

## Positioning of old and new biologicals and small molecules in the treatment of inflammatory bowel diseases

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**Author contributions:** All the authors contributed to the writing of the manuscript.

**Conflict-of-interest statement:** Bessissow T has been a speaker and/or advisory board member for: AbbVie, Janssen, Takeda, Pfizer, Merck, Shire, Ferring and Pendopharm and has received unrestricted research grant from: AbbVie, Janssen, Pentax and Echosense; Lakatos PL has been a speaker and/or advisory board member: AbbVie, Celltrion, Falk Pharma GmbH, Ferring, Genetech, Jansen, Kyowa Hakko Kirin Pharma, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka Pharma, Pharmacosmos, Pfizer, Roche, Shire and Takeda and has received unrestricted research grant: AbbVie, MSD and Pfizer. There are no conflicts of interest to report from other authors

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**Manuscript source:** Invited manuscript

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Received: March 29, 2018

Peer-review started: March 29, 2018

First decision: April 26, 2018

Revised: May 9, 2018

Accepted: June 25, 2018

Article in press: June 25, 2018

Published online: August 28, 2018

### Abstract

The past decade has brought substantial advances in the management of inflammatory bowel diseases (IBD). The introduction of tumor necrosis factor (TNF) antagonists, evidence for the value of combination therapy, the recognition of targeting lymphocyte trafficking and activation as a viable treatment, and the need for early treatment of high-risk patients are all fundamental concepts for current modern IBD treatment algorithms. In this article, authors review the existing data on approved biologicals and small molecules as well as provide insight on the current positioning of approved therapies. Patient stratification for the selection of specific therapies, therapeutic targets and patient monitoring will be discussed as well. The therapeutic armamentarium for IBD is expanding as novel and more targeted therapies become available. In the absence of comparative trials, positioning these agents is becoming difficult. Emerging concepts for the future will include an emphasis on the development of algorithms which will facilitate a greater understanding of the positioning of novel biological drugs and small molecules in order to best tailor therapy to the patient. In the interim, anti-TNF therapy remains an important component of IBD therapy with the most real-life evidence and should be considered as first-line therapy in patients with complicated Crohn's disease and in acute-severe ulcerative colitis. The safety and efficacy of these 'older' anti-TNF therapies can be optimized by adhering to therapeutic algorithms which combine clinical and objective markers of disease severity

and response to therapy.

**Key words:** Inflammatory bowel disease; Small molecule; Positioning; Biologic; Therapeutic

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**Core tip:** Anti-tumor necrosis factor therapy should be considered as first-line therapy in patients with complicated Crohn's disease and in acute-severe ulcerative colitis. Beyond these specific circumstances, the positioning of novel biologics and small molecules depends on the patient's medical history, preference and disease phenotype. The efficacy and safety of using immunomodulatory therapy can be enhanced by adhering to therapeutic algorithms and using a 'treat-to-target' approach. The risks for adverse events due to poor disease control outweigh the risks associated with early aggressive therapy. In the setting of clinical and biochemical remission, following at least 6 mo of combined immunosuppressive therapy, consideration can be made to withdrawing thiopurine therapy in the correct patient with close follow-up.

Reinglas J, Goncz L, Kurt Z, Bessissow T, Lakatos PL. Positioning of old and new biologicals and small molecules in the treatment of inflammatory bowel diseases. *World J Gastroenterol* 2018; 24(32): 3567-3582 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v24/i32/3567.htm> DOI: <http://dx.doi.org/10.3748/wjg.v24.i32.3567>

## INTRODUCTION

Therapeutic trials for inflammatory bowel disease (IBD) began nearly 100 years after the first case report of IBD was published by Sir Samuel Wilks in 1859 who used the term "ulcerative colitis (UC)" to describe a condition similar to what is understood as UC today<sup>[1]</sup>. Approximately 10 years following the original study by Sir Sidney Truelove which revealed the efficacy of corticosteroid therapy in UC, the first clinical trial evaluating steroids in Crohn's disease (CD) was conducted in 1966 by Jones and Lennard-Jones<sup>[2]</sup>. Prior to these landmark trials, the treatment of IBD was limited to supportive care and surgical intervention.

Knowledge regarding the adverse effects of chronic steroid therapy in UC ultimately led to the first positive double blind randomized controlled trial (RCT) evaluating the efficacy of sulfasalazine in 1962<sup>[3,4]</sup>. Unfortunately, many patients were unable to tolerate the side-effects from sulfasalazine which prompted additional studies to uncover the active ingredient, 5ASA<sup>[5]</sup>. Since, 5ASA has repeatedly demonstrated its efficacy and improved safety profile as compared to sulfasalazine in mild to moderate UC<sup>[6-8]</sup>. In contrast, 5ASA therapy has been abandoned in CD due to its inability to prevent quiescent

disease relapse<sup>[9]</sup>. As steroid-refractory disease became more prevalent, reports on the use of ciclosporin began appearing and the first successful trials were conducted in 1989 and 1994 for steroid resistant severe CD and UC, respectively<sup>[10,11]</sup>. Due to ciclosporin's narrow therapeutic window, alternative steroid-sparing agents such as thiopurines were investigated. Although they have demonstrated fair efficacy in IBD, it may take up to 3-6 mo for them to reach their full therapeutic effect thereby limiting their potential as a strong induction agent<sup>[12]</sup>. Despite their slow onset of action and risks, thiopurines may be used strategically to reduce immunogenicity associated with biologic therapy and augment the rate of remission<sup>[13,14]</sup>. Budesonide, a corticosteroid which undergoes significant first-pass metabolism in the liver resulting in low systemic exposure, has also established its position in the therapeutic armamentarium since Rutgeerts *et al.*<sup>[15]</sup>'s original study demonstrating its non-inferiority to prednisolone therapy for CD patients in 1994. Budesonide has since repeatedly demonstrated its efficacy and safety making it the preferred means of inducing remission in patients with mild Crohn's ileitis<sup>[16]</sup>. A newer formulation with a delayed release (budesonide-MMX<sup>®</sup>) can be efficacious in moderate UC as well<sup>[17]</sup>.

Alongside the advent of new biological therapies, the therapeutic approach has evolved over the past decade to include the use of objective markers of disease severity and response to therapy in tandem with the historical clinical scores<sup>[18,19]</sup>. In this article, authors review the existing data and provide a rationale for the positioning of the 'old' and 'new' biologicals and small molecules. Strategies for the use of available therapies based on recent guidelines will be reviewed.

## CD

### **Anti-tumor necrosis factor**

**Infliximab:** Four years after the FDA approved the use of infliximab in CD, the first large RCT; ACCENT I, was published in 2002 which evaluated infliximab maintenance therapy in 573 patients with a CDAI of at least 220 whom had responded well to an initial infusion of infliximab<sup>[20]</sup>. At the 30 and 54 wk follow-up, patients receiving infliximab maintenance therapy were more likely to be in remission (CDAI < 150) as compared to those without maintenance therapy (30 wk: OR = 2.7, 95%CI: 1.6-4.6) with a similar incidence of infection across all groups<sup>[20]</sup>. Besides demonstrating infliximab's efficacy, this study also provided a rationale for dose escalation in patients losing response to therapy<sup>[21]</sup>. Although effective for luminal disease, it was unclear if infliximab would also be effective for fistulising disease, thus the ACCENT II trial was published 2 years later which included 306 patients with one or more draining abdominal or perianal fistulas of at least 3 mo duration<sup>[22]</sup>. In this trial, the patients who were undergoing infliximab maintenance therapy demonstrated a significant fistula response wherein 36% (vs 23%,  $P = 0.009$ ) had

complete resolution of fistula draining at 54 wk<sup>[22]</sup>. Additionally, ACCENT II demonstrated a significant reduction in the requirement for hospitalization and surgery due to fistulising disease (8.6% vs 18.9%,  $P < 0.05$ )<sup>[23]</sup>. Early initiation of infliximab was further supported in a large study conducted by the GETAID group which evaluated the use of dual therapy vs monotherapy over 52 wk in 113 steroid-dependant CD patients<sup>[13]</sup>. Both GETAID and ACCENT- I studies identified incongruence amongst endoscopy and clinical scores, such as the CDAI. In a sub-study of ACCENT- I, 18% of moderate to severe CD patients as determined by the CDAI score had no active CD on endoscopy<sup>[24]</sup>. This prompted a rationale to include more objective end points and markers of disease severity (e.g., CRP and mucosal healing) in future studies, as was included in the Study of Biologic and Immunomodulator Naive Patients in Crohn's Disease (SONIC) conducted in 2010<sup>[14]</sup>. In this landmark RCT involving 508 biologic- and immunosuppressive-naïve patients, the superiority of infliximab over azathioprine as well as the therapeutic advantage of combining therapies over monotherapy with either infliximab or azathioprine alone at the 30 and 50 wk follow-ups was demonstrated.<sup>[14]</sup>

**Adalimumab:** In an attempt to possibly reduce the immunogenic responses induced by chimeric antibodies, such as infliximab which contains 25% mouse sequences, adalimumab was designed as the first fully human monoclonal antibody against tumor necrosis factor (TNF)-alpha<sup>[25]</sup>. The results of three pivotal trials (CLASSIC- I, CHARM and GAIN) established regulatory approval of adalimumab for the induction and maintenance of remission of CD in 2007. CLASSIC- I was the first human trial to evaluate induction of remission using adalimumab in 299 moderate to severe CD patients naïve to anti-TNF therapy<sup>[26]</sup>. A linear dose-response curve was appreciated at the 4 wk follow-up, with the greatest clinical remission rate associated with the highest dose studied (160 mg and 80 mg at weeks 0 and 2, respectively)<sup>[25]</sup>. As a ceiling effect was not achieved, it is unclear if higher dosing would be more efficacious, studies evaluating this are underway. The use of adalimumab as a second line induction agent following the failure of infliximab due to intolerance or poor response was evaluated in the GAIN trial which included 325 patients who had either lost response or become intolerant to infliximab<sup>[27]</sup>. At the 4 wk follow-up, 21% (34 of 159) of patients in the adalimumab group vs 7% (12 of 166) of those in the placebo group achieved clinical remission.

The efficacy of adalimumab for maintenance therapy was evaluated in the CLASSIC-II and CHARM studies. CLASSIC-II followed up with 276 patients from the CLASSIC- I study at 56 wk after randomizing patients to receive maintenance dosing or placebo. A greater proportion of patients receiving adalimumab 40 mg SC weekly or biweekly were in remission as compared to those receiving placebo (83% and 79% vs 44%,

respectively)<sup>[28]</sup>. Additionally, although most patients responded to therapy within the first week, some patients only responded to therapy after week 12<sup>[28]</sup>. This suggests that an observational period may need to occur prior to modifying therapy in patients who do not respond to induction following 1 wk. In the largest open-label study, CHARM enrolled 854 patients in order to evaluate the efficacy of adalimumab for induction and maintenance in CD patients not responding to alternative immunosuppressive therapy, including those whom had failed infliximab<sup>[29]</sup>. Although the induction dose of adalimumab was half of that provided in the CLASSIC trials, the response rate was similar. At week 56, biweekly and weekly dosing was equally effective at maintaining remission as compared to placebo (36% and 41% vs 12%, respectively). Of note, a greater proportion of patients receiving placebo discontinued treatment due to adverse events as compared to those receiving adalimumab<sup>[29]</sup>. This suggests the risks of complications associated with poorly controlled disease outweigh the risks associated with therapy. To corroborate the findings from the previous studies demonstrating clinical remission, the EXTEND trial conducted in 2012 which involved 135 patients with moderate to severe ileocolonic CD demonstrated a trend towards mucosal healing with adalimumab at week 12 as compared to placebo (27% vs 13%, respectively) as well as a significant difference at week 52 (24% vs 0%, respectively ( $P < 0.001$ ))<sup>[30]</sup>. Again, this suggests 12 wk may not be sufficient in all patients to determine response to therapy.

**Certolizumab:** Certolizumab pegol is a pegylated humanized monoclonal antibody Fab' fragment linked to polyethylene glycol that has a high affinity to tumor necrosis factor alpha<sup>[31]</sup>. Certolizumab was proposed as a potential alternative to infliximab due to its ease of delivery (SC as oppose to infusion) and longer half-life which may reduce the need for frequent dosing and risk for immunogenicity, theoretically<sup>[32,33]</sup>. The risks for side effects were presumed to be lower due to the lack of an Fc region which would be responsible for activating the compliment pathway leading to cellular apoptosis<sup>[32,33]</sup>. The largest phase II trial in 2005 by Schreiber *et al*<sup>[33]</sup> in 292 patients with moderate to severe CD demonstrated a significant dose-response relationship with clinical benefit demonstrated up until week 10, then lost significance at week 12 which was presumed to be secondary to greater placebo rates in patients with lower CRP values<sup>[33]</sup>. The potential placebo effect was addressed in the PRECISE- I trial which stratified 662 patients with moderate to severe CD based on their CRP prior to randomization to treatment groups<sup>[31]</sup>. Although response rates at week 6 and 26 were found to be modestly significant, induction of remission rates were not. However, in patients responding to certolizumab, maintenance of remission was successfully demonstrated in the PRECISE- II and PRECISE- III follow-up trials through 5 years<sup>[34,35]</sup>. The MUSIC trial conducted in 2013 confirmed certolizumab's efficacy with respect to mucosal

healing following 54 wk of therapy after evaluating 89 patients with active endoscopic disease (ulceration in  $\geq 2$  intestinal segments with a Crohn's Disease Endoscopic Index of Severity (CDEIS) score  $\geq 8$  points)<sup>[36]</sup>. As early as week 10, endoscopic remission was achieved in 37% of patients.

### Anti-integrin

**Natalizumab:** Natalizumab blocks the adhesion and subsequent migration of leukocytes from circulation into the gut by binding alpha-4 integrin which is expressed on all circulating leukocytes except neutrophils. Originally designed for multiple sclerosis patients, natalizumab demonstrated good efficacy for induction and maintenance of remission for CD in a large meta-analysis which included 5 trials<sup>[37]</sup>. The largest trials to be performed were ENACT- I , ENACT- II and ENCORE. ENACT- I included 905 patients with CD randomized to either placebo or natalizumab induction groups<sup>[38]</sup>. Although there was a subtle but significant difference in the response rate favoring natalizumab (56 percent and 49 percent, respectively), there was no difference in remission rates between groups for induction. ENACT- II included 339 responders to natalizumab from ENACT- I and randomized them to maintenance therapy every 4 wk or placebo<sup>[38]</sup>. In contrast to the first trial, significantly higher rates of remission occurred through 36 wk as compared to placebo (44% vs 26%). Induction of remission was reassessed in the ENCORE study which included 509 patients with CD evaluated through 3 induction doses over 8 wk. At week 12, a greater proportion of patients on natalizumab were in remission as compared to placebo, 28% vs 16% respectively<sup>[39]</sup>.

Although natalizumab demonstrated good efficacy in luminal CD, concerns related to serious infection surfaced. In an open-label extension of the ENACT- II trial, one patient died from JC virus-associated progressive multifocal leukoencephalopathy (PML)<sup>[40]</sup>. The association with PML and natalizumab was described in two other case reports on patients receiving treatment for multiple sclerosis<sup>[41,42]</sup>. Since the estimated risk for PML is 1 per 1000 patients, JC virus antibody testing should be considered if natalizumab will be used in IBD.

**Vedolizumab:** Vedolizumab reduces lymphocyte migration into the gut by antagonizing the  $\alpha_4\beta_7$  integrin mediated reactions. In contrast to natalizumab it does not act on  $\alpha_4\beta_1$  integrin, which is involved in brain lymphocyte trafficking, thus may have lower risk for PML<sup>[43]</sup>. Efficacy for its use as an induction and maintenance agent in CD was demonstrated in the GEMINI- II trial<sup>[44]</sup>. In the induction component of the trial, 368 patients were randomized to placebo or vedolizumab and 747 patients received open-label vedolizumab. Approximately 50% of all patients had failed at least one anti-TNF prior to enrolling in the study. Although clinical remission was achieved in a significantly greater proportion of patients taking vedolizumab as compared to placebo at week 6

(14.5% vs 6.8%, respectively), there was no significant difference in CDAI scores greater than 100 (CDAI-100 score) or CRP levels between groups. However, nearly twice as many patients in the vedolizumab maintenance groups were in clinical remission as compared to the placebo group (39% vs 21.6% respectively). Significant differences in favor of maintenance therapy over placebo were demonstrated in the CRP and the CDAI-100 score. Fistulization also improved as compared to placebo in the small group of patients on vedolizumab every 8 wk ( $n = 17$ ) but not in the small group taking vedolizumab every 4 wk<sup>[44]</sup>. Acknowledging that subjects recruited for this study had likely more aggressive disease than the aforementioned biologic-naïve anti-TNF studies discussed, vedolizumab is efficacious for luminal and possibly fistulising disease but may not provide as effective and efficient induction as compared to anti-TNF therapy. This has also been supported in network meta-analyses<sup>[45]</sup>. As such, if rapid induction is required then physicians prescribing vedolizumab should be aware of the potentially slower onset of action and consideration for the concomitant use of faster-acting induction agents (e.g., corticosteroids) to bridge the patient symptomatically.

A common reason for using vedolizumab as first line treatment in IBD is the assumption of the reduced risk for infection given the attenuation of the immune response is localized to the gut. This has been previously supported in a review which included six trials evaluating the use of vedolizumab in UC and CD (2380 patients with 4811 person-years of vedolizumab exposure)<sup>[46]</sup>. Within this study however, 16 patients with CD in the vedolizumab group developed clostridium difficile infection as compared to none in the placebo group. Additionally, more patients on vedolizumab had gastroenteritis and developed tuberculosis infection (despite negative tuberculosis screening at enrollment). In the aforementioned GEMINI- II trial, vedolizumab also had a higher rate of infections (44.1% vs 40.2%), and serious infections (5.5% vs 3.0%) as compared to placebo<sup>[44]</sup>. Head to head trials are needed to better describe the risk for infection in patients taking vedolizumab as compared to other biologics.

**Ustekinumab:** IL-12 p35-p40 and IL-23 p19-p40 are two proinflammatory heterodimeric cytokines that are induced in the inflamed mucosa of CD patients<sup>[47,48]</sup>. Ustekinumab is a human monoclonal IgG<sub>1k</sub> antibody which blocks the P40 sub-unit of IL-12 and IL-23 on T cells, natural killer and antigen presenting cells<sup>[49]</sup>. Originally successful in the treatment for plaque psoriasis and psoriatic arthritis, ustekinumab demonstrated its efficacy for CD in the UNITI trials which included 1300 CD patients with moderate to severe disease<sup>[50]</sup>. UNITI- I included 741 patients whom had failed anti-TNF therapy due to non-response or intolerance. The induction component of the trial revealed a significantly better clinical response in the ustekinumab treatment groups as com-



pared to placebo (34% vs 22%, respectively). UNITI-II included 628 patients whom were anti-TNF naïve but failed conventional immunosuppressive therapy due to poor response or intolerance. The UNITI-II cohort also had a significant improvement in their CDAI scores for induction by approximately 25% as compared to placebo. Patients receiving maintenance therapy every 8 wk and every 12 wk demonstrated a significantly greater remission rate at week 44 as compared to placebo (53% and 49% vs 36%, respectively). Of note, the secondary analyses demonstrated a non-significant difference in CDAI scores compared to placebo in the UNITI-I group as compared to the UNITI-II group, albeit the trend still favored ustekinumab therapy<sup>[50]</sup>. Lack of significance is most likely due to a lack of power to properly evaluate the difference amongst sub-groups, however this trend is expected; patients in UNITI-I have more refractory disease thus less likely to respond to ustekinumab as compared to the biologic-naïve patients in UNITI-II. Significant improvements in fecal calprotectin and CRP were also noted and able to be seen as early as 3 wk supporting its usefulness in acute severe flares.

## UC

### Anti-TNF agents

**Infliximab:** The first two large-scale studies to assess the therapeutic potential of infliximab were the ACT 1 and ACT 2 trials published in 2005, prior to this, biologic therapy for UC was not established<sup>[51]</sup>. ACT 1 evaluated 364 patients with moderate to severe UC following their induction and maintenance dosing until 54 wk. ACT 2 evaluated the same number of patients and maintained the same induction, maintenance and follow-up regimen as ACT 1 except maintenance dosing ceased after 22 wk. Nearly 60% of patients in both cohorts were steroid dependent. In both studies, a significant clinical response was demonstrated with remission occurring in approximately 35% and 31% of patients taking infliximab as compared to 15% and 6% of patients on placebo at week 8 in ACT 1 and ACT 2 studies, respectively. Sustained remission was achieved over the study period in approximately 20% of patients on infliximab as compared to 5% of patients in the placebo group. Additionally, a greater proportion of patients were able to be weaned off their steroids following the initiation of infliximab. Mucosal healing, considered to be the greatest risk factor for malignancy, was markedly improved throughout the study period and significantly better than placebo as early as week 8, approximately 60% vs 30% respectively. No difference between the two doses prescribed, 10 mg/kg and 5 mg/kg, was identified with respect to efficacy<sup>[51]</sup>.

Given the toxicity associated with cyclosporine and limited therapies available, GETAID compared the efficacy of infliximab against cyclosporine in an open-label RCT involving 115 patients with severe ulcerative colitis whom had failed high dose intravenous steroid therapy. The results were positive for both agents with no

significant difference in treatment failure or side effects between the infliximab and the cyclosporin groups (54% vs 60%, respectively)<sup>[52]</sup>.

**Adalimumab:** Five years following the approval for infliximab use in UC, adalimumab became the second biologic approved for use in UC based on the results from the ULTRA trials. ULTRA 1 utilized two different induction regimens (160/80 mg vs 80/40 mg SC at weeks 0 and 2 followed by 40 mg every 2 wk) to evaluate if adalimumab was effective in 186 moderate to severe UC patients<sup>[53]</sup>. At week 8, 19% vs 9% were in remission in the 160/80 mg group as compared to placebo, respectively. As noted in the CD trials, a ceiling effect was not achieved thus the optimal dose is still under investigation. ULTRA 2, which included 518 patients with moderate to severe UC, was conducted to evaluate the long-term efficacy of adalimumab as a maintenance agent<sup>[53]</sup>. Following 1 year, remission was achieved in 17% of patients on regular maintenance dosing as compared to 9% of patients in the placebo group. Similarly, mucosal healing was also higher in the adalimumab group as compared to placebo at both week 8 and 52 follow-up intervals, 41% and 25% vs 32% and 15%, respectively. This study also demonstrated that biologic naïve patients were more likely to achieve clinical remission as compared to patients previously on infliximab (Week 8: 21% vs 9% and Week 52: 22% vs 10%, respectively), which highlights prior biologic use as a potential risk factor for difficult to treat or aggressive disease. Long-term maintenance therapy using adalimumab was further evaluated over 4 years in ULTRA 1 and 2 trials as well as in an open-label study (ULTRA 3)<sup>[54]</sup>. With respect to patients observed as nonresponder imputation (NRI), 25% and 28% of the 199 patients from ULTRA 1 and 2 whom were still on adalimumab at the 4 year follow-up maintained clinical remission and mucosal healing respectively. In contrast, the ULTRA 3 open-label trial demonstrated clinical remission and mucosal healing rates to be considerably greater (64% and 60%, respectively), albeit difficult to compare in the absence of randomization.

**Golimumab:** Golimumab is a fully human monoclonal immunoglobulin delivered subcutaneously which targets a unique epitope on the TNF molecule as compared to infliximab and adalimumab. The PURSUIT trials which evaluated 1064 biologic naïve patients with moderate to severe UC were responsible for establishing regulatory approval for it in 2014. The induction trial, PURSUIT-SC, revealed a significantly greater proportion of patients in clinical remission following 6 wk using 200/100 mg and 400/200 mg induction doses as compared to placebo, 51% and 55% vs 30% respectively<sup>[55]</sup>. The extension of this trial, PURSUIT-M, which included 464 patients with moderate to severe UC whom had responded favorably to golimumab in the induction trial also demonstrated greater efficacy than placebo at maintaining clinical remission following 54 wk. At study end, 42% of patients

taking golimumab 100 mg every 4 wk were found to be in clinical remission as compared to 27% of patients taking placebo<sup>[56]</sup>. The rate of mucosal healing was significantly greater for patients taking golimumab in both the induction and maintenance studies, the differences were able to be appreciated as early as 2 wk. Golimumab, although not formally assessed in clinical trials, has been reported to be efficacious as a second and third-line anti-TNF agent in real life settings<sup>[57]</sup>.

### Anti-integrin agent

**Vedolizumab:** GEMINI-1 evaluated the efficacy of vedolizumab in a treatment resistant group of 895 moderate to severe UC patients (approximately 40% of patients failed  $\geq 1$  anti-TNF therapy)<sup>[58]</sup>. In the induction phase of the trial, 17% of patients taking vedolizumab were in clinical remission as compared to 5% of patients taking placebo by week 6. Mucosal healing was also nearly twice as apparent in patients taking vedolizumab as compared to placebo (41% vs 25% respectively). At 52 wk, clinical remission was maintained in approximately 44% of patients taking vedolizumab as compared to 16% of patients on placebo. No significant difference was identified between treatment groups receiving every 4 or 8 wk dosing regimens. In contrast to GEMINI- II for CD, there was no difference in infection rates in the treatment group as compared to placebo<sup>[44,58]</sup>.

## SMALL MOLECULES

### JAK inhibitors

**Tofacitinib:** Tofacitinib is a new oral medication which suppresses cytokine signalling in mucosal immune cells by inhibiting janus kinase's 1 and 3 (JAK 1 and 3). The oral route of administration and ability to target multiple cytokine pathways makes JAK inhibitors an attractive therapeutic option.

Although the efficacy for tofacitinib has not been established in CD yet, it has been established in UC as demonstrated by the OCTAVE trials<sup>[59]</sup>. Of the 905 patients with moderate to severe UC randomized to treatment in the induction trials, approximately 18% achieved clinical remission as compared to 6% of patients in the placebo group at 8 wk. Onset to effect was rapid, with improvements in their partial mayo score demonstrated as early as 2 wk. Although over 50% of patients within the induction groups had prior exposure to anti-TNF therapy, the treatment effect was similar in comparison to patients whom were biologic naïve despite OCTAVE's more stringent criteria for clinical remission as compared to the aforementioned trials (*i.e.*, partial mayo rectal bleeding subscore of 0). The OCTAVE-Sustain extension trial, which included 593 patients who had a clinical response to induction therapy, also demonstrated good maintenance of remission after 52 wk in both 5 mg and 10 mg twice daily treatment groups as compared to placebo (34% and 41% vs 11%, respectively). Mucosal healing and steroid-free remission was achieved and

maintained in a similar proportion of patients. With respect to adverse events, serious infections occurred more frequently in the induction but not maintenance trial. However, herpes zoster infection did occur more frequently in the tofacitinib 10mg maintenance group as compared to placebo<sup>[59]</sup>. Of note, tofacitinib received a recommendation for the treatment of UC by the GIDAC-FDA in March 2018 a final decision is anticipated by June 2018<sup>[60]</sup>.

## BIOSIMILARS

According to the FDA, a biosimilar is defined as a biological product that is highly similar to the reference product notwithstanding minor differences in clinically inactive components which result in no clinically meaningful differences in the purity, safety and efficacy of the product<sup>[61]</sup>. The use of biologic anti-inflammatory medications is increasing and the cost has become a significant economic burden on many national health-care systems around the world<sup>[62]</sup>. In Canada, the growth of Canadian sales of biologic anti-inflammatory drugs has nearly doubled since 2010. The top-selling biologic, remicade (infliximab), has cost the Canadian Government \$224 million in 2015 and \$4.8 billion since it was approved 10 years ago. Based on a Market Intelligence Report published by Health Canada, the use of a biosimilar such as Inflectra could have resulted in a \$41.7 million reduction in drug expenditures in 2015<sup>[62]</sup>. Several biosimilars to remicade (flixabi, inflectra, remsima) and adalimumab (cyltezo and imraldi) have already been approved for use in IBD.

Infliximab-dyyb (or CT-P13), was the first biosimilar for remicade (infliximab) to be approved and has the greatest amount of 'real world' observational data evaluating its efficacy and safety<sup>[63]</sup>. Infliximab-dyyb was first approved in South Korea and thereafter in Europe in 2013 following the results of two large randomized and double-blind clinical studies evaluating its safety and efficacy in rheumatoid arthritis as compared to remicade, PLANETRA and PLANETAS<sup>[64,65]</sup>. No significant differences were found with respect to safety, efficacy and immunogenicity thus it was approved for use in all labelled indications remicade was approved for. However, small retrospective studies in IBD have demonstrated mixed results<sup>[66-68]</sup>. A larger prospective nationwide multi-center study performed in Hungary involving 126 CD and 84 UC patients reported excellent induction rates<sup>[69]</sup>. At week 14, 81% of patients with Crohn's disease and 78% of patients with ulcerative colitis had a clinical response (CDAI reduction > 70) and 54% and 59% respectively, were in clinical remission (CDAI < 150). Comparable results were also seen in another large observational cohort study including 313 CD and 234 UC patients<sup>[70]</sup>. Response rates at 8 wk were greater than 90% for all patient groups, including patients whom switched from remicade to infliximab-dyyb. At week 24, response rates were 73.7%, 62.2% and 78.9% for biologic naïve,

**Table 1** Currently approved biologic treatments for inflammatory bowel diseases<sup>[16,117,118]</sup>

Medication	Route of administration (IV, SC, PO)	Approved dose
Infliximab	IV	Induction: 5-10 mg/kg (weeks 0, 2, and 6) Maintenance: 5-10 mg/kg every 4-8 wk
Adalimumab	SC	Induction: 160 mg (week 0), 80 mg (week 2) Maintenance: 40 mg every 7-14 d
Golimumab	SC	Induction: 200 mg (week 0), 100 mg (week 2) Maintenance: 100 mg every 4 wk
Certolizumab	SC	Induction: 400 mg (weeks 0, 2, and 4) Maintenance: 400 mg every 4 wk
Vedolizumab	IV	Induction: 300 mg (weeks 0, 2, and 6) Maintenance: 300 mg every 4-8 wk
Ustekinumab	IV SC	Induction: < 55 kg: 260 mg 55-85 kg: 390 mg > 85 kg: 520 mg Maintenance: 90 mg every 8 wk

pre-exposed and switched respectively. The efficacy, immunogenicity and safety profiles in both studies were considered comparable to that of the originator drug infliximab.

To date, studies which have evaluated switching from originator to biosimilar have been largely positive<sup>[71,72]</sup>. The longest evaluation period occurred over 52 wk in the NOR-SWITCH study which was a randomised, non-inferiority, double-blind, phase 4 trial involving 482 patients across 40 Norwegian centres with various inflammatory diseases maintained in remission on infliximab for at least 6 mo. Of the 482 patients, 155 (32%) and 93 (19%) were CD and UC respectively<sup>[73]</sup>. At study end, there was no difference in disease worsening, safety or immunogenicity amongst any of the groups. Although switching therapies in the setting of controlled disease would be a reasonable option and is supported by the evidence as well as the European Crohns and Colitis Organization; switching in the setting of failing the originator drug would be ill-advised<sup>[71]</sup>. Ben-Horin *et al.*<sup>[74]</sup> studied the cross reactivity of antibodies to remicade and infliximab-dyyb in 125 patients with IBD and healthy individuals as negative controls. They demonstrated that anti-remicade antibodies recognize and inhibit infliximab-dyyb as well. These results suggested that there was similar immunogenicity and shared immunodominant epitopes. Although this supported the safety of biosimilars and the use of the same assay as the originator drug to detect antibodies, this study also supported not using the biosimilar in the setting of originator failure<sup>[71,74,75]</sup>.

### **Evolution of treatment strategies of IBD and positioning currently approved biologics and small molecules in clinical practice**

As the therapeutic armamentarium for IBD continues to expand, so follows the complexity associated with managing IBD patients in clinical practice. The needs for algorithms are required in order to assist health care practitioners determine the relative positioning of each agent and their use in combination with other therapies. Until the results of head to head biologic and small

molecule trials become available, we can only speculate the positioning of therapeutic agents based on the current available literature as summarized in this section (Table 1).

### **Positioning the 'old' biologics: Anti-TNFs first, alone or in combination?**

As newer and more targeted therapies in IBD become available, questions related to maintaining anti-TNF agents as first line therapy arise. Based on decades of data, anti-TNFs currently provide the best long-term evidence of efficacy in CD and UC, with a known safety profile. They are effective for both induction and maintenance therapy, decrease corticosteroid exposure and promote sustained mucosal healing<sup>[76,77]</sup>. The most important safety concern is the risk of serious infection. However, in younger patients without co-existing medical problems, this risk is fairly low<sup>[78]</sup>.

Comparing efficacy of TNF inhibitors is difficult due to the lack of high-quality, head-to-head trials (Table 2). Network meta-analyses indirectly comparing anti-TNF agents have reported mixed results<sup>[45,79-81]</sup>. Based on 'real world' data, an analysis of retrospective and comparative effectiveness database studies revealed subtle differences regarding hospitalisation and surgery rates as well as the steroid sparing effect between infliximab and adalimumab, favouring infliximab at currently recommended doses. Of note, clinical trials of higher-dose adalimumab for both UC and CD are currently underway<sup>[82,83]</sup>.

Deciding between which anti-TNF agent to use depends on the clinical circumstances, treatment history and patient preference. In the absence of head-to-head comparisons, there exists few specific scenarios in which the evidence supports the use of specific anti-TNF agents. In the setting of a hospitalized patient with severe UC, only infliximab has demonstrated its efficacy as a 'rescue' therapy<sup>[84]</sup>. Patients with perianal disease can benefit from either infliximab or adalimumab, albeit the evidence is based on a post-hoc analysis for adalimumab and lacking for other anti-TNF agents<sup>[23,85]</sup>. Golimumab

**Table 2** Biologic agents which have demonstrated efficacy in inflammatory bowel diseases and rheumatology

	Mechanism of action	UC	CD	<sup>2</sup> Fistulization	Ankylosing Spondylitis	Psoriasis
Anti-TNF						
<sup>1</sup> Infliximab <sup>[20,22,51,119]</sup>	Chimeric monoclonal antibody	x	x	x	x	x
Adalimumab <sup>[26,28,54,120,121]</sup>	Fully human monoclonal antibody	x	x	x	x	x
Certolizumab <sup>[31,122,123]</sup>	Pegylated humanized monoclonal antibody Fab' fragment		x	+/-	x	x
Golimumab <sup>[57,122,124]</sup>	Fully human monoclonal antibody	x			x	x
Anti-integrin						
<sup>4</sup> Natalizumab <sup>[39]</sup>	Chimeric monoclonal antibody against $\alpha 4$ integrin		x			
<sup>3</sup> Vedolizumab <sup>[46,96]</sup>	Chimeric monoclonal antibody against $\alpha 4\beta 7$ integrin	x	x	+/-		
Ustekinumab <sup>[50,125,126]</sup>	Fully human monoclonal antibody against P40 sub-unit of IL-12 and IL-23		x	+/-	x	x

<sup>1</sup>Infliximab is the only biologic which has been evaluated to be an effective 'rescue' agent. Evidence is lacking for the remaining biologics; <sup>2</sup>Improvement in fistulizing disease was evaluated as a primary outcome only in infliximab. Efficacy was otherwise determined indirectly from secondary outcomes, subgroup analyses and small scale studies for the remaining biologics; <sup>3</sup>Consider the use of vedolizumab as a first-line biologic agent in patients at high risk for infectious complications. Vedolizumab has a slower onset of action (approximately 6-8 wk) as compared to alternate biologics; <sup>4</sup>Use of natalizumab is contraindicated if the patient is JC virus antibody positive due to the risk of progressive multifocal leukoencephalopathy. UC: Ulcerative colitis; CD: Crohn's disease.

has demonstrated efficacy in UC as a second or third line anti-TNF agent in small cohorts of patients but not for CD. Similarly, certolizumab can be considered in the same context for CD but lacks evidence for UC. Ease of administration may influence one's decision thus patients who would rather less frequent dosing may prefer the IV infusion infliximab as compared to the other anti-TNF agents which are delivered SC by the patient.

The relatively high costs of anti-TNFs and the expiration of patents have triggered the development of biosimilar monoclonal antibodies. Multiple regulatory agencies have approved the use of biosimilars in IBD based on extrapolation of data on safety and efficacy. Since then, real-world data and randomised controlled trials on switching from originator to biosimilar infliximab has shown similar results in terms of efficacy and safety<sup>[72]</sup>. Following the introduction of vedoluzimab and ustekinumab, anti-TNF therapy may not be the first-line biologic agent in all IBD patients. However, the lower cost of biosimilars probably makes the use of anti-TNF agents still very attractive.

Optimizing the efficacy of the initial anti-TNF therapy prior to switching to another biologic, either in or out of class, is a critical principle when managing IBD patients. Studies have repeatedly demonstrated that patients failing their first biologic have poorer outcomes following initiation of their second or third biologic<sup>[50,58]</sup>. The ability to differentiate the cause for a loss of response to anti-TNF therapy has been facilitated with therapeutic drug monitoring (TDM)<sup>[86]</sup>. Based on TDM results, an educated decision regarding dose optimization and switching in or out of class can now be determined<sup>[16,87]</sup>. However, the frequency of TDM is still up for debate. Few retrospective studies have demonstrated benefit with proactive TDM<sup>[88,89]</sup>. The recent multicentre prospective RCT involving 167 patients with active CD, TAILORIX, demonstrated that there was no benefit in patients receiving infliximab dose escalation based on TDM as compared to clinical scoring<sup>[89]</sup>. Although more patients in the

clinical dose escalation group received dose escalation as compared to the TDM group, thus the benefit seen from the clinical group may be over-inflated. Similarly, the TAXIT study, which was a 1 year RCT involving 178 CD and 85 UC patients performed at a single tertiary referral center, did not find benefit in proactive vs reactive (*i.e.*, symptom based) TDM<sup>[88]</sup>. However, the results from the TAXIT study should be interpreted with caution since dose optimisation occurred in both groups at study start. Prospective, multi-center studies are needed to further investigate the positioning of TDM.

The decision to initiate combination therapy involves balancing the benefits of improved efficacy and lower immunogenicity of therapy against the heightened risks for infection and malignancy. The SONIC trial revealed the steroid-free remission rate in CD patients at week 26 was significantly greater in the combination azathioprine and infliximab group as compared to infliximab or azathioprine alone (57% vs 44% vs 30%, respectively)<sup>[14]</sup>. The SUCCESS trial, which was a 16 week RCT involving 239 patients with moderate to severe UC, revealed similar results. Steroid-free remission was achieved in 40% of patients on dual therapy as compared to 22% and 24% on infliximab and azathioprine monotherapy, respectively<sup>[90]</sup>. Supporting this strategy was the open label prospective DIAMOND study which evaluated 176 Japanese patients with CD over 52 wk. This study demonstrated that the efficacy of using dual therapy was not limited to only infliximab but also to adalimumab. Mucosal healing was significantly better in the combination group as compared to the azathioprine monotherapy group at week 26 (84% vs 64%, respectively)<sup>[91]</sup>. Although the difference in clinical remission was not significant, likely due to a small cohort and lower thiopurine dosing, a trend was maintained in favor of combination therapy. The infection and serious complication risks were not greater on dual therapy as compared to monotherapy in either of the aforementioned studies. In contrast, the SONIC trial



demonstrated the lowest risk for infection to be present in the dual therapy group (3.9%) as compared to the infliximab or azathioprine monotherapy groups (4.9% and 5.6%, respectively). This suggests that poorly controlled disease is a stronger risk factor for infection instead of intensified immunosuppression. Ultimately, the risk for hepatosplenic T-cell lymphoma (especially in young/adolescent males after 2 years of therapy), myelosuppression and opportunistic infections must be weighted individually<sup>[92,93]</sup>. Consideration can be made to initiating therapy with both combined thiopurine and anti-TNF therapy than stopping thiopurine therapy after 6 mo in the setting of clinical and biochemical remission and a therapeutic drug level, which has been supported in the literature<sup>[94,95]</sup>.

### **Positioning 'new' agents: First or second-line?**

Vedolizumab has emerged as a first-line agent for induction of remission for moderately active UC patients failing conventional therapy<sup>[58]</sup>. In CD, clinicians should be aware of the potentially slower onset of action of vedolizumab. Concomitant use of corticosteroids may be necessary during the induction period. For these reasons, anti-TNFs or ustekinumab may be more favourable first line choices in CD patients with severe disease activity at present. There is also no considerable data from RCTs on the efficacy of vedolizumab in fistulizing CD and acute severe UC. Ongoing phase IV trial will determine its effectiveness<sup>[96]</sup>. Vedolizumab is currently being positioned in some jurisdictions as a second-line biologic agent following anti-TNFs, although the ongoing LOVE studies are evaluating the use of vedolizumab in early vs. late UC and CD<sup>[97,98]</sup>. Given their effectiveness in the medium to long term and the favourable safety profile, it is expected that gut-selective anti-integrin agents will increasingly be used as maintenance therapy or even as part of a combination biological therapy. A clinical trial evaluating the efficacy of adalimumab, methotrexate and vedolizumab triple combination therapy is ongoing<sup>[99]</sup>.

Ustekinumab is the most recently approved biologic agent for CD<sup>[50]</sup>. Presently, there is no data available describing its efficacy in UC or fistulising CD. An indirect comparison amongst the anti-TNF and UNITI trials suggests ustekinumab may be safer and have a lower rate of immunogenicity which may make it the preferred biologic for some CD patients<sup>[77]</sup>. More comprehensive data on efficacy in certain patient subgroups and mucosal healing is needed.

Finally, tofacitinib is a small molecule awaiting final approval for the treatment of UC<sup>[59,60]</sup>. Their oral route of administration makes them particularly attractive. Their safety profile has been suggested to be similar to that of thiopurines. Due to their mechanism of action, they are not limited by immunogenicity and subsequent loss of response. Their positioning and use as mono- or combination therapy has yet to be elucidated.

### **The evolution of treatment strategies and objective monitoring: Early aggressive or tailored therapy?**

The introduction of highly effective therapies early in

the disease course alongside objective patient monitoring can modify the disease trajectory and reduce morbidity. However, it is also important to recognize that approximately 20% of patients with IBD may have an indolent disease course, and available population-based data suggests that approximately half of patients with CD can be symptomatically controlled 10 years after diagnosis<sup>[100,101]</sup>. Risk stratification can guide early introduction of highly effective therapy in patients with a poor prognosis and prevent overtreatment in low-risk patients. Unfortunately, current patient stratification relies on clinical factors. Most of these are indicators rather than predictors of a complicated disease course (e.g., presence of perianal disease, age < 40 years old at diagnosis and need for steroids during the first flare)<sup>[102]</sup>. Molecular makers for predicting an aggressive phenotype have yet to be identified but studies are ongoing<sup>[103,104]</sup>.

In the absence of objective predictors for disease severity, studies have attempted to better elucidate the risks and benefits of aggressive therapy. The TOP-DOWN trial was the first to assess and compare different treatment algorithms in IBD<sup>[105]</sup>. Treatment-naïve early CD patients were randomly assigned to receive early aggressive therapy ('top-down') with an immunosuppressant and anti-TNF agent or less aggressive ('step-up') therapy with steroids and a possible transition to immunosuppressant and biologics if necessary. The authors found that the 'top-down' strategy was more effective than the conventional 'step-up' strategy for achieving corticosteroid-free remission at week 52 (61.5% vs 42.2%,  $P = 0.027$ ). Similar conclusions were demonstrated in both the SONIC and UC-SUCCESS trials whereby the efficacy of therapy was improved despite comparable adverse events between groups.

The strengths of objective patient monitoring are becoming more evident as study designs continue to improve and include more objective markers of disease severity and response to therapy. An example is the cluster randomisation trial, REACT<sup>[106]</sup>. In this trial, 1982 patients with CD were randomized to receive either algorithm-based treatment optimization vs. conventional management (therapeutic decisions based on community physician assessment). The composite endpoint of hospitalization, surgery and serious disease related complications was lower in patients treated with the algorithm-based strategy at 24 mo (27.7% and 35.1%, hazard ratio: 0.73, 95%CI: 0.62 to 0.86,  $P < 0.001$ ), despite no differences in serious drug-related adverse events as compared to the conventional treatment group. In UC, evidence is less straightforward on whether 'top-down' therapy alters the long-term disease outcomes. Although several studies have shown that the severity and extent of UC at diagnosis may have a major impact on the subsequent course of the disease with elevated risks of recurrent hospitalization, colectomy, cancer and mortality<sup>[101,107,108]</sup>. In a population-based inception cohort from Norway, the extent of disease, need for systemic steroids and high CRP at diagnosis were independently associated with colectomy<sup>[109]</sup>. Consequently, patients presenting with extensive colitis and signs of severe disease

**Table 3 Recommendations for treating to target in Crohn's disease by the International Organization for the Study of Inflammatory Bowel Diseases<sup>[19]</sup>**

Crohn's disease	Ulcerative colitis
The consensus target is a combination of: Clinical/ <sup>1</sup> PRO remission defined as resolution of abdominal pain and diarrhea or altered bowel habits which should be assessed every 3 mo until resolution then 6-12 mo thereafter. and Endoscopic remission <sup>2</sup> defined as resolution of ulceration at ileocolonoscopy which should be assessed at 6-9 mo intervals during the active phase	Clinical/ <sup>1</sup> PRO remission defined as resolution of rectal bleeding and diarrhea or altered bowel habits which should be assessed every 3 mo until resolution then 6-12 mo thereafter. and Endoscopic remission <sup>2</sup> defined as resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy <sup>3</sup> which should be assessed at 3 mo intervals during the active phase
Adjunctive measures of disease activity that may be useful in the management of selected patients but are not a treatment target include: •Faecal calprotectin	Adjunctive measures of disease activity that may be useful in the management of selected patients but are not a treatment target include: •CRP •Faecal calprotectin •Histology
Measures of disease activity that are not a target: •Histology •Cross-sectional imaging	•Cross-sectional imaging

<sup>1</sup>Patient reported outcomes; <sup>2</sup>When endoscopy cannot adequately evaluate inflammation, resolution of inflammation as assessed by cross-sectional imaging can be substituted; <sup>3</sup>While Mayo subscore of 0 may be defined as the target, there is currently insufficient evidence to recommend it in all patients; only Mayo subscore of 0-1 can be systematically recommended in practice.

at diagnosis could benefit from top-down therapy.

'Treat to target', a strategy that uses objective clinical and biochemical outcome measures to assist clinicians in making decisions related to modifying therapy, has been gaining popularity since the REACT study demonstrated that disease activity correlates relatively poorly with objective measures of inflammation, and clinical remission in the absence of mucosal healing may not necessarily decrease the risk of future complications in CD<sup>[106]</sup>. The CALM study supported this logic as well and demonstrated that early and stringent control of disease using objective markers of inflammation (*e.g.*, CRP and fecal calprotectin) was efficacious and safe in their sample population of 244 patients with CD<sup>[18]</sup>. Their primary end-point, mucosal healing at 48 wk, was achieved in 46% vs 30% of the patients in the 'tight control' group as compared to the 'clinical management' group. Deep, biological and steroid-free remissions were greater in the 'tight control' group as well, whilst the adverse events not significantly different between groups. The recent systematic review and expert opinion of 28 IBD specialists on 'Selecting Therapeutic Targets in Inflammatory Bowel Disease' (STRIDE) also suggested the importance of using objective markers and recommends that therapeutic targets for CD and UC should move away from composite disease activity indices to separate patient-reported outcomes and objective measurements of inflammation (Table 3)<sup>[19]</sup>. However, the open-label multicentre RCT 'CALM' suggested that biomarkers such as fecal calprotectin be considered as additional targets to therapy in their cohort of 244 patients with active CD. Besides acting as a treatment target, biomarkers can facilitate the monitoring of a patient. For example, elevated c-reactive protein or fecal calprotectin should prompt further endoscopic and/or radiologic evaluation irrespective of clinical scores. Although intensified regimens are efficacious, they are also more likely to

encounter difficulties with patient compliance. Additional guidance regarding the use of endoscopic findings as treatment targets will come following the completion of the REACT- II prospective trial.

## FUTURE PERSPECTIVES

Data obtained from head to head biologic and small molecule trials will eventually be applied to clinical practice in order to better individualize and optimize therapy. The determination of which therapies can be combined best will be further elucidated as well. For instance, combining anti-TNF therapy with vedolizumab is being evaluated in studies for patients with refractory disease because it combines a rapidly acting systemic agent with a slower acting gut-specific therapy. The development of oral medications with specific targets (*e.g.*, filgotinib) will open the door to a large range of potential therapeutic combinations which will enable therapy to be individualized further<sup>[110]</sup>. Specific therapies such as anti-fibrotics, SMAD7 inhibitors, sphingosine 1-phosphate receptor modulators and phosphodiesterase inhibitors are quickly making their way through trial phases and can be expected to hold a place in the IBD armamentarium in the near future<sup>[111-113]</sup>. As in Oncology, omics will enable us to determine which patients are at greatest risk for a complicated disease course thus provide a rationale for initiating intensified immunotherapy at diagnosis and individualize therapy best<sup>[114]</sup>. Molecular imaging and pre-treatment genetic and biomarker analysis may be able to predict response to a proposed therapy in the future and are currently being investigated<sup>[103,104,115,116]</sup>.

## CONCLUSION

As the quality of trial designs improved over the decades, so followed our understanding of IBD. This has enabled

us to tailor therapy and develop effective treatment algorithms using clinical symptoms/PROS, biomarkers and endoscopic indices to help guide therapy. Anti-TNF therapy remains an important component of IBD therapy with the most real-life evidence and should be considered as first-line therapy in patients with complicated CD and in acute-severe UC. Novel mono- and combination therapies have only begun to be approved and offer the ability to tailor therapy further. However, clinicians will be faced with important challenges in defining the optimal use of these new therapies and their relative position in treatment algorithms. The next generation of clinical trials will need to ascertain the answers to these questions.

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**P- Reviewer:** M'Koma AE, Nakase H, Sivandzadeh GR  
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