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The Current State of the Inflammatory Bowel Disease Drug Pipeline: A Promising Time



Jason R. Goldsmith



Peter D.R. Higgins

The pipeline for IBD therapies has exploded in recent years, as advances in our understanding of the pathogenesis of IBD have led to new therapeutic targets. This includes multiple new mechanisms of action, ranging from biologic-based immunosuppression to mucosal barrier repair. This article reviews the promising mechanisms of action and specific agents currently in clinical trials for IBD.

BACKGROUND

In recent years, basic and translational science research into the pathogenesis of inflammatory bowel diseases (IBD) have resulted in a boom of new therapeutics for IBD. This started with the anti-TNF therapies, but has significantly broadened since. This article reviews the current state of the IBD drug pipeline (Figure 1). In this pipeline, several broad mechanisms of action (MOA) show significant promise, with multiple drugs in the pipeline, with many in late phase trials and one recent FDA approval. These MOAs include anti-adhesion therapies, anti-IL12/23 therapies, and Janus kinase (JAK) inhibitors. Other MOAs are less developed, but show promise as novel mechanisms. This includes therapies that directly modulate the immune response, therapies that alter the microbiome, and therapies that enhance/repair the intestinal barrier, as well as a new appreciation of the anti-inflammatory properties of several natural products.

Jason R. Goldsmith MD, PhD¹ Peter D.R. Higgins MD, PhD, MSc² ¹Department of Medicine, ²Department of Gastroenterology, University of Michigan, Ann Arbor, MI

Anti-Adhesion and Chemotaxis Therapies

Anti-adhesion therapies prevent the interaction between the endothelium of blood vessels and the integrins on a subset of white blood cells, preventing immune cell infiltration into organs and thus tamping down the immune response. Natalizumab (Tysabri) was the first drug in this class to be approved for use in CD, after the Phase 3 ENCORE trial demonstrated efficacy.¹ A monoclonal antibody targeting the $\alpha 4$ integrin subunit, it had broad effects, blocking the gut-specific $\alpha 4\beta 7$ integrin as well as the brain $\alpha 4\beta 1$ integrin. Thus, the antibody was also effective in the treatment of multiple sclerosis, by reducing immune surveillance in the brain. Unfortunately, long-term natalizumab has been associated with increased susceptibility to JC virus infection and subsequent development of progressive multifocal leukoencephalopathy (PML).²

Because of this risk of PML, development of gut-specific anti-integrin therapies were undertaken, culminating in the FDA approval of vedolizumab (Entyvio), a $\alpha 4\beta 7$ -specific monoclonal antibody.³

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Other second-generation anti-adhesion therapies are still in clinical trials. In phase 2 trials for UC and CD, abrilumumab (AMG181/MEDI7183) targets $\alpha4\beta7$ on WBCs like vedolizumab. Etrolizumab,⁴ which targets only the $\beta7$ subunit on WBCs, is currently in Phase 3 trials for UC. PF-00547659,⁵ which targets enterocyte Mucosal Addressin Cell Adhesion Molecule-1, has completed phase 2 for UC and CD.

Because these second generation anti-adhesion therapies are designed to be gut-specific, there is a hypothesis that they may result in lower risk of infections (supported based on extensive impressive data with vedolizumab) than existing anti-TNF therapies. Consequently, head-to-head trials between anti-adhesion therapies and anti-TNF therapies are needed to determine whether these new therapies provide equivalent efficacy with improved safety; as it stands there is currently a set of two trials registered on clinicaltrials.gov to compare Etrolizumab vs adalimumab (Humira), but they are not yet in the recruiting phase.

In contrast to the aforementioned gut-specific injectable therapies, Ajinomoto Pharmaceutical has tested an oral small-molecule inhibitor (AJM300) of the $\alpha4$ integrin subunit,⁶ demonstrating short-term efficacy. The authors hope that the pharmacokinetics of this drug, with its short half-life, will facilitate easy cessation should PML occur, and that the subsequent resumption of immune activity would prevent significant brain damage. However, given the significant harm caused by PML, the evidence level required for such a $\alpha4$ agent to reach market will be quite high for the FDA and the European Medicines Agency. A biologic targeting $\alpha2$ integrin, vatelizumab, is in Phase 2 studies for UC, but would likely encounter similar safety concerns to natalizumab and now AJM300.

A related approach involves inhibition of immune cell chemotaxis: the signaling that targets immune cells to different tissues. Several therapies are being pursued in this vein, including: 1) RPC1063, a sphingosine 1-phosphate 1 receptor modulator that inhibits lymphocyte egress from lymph nodes, which recently completed phase 2 trials for UC; 2) GS-5745, a monoclonal antibody targeting matrix metalloproteinase-9 (MMP-9), a pro-inflammatory enzyme involved in wound repair and chemotaxis, in phase 1 trials for UC; 3) GSK3050002, a monoclonal antibody targeting chemokine (C-C motif) ligand 20, in phase 1 trials for

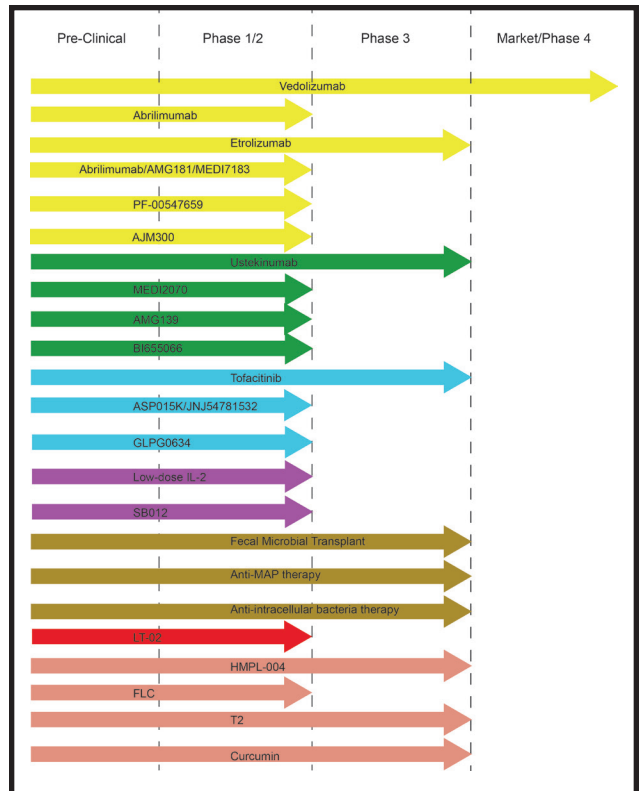


Figure 1. IBD Drug Pipeline

An overview of many of the therapies currently in the IBD therapy pipeline, divided by clinical trial phase (pre-clinical, phase 1 or 2, phase 3, and phase 4) and color-coded based on drug class. Anti-adhesion: yellow, anti-IL12/23: green, JAK inhibitors: blue, immune-cell modulation: purple, microbiome: brown, mucosal barrier enhancement: red, natural products: pink. Abbreviations: MAP: mycobacterium avium paratuberculosis, FLC: flaxseed lignan complex.

UC; and 4) E6011, a monoclonal antibody inhibitor of chemotaxis being explored in Japan in Phase 1/2 trials.

Anti-IL-12/23 Therapies

Ustekinumab (Stelara) is a monoclonal antibody targeting p40, a subunit of both IL-12 and IL-23. It is on the market for psoriasis, and has proven effective in phase 3 trials for Crohn's disease. It is believed to act through both inhibition of IL-12-mediated maturation of Th1 cells, and IL-23 mediated stimulation of Th17 cell survival and proliferation. With the completion of phase 3 trials, ustekinumab is anticipated to reach market within the next two years. Other compounds in this class include MEDI2070, an IL-23 specific agent that has finished recruitment for a phase 2 study. AMG139 is another IL-23 specific agent, which is in

phase 1 dose-ranging studies for CD, and BI655066 is an IL23p19 sub-unit specific monoclonal antibody in phase 2 trials for CD. Based on the pipeline, it appears as if several therapies targeting this pathway will be available for CD in the future.

JAK Inhibitors

JAK inhibitors work by blocking the activation of the intracellular enzymes Janus Kinases 1-3, which transduce cytokine signals and generally activate immune cells. The different agents under investigation vary in their selectivity for the different JAK molecules. Tofacitinib (Xeljanz) is a small-molecule oral JAK inhibitor which is FDA approved for rheumatoid arthritis, and in a head-to-head trial with adalimumab was found to be numerically superior without reaching statistical significance.⁷ Tofacitinib is currently in phase 3 clinical trials for UC and in phase 2 trials for CD. ASP015K/JNJ54781532 is another JAK inhibitor (selective for JAK1/3) in phase 2 trials for UC, while GLPG0634 is a JAK inhibitor with similar selectivity in phase 2 trials for CD. Given the approval of Tofacitinib for rheumatoid arthritis (RA), it is likely that JAK inhibitors will reach the market soon, assuming they prove safe and effective in IBD. With the recent rejection of agent for RA in Europe on the basis of safety data, the fate of Tofacitinib for IBD is not a foregone conclusion in the USA.

Immune Cell Modulation

Other therapies focus on modulating the aberrant T-cell responses thought to be an important underpinning in the pathogenesis of IBD. One interesting approach being used in UC is directly tamping down the Th2-immune response believed to be involved in the pathogenesis of IBD. SB012, which is being investigated in a Phase 1/2 trial currently, is a rectally administered formulation of a DNzyme that degrades GATA-3, a key transcription factor mediating the Th2 response. Another approach involves therapies to expand the regulatory T-cell (Treg) compartment that regulates inflammation. Low dose IL-2 has been shown to expand Treg populations and has clinical evidence supporting efficacy in autoimmune conditions, including alopecia⁸ and graft-vs-host disease.⁹ This approach is now being investigated in a phase 1&2 trials in UC and CD patients.

Similar immune modulation is being explored by Qu Biologics in phase 1/2 CD studies with a proprietary technology they have labeled site-specific

immunomodulators derived from bacterial products, which are believed to alter macrophage function.

Microbiome-Targeted and Anti-Microbial Therapies

With the continuously evolving understanding of the host-microbiome interactions that underpin IBD, therapies designed to target the microbiome have received significant attention in recent years. Unfortunately, both probiotics¹⁰ and fecal microbiota transplant (FMT)¹¹ have not yielded consistent results in IBD and further work is still being undertaken. FMT in particular is seeing a large amount of continued research activity, given its low cost of acquisition and use. A phase 1 trial is ongoing in CD patients, and a phase 2/3 trial for FMT in pediatric IBD patients has been registered but is not yet open to enrollment. A phase 2 FMT trial is currently in the recruitment phase for patients with UC-associated pouchitis, and a phase 1 trial exploring pre- and post-FMT shifts in host microbiota population in patients with mild to moderate UC is also recruiting. One hypothesized problem with FMT in IBD is that the increased immune response in IBD patients may overwhelm the transplanted microbiota; to test this theory a phase 1/2 trial using serial FMTs is being pursued in CD patients. Another phase 4 study is looking at antimicrobial ablation with FMT rescue therapy in UC and Crohn's colitis patients.

With the failure of probiotic studies in recent years, attention has shifted to prebiotics – compounds that shift the microbial composition, usually by serving as preferential metabolites for “good bacteria” to increase their relative presence. Synergy-1, a 1:1 oligosaccharide/inulin mixture, has recently completed a Phase 2 trial in UC patients and results are pending. Unfortunately, previous pilot trials of fructo-oligosaccharides were very poorly tolerated by IBD patients due to high rates of bloating and discomfort, with 26% (vs. 8% in placebo) choosing to discontinue in the FOS arm, and additionally did not demonstrate clinical benefit.¹² In a related vein, studies of partial enteral nutrition, as a potential replacement to the poorly tolerated enteral nutrition approach, are being pursued in CD patients.

A third, perhaps more traditional approach, involves ablation of perceived “bad” gut microbiota that may be contributing to IBD. One approach being pursued in CD patients is the ablation of intra-macrophage bacteria using a combination of ciprofloxacin, doxycycline, and hydroxychloroquine. Another antimicrobial trial

explores the hypothesis that CD is caused by an infection by mycobacterium avium subspecies paratuberculosis (MAP) using a combination anti-MAP therapy of clarithromycin, rifabutin, and clofazimine.

Mucosal Barrier Enhancement

A different approach to treating IBD involves enhancing the mucosal barrier, as opposed to suppressing the immune system. The pathway with the strongest evidence using this approach is phosphatidylcholine, a key component of the mucosal barrier. Recent phase 2 trials of LT-02, a delayed release formulation of phosphatidylcholine, showed efficacy in UC patients,¹³ and phase 3 trials are being planned.

Natural Products

Herbal compounds used in other medical cultures, along with other natural products, have received increasing amounts of attention as potential therapies for IBD; especially as anti-inflammatory claims become backed by experimental evidence. Andrographis paniculata extract (HMPL-004) is a plant extract with broad anti-inflammatory properties (inhibiting TNF, NF- κ B, and IL-1B)¹⁴ currently in phase 3 trials for UC as an alternative to mesalamine.^{15,16} Flaxseed lignan-enriched complex (FLC), is another dietary extract with anti-inflammatory properties that is currently being investigated in phase 2 trials for UC. STW5 is an herbal preparation that has been shown to be efficacious in IBS¹⁷ and in murine colitis¹⁸ and a phase 2 trial has been registered at clinicaltrials.gov for UC patients. Tripterygium glycosides (T2), an extract of Tripterygium wilfordii Hook F, is a traditional Chinese medicine used in inflammatory conditions now being investigated in phase 2/3 trials for CD. Curcumin, a potent NF- κ B inhibitor,¹⁹ is being explored alongside thiopurines in phase 3 trials to prevent post-op recurrence of CD. Milk-derived gangliosides, believed to be anti-inflammatory,²⁰ are being explored in early phase 1 trials in IBD patients.

Other Therapies

There are several other therapies in the pipeline for IBD that cover a wide range of modalities. Recruitment has opened for a Phase 2/3 clinical trial exploring hyperbaric oxygen for the treatment of UC. The mechanism of action is believed to be broad anti-inflammatory properties.²¹ Other novel mechanisms of action under active clinical investigation include: 1) an oral antisense

inhibitor of SMAD7 (Mongersen) which has completed phase 2 studies in CD; 2) small-molecule inhibition of toll-like receptor (TLR) 2 and TLR4 (via CD14): VB-201, in phase 2 trials for UC; 3) umbilical cord blood stem cells (FURESTEM-CD) in phase 1/2 trials for CD; 4) placenta-derived cells (PDA001) in phase 1 trials for CD, 5) allogenic mesenchymal stromal cells in phase 1 trials in pediatric CD, and 6) AVX-470, a parenteral bovine anti-TNF that is oral bioavailable in the gut, which just completed phase 1 trials in UC patients.

CONCLUSION

The recent advances in our understanding of the pathogenesis of IBD have led to an explosion of drugs in IBD pipeline. In particular, MOA with multiple drugs in late-stage development include anti-adhesion therapies, anti-IL12/23 therapies, and JAK inhibitors. Barrier enhancing and microbiome-altering therapies are also being pursued, but these pipelines are less robust.

In addition to the aforementioned successes and promising candidates, there have also been several failures in recent years. Most notably, the recent negative trial of Trichuris suis ova appears to be the end of parasitic therapy, although the parasitic enzyme P28GST, derived from Schistosoma, is being explored as a post-resection agent in CD patients in phase 2 trials to prevent the recurrence of ileo-colonic disease. The negative trials for anti-IL-13 (tralokinumab) and anti-IL-17 (secukinumab) therapies have led to refocused basic mucosal immunology questions, continuing the feedback loop between bench and bedside research.

Additionally, phase 3 trials are limited in their ability to inform us how to best use a given therapy, demonstrating only clinical superiority to placebo. For instance, we have had access to infliximab since 1998, but we still continue to study how to best optimize its use.^{22,23} Currently, our approach to medical management of IBD is largely one of trial and error, starting with less potent drugs with safer side effect profiles, and escalating after clinical failure. We select more potent agents largely by fiat, as head-to-head trials of more potent agents, such as anti-TNFs or anti-TNFs and vedolizumab, are just starting to be performed. As we move forward, work is being done to move towards a more evidence-based approach. Future predictive models that could include genetic and clinical markers may be able to predict which patients are more likely to respond to or fail a given therapy, to avoid the slow,

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