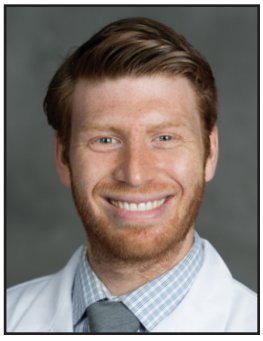
Seymour Katz, M.D., Series Editor

The IBD Therapeutic Pipeline is Primed to Produce



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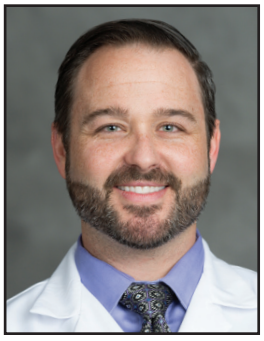

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INTRODUCTION

There has not been a more exciting time in the treatment of inflammatory bowel disease (IBD) since the approval of infliximab in 1998. In addition to multiple recently approved medications including vedolizumab, ustekinumab, and recently tofacitinib, the IBD pipeline continues to expand at a remarkable rate. There are multiple emerging therapies in known and effective drug classes as well as multiple potential therapies with novel mechanisms of action (MOA). Therapies currently on the market employ a variety of different MOAs including anti-tumor necrosis factor (TNF) (infliximab, adalimumab, certolizumab, and golimumab), immune system modulation (azathioprine, 6-MP), anti-integrin or anti-adhesion (vedolizumab), anti-interleukin 12/23 (ustekinumab), and Janus lkinase (JAK) inhibitors (tofacitinib). The IBD pipeline now boasts additional therapies in each of these broad MOA groups, as well as therapies with completely novel mechanisms including regenerative therapy, immune cell modulation, microbiome targeting, nutrition-based, apheresis, hormone modulation, and PDE-4 inhibitors. This review will provide an update on the current and future IBD drugs, focusing on promising therapies currently in late stage or advanced human clinical trials.

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CYTOKINES

TNF-α Inhibitors

The modulation of cytokines is a pivotal modality for the treatment of inflammatory bowel disease, and there are several pipeline drugs targeting various different cytokines. While the intricate and complicated roles of many cytokines remain to be elucidated, several have emerged as targets in inflammatory diseases such as Crohn's disease (CD) and ulcerative colitis (UC).

The first approved specific cytokine-targeting drug to treat inflammatory bowel disease was the TNF-α inhibitor infliximab. Infliximab was approved in the United States (US) for Crohn's disease in 1998 under the trade name Remicade. Three other TNF-α inhibitors have since been approved for use in inflammatory bowel disease, adalimumab (Humira) for CD and UC, certolizumab (Cimzia) for CD, and golimumab (Simponi) for UC. At this time several new TNF-α inhibitors have been studied in Crohn's disease. DLX 105 (ESBATech) is an anti-TNF-α antibody,

and its use for fistulizing Crohn's disease has been studied as a fistula-targeted local injection in a phase II trial (ClinicalTrials.gov NCT01624376), but no results are available. Two oral anti-TNF-α therapies, V565 (VHsquared) and OPRX-106 (Protalix Bio), are in the pipeline. V565 is currently recruiting for a phase II trial for patients with moderately to severely active CD (NCT02976129) after reportedly favorable results in a phase Ib trial (NCT03010787). OPRX-106 demonstrated efficacy in clinical and biomarker improvement in a phase II trial of patients with mild to moderate UC.[1] These exciting therapies are worth watching as the oral mode of administration could be of clinical benefit with a much easier mode of administration than currently available TNF-α inhibitors.

In addition to more novel TNF-α inhibitors, biosimilar agents to infliximab have recently entered the market. In 2016 the FDA approved Inflectra (Remsima)(Pfizer), a biosimilar of infliximab, and this has been followed by Renflexis (Flixabi)(Merck). The FDA approved Cyltezo (adalimumab-adbm) (Boehringer-Ingelheim) in 2017 and Hyrimoz (adalimumab-adaz) (Sandoz) in 2018, both biosimilars to Humira. In September of 2018, Hulio (Mylan and Fujifilm Kyowa Kirin Biologics), another biosimilar to adalimumab, was approved for use in IBD in Europe.

The approval of biosimilars is based largely on extrapolation from efficacy trials in other inflammatory conditions, as the biosimilar is nearly identical to the reference medication and therefore should have the same clinical effects in the same diseases.[2] While this rationale is not uncontested, early evidence in multiple studies from Europe supports their use.[2–4] Furthermore, several clinical trials investigating the clinical use of biosimilars compared to infliximab in CD and UC are in progress (NCT02452151, NCT03308357, NCT02846961, NCT02998398, NCT02925338). Given the substantial cost of biologic medications and the ever-present need to provide cost-effective treatment strategies, the use of biosimilars is likely to increase, and many more biosimilar medications are likely to come to market in the near future.

Anti-Interleukins

Several interleukins (ILs), a subset of cytokines, play a critical role in gut inflammation and the pathogenesis of IBD and have been identified as important treatment targets. Perhaps the most promising target interleukin is IL23 with or without concomitant inhibition of IL12. IL23 and IL12 are critical mediators of T cell differentiation and function.[5] While the exact role of IL12 and IL23 in the pathogenesis of Crohn's disease is unclear, IL23 in particular is thought to be important in the pathogenesis of CD through induction of IL22 expression.[6] Ustekinumab (Stelara) (Janssen) is an inhibitor of IL12 and IL23 through direct action on P40, a subunit of both interleukins.[5] In 2016 ustekinumab became the only approved IL12/23 inhibitor in inflammatory bowel disease (CD), and a recent phase III long-term extension trial demonstrated reduction in the incidence of CD-related hospitalization, surgery, and alternative biologic therapy at two years in patients treated with ustekinumab compared to placebo.[7]

There are several specific IL23 inhibitors currently in clinical trials. Two of the most promising IL23 inhibitors currently in the pipeline, are MEDI2070 (brazikumab) (Allergan) and risankizumab (AbbVie). Both MEDI2070 and risankizumab are selective inhibitors of IL23 via selective binding of the p19 subunit, a component of IL23 but not IL12.[6,8] MEDI2070 recently demonstrated efficacy in a phase IIa trial for patients with moderate to severe CD who had previously failed anti-TNF therapy.[6] In this double-blind, placebo-controlled study, 119 patients received either placebo or 700mg MEDI2070 IV at weeks 0 and 4, followed by open-label MEDI2070 210 mg subcutaneously every 4 weeks from week 12-112. The primary outcome of clinical response at week 8, (either remission defined as a Crohn's disease activity index [CDAI] score <150, or a decrease in CDAI score of 100 from baseline), was achieved in 49.2% of the MEDI2070 group compared to 26.7% of the placebo group (p=0.010). In the open label phase of this study, 53.8% of patients that continued to get MEDI2070 and 57.7% of patients who had received placebo then transitioned to open label MEDI2070 achieved clinical response at week 24. A phase IIb/III trial of MEDI2070 in patients with moderate to severe CD is currently active (NCT03759288) as is a phase II trial of MEDI2070 in patients with UC (NCT03616821).

More recently, risankizumab demonstrated

efficacy in a phase II, randomized, double-blind, placebo-controlled trial for patients with moderate-to-severe CD.[8] In this study 121 patients were randomized, and the primary outcome was clinical remission (CDAI score <150) at week 12. Patients received intravenous infusions of either risankizumab 200 mg, risankizumab 600 mg, or placebo at weeks 0, 4, and 8. The primary outcome was achieved in 31% of the pooled risankizumab arm versus 15% of the placebo arm ($p = 0.0489$). When separating the risankizumab dose groups, 24% of the 200mg group and 37% of the 600 mg risankizumab group achieved clinical remission ($p = 0.31$ and $p = 0.0252$ respectively). A long-term extension phase II trial of risankizumab in patients with moderately to severely active CD is currently underway (NCT02513459), as well as three phase III studies for use in CD that are currently either recruiting or planned (NCT03105128, NCT03104413, NCT03105102).

Several other IL23 specific inhibitors are rapidly entering clinical trials for CD and UC, including mirikizumab (LY3074828) (Eli Lilly), tildrakizumab (Sun Pharma), and guselkumab (Janssen).[9] Of the three, mirikizumab is farthest along in development with two phase II clinical trials recruiting, one for active CD (SERENITY) and another for moderate to severe UC (NCT02891226, NCT02589665 respectively). Guselkumab recently started recruiting for a combined phase II/phase III trial in CD (GALAXI)(NCT03466411) with an expected enrollment of over 2000 participants with a smaller phase IIa trial in UC patients (NCT03662542).

The selective inhibition of IL23 and sparing of IL12 may add increased safety, as IL12 plays a role in defense against intracellular pathogens and may be important in susceptibility to mycobacterial disease.[9] Furthermore, risakizumab demonstrated superiority over ustekinumab in a phase II trial for patients with moderate-to-severe plaque psoriasis.[10] This further supports the notion that selective IL23 blockade may be superior to combined IL12/23 inhibition for use in inflammatory or autoimmune conditions.

The positioning of ustekinumab and other inhibitors of interleukin 23 for use in clinical practice is still being sorted out. One patient subset that may be ideally suited for use of IL12/23 inhibition is patients with CD as well as psoriasis, or those that develop psoriasis induced by TNF-α inhibitors. These assertions are supported by the efficacy of ustekinumab in patients with CD and severe psoriasiform lesions and/or alopecia secondary to TNF-α inhibitor use.[9] Additionally, ustekinumab has been proposed as a potential first line agent for moderate to severe CD given comparable efficacy and more favorable safety profile than TNF-α inhibitors,[9] although head-to-head data is lacking and more research is needed.

In addition to the IL12/23 pathway, there is a drug in development that targets IL17 indirectly. Vidofludimus (4SC) is an oral inhibitor of dihydroorotate dehydrogenase (DHODH), which inhibits the proliferation of lymphocytes and IL17 production.[11] In an open label, uncontrolled study (ENTRANCE), 8 out of 14 (57.1%) patients with CD and 6 out of 12 (50.0%) patients with UC experienced steroid-free clinical remission at week 12 using CDAI< 150 for CD and clinical activity index (CAI) < 4 for UC.[12] Vidofludimus was also reported to be well tolerated, with no serious drug-related adverse events. A phase II dose finding clinical trial of IMU-838 (vidofludimus calcium) (Immunic Therapeutics) in patients with UC recently started recruiting (NCT03341962) with reported plans for a phase II trial in CD as well.

Inhibition of the pro-inflammatory cytokine IL6 with the fully human monoclonal antibody PF-04236921(Pfizer) has shown promising results for the treatment of CD in phase II trials (ANDANTE I and II).[13] These multicenter, randomized trials included an induction study and an open label extension. Patients in this trial had failed ≥ 1 anti-TNF therapy. This trial randomized 249 patients to receive placebo or treatment with PF-04236921 subcutaneously at doses of 10mg, 50mg, or 200mg on days 1 and 28, however enrollment in the 200mg group was discontinued early due to fatalities in a trial for aystemic lupus erythematosus (SLE), and this group was not included in the primary efficacy analysis. The primary endpoint for the induction study was CDAI-70 response rate at weeks 8 or 12, and the primary objective of the open label extension was safety. In the induction study PF-04236921 met the primary endpoint in 49.3% vs. 30.6% for placebo at week 8 ($p < 0.05$), and 47.4%

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vs. 28.6% at 12 weeks ($p < 0.05$). In the open label extension study, a one-time dose escalation to 100 mg was allowed for non-responders beginning at week 8, and 77.8% had their dose escalated to 100mg. Despite the drug's efficacy, there is some concern regarding signals of gastrointestinal abscess and perforation, which have been reported with other IL6 inhibitors as well. While this does not exclude anti-IL6 therapy from consideration, especially in a treatment refractory population, careful patient selection may be prudent for anti-IL6 therapies going forward.

An additional cytokine modulator in the pipeline is PF-06480605 (Pfizer). This therapy is also an inhibitor of a cytokine, a blocker of the TNF ligand known as TNFSF15 (TNF super family 15). A phase II trial for patients with UC has reportedly completed enrollment, however no data on efficacy has been published yet (NCT02840721).[14]

A phase II trial of GSK1070806 (GlaxoSmithKline), a monoclonal antibody to IL18, was recently registered for patients with moderate to severe CD after a single arm phase I trial demonstrated safety in healthy and obese subjects.[15]

Tumor necrosis factor receptors (TNFRs) have become targets for novel therapeutics. OX40 is a member of the TNFR family. The novel OX40 inhibitor KHK4083 (Kyowa Hakko Kirin) has demonstrated safety and tolerability in a phase I trial for patients with plaque psoriasis.[16] KHK8043 is currently being investigated in a phase I (NCT02985593) and a phase II (NCT02647866) clinical trial for patients with UC.

The importance of cytokines in the pathogenesis of inflammatory bowel disease is highlighted by the numerous promising therapeutics either in use or under investigation that target them. Cytokine modulation is and will certainly continue to be a cornerstone of the treatment of CD and UC. We anticipate that the cytokine modulator pipeline will continue to grow in this arena as our understanding of these pathways continues to evolve.

Regeneration

Utilizing the innate potential of the stem cell, or modulating the body's own regenerative capacity to heal disease, is an exciting and active area of research in many diseases including inflammatory bowel disease. Despite many inherent challenges to this type of therapy, advances are being made at a fast pace. It is likely that regenerative medicine will become a powerful and prominent tool for many disease states including inflammatory bowel disease.

Stem cell therapy (SCT) for inflammatory bowel disease is beginning to emerge as a potentially viable treatment option for some patients. There are numerous clinical trials either published or registered with Clinicaltrials.gov for use of stem cells in CD and UC. Therapies may include stem cells that are hematopoietic, bone marrow-derived, adipose-derived, or mesenchymal. Both autologous and non-autologous stem cells have been studied. The route of administration can be either systemic or locally injected/delivered.

In March of 2018, the European Commision approved Alofisel (formerly Cx601) (Takeda, TiGenix), the allogeneic expanded, adipose-derived stem cell therapy for the treatment of complex perianal fistulas in adult patients with Crohn's disease who have shown inadequate response to at least one conventional or biologic therapy. Approval was based on a randomized, double-blind, parallel-group, placebo-controlled phase III trial (ADMIRE-CD) of Cx601 injection for complex perianal fistulas in adult patients with Crohn's disease demonstrating safety and efficacy.[17] In this study 202 patients received a single injection of either Cx601 or placebo (saline solution) into the lesion. The primary endpoint was combined remission, defined as clinical closure of all treated external openings that were draining at baseline, and no collections of greater than 2 cm of treated fistulas on MRI. This was achieved in 50% of the treatment group compared to 34% of the placebo ($p = 0.024$). This study was also continued for a 52-week period evaluating efficacy endpoints of combined remission (as above), and clinical remission (absence of draining fistulas). At 52 weeks 56.3% of the treatment group achieved combined remission compared to 38.6% in the control group ($p = 0.021$); and 59.2% of the treatment group compared to 41.6% of the control group achieved clinical remission ($p = 0.013$). Cx601 also proved to be safe, with similar rates of adverse events in both groups.[17] A large,

multicenter, phase III trial (ADMIRE-CD II) in underway to gain FDA approval (NCT03279081).

Additional promising stem cell therapies in the pipeline include Furestem-CD (Kangstem Biotech) (NCT02000362, NCT02926300) in phase I and II trials for CD, PROCHYMAL (NCT00482092, NCT00543374, NCT01233960) in phase III trials for CD, and MultiStem (NCT01240915) in a phase II trial for UC.

A recent meta-analysis of stem cell therapy (SCT) for CD analyzed 21 studies that included 514 patients.[18] This study found that systemic infusion of SCT resulted in 56% of patients achieving clinical response using random-effects meta-analysis (95% confidence interval [CI] 33-76, n=150). Efficacy was also demonstrated when evaluating clinical and endoscopic remission, and for patients with perianal CD. This analysis suggests that SCT may be effective, however the rate of severe adverse events (SAEs) was also significant. In this meta-analysis, the overall pooled rate of SAEs was 12%. The pooled rate of SAEs related to SCT was 8%. Severe adverse effects of SCT could be a significant obstacle to the use of these therapies. The use of adipose-derived mesenchymal stem cells as intralesional injection therapy for perianal fistulae in CD is perhaps closest to mainstream clinical use in the US. These studies, combined with the meta-analysis previously discussed, enabled the use of this therapy in Europe, and suggests that intra-fistula injection of adipose-derived stem cells may soon become a readily available treatment options for these patients in the US. In addition to therapies that utilize administration of actual stem cells, several emerging therapies aim to modulate or induce the regenerative capacity of a patient's own stem cells.

Preliminary evidence suggests that regenerative therapies hold great promise as treatments for IBD. While many barriers to their widespread use remain, this is an area that is likely to occupy a significant role in the treatment of IBD in the future.

Barrier and Mucosal Agents

The use of barrier or mucosal augmentation agents to help reconstitute and protect the intestinal mucosa is an exciting potential therapeutic area under investigation. These are directly acting, mechanistically based, and ideally not systemically absorbed. The investigators postulate that barrier agents may be uniquely suited to be low toxicity augmentations to other therapies, or potentially non-systemic maintenance therapy.

For patients with ulcerative colitis, the administration of oral phosphatidylcholine represents perhaps the most promising potential barrier augmentation therapy. The concentration of phosphatidylcholine in intestinal mucous has been shown to be lower in patients with UC compared to both patients with Crohn's disease and healthy controls.[20] It is for this reason that re-constituting this barrier with delayed release phosphatidylcholine has been studied as a potential therapy in several clinical trials for patients with UC.[21] One such therapy is LT-02 (Nestlé Health Science), which demonstrated promising early results in clinical trials, including a phase II trial for UC patients refractory to mesalazine.[22] This was a double-blind, randomized, placebo-controlled superiority study that analyzed 156 patients with UC and a deficient response to mesalazine therapy. Co-medication with 5-ASA, systemic steroids, azathioprine, and 6-mercaptopurine was allowed if specific dosing and duration criteria were met. Patients receiving rectally applied aminosalicylates or steroids, or oral topically acting steroids were excluded. The primary endpoint was change in the simple clinical colitis activity index (SCCAI). This study compared placebo to LT-02 doses of 0.8g, 1.6g, and 3.2g, and demonstrated a SCCAI score decrease of 33.3% in the placebo group vs. 44.3% in the 0.8g, 40.7% in the 1.6g, and 51.7% in the 3.2g doses ($p>0.05$, $p>0.05$, and $p=0.030$ respectively). Remission for placebo vs. 3.2g was 15% vs. 31.4% ($p=0.089$). Interestingly, despite a modest clinical improvement in patients receiving LT-02 vs. placebo, histologic remission was achieved in 20% of placebo patients compared to 40.5% LT-02 patients ($p=0.016$). Patients achieved mucosal healing in 32.5% for placebo vs. 47.4% for LT-02($p=0.098$). Furthermore, the safety profile was very favorable.

These promising results led to the study of LT-02 in phase III trials. Three phase III trials for LT-02 in UC have been initiated, PROTECT-1 (NCT02142725), PROTECT-2 (NCT02280629), and PROTECT-3 (NCT 02849951). PROTECT-1

investigated LT-02 at two doses compared to placebo for remission induction in patients with UC refractory to mesalamine, but was unfortunately terminated. PROTECT-2 is investigating LT-02 at the 3.2g dose for maintenance of remission over 48 weeks, and is currently recruiting. PROTECT-3 investigated LT-02 as an add-on therapy for the induction of remission in UC patients refractory to mesalamine, but unfortunately has also been terminated. Given the termination of two studies aimed at induction of remission, it is reasonable to deduct that LT-02 may have more promise as maintenance therapy with a favorable safety profile for UC patients already having achieved remission.

Other therapies that address the unique needs of the inflamed colonic mucosa rather than creating a mechanical barrier have been investigated. Luminal short-chain fatty acids (SCFAs) are thought to be important for colonic integrity, blood flow, motility, and mucous.[23,24] Two small studies of SCFA delivered topically as enemas have been performed without compelling evidence for efficacy.[25,26] L-Carnitine is critical in fatty acid transport/metabolism, and propionyl-L-carnitine (PLC) is thought to potentially represent a colonic reserve of propionyl-coenzyme-A and L-carnitine in the colon of patients with UC.[23] PLC is also thought to be anti-inflammatory and have antioxidant effects in the intestinal mucosa of UC patients.[27] PLC has been studied in a phase II trial for patients with UC due these potential effects on SCFA metabolism as well as protective effects on reactive oxygen species present in states of inflammation.[23] This double-blind, parallel-group trial randomized 121 patients with UC on stable aminosalicylate or thiopurine therapy to receive 1g/day PLC, 2g/day PLC, or placebo.[23] The primary endpoint was "clinical/endoscopic response" using the disease activity index (DAI) as the measure. The study reported good results for both dose groups, with 72% of PLC treated patients achieving clinical/endoscopic response vs. 50% in the placebo group (p=0.02). The remission rates did not achieve statistical significance for PLC treated vs. placebo. Unfortunately, two phase III clinical trials of propionyl-L-carnitine hydrochloride (ST 261) were terminated due to low probability of success (NCT01538251, NCT01567956.) Despite these failures, the general concept of mucosal function augmentation with safe and tolerable oral supplementation such as PLC persists as a potential therapeutic avenue.

Alkaline phosphatase (AP) is a highly important and prevalent enzyme in many living organisms including humans.[28] AP is expressed as an apical brush border enzyme in the intestinal tract and is thought to play an important role in mucosal defense through dephosphorylation of inflammatory molecules.[28,29] An exploratory open label study of exogenous AP in 21 patients with refractory UC reported improvement in short term disease activity scores as well as lower levels of C-reactive protein(CRP) and fecal calprotectin.[29] Of note, in this study the exogenous AP was administered intraduodenally via naso-duodenal tube daily for 7 days. Previously, exogenous AP has been studied intravenously for safety in a variety of conditions. Since then AM-Pharma has developed a fully human recombinant form of AP known as recAP, and is currently studying intravenous recAP in a phase II trial for acute kidney injury due to sepsis (NCT02182440).[30] The authors could not find active clinical trials in UC. Alkaline phosphatase appears to be a promising agent to promote protection from inflammation at the mucosal barrier of the intestine, but there remain significant challenges in drug delivery. Should a stable intestinal-release oral formulation become feasible, human AP could represent another safe mucosal-based therapy for UC.

The future direction of barrier reconstitution and augmentation therapies appears promising, and the authors anticipate their incorporation into the UC armamentarium in the near future.

JAK Inhibitors

Therapeutics targeting the Janus kinase (JAK) pathway offer a particularly promising class for the treatment of IBD. JAKs are a family of receptor-associated tyrosine kinases that are crucial in cytokine signaling.[31] Their importance in cytokine signaling makes JAK signaling a key pathway in autoimmune disorders including rheumatoid arthritis and inflammatory bowel disease.[31] JAK antagonists are actively being used or investigated for several disease states, including inflammatory bowel disease. Thus far several JAK inhibitors have

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demonstrated promising efficacy for the treatment of Crohn's disease and ulcerative colitis, and their oral delivery represents an additional potential benefit. As a class, JAK inhibitors do exhibit significant side effects including lymphopenia, leukopenia, liver enzyme elevations, dyslipidemia and herpes zoster reactivation.[32]

Tofacitinib (Xeljanz**)** (Pfizer) is a pan-JAK inhibitor with a preference for JAK1 and JAK3 that has demonstrated efficacy in the treatment of ulcerative colitis.[33] As a result, Tofacitinib was recently approved in the United States and Europe for moderate to severe active ulcerative colitis (UC) based on phase II and phase III trials. Phase III trials, titled **O**ral **C**linical **T**rials for tof**A**citinib in ulcerati**VE** colitis (OCTAVE), were published in May 2017. OCTAVE Induction 1 included 614 randomized patients assigned to placebo, tofacitinib 10 mg twice daily, or tofacitinib 15 mg twice daily. The primary endpoint was remission at 8 weeks, defined a Mayo score ≤ 2, no subscore > 1, and rectal bleeding subscore = 0. Mucosal healing, defined as a Mayo endoscopic subscore ≤1, was a secondary endpoint. Remission occurred in 18.5% of the 10 mg tofacitinib group compared to 8.2% of placebo (p=0.007). Mucosal healing was achieved in 31.3% in the 10 mg tofacitinib group vs. 15.6% in the placebo group(p<0.001). OCTAVE Induction 2 examined the same endpoints in 547 randomized patients. Remission was achieved in 16.6% of the 10 mg tofacitinib group vs. 3.6% of the placebo group(p<0.001). Mucosal healing was achieved in 28.4% of the 10 mg tofacitinib group vs. 11.6% of the placebo group (p<0.001).[33]

The OCTAVE Sustain trial randomized 593 patients that had completed OCTAVE Induction 1 or 2 and had a clinic response to receive placebo, tofacitinib 5 mg twice daily, or tofacitinib 10 mg twice daily. The primary endpoint of remission at 52 weeks was achieved in 11.1% of placebo, 34.3% of the tofacitinib 5 mg group, and 40.6% of the tofacitinib 10 mg group (p<0.001) for each treatment compared to placebo. The secondary

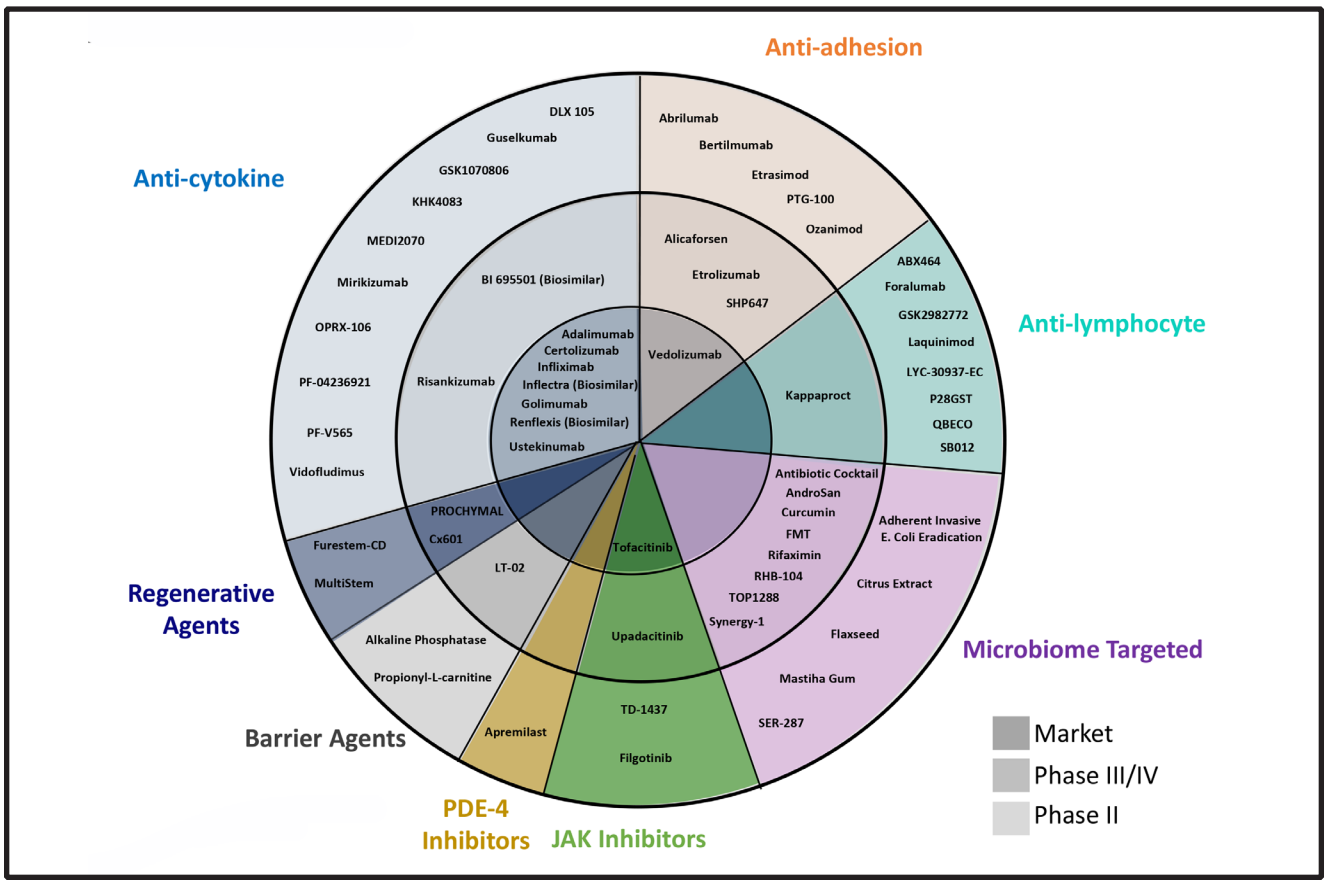

Figure 1. IBD Drug Pipeline

endpoint of mucosal healing was also significantly higher for both treatments compared to placebo. Unfortunately tofacitinib failed to demonstrate efficacy based on the CDAI as induction or maintenance therapy in two phase II studies for moderate-to-severe Crohn's disease, despite significant decreases in CRP and FCP.[35,36]

Another exciting JAK inhibitor is filgotinib (GLPG0634/GS-6034)(Galapagos), which is a selective inhibitor of JAK1.[37] Filgotinib has demonstrated efficacy in several phase II trials for rheumatoid arthritis.[38–40] Filgotinib also delivered promising results in a phase II clinical trial for moderate to severe Crohn's disease.[41] This trial was a randomized, double-blinded, placebo-controlled trial that enrolled 174 patients. This study compared filgotinib 200 mg daily given orally to placebo. The primary endpoint was clinical remission, defined as Crohn's Disease Activity Index less than 150 at week ten. At week ten, 47% of the filgotinib group achieved clinical remission compared to 23% of the placebo group (p=0.0077). These early results are certainly promising, and there are currently multiple registered clinical trials for filgotinib in inflammatory bowel disease, all of which are currently recruiting. Phase II trials that are recruiting include studies investigating filgotinib for the treatment of small bowel Crohn's disease (NCT03046056), and for perianal fistulizing Crohn's disease (NCT03077412). Phase III trials include investigating filgotinib for moderately to severely active Crohn's disease (NCT02914561), for moderately to severely active ulcerative colitis (NCT02914522), and long-term extensions for patients with Crohn's disease (NCT02914600) and ulcerative colitis (NCT02914535).

Upadacitinib (ABT-494) (AbbVie) is a more potent JAK1-selective inhibitor that is currently being investigated for use in Crohn's disease, ulcerative colitis, rheumatoid arthritis, atopic dermatitis, and psoriatic arthritis.[42] CELEST (NCT02365649) was a phase II, randomized, double-blinded, placebo-controlled study investigating upadacitinib for patients with moderately to severely active Crohn's disease.[43] The study which required intolerance or poor response to TNF inhibitors or immunomodulators, enrolled 220 patients, and investigated an array of dosages of upadacitinib compared to placebo. Efficacy was seen with regards to clinical response and remission as well as endoscopic remission at 16-weeks. Similarly, a 52 week maintenance extension showed maintenance of response at 52 weeks.[44] A phase II study evaluating long term efficacy, safety and tolerability in patients with Crohn's disease is ongoing with expected completion in 2022 (NCT02782663). Additionally, upadacitinib is being studied in a phase II trial for induction and maintenance in patients with moderately to severely active ulcerative colitis (NCT02819635). Currently recruiting/enrolling phase III trials of upadacitinib include a trial for patients with Crohn's disease and intolerance or inadequate response to conventional therapies but not biologics (NCT03345849), a maintenance and long term extension study in patients with Crohn's disease (NCT03345823), a study of patients with Crohn's disease and inadequate response or intolerance to biologic therapy (NCT03345836), and a study of long term safety and efficacy in ulcerative colitis (NCT03006068).

TD-1473 (Theravance Biopharma) is a gut-selective multi-JAK inhibitor that has reportedly demonstrated promise in a small phase Ib trial for moderate to severe UC according to a press release by Theravance Biopharma.[45] While data is extremely preliminary, TD-1473 is gut-selective. The potential to avoid systemic side effects from JAK inhibition with a localized gut-selective agent is very appealing, making this agent another exciting pipeline therapy in the JAK inhibitor class. A phase IIb evaluation of the efficacy and safety of induction and maintenance therapy with TD-1473 in subjects with moderately-to-severely active ulcerative colitis was recently registered (NCT03758443), however recruitment has not started.

In addition to the promising efficacy of JAK inhibitors in IBD, their oral delivery represents an additional potential benefit to both patients and physicians. These benefits must be weighed against factors such as cost, risks, and side effects. Shingles is the most prominent adverse event in tofacitinib trials, which seems likely to be ameliorated by prior use of the recombinant Shingrix vaccine. Similarly, it is expected that the JAK-1 specific inhibitors will have less occurrence of shingles, but this remains to be proven in clinical trials. The

authors anticipate that additional selective JAK inhibitors will achieve approval for ulcerative colitis and Crohn's disease in the near future.

Anti-Adhesion and Chemotaxis Therapies

Anti-adhesion therapies aim to prevent the interaction between adhesion molecules expressed on the endothelium of blood vessels and molecules expressed on the leukocyte cell surface, primarily integrins. By preventing this interaction, leukocytes are unable to migrate into gut tissue from the vasculature and propagate tissue inflammation. Natalizumab (Tysabri) was the first drug in this class to be approved for use in CD, after the phase III ENCORE trial demonstrated efficacy.[46] As a monoclonal antibody targeting the α4 integrin subunit, it was designed to have broad effects, blocking the gut-specific α4β7 integrin for Crohn's disease as well as the α4β1 integrin in the brain for multiple sclerosis. Unfortunately, long-term natalizumab use was associated with increased susceptibility to JC virus infection in the brain and subsequent development of progressive multifocal leukoencephalopathy (PML).[47] As a result, the FDA suspended its use in general clinical practice and clinical trials in February of 2005 and it is currently restricted to registered providers in select circumstances through the TOUCH prescribing program.

Vedolizumab (Entyvio) (Takeda), a monoclonal antibody targeting the gut-specific α4β7 integrin, has since been developed and showed efficacy in phase III trials (GEMINI) for induction and maintenance in Crohn's disease and ulcerative colitis and was approved by the FDA in May of 2014.[48,49] Abrilumab (AMG 181/MEDI 7183) (Amgen) was designed as an antibody against gut specific α4β7-integrin with reduced immunogenicity as compared to Vedolizumab. Unfortunately, phase II trials failed to demonstrate efficacy in inducing remission rates at 8 weeks in moderate to severe Crohn's disease, though modestly increased response rates were observed.[50] Abrilumab demonstrated improved rates of remission, response, and mucosal healing at doses of 70mg and 210mg. This was seen in all subjects as well as subjects who previously failed anti-TNF.[51] A phase II trial of PTG-100 (Protagonist Therapeutics)(NCT02895100), an oral gut-specific α4β7 integrin antagonist, was initially terminated due to lack of efficacy. However, an independent, blinded, re-read of endoscopies demonstrated higher rates of clinical remission relative to placebo. The initial lack of response was attributed usually high placebo effect due to "misread endoscopy reports". An official report is expected to be published in 2019.

Etrolizumab (RG7413/rhuMAb Beta7) (Roche) is a monoclonal antibody that targets the β7 subunit of α4β7 and αEβ7 integrin (involved in T cell retention via interaction with E-cadherin) on T lymphocytes. A phase II clinical trial, EUCALYPTUS, demonstrated efficacy of Etrolizumab in inducing and maintaining remission in patients with UC.[52] The recently published phase III BERGAMOT trial demonstrated higher rates of symptomatic remission and endoscopic remission as early as 6 weeks and sustained through week 14 in CD patients refractory/intolerant to anti–TNFα agents. The maintenance phase of this trial is still ongoing.[53] Etrolizumab is currently being studied in seven additional phase III clinical trials in both UC and CD in both anti-TNF naive and exposed patients (NCT02100696, NCT02163759, NCT02171429, NCT02165215,, NCT02118584, NCT02136069, NCT02394028, NCT02403323).

AJM300 (Carotegrast) (EA Pharma) is an oral small molecule directed against the α4 integrin involved in lymphocyte homing to the gut and brain. Phase II clinical trials in UC demonstrated significantly higher rates of clinical response, remission, and mucosal healing at 8 weeks compared to placebo,[54] however no significant difference was noted in patients with CD.[55] Phase III development for ulcerative colitis is ongoing in Japan. Although there is a theoretical risk of PML with AJM300, given the presence of α4 in brain lymphocytes, the manufacturer speculated that the short half-life of this thrice daily small molecule could facilitate rapid cessation should PML occur, and that the subsequent resumption of immune activity might prevent significant brain damage. However, given the significant potential for harm caused by PML, the evidence level required for any future α4 agent to reach market is expected be extremely high.

Based on the success of targeting integrins, investigation has also focused on preventing

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lymphocyte migration and tissue infiltration by inhibiting the mucosal addressin-cell adhesion molecule 1 (MAdCAM-1) present on intestinal and colonic vascular endothelial cells. This molecule is the target of the α4β7 integrin blocked by vedolizumab and etrolizumab. SHP647 (previously known as PF-00547659) (Shire, previously Pfizer) is an anti-MadCAM-1 antibody that was shown in phase II studies to be significantly more effective than placebo in achieving clinical remission, clinical response, and mucosal healing in patients with UC who failed prior therapy (TURANDOT).[56] Results of phase II studies in patients with CD (OPERA-1) did not show significant efficacy as induction therapy,[57] however, the results of the maintenance part of the phase II study (OPERA-2) suggested sustained efficacy over 72 weeks, but not a clear dose-reponse signal.[58] Phase III trials of SHP647 in patients with moderate to severe ulcerative colitis have recently started ruiting (NCT03259334, NCT03259308) with plans to start recruiting for a phase III long-term maintenance trial (CARMEN CD 305, 306 307) in patients with moderate to severe Crohn's disease (NCT03345849, NCT03627091, NCT03559517). However, development of this promising therapy may be further slowed by the purchase of Shire by Takeda, and the required sale of this drug to another company as it competes with vedolizumab.

Eldelumab (BMS-936557) (Bristol-Myers Squibb) is a monoclonal antibody that binds to Interferon-γ-inducible protein-10 (IP-10, also known as CXCL10) and blocks lymphocyte migration into intestinal epithelial cells. Results of phase II clinical trials of Eldelumab in UC and CD did not demonstrate significant efficacy in induction therapy.[59,60]

"Lymph node trapping" through modulation of sphingosine-1-phosphate (S1P) receptors has emerged as an exciting target for modulating gut inflammation in IBD. S1P signaling is thought to play a critical role in migration of lymphocytes from peripheral lymph nodes to gut lymphoid tissue.[61] Ozanimod (formerly RPC1063) (Celgene) is an oral S1PR1 and S1PR5 agonist, that produced increased clinical remission rates in ulcerative colitis after 8 weeks of induction(TOUCHSTONE) and Crohn's disease (STEPSTONE) when compared to placebo in phase II clinical trials.[62] Two phase III open-label extension studies are currently ongoing for patients with moderate to severe UC who were treated with ozanimod in previous trials (NCT02531126, NCT02435992). Phase II trials of Amiselimod (MT-1303) (Biogen), a S1PR1 modulator, were recently discontinued while phase II trials of Etrasimod (APD334) (Arena), another oral S1PR1 modulator, are still ongoing recently demonstrated positive results in patients in UC patients. Reportedly phase III trials are planned, however, have not been registered.

Alicaforsen (ISIS 2302) (ISIS Pharmaceuticals) is a 20-base antisense oligonucleotide that is highly selective for intercellular adhesion molecule-1(ICAM-1) mRNA resulting in ICAM-1 down regulation. ICAM-1 is an adhesion molecule involved in leukocyte migration and trafficking in the gut. While phase II trials demonstrated that topical alicaforsen was more effective than placebo in inducing long term remission in patients with distal UC, there was no significant difference when compared to mesalamine enemas.[63] Results of a phase II clinical trial investigating IV Alicaforsen in patients with CD were similarly disappointing.[64] There is evidence that Alicaforsen may be effective in chronic refractory pouchitis.[65] Vercinon (CCX282-B) (GSK-1605786) (GlaxoSmithKline) is an oral small molecule that binds to and blocks CCR9 receptors on the surface of lymphocytes which are involved in lymphocyte trafficking. This was studied in a phase III clinical trial (SHIELD-1), however results did not show significant efficacy compared to placebo in patients with CD and the program was discontinued in August of 2013.[66]

Immune Cell Modulation

Lymphocytes play a critical role in gut inflammation and the pathogenesis of IBD. Therapeutic strategies targeting aberrant lymphocyte differentiation, activation, survival, and functioning represent an important area of interest with variable success. Early attempts at modulating lymphocyte function with rituximab, (an anti-CD20 monoclonal antibody),[67] and lenalidomide, (a derivative of thalidomide used in multiple myeloma),[68] demonstrated no efficacy in treating IBD. IL2 plays an important role in promoting regulatory

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T cell (Treg) proliferation and survival as well as differentiation into proinflammatory effector T cells including Th17. Unfortunately, daclizumab, a monoclonal antibody to the IL2 receptor (CD25) showed no effect in phase II trials in UC.[69]

T cell activation occurs by simultaneous engagement of the T cell receptor, co-receptor complex (CD3), and co-stimulatory molecule (CD28) by antigen presenting cells. Both CD3 and CD28 have been proposed as therapeutic targets. Visilizumab (HuM291) (Nuvion) is a monoclonal antibody to the CD3 chain of the T-cell receptor complex which has been shown to diminish cytokine release and T cell activation while inducing T cell apoptosis. Unfortunately, visilizumab was not effective for severe, corticosteroid-refractory UC and was associated with increased infectious, cardiac, and vascular adverse events[70] despite positive phase I and phase II studies at higher doses.[71,72] As a consequence, the clinical development of visilizumab was halted.

Another T cell targeting agent, foralumab (NI-0401/TZLS-401) (Tiziana), a human anti-CD3 antibody was evaluated in a phase II clinical trial in patients with moderate to severely active Crohn's disease (NCT00630643), however results of this study remain unpublished. Abatacept (BMS-188667) (Orencia) (Bristol-Myers Squibb), which inhibits T cell co-stimulatory signaling by binding to C80/CD86 on antigen presenting cells, thus preventing CD28-mediated co-stimulation, was also unsuccessful in phase III trials of patients with moderate to severe UC and CD.[73]

Laquinimod (TV-5600, previously ABR-215062) (TEVA) is a novel oral therapy with a proposed mechanism of direct inhibitory effect on antigen presenting cells and T cells, resulting in downregulation of pro-inflammatory cytokines. Phase II trials demonstrated significantly higher rates of remission and response compared to placebo in patients with CD.[74] Currently phase III trials are underway for MS but no trials are registered at clinicaltrials.gov for IBD as of yet.

Upregulation of immunoregulatory cytokines, such as TGF-β, has been an exciting area of investigation. TGF-β suppresses the activation and functioning of pro-inflammatory effector T cells. High concentrations of intracellular SMAD7 inhibit TGF-β pathways leading to development of colitis in animal models[75]. Mongersen (Formerly GED-0301) (Celgene) is an oral pH controlled 21base single-stranded oligonucleotide that binds and facilitates degradation of SMAD7 mRNA. Phase II trials demonstrated significant efficacy in clinical remission compared to placebo,[76,77] with minimal data on biologic remission. After studies including an endoscopic endpoint in 2017, Celgene shut down four planned and ongoing phase III clinical trials testing the safety and efficacy of mongersen (NCT02641392, NCT02685683, NCT02596893, and NCT02974322).

Kappaproct (Cobitolimod) (DIMS0150) (InDex) is a locally administered DNA-based immunomodulatory sequence that binds to the toll-like receptor 9 (TLR9). This leads to the release of anti-inflammatory cytokines such IL10 and type I interferons to reduce intestinal inflammation and induce mucosal healing.[78,79] A phase III clinical study demonstrated increased rates of symptomatic remission as well as histological remission compared to placebo in patients with ulcerative colitis at week four. This was seen after two doses of topically administered drug during colonoscopy at weeks 0 and 4.[80] It remains to be seen whether oral administration will have comparable efficacy with results expected by the end of 2018.

Another interesting approach currently being investigated involves hampering Th2-mediated inflammation which has been shown to play a role in the pathogenesis of UC. SB012 (Sterna Biologicals) is a rectally delivered DNAzyme-based GATA-3 antagonist. GATA-3 is a transcription factor that plays a key role in regulating Th2 differentiation, activation, and proinflammatory cytokine release such as IL4, IL5, and IL13. Preclinical studies demonstrated that inhibition of GATA-3 mRNA expression in T cells resulted in suppressed colitis in experimental mice models.[81] In May of 2014 recruitment for a phase II trial, SECURE (NCT02129439) was initiated in patients with UC which recently concluded in March of 2018 with published abstract suggesting safety and efficacy in disease activity improvement at 28 and 56 days.[82]

In addition to lymphocytes, the activity of macrophages and NK cells is being investigated as an area of interest. ABX464 (Abivax) is an oral small molecule that has been shown in

mouse models to reduce colonic production of macrophage-induced inflammatory cytokines such as IL6 and TNF-α and increase tissue repair via cytokine IL22.[83] A recent phase 2a induction trial of ABX464 reportedly demonstrated significant increase in clinical remission and mucosal healing over placebo in patients with moderate to severe active ulcerative colitis who failed or were intolerant to other therapy with an extension study evaluating the long-term safety and efficacy currently recruiting (NCT03368118). Interestingly, ABX464 is also currently being investigated in HIV due to its ability to block HIV replication. In March of 2017 recruiting for a phase IIa trial (NCT03093259) of Abivax in moderate-to-severe active UC began.

Another cell-targeting therapy, NNC0142-0002 (Janssen) is an antibody directed against the natural killer group 2D (NKG2D) protein, demonstrated increased clinical remission after week 12 in patients with CD in a phase II study as well as a significant improvement in a biologic non-failure subgroup from week one onward despite not meeting their primary endpoints (clinical response at 4 weeks).[84] Two new clinical studies with the anti-NKG2D biologic have reportedly been planned for moderately to severely active Crohn's, but as yet they have not been registered with clinicaltrials.gov.

Bertilimumab (Immune Pharmaceuticals) is a monoclonal antibody that targets eotaxin-1, a chemokine involved in eosinophils migration to inflamed tissue. A randomized, double blind phase 2 trial is actively enrolling patients with severe UC (NCT01671956), however recruitment has been ongoing for over 2 years.

TOP1288 (TopiVert Pharma) is a rectally administered, non-absorbed, narrow spectrum protein kinase inhibitor (NSKI) that has been shown to be effective in reducing inflammation in mouse models of colitis.[85] TOP1288 is currently undergoing a randomized, double-blind, placebo-controlled multicenter phase IIa clinical trial for patients with moderate to severe UC (NCT02888379) and a phase I clinical trial with the non-absorbed oral formulation (NCT03071081).

P28GST (Satt Nord) is a recombinant protein glutathione-S-transferase. It is found in the intestinal helminth parasite *Schistosoma*. It has been shown to promote Th2 mediated cytokine release and reduce intestinal inflammation as well as decrease colitis in experimental mouse models.[86,87] This is currently being investigated as a therapeutic vaccine in a phase II, multicenter clinical trial in patients with moderate CD (NCT02281916).

GSK2982772 (GlaxoSmithKline) is a first in class small molecule inhibitor of receptor-interacting protein-1 (RIP1) kinase, which is involved in necroptosis (programed inflammatory cell death) and inflammation via TNF dependent cellular responses.[88] Currently GSK2982772 is being evaluated in a phase II, multicenter, randomized, placebo-controlled study is patients with UC (NCT02903966).

LYC-30937-EC (Lycera) is a first in class, oral, gut-directed ATPase modulator, designed to selectively target and induce apoptosis in lymphocytes. Currently two phase II trials have completed recruiting in patients with active UC (NCT02762500, NCT02764229), but did not show statistically significant benefits.

QBECO SSI (Qu Biologics) is an investigational immunotherapy that is derived from inactivated E. coli bacteria and is designed to restore innate immune function in the gastrointestinal (GI) tract. Phase I/II trials demonstrated safety and efficacy in patients with both CD and UC. A larger phase II trial of both induction and maintenance therapy in patients with moderate to severe CD is currently recruiting at five centers in Canada (NCT03472690).

Microbiome Targeted Therapies

Multiple studies have demonstrated that intestinal dysbiosis plays a key role in the development and exacerbation of IBD through aberrant mucosal inflammation.[89] As a result, various therapeutic strategies aimed at manipulating the intestinal microbiome are currently in development. Investigation has focused on diet, probiotics, prebiotics, antibiotics, and fecal microbiota transplant (FMT).

Diet and Nutritional Supplementation

Dietary approaches to managing IBD represent an under-resourced, difficult, but important area of study. This was highlighted by an online

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questionnaire showing that 71% of IBD patients believe that diet affects their disease and that 61% of patients believe their specialist disregarded the importance of diet the management of their disease.[90] Despite the patient perspective on diet and nutritional supplementation in the management of IBD, very few rigorously designed prospective trials exist.

Diets of popular interest include the semi-vegetarian diet (SVD), the specific carbohydrate diet (SCD), the exclusive enteral nutrition (EEN), the low fermentable oligosaccharide, disaccharide, monosaccharide, and polyol (FODMAP) diet, and the allergen elimination diet. A small prospective trial in Japan demonstrated that a semi-vegetarian diet, with small portions of meat offered once every two weeks and fish weekly, had higher rates of remission and prevention of relapse compared to omnivores in hospitalized patients with CD.[91,92] Exclusive enteral nutrition (EEN) has been shown in pediatric CD patients to be as effective as corticosteroids in inducing disease remission with higher rates of histological improvement.[93] Unfortunately, these results have not been reproduced in adult studies.[94] Specific carbohydrate diets, consisting of mostly meat, fruits, vegetables, nuts, oils, and honey with the elimination of most grains, have shown some efficacy in pediatric patients with IBD in retrospective and small single arm clinical trials.[95,96] Multiple additional early phase trials have been registered and are recruiting in both pediatric (NCT02610101, NCT03301311) and adult patients (NCT03058679, NCT02412553, NCT02858557). Multiple small observational studies [97,98] and one small randomized cross-over study[99] have demonstrated that low FODMAP diets (elimination of poorly absorbed short-chain carbohydrates) are effective in improving clinical symptoms of pain, bloating, and distention in patients with IBD, however larger prospective clinical trials are needed. Currently a 30 participant randomized trial of a low FODMAP diet compared to a control diet is recruiting patients with UC (NCT02469220). A large, randomized, controlled trial, conducted at three London teaching hospitals showed improvement in quality of life in CD patients with the implementation of an IgG4-targeted elimination diet. The research group used IgG4 reactivity to guide exclusion of the four food types with the highest IgG4 titers in the treatment group compared to the elimination of the four food types with the lowest IgG4 titers in the sham control group.[100]

Omega-3 free fatty acids (Epanova) (AstraZeneca) were evaluated in Crohn's disease patients in two large randomized, double-blind, placebo-controlled studies (EPIC-1 and EPIC-2), and did not show efficacy in maintaining remission.[101] However, recently published results of a phase II clinical trial evaluating the efficacy of eicosapentaenoic acid (TP-252) (Thetis) in maintaining remission for patients with UC, the major component of fish oil, demonstrated significant improvements in fecal calprotectin levels and maintenance of clinical remission at six months.[102]

A large, multi-center, randomized, control trial of curcumin, the biologically active component of turmeric with anti-inflammatory and antioxidant effects, showed higher rates of remission as well as improved clinical and endoscopic scores in patients with UC when added to standard therapy compared to standard therapy alone.[103] Additional phase III clinical trials evaluating the efficacy of curcumin have recently been registered in both pediatric (NCT02277223) and adult patients (NCT02683759) with UC. A randomized, double-blind, placebo-controlled study of vitamin D administration (2000 IU/day) demonstrated increased plasma cathelicidin, improved intestinal permeability (measured by urinary sugar excretion), lower CRP, and higher QoL in patients with CD.[104]

Andrographis paniculata extract (HMPL-004) (Hutchison Medi Pharma), a plant extract with broad anti-inflammatory properties (inhibiting TNF-α, NF-κB, and IL1β),[105] demonstrated efficacy in phase II clinical trials.[106] However phase III clinical trials further evaluating effectiveness of HMPL-004 in induction therapy (NCT01805791) and maintenance therapy (NCT01882764) were terminated due to an interim analysis which demonstrated futility in continuing its development. AndoSan (ACE Co. Ltd) is an extract from the *Agaricus blazei Murill,* a mushroom from Brazil with anti-inflammatory properties that has been evaluated in a phase II/phase III trial. This randomized, single-blinded, placebo controlled

trial demonstrated improvement in symptom score, fatigue, and health related quality of life compared to placebo in patients with UC.[107] Additional trials of anti-bacterial and anti-inflammatory mastiha gum, derived from the mastic tree in Greece, are currently ongoing (NCT02796339), as are studies of the effects of citrus extract (NCT03225261) and flaxseed lignan-enriched complex (NCT02201758).

Probiotics and Prebiotics

Augmentation of the protective functions of "good" bacteria in the GI tract through the use of probiotics and prebiotics have recently emergent as an area of interest. Single probiotic strains of non-pathogenic *E. coli* Nissle 1917[108] and *Lactobacillus GG*[109] demonstrated effectiveness in single trials in maintenance of remission in UC patients. Several trials have demonstrated that VSL#3 (a cocktail of eight different bacteria species) may be effective in inducing and maintaining remission in UC[110,111] and preventing the development and recurrence of pouchitis.[112–114] Several clinical trials investigating the role of probiotics for CD induction and maintenance therapy have failed to yield positive results.[115,116]

Another multi-probiotic, SER-287 (Seres Therapeutics), consists of live bacterial spores that proliferate and replace pathogenic "bad" gut bacteria. SER-287 reportedly showed benefit in clinical remission rates and endoscopic scores in patients with UC in a phase Ib placebo-controlled trial (NCT02618187).

In recent years, attention has shifted to prebiotics, which are non-digested compounds that shift microbial composition to promote protective "good bacteria" growth. This is achieved by serving as preferential metabolites for these bacteria. In preclinical studies, prebiotics have shown improved growth of "good bacteria",[118,119] reduced inflammatory cytokine production,[120] and reduced fecal calprotectin levels.[121] Clinical use has been limited by high participant dropout due to bloating and discomfort among IBD patients.[122,123] Currently, a phase II, single-group, clinical trial of Synergy-1, which is a combination of a probiotics and prebiotic (known as a synbiotic) containing a 1:1 oligosaccharide/inulin mixture, has been completed without published results for patients with mild to moderately active UC (NCT02093767). An additional randomized placebo-controlled trial evaluating the efficacy of Synergy-1 for maintenance therapy in patients with UC is currently recruiting (NCT02865707).

Antimicrobial Therapy

Antimicrobial therapy aims to alter the composition of the microbiota by reducing the concentration of potentially pathogenic bacteria that may be playing a role in the pathogenesis and disease course of patients with IBD. While the use of ciprofloxacin and metronidazole have demonstrated modest efficacy in inducing and maintaining remission in patients with active colonic Crohn's disease and in preventing postoperative recurrence in patients with ileocolonic anastomosis, their routine use is not recommended outside of suppurative complications.[124] Rifaximin, a minimally absorbed antibiotic, has gained attention recently due to its efficacy in other intestinal diseases. Several studies have shown that rifaximin may be effective in inducing and maintaining clinical remission in patients with CD compared to placebo,[125,126] however studies have thus far failed to show improvement in patients with UC.[127] Multiple additional trials of Rifaximin for induction therapy in CD patients (NCT02240108, NCT00603616, NCT02240121) and in the prevention of postoperative recurrence in CD patients (NCT03185624, NCT03185611) are currently underway. Additional studies investigating the role of antibiotics in IBD include the use of wide-spectrum antibiotic cocktails with doxycycline, amoxicillin, and metronidazole (NCT02345733) and oral vancomycin, neomycin, ciprofloxacin, lavage with PEG, +/- fluconazole in active CD that is refractory to conventional immunosuppressive therapy (NCT02765256).

Antimicrobial therapy targeting specific aberrant bacterial triggers of IBD is currently under investigation. Specifically, the ongoing randomized controlled trial TEOREM (Evaluation of Adherent Invasive *E coli* Eradication in Adult Crohn Disease) plans to assess whether 12 weeks of treatment with ciprofloxacin and rifaximin is superior to placebo in obtaining endoscopic remission in patients with ileal Crohn's disease colonized with adherent invasive *E coli* (NCT02620007). Adherent invasive *E coli* is a bacteria which has been associated with the pathogenesis of IBD. RHB-104

(Redhill Biopharma) is a fixed oral antibiotic combination therapy of clarithromycin, rifabutin, and clofazimine with potent intracellular, anti-mycobacterial, and anti-inflammatory properties that targets *Mycobacterium avium* subspecies *paratuberculosis* (MAP). MAP may play a role in the pathogenesis of Crohn's disease.[128] RHB-104 has recently completed a phase III clinical trials (MAPUS) in patients with CD (NCT01951326).

Fecal Microbiota Transplant

Fecal microbiota transplant (FMT) has the potential to restore microbial diversity that is often lost in IBD patients and has gained significant attention due its low cost, "ick factor", and relative safety profile.[129] In February of 2017, the FOCUS study demonstrated improved steroid-free clinical remission, steroid-free clinical response, and steroid-free endoscopic response at 8 weeks in patients who received one multi-donor FMT colonic infusion followed by multi-donor FMT enemas 5 days per week for 8 weeks.[130] The success of this trial was attributed to the intensity of the FMT administration. These results were also supported by a phase III uncontrolled trial in Turkey, where a single 500 mL fecal suspension was endoscopically delivered into the proximal terminal ileum along with loperamide (to provide adequate time for colonization). This study showed a 70% clinical response with 13% having clinical and endoscopic remission at 12 weeks.[131]

An earlier trial conducted in Canada demonstrated a significantly higher frequency of clinical and endoscopic remission in patients with UC at 7 weeks compared to placebo after receiving one FMT enema per week for 6 weeks.[132] A recently published abstract demonstrated that FMT can be effective with shorter duration and lower intensity protocols as well. This multi-center, randomized, placebo-controlled trial demonstrated that FMT delivered as one week of induction therapy, (administered via colonoscopy on day 0 followed by two enemas by day 7), had higher rates of steroid-free clinical and endoscopic remission compared to placebo (autologous FMT).[133] Given the invasive and "icky" nature of FMT administered by endoscopy, enteral access, or enema, there is currently a phase II trial evaluating the effectiveness of fecal transplantation via oral frozen capsules (NCT03273465).

Currently there is no published data on the efficacy of FMT in Crohn's disease, however there are currently multiple trials underway (NCT02227342, NCT02330211, NCT03078803, NCT02417974). A phase II trial of FMT in UC-associated pouchitis is currently recruiting as well (NCT02049502). Two studies looking at antimicrobial ablation with FMT rescue therapy in IBD patients are currently underway (NCT02606032, NCT02033408). Several additional studies with variations in FMT protocols are underway as well.

Extracorporeal Leukocytapheresis and Small Molecule Absorbents

Leukocytapheresis is a non-pharmacologic approach to the treatment of IBD that purportedly works by removing activated circulating leukocytes in the colonic mucosa through the use of beads or filters.[134] Leukocytapheresis has the potential for improved treatment efficacy in steroid refractory and steroid dependent patients as well as improved safety through steroid and biologic sparing. Adacolumn (JIMRO) is a device column packed with cellulose acetate beads capable of extracting granulocytes and monocytes from the patient's plasma. Cellsorba (Asahi KASEI) is a leukocyte apheresis device consisting of fine polyester fibers that removes lymphocytes in addition to granulocytes and monocytes. Small uncontrolled studies, primarily conducted in Japan, have demonstrated some efficacy as a steroid-sparing treatment modality.[135] However larger, sham-randomized phase III North American trials failed to demonstrate any efficacy of the Adacolumn for induction therapy for patients with moderate-to-severe UC[136] or active CD.[137] Two recent single group assignment trials have shown efficacy in inducing remission for steroid dependent ulcerative colitis demonstrating a potential role in this subclass of patients.[138,139]

ST-120 is a spherical carbon adsorbent that absorbs small molecular weight toxins, inflammatory mediators, and bile acids in the GI tract. ST-120 demonstrated significant efficacy in fistulizing CD in small Japanese studies.[140] Unfortunately, a large phase III, multicenter,

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randomized, placebo-controlled study (FHAST-1) did not meet primary endpoints (50% reduction in the number of draining fistula) in patients with active fistulizing CD.[141]

Phosphodiesterase 4 (PDE4) inhibitors

Phosphodiesterase 4 (PDE4) inhibitors block the breakdown of cAMP, which is an important intracellular signaling molecule that plays a role in the suppression of the NF-κB dependent inflammation including TNF-α production.[142] Apremilast (Otezla) (Celgene), is a PDE4 inhibitor approved by the FDA for psoriasis and psoriatic arthritis. A recent phase II, multicenter, randomized, placebo-controlled trial demonstrated significantly higher rates of clinical remission, mucosal healing, and biomarker improvement in patients with UC.[143]

While PDE4 inhibition represents a potentially efficacious target in IBD pathogenesis, multiple phase II and phase III trials of the PDE4 inhibitor tetomilast (OPC-6535) (Otsuka Pharma) failed to show any difference compared to placebo in patients with UC.[144,145] The trial was limited by high drop-out rate due to upper gastrointestinal symptoms, and a *post hoc* analysis suggests that tetomilast may have some clinical efficacy in those able to tolerate the drug.

Hyperbaric Oxygen Therapy

Hyperbaric oxygen therapy (HBOT) was investigated in a small phase II clinical trial based on systematic review suggesting improvement in clinical response.[146] HBOT has been shown to reduce pro-inflammatory cytokines, improve microbiome diversity, and increase growth factor synthesis. A recent phase 2A, randomized, double-blind, sham-controlled trial demonstrated significantly higher rates of clinical remission at 5 and 10 days in patients hospitalized for moderate-severe UC flare treated with HBOT and steroids compared to sham plus steroids despite early termination due to poor recruitment.[147] Despite these encouraging results, availability and costs of administering hyperbaric oxygen therapy remains a major barrier to widespread use outside of highly specialized academic centers.

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CONCLUSION

Advances in our understanding of the pathogenesis of IBD have begun to unravel the complexity of gut inflammation. With contributions from the immune system, genetics, microbiome, pathogens, and the environment, the multiple facets of IBD can be daunting. This complexity also allows for immense opportunity, offering multiple targets on which to intervene. The IBD pipeline can therefore be expected to continue to grow and mature.

Identifying safe and efficacious targets is only the first hurdle. Critical questions regarding optimal overall treatment approach and drug selection remain unanswered. The question of which therapy to initiate in the treatment naïve patient, or which drug to try next, remain largely uninformed and often clinical practice relies on anecdotal or cost-driven step-up therapy in the absence of an evidence-based overall strategy. Studies aimed at answering these questions have been performed and some headway has been made, particularly with regard to the benefits of combination therapy demonstrated in the SONIC[148] trial for CD and the SUCCESS[149] trial for UC. Newer studies, including REACT[150] and CALM,[151] have shown benefit in rapid step-up and treat-to-target strategies. REACT was an open-label, cluster randomized controlled trial that compared early combined immunotherapy (ECI) with an anti-TNF-α and an antimetabolite therapy to conventional management. This study found that ECI was not more effective than conventional management for symptom control in CD, but had improved rates of major adverse outcomes.[150] CALM was an open-label, randomized phase III study comparing a 'tight control' management strategy that utilized the biomarkers fecal calprotectin and C-reactive protein in conjunction with clinical symptoms vs. a strategy using only clinical symptoms. This study found that patients in the tight control group had better clinical and endoscopic outcomes than those in the clinical management alone, supporting a treat-to-target strategy that utilizes biomarkers in conjunction with clinical evaluation.[151]

Optimal treatment strategies remain elusive due to a number of factors including an incomplete understanding of the pathogenesis of IBD, a lack of head to head treatment trials (further complicated by the rate of emerging new therapies), and the

mixed data on prospective drug levels. The field will benefit from head to head treatment trials and algorithmic strategy studies at the population level. However, the heterogeneity of patient response highlights the need for predictive models that can identify the next optimal therapy for each patient.

As our understanding of IBD expands, so too does the drug pipeline but also the number of unanswered questions regarding the best way to use these treatments. These complex diseases offer many challenges, but great opportunity to improve patients' quality of life and outcomes. This is an exciting time in the treatment of IBD, and we are only just beginning. ■

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