Although antagonists of tumor necrosis factor have resulted in major therapeutic benefits in inflammatory bowel disease, the magnitude and durability of response are variable. Similar to previously available drugs such as 5-aminosalicylates and immunomodulators, the therapeutic effect is not universal leaving many people searching for options. The development of newer agents has benefited from advances in the understanding of the pathophysiology of the disease. Uncontrolled activation of the acquired immune system has an important role, and lymphocytes, cytokines, and adhesion molecules are broadly targeted for therapeutic intervention. There is increasing evidence of an important role of the innate immune system and the intestinal microbiome. This has led to a deeper understanding of the immunologic pathways leading to IBD and, most importantly, to the development of targeted therapies. In this review, we explore the limitations of current therapy as well as mechanisms of actions of new drugs and the efficacy and adverse events from data from clinical trials.

INTRODUCTION

The inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) are thought to be the result of an overly aggressive immune response toward an environmental trigger within a genetically susceptible host. Recent work has elucidated the host-microbe interaction identifying the complex interplay between genetic susceptibility, environmental factors, and the intestinal microbiome. This has led to a deeper understanding of the immunologic pathways leading to IBD and, most importantly, to the development of targeted therapies. For CD and UC not responding to 5-aminosalicylates (5-ASA), immunosuppression with corticosteroids, azathioprine, and anti-tumour necrosis factor (anti-TNF)
antibodies have been the mainstay of treatment\textsuperscript{[2]}\textsuperscript{8}. Even the most potent combination of immunomodulator and anti-TNF therapy in combination in recently diagnosed CD only achieves steroid free remission in 57% of patients\textsuperscript{[2]}\textsuperscript{8}. Given the persistent and sizable population of patients who are not served with current therapy, there has been great interest in new pathways of inflammation that would be amenable to pharmacologic intervention. This paper focuses on the most promising pathways and medications that appear closest to clinical availability.

\textbf{LIMITATIONS OF CONVENTIONAL THERAPY}

\textbf{Corticosteroids}

The significant benefit of corticosteroid therapy in IBD was established in the 1950s and 1960s for UC and later in the 1970s and 1980s for CD\textsuperscript{[2]}\textsuperscript{6}. In general, corticosteroids centrally suppress nuclear factor (NF)-\kappaB activation, which is the primary transcription factor mediating inflammatory response in both the innate and adaptive immune systems. In active IBD, corticosteroids are still a viable first-line treatment, but patients and clinicians have to be aware of significant short- and long-term side effects. Opportunistic infections, steroid-induced psychosis, steroid dependence, diabetes, and osteoporosis are among the most common side effects\textsuperscript{[8]}. Clinicians should also be aware of the variability of clinical response to these agents. Corticosteroids are unlikely to induce mucosal healing or maintain clinical remission, so its use is limited to induction of remission\textsuperscript{[6]}.

\textbf{Thiopurines}

Thiopurines, also referred to as immunomodulators, are derivatives of thioguanine and act as purine antimetabolites. Following metabolism into 6-thioguanine nucleotides, immunosuppression is in part the result of incorporation into the DNA/RNA of rapidly dividing inflammatory cell lines\textsuperscript{[7]}. This induces effector T cell apoptosis by suppression of the Rac1 and Vav-Rac1 signaling pathways and decreases NF-\kappaB activation, which leads to a decrease in pro-inflammatory cytokine secretion. Up to one third of patients with IBD are intolerant to thiopurines and a further 10% are unresponsive to them\textsuperscript{[8]}. In the majority of patients who do respond, the benefits of thiopurines take 3-6 mo to appear\textsuperscript{[8]}. Significant risks of thiopurines include lymphoproliferative disease (non-Hodgkin’s lymphoma), as high as 4-5 fold compared with unexposed IBD patients and further increased when used in combination with anti-TNF\textsuperscript{[9]}. Other side effects include early hypersensitivity reactions such as fever and pancreatitis, bone marrow suppression and hepatotoxicity requiring frequent lab monitoring during treatment\textsuperscript{[10]}. Finally, one in 300 patients harbor a homozygous \textit{TPMT} mutation and use of these agents is generally avoided\textsuperscript{[11]}.

\textbf{Methotrexate}

For patients with CD unresponsive to thiopurines, methotrexate has been the alternative. In a recent study from 2011, Kozarek \textit{et al.}\textsuperscript{[12]} showed that in patients who had failed azathioprine treatment, methotrexate was effective in maintaining clinical benefits in 63% of patients at 1 year. And in this group, 26% required side effects sufficient enough to discontinue therapy, and most of these adverse events occurred in the first 6 mo. This study shows that methotrexate is well tolerated in the long term and is a viable option in patients who cannot receive thiopurines. However, methotrexate has lower mucosal healing rates compared to biologics and azathioprine\textsuperscript{[13]}.

Methotrexate is an antimetabolite and acts specifically during DNA and RNA synthesis and therefore its effect is mainly seen on rapidly dividing cells (such as gastrointestinal and oral mucosa, and effector T-cells). This mechanism of action explains the most frequently observed side effects of myelosuppression and liver. Furthermore, its absolute contraindication in pregnancy makes this drug less desirable to use in reproductive aged women\textsuperscript{[14]}. Unlike, thiopurines methotrexate is not effective in inducing or maintaining remission in UC\textsuperscript{[14]}. In addition, a significant percentage of prescribing gastroenterologists were unfamiliar and uncomfortable with its use in the management of CD, further limiting its use in the United States\textsuperscript{[15]}.

\textbf{Biologic therapy}

\textbf{Anti-TNF-\alpha inhibitor therapy:} TNF-\alpha is a key pro-inflammatory cytokine involved in the systemic inflammatory cascade and is a member of a group of cytokines that stimulate the acute phase reaction. In response to lipopolysaccharide and other bacterial products presented by antigen-presenting cells, activated intestinal T cells, macrophages, produce TNF-\alpha and natural killer cells. In IBD, the number of TNF-\alpha secreting T cells in the lamina propria is increased and specific agents directed at these T cells were developed\textsuperscript{[16]}.

The United States Food and Drug Administration (FDA) approved the first anti-TNF agent for CD, infliximab, in 1998. This was followed by additional in category drugs, adalimumab in 2007, which had the benefit of subcutaneous administration, and certolizumab in 2008.

While various trials have confirmed the significant clinical benefit of anti-TNF-\alpha therapy, it is apparent that there are major limitations in the use of these agents, ranging from cost-effectiveness issues to morbidity and mortality, and the side effect profile is significant\textsuperscript{[17]}. Data from large treatment registries suggest that patients receiving both anti-TNF-\alpha agents and other immunosuppressants such as azathioprine and corticosteroids are at a higher risk of developing opportunistic infections and lymphoma\textsuperscript{[18]}. In addition, approximately 10% per year of patients lose response to this therapy, often but due to the development of anti-drug antibodies\textsuperscript{[18,19]}.

\textbf{Therapies targeting other cytokine pathways}

\textbf{Natalizumab:} Natalizumab, a human anti-\alpha4 integrin antibody, has been studied in CD\textsuperscript{[20]} and a recent meta-analysis concluded that it was superior to placebo in
controlling symptoms and inducing mucosal healing\textsuperscript{16}. However, its adoption was limited by the discovery of the development of progressive multifocal leukoencephalopathy in 1:1000 patients\textsuperscript{21}. After initially being removed from the market, it’s currently available only through enrollment in a specialized FDA risk minimization program known as TOUCH (https://www.touchprogram.com/TPP) that details the risk of progressive multifocal leukoencephalopathy (PML).

**New therapeutic goals: Mucosal healing and deep remission:** In recent years, mucosal healing has emerged as a major therapeutic goal in IBD. However, the definition of mucosal healing varies across studies, and there is no validated definition of mucosal healing or endoscopic remission in IBD\textsuperscript{23}. Current therapeutic goals are to induce remission both clinically, biochemically and endoscopically\textsuperscript{25}.

“Deep remission” in CD is defined as a combination of endoscopic and clinical indicators of disease activity, a CD activity index (CDAI) below 150 together with complete mucosal healing. Deep remission has been associated with better long term disease-specific quality of life, fewer flares and Crohn’s related hospitalizations, greater work productivity, and less activity impairment compared to mucosal healing alone\textsuperscript{26}. In UC, there is no proposed definition of deep remission.

Another area of consensus regarding potential therapy is prevention of bowel damage in CD by earlier introduction potent of therapy. In a population-based cohort study from Olmsted County, United States, among patients with CD diagnosed from 1970 to 2004, the cumulative risk of developing complications (STRUCTURING should be stricturing or penetrating disease) was 34% at 5 years and 51% at 20 years after diagnosis\textsuperscript{27}. These observations highlight the importance of creating tools that are able to measure cumulative bowel damage in CD. The development of an appropriate index is underway and has been named the CD digestive damage score (the Lemann score)\textsuperscript{28}. It addresses damage location, severity, extent, progression and reversibility, as measured by diagnostic imaging modalities and the history of surgical resection. The Lemann score may be used to assess the effect of various pharmacological therapies, function as a clinical trial endpoint and allow better identification of high-risk patients in regard to identification or progression of bowel damage.

The concept of early treatment to avoid later complications and the need for surgical intervention in CD is gaining momentum, and these new scoring systems might be able to help to identify patients at risk and help caregivers determine the timing for introduction of disease modifying agents. In a population-based study from Cardiff, United Kingdom, Ramadas et al\textsuperscript{29} reported that early thiopurine use (within the first year of diagnosis) was associated with lower rates of surgery. Subgroup analysis from placebo-controlled trials with anti-TNF-\(\alpha\) agents have also suggested that patients with early CD may experience greater efficacy than patients with established disease\textsuperscript{30}.

Complicated CD can be defined as the presence of bowel damage (stricture, abscess and/or fistula) and/or the requirement for surgery. The clinical factors associated with complex CD include: ileal disease, upper gastrointestinal involvement, smoking, complicated behavior (stricturing or penetrating), young age at diagnosis, perianal disease and some genetic factors such as nucleotide oligomerization domain 2 (NOD2), interleukin 10 (IL10) or IL-10R mutations\textsuperscript{31}. The most widely studied genetic marker in CD is the presence of variants of the NOD2 gene and its association with a more complex disease course and requirement for surgeries\textsuperscript{32}. The IBD CHIP project, a new DNA array-based diagnostic system which uses a DNA array to detect IBD mutation to predict the clinical evolution for CD, found that the NOD2 gene was the most important genetic association, was an independent predictive factor for need for surgery, and the strongest factor associated with a complicated disease course. However, a more recent study has reported that associations with gene variants are not accurate in predicting the course of CD. Currently, serological and genetic markers are not routinely used in clinical practice, as data are available in the predictive value of these markers\textsuperscript{33-35}.

Aggressive UC was recently defined as disease that is associated with a high relapse rate, the need for surgery, the development of colon cancer and/or the presence of extra-intestinal manifestations\textsuperscript{36}, though this marks a very heterogeneous group of patients. Clinical risk factors include extensive colitis and a young age at diagnosis. As in trials for rheumatoid arthritis, new emphasis is being placed on disease modifying drugs which limit mucosal damage. This marker of therapy may be used in upcoming disease-modification trials as well as in our clinical practice to promote early intervention with disease modifying agents in patients having such factors\textsuperscript{37}.

Emerging concepts in the management of IBD patients are tight monitoring and accelerated step up approaches\textsuperscript{38}. These require endoscopy, imaging (magnetic resonance imaging) and colonoscopy, C reactive protein, and/or fecal markers at 3-6 mo after introduction of disease-modifying agents (thiopurines and anti-TNF-\(\alpha\)) to identify objective signs of inflammation, and escalation of treatment. Further clinical trials are needed to evaluate the value of this strategy.

In CD patients with mild disease, corticosteroids are appropriate on an as needed basis, and in patients with moderate active disease without poor prognostic indicators, steroids and thiopurines still remain the standard first-line therapy. Anti-TNF-\(\alpha\) therapy should be considered as first-line therapy in patients with CD with bowel damage (stricture/fistula/abscess) and/or poor prognostic factors, severe disease, or complex perianal disease\textsuperscript{31,39}.

In UC, a proposed treatment algorithm for accelerated step-up therapy after “5-ASA failure” indicates that steroids and azathioprine should be considered. If
in case of is steroid-dependent disease and persistent signs of inflammation, then long term maintenance therapy with thiopurines or anti-TNF-\(\alpha\) agents should be considered\(^{[34,37]}\).

Despite therapeutic advances over the past several years and introduction of multiple new anti-TNF agents, including infliximab, adalimumab, certolizumab, golimumab, and natalizumab (CD only), there is still a large subset of patients that do not respond to these drugs or are unable to maintain remission long-term\(^{[38-41]}\). It is likely that these patients have disease that is driven by other factors. The best management approach toward these patients is unclear, but the development of new non anti-TNF based therapies may be a promising avenue of treatment. Three new agents in the “pipeline” which appear to be promising, and are closest to being commercially available in the United States are ustekinumab, tofacitinib, and vedolizumab. Ustekinumab already has FDA approval for psoriasis, and tofacitinib has FDA approval for rheumatoid arthritis, vedolizumab will soon be evaluated by the FDA for approval as IBD therapy\(^{[33]}\), and is expected to be approved in 2014.

**Targeting IL-12/23:** IL-12 and IL-23 are inflammatory cytokines produced by antigen-presenting cells, which promote T cell maturation into T-helper (Th)1 and Th17 phenotypes, respectively. The cytokines were identified to be significant to the pathology IBD in genome wide association studies\(^{[42]}\). IL-12 and IL-23 share a common p40 subunit, and it is known that when IL-12 (p35 + p40) is present, T cells differentiate into Th1 cells producing interferon-\(\gamma\) and TNF. On the other hand, when IL-23 (p19 + p40) is present together with transforming growth factor-\(\beta\) and IL-6, the Th17 subset preferentially develops and produces IL-6, IL-17A, IL-17F, IL-22 and IL-21\(^{[43]}\). Since both pathways are activated in CD patients, and contribute to tissue damage by the production of inflammatory cytokines, this makes neutralizations of the p40 subunit an attractive therapeutic target. Ustekinumab (Stelara) and briakinumab (Ozespa, previously ABT-874; Abbott, Abbott Park, IL, United States) are monoclonal IgG1 antibodies that target the p40 subunit of the IL-12/IL-23. Although Phase II trials in briakinumab were negative, however ustekinumab showed promising results in CD and is being further evaluated\(^{[43,44]}\).

The efficacy of ustekinumab was initially investigated in a double-blind, cross-over trial with 104 moderate to severe CD patients. In this group, clinical response rates for the patients given ustekinumab and placebo were 53% and 30%, respectively \((P = 0.02)\) at weeks 4 and 6, and 49% and 40% \((P = 0.34)\) at week 8. Further subgroup analysis showed that patients who received infliximab in the past (neither primary nor secondary non responders) had a significantly greater response to ustekinumab \((P < 0.05)\) through week 8. Based on the results of this study it was noted that ustekinumab induced clinical response in patients with moderate to severe disease, especially in those with prior exposure to infliximab. These results led to further evaluation of ustekinumab in inducing and maintaining remission in patients with CD refractory to anti-TNF agents. During induction, 526 patients were randomly assigned to receive intravenous ustekinumab (at dose 1, 3, or 6 mg/kg of body weight) or placebo at week 0. In the maintenance phase, the 145 patients who had a response to ustekinumab at 6 wk underwent a second randomization to receive subcutaneous ustekinumab (90 mg) or placebo at weeks 8 and 16, the primary endpoint was clinical response at week 6 defined as decrease in CDAI of 100 points from baseline. The proportions of patients who met the primary endpoint were 36.6%, 34.1%, 39.7% for 1, 3 and 6 mg of ustekinumab, respectively \(P = 0.03\) at 22 wk. Serious infections occurred in 7 patients (6 receiving ustekinumab) during induction and 11 patients (4 receiving ustekinumab) during maintenance therapy\(^{[43,45]}\) (Table 1).

We await the results of an ongoing phase 3 study. If the data are confirmed, this therapy may become a useful option for patients who have failed anti-TNF therapy.

**ANTIADHESION MOLECULES**

Drugs targeting adhesion molecules interfere with the migration of leukocyte subsets from the blood to the sites of inflammation\(^{[46]}\). The first drug in this category to be used in IBD was a monoclonal antibody against the \(\alpha4\) integrin, natalizumab. The blockade of \(\alpha4\)-integrins not only interferes with the \(\alpha4\beta7\) MadCAM1 interaction, associated with IBD, but also with \(\alpha4\beta1\) vascular cell adhesion molecule-1 interaction which is needed for patrolling effector T cells to contain JC virus and prevent it from infecting the brain. Following these results, therapies targeting \(\alpha4\beta7\) more specifically for the gut vasculature were developed in order to avoid the risk of PML\(^{[47]}\).

Vedolizumab (formerly called MLN002, Millennium; Takeda) binds specifically to the \(\alpha4\beta7\)-integrin dimer which is involved in recruitment of lymphocytes to the gut. Two large phase 3 studies under the GEMINI study group, one in UC (GEMINI 1) and one in CD (GEMINI 2) have recently been published and demonstrate a beneficial effect of vedolizumab in induction and maintenance of remission of UC and CD. GEMINI 1 and 2 are randomized, blinded, placebo-controlled multicenter trials to examine the efficacy of vedolizumab for induction and maintenance in moderate to severe UC and CD, respectively.

In the induction trial of the GEMINI 1 study, 374 patients received vedolizumab or placebo at week 0 and 2, and 521 patients received open-label vedolizumab at weeks 0 and 2 with disease evaluation at week 6. Patients
who had a response at week 6 were then randomly assigned to continue receiving vedolizumab every 8 or 4 wk or were switched to placebo for up to 52 wk. The primary outcome was clinical response at week 6 defined at a reduction in the Mayo score of at least 3 points and a decrease of at least 30% from the baseline score. Response rates at week 6 were 47.1% and 25.5% among patients in the vedolizumab group and the placebo group, respectively (P < 0.001). At week 52, 41.8% of patients who continued to receive vedolizumab every 8 wk and 44.8% of patients who received vedolizumab every 4 wk were in clinical remission, as compared with 15.9% of patients who switched to placebo (P < 0.001 for both groups).

The frequency of side effects was similar in both groups and serious adverse events were not more common in the vedolizumab group. All patients in the trial had an eligibility criterion of an unsuccessful previous treatment (lack of response, or unacceptable side effects), with one or more of the following medications: glucocorticoids, immunosuppressive medications (azathioprine or 6-mercaptopurine), or TNF antagonists. Patients were allowed to continue 5-ASA drugs during the study. This study shows that vedolizumab is more effective than placebo as induction and maintenance therapy in UC and more importantly, shows response in patients who had failed previous therapy.

In the induction trial for GEMINI 2, 368 patients were randomly assigned to receive vedolizumab or placebo at weeks 0 and 2 and 747 patients received open label vedolizumab at weeks 0 and 2; disease status was assessed at week 6, and the two primary endpoints were clinical remission (CDAI < 150) and CDAI-100 response (> 100 point decrease in CDAI score) at week 6. In the maintenance trial, 461 patients who had had a response to vedolizumab were re-randomized to placebo or vedolizumab every 8 or 4 wk until week 52. At week 6, a total of 14.5% of patients who received vedolizumab were in clinical remission, compared to 6.8% of patients who received placebo (P = 0.02). A total of 31.4% and 25.7% of patients in the treatment vs placebo group had a CDAI-100 response (P = 0.23). Among the 461 patients who had an initial response, 39.0% and 36.4% of those assigned to vedolizumab every 8 or 4 wk were in clinical remission at week 52, compared to 21.6% of those assigned to placebo (P < 0.001 and P = 0.004, for the two vedolizumab groups, respectively). Vedolizumab, as compared with placebo, was associated with a higher rate of serious adverse events (24.4% vs 15.3%), infections (44.1% vs 40.2%), and serious infections (5.5% vs 3.0%). Eligible patients for the trial had had no response to or had had an unacceptable side effects from one or more of the following: glucocorticoids, immunosuppressive agents (azathioprine, 6-mercaptopurine, or methotrexate), or TNF antagonists. This study shows that vedolizumab-treated patients with active CD were more likely than patients receiving placebo to have a remission, but not a CDAI-100 response, at week 6 (primary endpoint); and that those patients with an initial clinical response were more likely to be in clinical remission at week 52.

Both these reports are among the largest clinical studies in patients with IBD and combined consist of 2010 patients. Primary and secondary endpoints were met in the GEMINI 1 study (UC), however it seems that vedolizumab was less effective in patients with CD, although maintenance of remission was noted in the treatment group, and that patients with CD had a higher frequency of adverse events with treatment compared to placebo. It is possible that the underlying pathogenesis of the two diseases are different, and the selective blockage of gut-specific $\alpha\beta_4$-mediated leukocyte trafficking is more beneficial in UC, which is confined to the mucosa and the large intestine, compared to CD which might represent a more systemic disorder. More studies need to be done to assess the pharmacodynamics of vedolizumab.
To date, there have been no reported cases of PML. The results of these two recent studies suggest a promising new therapy for IBD.

TARGETING JANUS KINASE RECEPTORS

Besides specific neutralization of specific cytokines with antibodies, control of inflammation can be achieved by interfering with conserved elements associated with cytokine receptors, thus allowing a broader action. The Janus kinase (JAK) family of tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) plays a significant role in signal transduction of hematopoietin receptors type I and II. Tofacitinib (formerly CP-690, 550; Pfizer) is a JAK inhibitor that inhibits all four JAK family kinase members, with a functional cellular specificity for JAK1 and JAK3 over JAK2. Thus it can directly or indirectly modulate signaling for an important subset of proinflammatory cytokines including IL-2, -4, -7, -9, -15 and -21.

In a double-blind, placebo controlled, phase 2 trial, 194 patients with moderately to severely active UC were randomized to receive tofacitinib at a dose of 0.5, 3, 10 or 15 mg or placebo twice daily for 8 wk. Patients enrolled had to have a Mayo score of at least 6 with an endoscopic subscore of 2 or 3, and patients could receive oral mesalamine or oral prednisone at a stable dose of 30 mg or less per day, patients were not allowed to be on concurrent immunosuppressive therapy or therapy with anti-TNF agents. Approximately 30% of patients had prior anti-TNF exposure with failure of therapy. The primary outcome was clinical response at 8 wk, and occurred in 32%, 48%, 61% and 78% of patients receiving tofacitinib at a dose of 0.5 mg (P = 0.39), 3 mg (P = 0.55), 10 mg (P = 0.10) and 15 mg (P < 0.001), respectively, compared with 42% of patients receiving placebo. Clinical remission, defined as Mayo score < 2 with no subscore > 1, at 8 wk occurred in 13%, 33%, 48%, and 41% of patients receiving tofacitinib at a dose of 0.5 mg (P = 0.76), 3 mg (P = 0.01), 10 mg (P < 0.001) and 15 mg (P < 0.001), respectively, compared with 10% of patients receiving placebo. The most commonly reported adverse events was related to infection, and occurred in 6 patients on treatment with any dose of tofacitinib and 6 patients in the placebo group. There was a dose dependent increase in both high and low density lipoprotein cholesterol at 8 wk with tofacitinib which reversed after discontinuation of the study drug. Given the broad mechanism of action, opportunistic infections remain a valid concern and more data is required to determine the efficacy and safety of tofacitinib in the treatment of IBD. However, it’s oral method of administration will surely make this a popular avenue of treatment should it prove effective in larger scale treatment trials (Table 1).

CONCLUSION

Although IBD therapy has become much more efficacious with the introduction of anti-TNFs and the use of combination therapy, many patients still experience insufficient improvement on these agents. We are currently limited in option for patients who fail to respond to anti-TNF agents. In the near future, our patients may have access to IL-12/23 antibodies in CD, vedolizumab in CD and UC, possibly tofacitinib in both UC and CD. The promise of these agents is a bright light on the horizon for treatment of IBD.

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