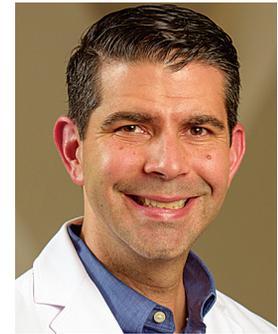


CROHN'S DISEASE: CURRENT AND FUTURE BIOLOGIC THERAPIES

John D. Betteridge, M.D.
Gastroenterologist
Regional GI



INTRODUCTION

In Crohn's disease, a dysfunctional immune system causes mucosal ulceration and chronic bowel wall damage that is typically progressive, especially in the first decade after diagnosis, and is often disabling. Most patients move from an initial "inflammatory" phenotype of bowel wall ulceration and injury to strictures of the lumen, or perforations that require surgery because of fistulas and/or abscesses.¹

The introduction of anti-tumor necrosis factor (Anti-TNF) biologics brought about a paradigm shift in Crohn's therapy. For the first time, medications are widely available that can alter the natural history of the disease and slow or halt its progression. Crohn's patients are experiencing an improved quality of life, with fewer operations or hospitalizations, and less steroid use.² However, about 30% of all Crohn's patients will not respond to anti-TNF biologics (infliximab, adalimumab, certolizumab); another 10% or more of responders will lose response each year; and a number of patients stop therapy because of intolerance to the medications. This all underscores the need for new biologic medications that offer novel mechanisms of action with comparable, or preferably superior, efficacy.^{3,4,5}

Hence, drug development of biologic agents for Crohn's disease has sped forward. Multiple new

products with unique mechanisms of action, including two other classes of biologics, are now commercially available, and several others are in the "pipeline" at different phases of development. These newer medications may have some advantages. For example, Vedolizumab theoretically offers "targeted" immune suppression with a reduced profile of side effects, and Ustekinumab also appears to be better tolerated than anti-TNF. However, neither drug appears to have superior efficacy, and they may be somewhat inferior in effectiveness. The economics of biologic therapies has also driven development of new, "biosimilar" medications that offer lower cost alternatives for biologics that are no longer protected by patent.

This article will review FDA-approved, commercially available biologic therapies for treatment of Crohn's disease, including anti-TNF, anti-TNF biosimilars, anti Integrin, and Anti IL12-23 agents (Table 1). It will also review briefly some medications currently in the development "pipeline." Since more than 200 molecules are currently registered with the Food and Drug Administration (FDA) and or European Medicines Agency (EMA), I will restrict the discussion to Biologic medications that are most likely to reach the market in the next two to three years, as well as those with unique mechanisms of interest. I will also discuss the cost burdens and shifts in the treatment of

Table 1. Current Biologics for Treatment of Crohn's Disease

| Medication | Target | Route | Treatment Schedule |
|---------------------------------|----------------|--------|--|
| infliximab, Remicade® (Janssen) | TNF | IV | Weight based loading 0, 2, 6 weeks. Then every 8 weeks in maintenance. |
| adalimumab, Humira® (Abbvie) | TNF | SQ | Load 160mg, 80mg day 1 and 15. 40mg every other week in maintenance. |
| certolizumab, Cimzia® (UCB) | TNF | SQ | Load 44mg week 0, 2, 4. 400mg every 4 weeks in maintenance. |
| vedolizumab, Entyvio® (Takeda) | α4β7, MadCam I | IV | 300mg, loading at 0, 2, 6 weeks. Then every 8 weeks. |
| Ustekinumab, Stelara® (Janssen) | IL 12-23 | IV, SQ | Loading weight based infusion x 1. 90mg SQ every 8 weeks in maintenance. |

Crohn's disease these medications have presented to our health system.

COMMERCIALLY AVAILABLE BIOLOGICS IN CROHN'S TREATMENT

Anti-TNF

Anti-TNF agents are the most widely used biologic agents, and are indicated for treatment of several diseases of immune system dysfunction. For example, adalimumab (Humira®, Abbvie) is labeled for 10 different indications and is the most widely prescribed biologic with over 1 million patients treated worldwide.^{6,7} Tumor Necrosis Factor is a cell-signaling protein (cytokine) with a variety of functions, including induction of fever and apoptosis, but most importantly induction of cell proliferation and differentiation. These properties make it an important amplification signal in acute phase responses, as well as in chronic inflammation fed by immune dysregulation.

Blockade of TNF has thus proven highly effective in treating patients with Crohn's disease.^{8,9} These are the first-line biologic agents in Crohn's disease, with more than 10 years of post-marketing data. There have been multiple positive Randomized Controlled Trials (RCT) for induction and maintenance of remission of Crohn's disease in patients with moderate to severe symptoms, or in those dependent on corticosteroids for symptom relief. There are currently three anti-TNF medications available in the United States.

Infliximab (Remicade®, Janssen) is given in Crohn's disease as a weight-based intravenous infusion, administered on a loading schedule of three infusions over the first six weeks, followed by a maintenance dose every eight weeks. Two other drugs, adalimumab and certolizumab (Cimzia®, UCB), are available as subcutaneous injections. These are also given in Crohn's disease with loading doses, followed by bi-weekly or monthly injections respectively for maintenance. All three medications have similar response rates, and though no head-to-head trials have ever been conducted, a meta-analysis of RCT data showed similar efficacy for all three medications in Crohn's disease.¹⁰

The impact of anti-TNF therapy for Crohn's disease cannot be overstated and has essentially changed the paradigms governing treatment. I now discuss with Crohn's patients not only the possibility of improvements in their symptoms and quality of life, but potentially changing the natural history of their

disease. The possibility of preventing complications that require surgery is a goal we still have not quite reached, but it is something previous generations of gastroenterologists couldn't even consider.

Still, several issues regarding both efficacy and safety remain. Regarding efficacy, as stated in the introduction, up to 30% of patients – known as primary non-responders – will have no response to initial treatment with anti-TNF. These patients are very unlikely to respond to a second anti-TNF agent. Also, each year about 10% of all responders – called secondary non-responders – lose responsiveness to the drug and require dose adjustments or a switch to another agent. Regarding safety, anti-TNF medications cause a 1.4- to 1.6-fold increase in the risk of serious infection.¹¹ There is also an increased risk of opportunistic or reactivation infections, like invasive fungal infections, tuberculosis, or hepatitis B.¹² Autoimmune reactions such as lupus-like syndrome and psoriasis (3-5% of Crohn's patients) can also complicate care. Anti-TNF biologics are also thought to potentially worsen or flare pre-existing conditions like congestive heart failure and multiple sclerosis.

More so than safety concerns, it's likely that cost considerations limit more widespread use of anti-TNF biologics. New, "biosimilar" anti-TNF drugs, similar to medications with expired patents, are coming to the marketplace in the United States.

BIOSIMILARS

A biosimilar is a copy version of an approved biologic medicine whose data protection has expired. Since they are similar to the parent molecule, they theoretically have similar efficacy and safety. Since generic equivalents for small molecule drugs provide up to 80% savings compared with their branded counterparts,¹³ it can be hoped that biosimilars might offer comparable savings, but they are not chemically identical like a generic drug is. Biologics are very large proteins, so differences in the manufacturing process (e.g. expression systems, growth conditions, and purifications) could create compounds that differ significantly from the parent compound, possibly with clinically meaningful effects. Still, the latter outcome is very unlikely, as it is known that even two batches of the parent biologic drug can have small differences due to the complex structure and function of large molecule proteins. The FDA and EMA have published guidelines regarding similarity, quality, purity, efficacy, and safety, and these compounds are strongly regulated. What is unique

about these guidelines is that biosimilars have to prove safety and efficacy in only one labeled indication for a biologic drug, and then are labeled for all indications of the parent molecule.

For example, CT-P13 (Inflixtra®), the only biosimilar available in the U.S., is a copy of infliximab and is already approved for use in Crohn's disease. It was approved based largely on a parallel group, Phase III Randomized Controlled Trial which showed no difference compared with infliximab *in patients with rheumatoid arthritis on methotrexate*.¹⁴

Since approval of Inflectra in Europe, smaller retrospective and cohort studies have shown positive results in IBD. Efficacy seems to be comparable to its parent molecule, infliximab. In general, efficacy is not a serious concern of mine, since translating results from one disease to another indication for the parent molecule is necessary to lower development costs, and to give relief to the marketplace. Most providers expect these medications to work in treatment naïve patients. Still, many others are concerned by the lack of data regarding interchangeability of these compounds.

As already discussed, biologics are large complex protein molecules that are chemically unique, and are distinct from small molecule generics for that reason. Because of their chemical composition, biologics create a significant immune response upon administration, and patients are warned against missing doses, because if the drug level falls below the therapeutic window, immunogenicity and formation of antibodies increases. This same phenomenon creates a potential problem when switching from a parent biologic to a biosimilar or vice versa, because the potential for immunogenicity can increase with each change. This effect has been observed already with biosimilars of erythropoietin, and cases of pure red cell aplasia.¹⁵

NOR-SWITCH, a recently published RCT, showed no significant difference in efficacy or safety when patients on infliximab were randomized to switch to a biosimilar or remain on infliximab, while efficacy, response rates, and immunogenicity (via antibody development) were observed.¹⁶ This is an important study, but has been criticized by some experts because it only showed that the first switch is safe, but offered no data on what multiple changes might bring. The FDA has not approved substitution of biosimilars, meaning pharmacists, infusion clinics, or health plans cannot substitute the biosimilar (or the original drug for that matter) without permission. This rule is important, as clinicians do retain control

over prescriptions now, but as more biosimilars are approved and costs decrease (a welcome advance), the pressure to switch a patient from the parent drug to a biosimilar will grow. Clinicians will need to show flexibility and understanding of which medications are being used by infusion centers, hospitals, and home infusion companies in their area.

Anti-Adhesion Molecules

Leukocyte trafficking (infiltration into the lamina propria of the intestinal wall) is a hallmark of the pathophysiology of IBD. Therefore, strategies that target the recruitment of leukocytes from the circulation into the site of inflammation could be a cornerstone of controlling the inflammatory cascade that leads to characteristic bowel wall injury in Crohn's disease.¹⁷ Integrins are cell adhesion transmembrane proteins integral to leukocyte migration through vascular endothelium after they've been "trapped" to the endothelium by L-selectin. The currently available biologic therapies that attack this mechanism are both anti-integrin molecules.

a. Natalizumab

Natalizumab (Tysabri®, Biogen) is an IgG4 humanized monoclonal antibody that antagonizes Alpha-4 integrin. It was first introduced as an effective medication in the treatment of multiple sclerosis, and was first shown to have efficacy in induction and maintenance of remission in Crohn's disease in 2003.¹⁸ Unfortunately, cases of progressive multifocal leukoencephalopathy (PML) due to reactivation of JC virus in the central nervous system (CNS) of patients treated with natalizumab have limited its use in Crohn's disease, and stopped further development of this drug. The blockade of $\alpha 4$ integrins blocks both the gut-specific $\alpha 4\beta 7$ subunit in cell adhesion molecule 1 (MadCAM-1), but also the $\alpha 4\beta 1$ -vascular cell adhesion molecule-1 (VCAM-1), which is necessary for leukocyte trafficking across the blood brain barrier. This latter action puts the CNS at risk for JC virus infection.¹⁷ Natalizumab is FDA approved for treatment of Crohn's disease after failure of anti-TNF biologics. (FDA, 2009)

b. Vedolizumab

Vedolizumab (Entyvio®, Takeda) is a humanized monoclonal antibody that specifically antagonizes the $\alpha 4\beta 7$ subunit by inhibiting its binding in cell adhesion molecule 1 (MadCAM-1), resulting in an

anti-inflammatory mechanism that is theoretically gut specific. The efficacy of vedolizumab in induction and maintenance of remission in Crohn's disease was established by the Gemini II trial. It included 368 patients in the induction study, and 461 patients in the maintenance study, and it showed statistically significant improvement in remission rates (14.5% vs. 7%, $p=0.02$) but not in response rates (31% vs. 26%, $P=0.23$) at week six.¹⁹

Several reasons have been proposed for these findings, but it seems possible the drug just takes longer to achieve the desired remission/response. This was demonstrated in Gemini III which primarily included patients who had failed or lost response to an anti-TNF. The delta between responders and non-responders continued to grow so that by week 10, it was statistically significant (47% to 25%, $P<0.0001$) while remission rates also grew (27% to 10%).²⁰ The maintenance trials of vedolizumab showed that responders could expect a durable response to the medication with clinical response and remission rates of 47% and 25% respectively at 52 weeks.¹⁹ This durability once a patient responds, compares favorably to all trials with anti-TNF biologics.

Vedolizumab has proven well tolerated both in clinical trials and in post marketing use. There is no increased risk for systemic or opportunistic infections. There is theoretically no increased risk for lymphoma and there has not been a single reported case of PML. As with anti-TNF and biosimilars, immunogenicity occurs, with 4.1% of patients positive for antibodies during FDA studies.¹⁹ For treatment in Crohn's disease there remain some question about efficacy for perianal disease and extra-intestinal manifestations. This, plus the possible slower onset of response, have led some experts to place vedolizumab behind anti-TNF and the medication discussed next, ustekinumab in the treatment of moderate to severe Crohn's disease.

c. Ustekinumab

Approved and available in the United States for use in Crohn's disease since September 2016, ustekinumab (Stelara®, Janssen) is the first commercially available biologic which decreases inflammation by blocking pro-inflammatory cytokines. Already available in the United States and Europe since 2010 for treatment of psoriasis and psoriatic arthritis, ustekinumab blocks biological activity of IL-12 and IL23 through their common p40 subunit, and

inhibits receptors for these two cytokines on T cells, antigen presenting cells, and natural killer cells.²¹

The efficacy of ustekinumab in Crohn's disease was investigated by the CERTIFI study group. In the induction study, patients were randomly assigned to receive one of several weight-based loading infusions, and 6mg/kg showed the greatest effect for inducing response or remission. Responders at week six underwent a second randomization, and received subcutaneous injections of 90mg every eight weeks in the maintenance phase of the study. At week 22, the ustekinumab group had higher rates of clinical remission (42% to 27%, $p=0.03$) and response (69% to 42.5%, $p <0.001$) than the placebo group.²² Interestingly, patients who had previously failed one or more immune suppressants, including anti-TNF, were more likely to respond to ustekinumab; patients with at least one bowel resection were more likely to fail. A large open label cohort study in Spain reported an 83% response rate to ustekinumab.²³

Given that ustekinumab has been on the market since 2010-2011, there is a good deal of safety data available from the dermatology literature. Multiple studies with five-year data suggest there is no increased risk of malignancy, major cardiovascular events, serious infection, or mortality.²⁴ As with vedolizumab, when the data are compared with data from the original anti-TNF studies, it seems that ustekinumab is slower in onset, and has somewhat muted response rates. but has a lower side effect profile, and yields more durable responses in those who do respond. The reasons for this behavior are unclear, but it is possible that some of these studies are identifying the individuals whose immune dysregulation is not TNF dependent, so they respond better to a different therapeutic mechanism. Another possibility suggested by the success of ustekinumab in anti-TNF failures, is that over time, an individual's Crohn's disease may change, maybe more so under pressure from TNF blockade.

BIOLOGICS IN THE PIPELINE

Based on the above experience, newer agents are coming to market, and similar considerations will be necessary when implementing them. As more biologics enter the marketplace, finding answers to these questions of differing responses, and moving toward a day of individualized therapeutics ("precision medicine"), will be topics of great import in IBD.

The majority of agents under study for future use in

Therapeutic Pipeline in Crohn's Disease

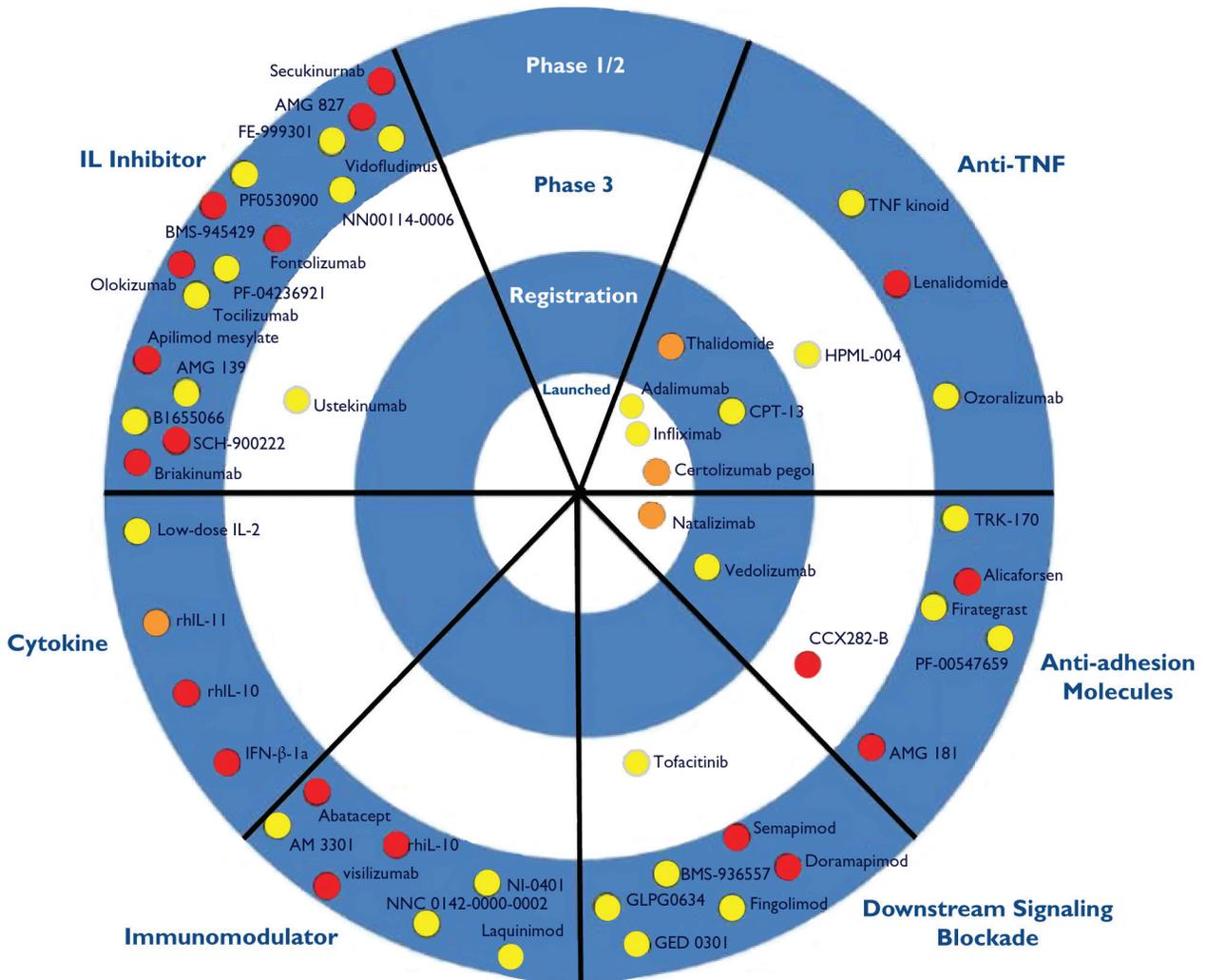


Fig. 1. Therapeutic Pipeline in Crohn's Disease. Drugs are categorized based on mechanism of action. Key: rh=recombinant human; IL=interleukin; TNF=tumor necrosis factor. From Amiot, A and Peyrin-Biroulet, L. Current and future biological agents on the horizon for the treatment of inflammatory bowel diseases. *Ther Adv Gastroenterol.* 2015. Vol. 8 66-82.

Crohn's disease target T-cell activation, adhesion molecules, or pro-inflammatory cytokines (Fig. 1). I will start with those biologics closest to market, with the most promise in early trials, or with a unique mechanism of action (MOA). I will only touch briefly on unique agents still in earlier phases of development, since many promising drugs in phase I or II never make it to market. I thus hope to avoid the alphabet soup that this type of review can become, since most of these drugs are not being targeted as first line agents in Crohn's disease.

a. Tofacitinib

Janus kinase (JAK) inhibitors block a variety of

pro-inflammatory cytokines by blocking the JAK/signal transducer and activator of transcription signaling pathway.²⁵ Tofacitinib is most likely to be the next biologic with a novel MOA to reach the market for IBD, but will likely be approved for ulcerative colitis (UC) only. It is already approved and available for rheumatoid arthritis. ABT-494 (AbbVie), a JAK inhibitor that is more JAK1-selective, is being evaluated for both ulcerative colitis and Crohn's disease. The JAK inhibitor filgotinib® (GLPG0634, Galapagos and Gilead) has positive phase 2 data in Crohn's disease and will undergo phase 3 testing in ulcerative colitis and Crohn's disease.

b. Laquinimod

This orally administered, small synthetic molecule, which initially showed success in MS, has shown efficacy in Crohn's disease. Its mechanism of action is not completely clear, but it has been shown to reduce circulating pro-inflammatory cytokines in Phase 2 and 2b studies. Interestingly, the lowest tested dose in these trials showed the best results.

c. Anti-TNF

HMPL-004, an *Andogaphis paniculata* extract which has been shown to reduce levels of TNF and IL1B, interferon, and IL-22, is currently being investigated in two Phase III studies. A novel approach to targeting TNF is to generate a polyclonal antibody response from the immune system of the patient. TNF-Kinoid, a recombinant human TNF conjugated to hemocyanin as a carrier protein, is inactivated, then adjuvanted with ISA-51; after encouraging early studies, it has had disappointing Phase II results.¹⁷

d. Smad7 antisense oligonucleotide

In Crohn's disease, defective activity of suppressive cytokine TGF- β 1 is observed due to high levels of Smad7, an intracellular protein that binds TGF- β 1. The oral SMAD7 antisense oligonucleotide drug called mongersenTM showed significant efficacy for inducing clinical remission in Crohn's disease. It is now in another phase 2 trial and will soon be in a phase 3 trial.²⁵

Lastly (but not completely), a number of biologics with activity in the IL 12-23 pathway are at various stages of development for use in Crohn's disease. A novel but early in development biologic is a met

metalloproteinase-9 antibody. This may have anti-inflammatory properties without significant immune suppression. It showed efficacy in a phase 1 study in ulcerative colitis and will be undergoing phase 2/3 trials in ulcerative colitis and Crohn's disease.²⁵

CONCLUSION

The pathophysiology of Crohn's disease remains incompletely understood despite the elucidation of many pathways that seem important in its pathogenesis. Years of research in animal models have enabled the development of a large panel of candidate biologic drugs, but several targeted cytokine pathways like IL-17 and IL-10 have failed to result in a usable drug that is safe and effective.

The success of TNF inhibitors has undoubtedly changed the treatment of this disease, and has proven the pivotal role of TNF in its pathogenesis, but these medications have several limitations including treatment failures, loss of response, and systemic immune suppression that can lead to unwanted side effects. New agents that target other pathways are emerging, but will undoubtedly have limitations like reduced efficacy for certain phenotypes, longer onset of action, or immunogenicity.

Ideally, new treatment approaches will be developed that might allow clinicians to select the best agent for any individual patient. In the future, tissue, stool, or blood testing hopefully may identify an individual in advance who might best respond to an anti-TNF, anti-integrin, or anti-IL 12-23 biologic. Clearly, we still have a lot to learn, but it is an exciting time to be taking care of patients with Crohn's disease.

John D. Betteridge, M.D.
Regional GI
2112 Harrisburg Pike, Suite 202
Lancaster, PA 17604-3200
301-758-3982
johnbett15@hotmail.com

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