight difference only noted at week 8. Greater histological remission, however, was noted at weeks 8 and 32.[60] It seems that ozanimod is a well-tolerated medication, but the TOUCHSTONE trial was underpowered from a safety perspective. Fingolimod, a similar agent used for multiple sclerosis has been associated with adverse events such as bradycardia and atrioventricular block and macular oedema. Serious infections, such as disseminated varicella zoster and herpes simplex infections are rare but have been observed.[61] There is also some concern with regard to the development of PML in natalizumab-naïve patients, and it is likely that all patients taking S1P receptor modulators will need full PML assessment for JC virus prior to, and during therapy.[62]

Phosphodiesterase 4 inhibitors

Phosphodiesterase 4 (PDE4) is an enzyme that controls the concentration of circulating cyclic adenosine monophosphate (cAMP). cAMP has been shown to affect NF-κ-B signaling in macrophages and T cells, therefore, giving it potential anti-inflammatory and immunosuppressive properties.[63] PDE4 inhibition also leads to reduced TNFα messenger ribonucleic acid expression *via* transcriptional modulation of NF-κ-B and increased synthesis of IL-10, an anti-inflammatory cytokine, *via* activation of protein kinase A (PKA).[64] PDE4 inhibitors have shown beneficial effects in murine studies of colitis.

Apremilast, which specifically targets PDE4, has been approved as an oral therapy for psoriatic arthritis (PsA), and as PsA shares several pathogenic mechanisms with IBD, has been proposed as a potential therapeutic agent. A recent phase II, randomized, double-blind, placebo-controlled trial by Danese and colleagues examined the efficacy of apremilast in active UC. Patients treated with apremilast 30 mg twice daily showed superior clinical disease indices, mucosal healing, CRP and FCP reduction when compared with placebo.[65] The drug is no longer being developed in IBD, and phase III trials will not be undertaken due to commercial decisions of the company, not a lack of phase II trial efficacy data.

Stem-cell transplant

There is emerging evidence that stem-cell therapy may be used as an alternative method to treating tissue damage caused by chronic inflammation in IBD through alteration of the mucosal immune response.[66] Results from ongoing clinical trials using both haematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) continue to be inconsistent. HSCs are multipotent cells isolated from bone marrow, umbilical cord or peripheral blood and have the ability to differentiate into blood and immune cells.[67] By migrating to damaged tissue, they may differentiate to epithelial or immune-modulatory cells to restore normal mucosal tissue and integrity.[68] MSCs are multipotent cells found in bone marrow, umbilical cord and adipose tissues. MSCs have immunomodulatory capability for downregulating mucosal immune reactivity by promoting regulatory T-cell formation,[69] including the inhibition of proliferation and function of Th1 and Th17 cells, promoting tissue healing.[70]

Current studies are focusing on autologous haematopoietic stem-cell transplant (HSCT). A Spanish trial showed drug-free clinical remission at 6 months in 70% of patients ($n = 29$).[71] A total of 15% of patients remained in drug-free remission at 5 years and of those who relapsed, 80% responded to subsequent medical therapy. The

largest trial to date, the ASTIC study, showed 3-month steroid-free clinical remission was seen in 38% of patients, half of whom achieved complete endoscopic healing. Best results were seen in patients with short disease duration and low baseline CDAI; however, there was a very high burden of adverse events, mainly infection in 23 of 40 participants and a single death.[72] The study failed to meet its primary endpoint.

The major advantage of using MSCs over HSCT are their low immunogenicity profile, and lack of requirement for whole-body irradiation or chemotherapy following transplant. The use of MSC therapy (MSCT) has been evaluated in the treatment of IBD in two ways. The first involves injection of MSCs directly into perianal fistulas to promote repair and second, IV administration to treat luminal UC and CD. Local injection at fistula sites of both autologous and allogenic MSCs have shown positive results in multiple case series and randomized controlled trials when compared with placebo.[72] A further phase I trial has shown an 83% rate of complete clinical healing and radiological evidence of response in complicated Crohn's fistulae treated with autologous MSCT directly to the fistula site.[73] IV autologous MSCT for luminal CD did not show sustained clinical remission, with worsening of symptoms in some patients.[74,75] However, a single trial of seven patients (four CD, three UC), treated with IV allogenic MSCs while on concomitant steroid or immunomodulatory therapy reported a significant reduction in clinical activity of disease in all patients, and full clinical remission in five out of seven (two CD, three UC), with significant endoscopic healing also being observed.[76]

The ADMIRE CD study was a double-blind study performed at 49 hospitals in Europe and Israel including 212 patients with CD and treatment-refractory, draining, complex perianal fistulas. As part of the phase III trial, patients were randomized 1:1 to groups given a local injection of 120 million Cx601 cells or placebo, in addition to conventional therapies. Efficacy endpoints at week 52 included combined remission classified as closure of all treated external fistulae draining at baseline, with an absence of collections > 2 cm confirmed by magnetic resonance imaging and clinical remission which was classified by an absence of draining fistulae. At week 24, combined remission was observed in 51.5% of patients given Cx601 compared with 35.6% in the placebo group ($p = 0.021$). At week 52, 56.3% of patients achieved combined remission *versus* 38.6% of the placebo group ($p = 0.010$), while 59.2% achieved clinical remission compared with 41.6% receiving placebo ($p = 0.013$). Adverse events occurred in 76.7% of patients in the treatment arm, compared with 72.5% of the placebo group. The phase III trial showed Cx601 to be a safe and effective treatment option for closing externally draining fistulae after 1 year.[77] Despite the findings of the above studies, the National Institute for Health and Care Excellence guidelines do not currently recommend the use of stem-cell transplant in the treatment of complex perianal fistulae in CD due to uncertainties surrounding the long-term benefits and cost effectiveness of the therapy.

Faecal microbiota transplant

Following the successful treatment of *C. difficile* infection with faecal microbiota transplant (FMT), attention was turned to its potential use in the treatment of IBD. Over the past 20 years, multiple studies have shown the pivotal role gut microbiota play in the pathogenesis of IBD.[78] Faecal bacterial of IBD patients has been shown to be different to healthy individuals, with a higher ratio of pathogenic bacteria, (*Escherichia coli, Campylobacter* spp., *Mycobacterium avium*) to commensal flora (*Bacteroides* and *Firmicutes* phyla) and a decreased bacterial load in areas of active inflammation.[79] Bacterial invasion of the mucosa has been demonstrated in IBD patients, while rarely found in healthy subjects.[80] A systematic review of 18 studies that used FMT as primary therapy in IBD showed that of 122 patients who underwent FMT, there was an overall remission rate of 45%.[81] Subgroup analysis indicated that CD patients were more likely to show response to FMT than UC, with 61% of patients achieving clinical remission, compared with 22% in UC. The most interesting study showed a benefit of FMT in UC-delivered FMT over FMT performed *via* nasoduodenal tube delivery, but also that donor effect may be extremely important with patients treated from a particular donor being most likely to respond. This suggests that there may be a role in the identification and transplantation of specific microbial species to restore intestinal homeostasis.[82] Reported adverse events associated with FMT include transient fever, and vomiting postduodenal infusions.[81] Serious events are rare but flares of IBD and infection have been reported.[83,84] It is important to realize, however, that all successful studies involved

more than a single FMT administration, resulting in an increased burden both on the patient who will require multiple endoscopies and the costs associated with this to the healthcare provider.

Conclusion

While the mainstay of treatment for IBD to date has included aminosalicylates, corticosteroids, immunomodulators and anti-TNFα inhibitors, a significant proportion of patients will fail to respond or lose response to these conventional therapies. As such, alternatives are need for those patients with refractory, and often severe disease. Anti-integrin therapy, IL-12/IL-23 inhibitors and SMDs show significant promise. Stem-cell transplant, particularly in fistulating CD, has been particularly promising. FMT needs more studies but it is clear that questions exist regarding standardized protocols, microbe selection or the best mode of delivery. It is clear that there is a need for drugs or drug combinations with good safety profiles that work in all patients.

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