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INFLAMMATORY BOWEL DISEASE (M REGUEIRO, SECTION EDITOR)

First-Line Biologics or Small Molecules in Inflammatory Bowel Disease: a Practical Guide for the Clinician

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Abstract

Purpose of Review Treating moderate-to-severe inflammatory bowel disease has become increasingly complex as the array of available biologics increases. Moreover, tofacitinib, the first small molecule approved for IBD, is available for use in ulcerative colitis. Choosing the right biologic, for the right patient, at the right time, can be a confusing and daunting task for clinicians.

Recent Findings In this review, we summarize the evidence for first-line use of the available biologics by disease state. Special circumstances for consideration including rapidity of action, safety, comparative effectiveness, postoperative Crohn's disease, fertility and pregnancy, and extraintestinal manifestations are discussed.

Summary In the moderate-to-severe UC patient, vedolizumab and infliximab are preferred first-line options. In the moderate-to-severe CD patient with a penetrating phenotype or with multiple EIMs, infliximab or adalimumab are the preferred first-line agents. In the moderate-to-severe CD patient with an inflammatory phenotype, anti-TNF, vedolizumab, and ustekinumab are all reasonable options.

Keywords Positioning biologics · Inflammatory bowel disease · Infliximab · Adalimumab, vedolizumab · Tofacitinib · Ustekinumab

Introduction

As the number of available biologics for inflammatory bowel disease (IBD) increases, clinicians must make choices regarding which medication to start based on individual patient characteristics and values. For more than a decade, TNF inhibitors (anti-TNFs) were the only biologics approved, but newer medications with different mechanisms of action are now available.

Though multiple algorithms exist to aid in decision-making, a "one-size-fits-all" approach is not altogether practical for patients with unique clinical characteristics or comorbidities. The aim of this review is to provide a practical guide for the clinician regarding choosing a first-line biologic in ulcerative colitis (UC) and Crohn's disease (CD). Special attention is paid to the newer biologic classes. Common clinical considerations that are frequently encountered by gastroenterologists are reviewed.

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Evidence for First-Line Biologic Therapy

Anti-TNFs

Anti-TNF therapy has been the mainstay of treatment for moderate-to-severe IBD for over 20 years, with infliximab being the first anti-TNF approved in August 1998. Anti-TNF therapies have been shown to improve clinical symptoms, lead to mucosal healing, and reduce hospitalizations and surgeries [1–11]. Infliximab and adalimumab are FDA-approved for both UC and CD, with golimumab only approved for UC and certolizumab only approved for CD. Infliximab is the only biologic therapy that is FDA-approved for managing fistulizing CD [12].

Starting therapy early in the disease course, prior to the development of irreversible bowel damage, optimizes remission rates and potentially alters the natural history of disease

[13]. In the landmark SONIC trial, moderate-to-severe CD patients, naïve to immunomodulators and biologics with an average disease duration of less than 2 years, were randomized to placebo, infliximab alone, or infliximab plus azathioprine [14]. Steroid-free remission rates were significantly higher in both the infliximab alone group versus placebo, and the infliximab plus azathioprine group versus placebo (44.4% versus 30.6%; $p = 0.009$ and 56.8% versus 30.6%; $p < 0.001$, respectively).

Despite the wealth of data demonstrating the efficacy of TNF antagonists in IBD, primary non-response rates can be as high as 30%. Additionally, up to 40% of patients may lose response by the end of the first year of therapy [1, 3, 6]. Dose optimization of anti-TNFs is critical before switching to another biologic [15].

Vedolizumab

Vedolizumab is a good candidate for first-line biologic therapy in patients with UC or CD. Vedolizumab is a monoclonal antibody targeting α4β7 that reduces lymphocyte trafficking by blocking interaction with mucosal vascular addressin cell adhesion molecule (MAdCAM-1) [16]. Vedolizumab is approved for use in moderate-to-severe UC and CD. Standard dosing for both UC and CD includes an initial dose of 300 mg at 0, 2, and 6 weeks followed by every 8-week maintenance dosing.

The GEMINI 1 trial was an integrated, double-blinded, randomized, placebo-controlled trial of 895 moderate-to-severe UC patients (521/895 open-label) [17]. The primary endpoint was clinical response at week 6 (decrease in the Mayo score by at least 3 points and 30% from baseline) after 2 doses. In the maintenance arm, responders at week 6 were re-randomized to vedolizumab every 4 weeks, every 8 weeks, or placebo, with an endpoint of clinical remission at week 52 (Mayo score ≤ 2 with no subscores > 1). Clinical response rates at week 6 were 47.1% for the vedolizumab and 25.5% for placebo ($p < 0.001$). Clinical remission rates at week 52 were 41.8% in the every 8-week arm ($p < 0.001$), 44.8% in the every 4-week arm ($p < 0.001$), and 15.9% in the placebo arm. Clinical remission and mucosal healing rates were higher in the vedolizumab arms in both induction and maintenance. Approximately 60% of the patients included in the GEMINI 1 trial were anti-TNF-naive. Stratifying by anti-TNF exposure, both anti-TNF-naïve and exposed groups had higher rates of clinical response at week 6 and remission at week 8. However, the absolute rates of response and remission were higher in the anti-TNF-naïve population.

The effectiveness of vedolizumab in UC for both anti-TNF-naïve and anti-TNF-exposed patients has been reproduced in both a systematic review and multiple observational studies [18–21]. Multiple studies have shown higher clinical remission and mucosal healing rates in vedolizumab-treated patients naïve to anti-TNFs [22, 23••]. In the multicenter VICTORY consortium, vedolizumab-treated patients with prior exposure to anti-TNFs had a reduced probability of achieving clinical remission (HR 0.53, 95% CI 0.38–0.75) and endoscopic remission (HR 0.51, 95% CI 0.29–0.88) [24].

The GEMINI 2 CD trial was similarly designed to the GEMINI 1 UC trial. Key endpoints were clinical remission (CDAI ≤150) and clinical response (decrease in CDAI > 100 points) at week 6 [16]. Clinical remission rates at week 6 were significantly higher in the vedolizumab versus placebo arm (14.5 versus 6.8%, $p = 0.02$). However, clinical response at week 6 did not reach statistical significance (31.4 versus 25.7%, $p = 0.23$). As in the GEMINI 1 UC trial, responders to vedolizumab at week 6 were re-randomized to maintenance vedolizumab every 4 weeks, every 8 weeks, or placebo. Clinical remission rates at week 52 were 39.0% in the every 8-week arm ($p < 0.001$), 36.4% in the every 4-week arm ($p = 0.004$), and 21.6% in the placebo arm. Clinical response and steroid-free remission rates were higher in the vedolizumab arms at week 52. Approximately 40% of GEMINI 2 patients were anti-TNF-naïve.

As in UC, multiple observational studies have confirmed the effectiveness of vedolizumab for CD, with higher rates of remission in the anti-TNF-naïve population [19, 24]. The VICTORY consortium showed that vedolizumab-treated patients with prior anti-TNF exposure were less likely to achieve clinical remission (HR 0.40; 95% CI 0.20–0.81) and mucosal healing (HR 0.29; 95% CI 0.12–0.73) compared with anti-TNF-naïve patients [24].

In summary, vedolizumab has consistently been shown to be effective in anti-TNF-naïve and exposed moderate-to-severe UC and CD patients, with greater efficacy rates in the biologic naïve population.

Ustekinumab

Ustekinumab is a monoclonal antibody targeting the p40 subunit shared by interleukin-12 (IL-12) and IL-23. Currently, ustekinumab is approved for use in moderate-to-severe CD. Trials of ustekinumab in UC have been promising, and an application for FDA approval is under review [25, 26]. Standard dosing includes an initial, weight range-based (260, 390, or 520 mg) infusion followed by 90-mg subcutaneous injections every 8 weeks [27].

In the double-blind, placebo-controlled UNITI-2 induction trial, moderate-to-severe Crohn's patients (CDAI scores 220 to 450) who had failed treatment with or were intolerant to immunosuppressants or glucocorticoids and without prior loss of response to anti-TNFs received an initial IV dose of ustekinumab (130 mg or 6 mg/kg) or placebo [27]. At week 6, clinical response (decrease in CDAI 100 or CDAI < 150) in the 130-mg group and the 6-mg/kg groups was 52% and 56%, respectively, compared with 29% in placebo-treated patients

($p < 0.001$). Clinical remission rates at week 6 in the 130 mg group (29%) and 6 mg/kg group (35%) were significantly higher than in placebo-treated patients (18%) ($p = 0.007$ and $p < 0.001$, respectively). Patients with a clinical response at week 8 were enrolled in the IM-UNITI maintenance study. Maintenance subcutaneous injections were 90 mg every 8 weeks or 12 weeks, or placebo. Clinical remission rates at week 44 with every 12 weeks (49%) and every 8 weeks (53%) were higher compared with placebo (36%) ($p = 0.040$ and $p = 0.005$, respectively).

Ustekinumab can be considered for first-line use for moderate-to-severe Crohn's disease. As ustekinumab is also approved for use in plaque psoriasis and psoriatic arthritis, patients with concomitant psoriasis and Crohn's disease certainly should be considered for first-line treatment with ustekinumab [28]. Crohn's disease patients with a relative contraindication to anti-TNFs such as a history of latent or active tuberculosis may be considered for first-line treatment with ustekinumab [29, 30]. Ustekinumab has also been shown to be efficacious in biologic naïve patients in the UNIFI trial and is pending indication approval for UC [26].

Tofacitinib

Tofacitinib is an oral, small-molecule, non-biologic, currently approved for use in moderate-to-severe UC. Tofacitinib is a pan-Janus kinase (JAK) inhibitor with preferential selectivity for JAKs 1 and 3 [31].

In the OCTAVE 1 and 2 parallel, double-blind, placebo-controlled induction trials studying tofacitinib in UC, adult patients with moderate-to-severe UC (Mayo score 6 to 12, with a rectal bleeding subscore of 1 to 3 and an endoscopic subscore of 2 or 3) who had treatment failure with or side effects from steroids, thiopurines, or anti-TNFs were eligible to received tofacitinib 10 mg twice daily or placebo [31]. Patients with ulcerative proctitis (< 15 cm of colitis) were excluded. Approximately half of patients enrolled in OCTAVE were TNF-naive.

Remission (Mayo ≤ 2, no subscore > 1 and rectal bleeding subscore of 0) at 8 weeks for tofacitinib versus placebo in OCTAVE 1 was 18.5% versus 8.2% ($p = 0.007$) and in OCTAVE 2 was 16.6% versus 3.6% ($p < 0.001$). Clinical response (decrease in Mayo score of 3 points and 30%) at week 8 for tofacitinib versus placebo in OCTAVE 1 was 60% versus 33% ($p < 0.001$) and in OCTAVE 2 was 55% versus 29% ($p < 0.001$), respectively. Patients who exhibited a clinical response went on to the 52-week maintenance study OCTAVE Sustain. At week 52, rates of remission were 41% and 34% for tofacitinib 10 mg and 5 mg, respectively, compared with 11% for placebo ($p < 0.001$).

Tofacitinib was approved for ulcerative colitis by the FDA in 2018. The original label indications and usage included standard treatment failures (e.g., corticosteroids, mesalamines) as well as biologic exposed patients. As of July 2019, given concerns from rheumatoid arthritis post-marketing clinical trials regarding increased occurrence of blood clots and death in patients treated with 10 mg twice daily, the indication for ulcerative colitis has been limited to "adults with moderate to severely active UC who have had an inadequate response or who are intolerant to TNF blockers" [32]. Though available safety data regarding the higher dose (10 mg) tofacitinib UC cohort in OCTAVE Sustain has not shown an increased risk of thrombosis as compared with placebo, long-term follow-up from the OCTAVE study is ongoing. Given these current safety warnings, we recommend tofacitinib should be used for TNF-exposed patients or first line for those with UC and concomitant uncontrolled rheumatoid arthritis or psoriatic arthritis. For UC patients who respond to tofacitinib, the lower 5-mg dose should be used for maintenance when feasible.

Special Considerations for Everyday Practice

The real-world patient frequently does not resemble the patients enrolled in the above described clinical trials [33]. For example, sicker patients are unable to wait for trial treatment during prolonged screening periods. Moreover, patients who have a history of malignancy and prior bowel surgery, or who are considering conception are usually excluded from clinical trials. Commonly, patients with IBD who are considering long-term treatment with biologic therapies have questions regarding comparative efficacy and safety. In the sections below, we explore a few of these common topics to aid the clinician in shared decision-making discussions with the patient.

Rapidity of Action

When choosing therapies for IBD patients, onset of action is a critical component of the decision-making process. A therapy that can potentially take weeks to months to work may need a "bridge" to keep the patients symptoms controlled during the induction period. It is also important to set expectations for the patient about when he or she can expect to see improvement.

Clinical experience has shown us that anti-TNF agents have a rapid onset of action, within days, in a subset of patients. Infliximab, in particular, has a faster onset of action as compared with other anti-TNFs [34]. To this point, infliximab, along with cyclosporine (in select institutions) is a mainstay of inpatient salvage therapy for steroid-refractory, severe UC with reduction in short-term rates of colectomy [35–37].

Although vedolizumab is effective in both anti-TNF-naïve and exposed patients, the response is faster in the anti-TNF-naïve population [38]. A post hoc analysis of the randomized placebo control trials of vedolizumab in both UC and CD was conducted to evaluate onset of action. In UC, vedolizumab patients had better symptom scores (rectal bleeding of 0 and stool

frequency score of 0 or 1) than placebo at week 2 (19.1% versus 10%), week 4 (28% versus 14.8), and week 6 (33.8% versus 16.8%). Symptom scores were higher in the anti-TNF-naïve UC population compared with anti-TNF exposed. In CD, only the TNF antagonist-naïve population had better symptom scores (stool frequency and abdominal pain) at week 0 and week 2 [38].

A pooled analysis of the GEMINI 2 and GEMINI 3 (anti-TNF-exposed CD patients) was performed to better understand response and remission rates in CD patients stratified by TNF exposure. Clinical remission rates at both week 6 and week 10 were higher in the vedolizumab-treated anti-TNF-naïve population compared with placebo. However, in anti-TNF-exposed patients, clinical remission rates at week 6 were not statistically significant. Only at week 10 did clinical remission reach significance [39].

Similar to infliximab, patients on tofacitinib may have significant improvement in their symptoms within days to weeks of starting therapy. In a post hoc analysis of the OCTAVE induction trials, tofacitinib showed a significant improvement in stool frequency, number of daily bowel movements, and rectal bleeding compared with placebo in just 3 days [40]. In a case series of 4 inpatient severe steroid refractory UC patients, high-dose tofacitinib (10 mg 3 times a day) with steroids induced clinical remission in 3 of 4 patients in 3 days [41]. This rapid onset of action of tofacitinib has the potential to minimize the cumulative exposure to corticosteroids.

Regarding ustekinumab in CD, the time to response is usually in the range of weeks. In the UNITI trial, week 3 clinical response and clinical remission rates were significantly higher in the weight-based ustekinumab arm over placebo (30.1% versus 17.8%, $p = 0.001$ and 12.9% versus 5.7%, $p = 0.005$, respectively). In addition, there was a significant decrease in the median C-reaction protein level at week 3 [27].

In summary, rapidity of action for both biologics and JAK inhibitors can potentially be within 2–3 weeks of starting therapy, depending on severity of disease, previous biologic exposure, among other factors. In a patient with more "severe" disease, using infliximab or tofacitinib may be appropriate given the fast onset of action. In a patient with more "moderate" disease naïve to biologics, vedolizumab or ustekinumab as first-line therapy is a reasonable option.

Safety

One of the biggest barriers to initiating biologic or immunosuppressive therapy is the concern regarding side effects. Discussing the safety implications of these therapies is critical in the shared decision-making process.

The TREAT registry was a prospective cohort study comparing long-term outcomes of 3400 CD patients on infliximab with over 20,000 patient-years of follow-up with 2833 patients on other treatments with 15,000 patient-years of follow-up [42]. Serious infection rates were higher in the infliximab-treated patients (RR = 2.46, 95% CI 1.8–3.4). Mortality and malignancy rates were similar between groups. Notably, narcotic and corticosteroid use were independently associated with both serious infection and mortality.

Siegel et al. performed a meta-analysis evaluating risk of lymphoma in 8905 CD patients with 21,178 patient-years of follow-up that were exposed to anti-TNF therapy [43]. Patients exposed to anti-TNFs had higher rates of non-Hodgkin's lymphoma than the general population (6.1 per 10,000 patient-years (PY) versus 1.9 per 10,000 PY).

Since vedolizumab is an anti-trafficking agent, mechanistically, one would expect lower rates of systemic infections, among other potential side effects. In a pooled analysis of six randomized controlled trials with 2830 IBD patients, adverse and serious adverse events were lower in the vedolizumab group than placebo [44••]. Serious infections occurred in less than 0.6% of patients. There was no increased signal for malignancy. Similar to the TREAT registry with anti-TNF agents, corticosteroid use and narcotic use were independent risk factors for serious infection. Observational, real-world studies have also demonstrated the favorable safety profile of vedolizumab [45, 46].

For ustekinumab, there were no increased rates of adverse events or serious adverse events in the UNIFI and UNITI data [26, 27]. In the psoriasis PSOLAR registry, there was a significantly increased risk of serious infections found with other biologics as compared with ustekinumab (HR = 1.96, $p < 0.001$). There was no increased risk of malignancy, mortality, or major cardiovascular events with any of the biologic agents in the registry including ustekinumab [47].

Since tofacitinib was approved by the FDA in May 2018, several safety concerns have surfaced. Low-density lipoprotein may increase up to 10% from baseline [48]. Lipids should be monitored within 2 months of starting tofacitinib. Shingles is another adverse event seen with tofacitinib. In the 1157 UC patients treated with tofacitinib in the OCTAVE trials and open-labeled extension, there has been a dose-dependent increased risk of shingles (5.6%) [49]. The median time to developing shingles was 324 days, with only 7.7% of patients having to stop drug. Finally, thrombotic risk has been shown in the rheumatoid arthritis (RA) population. In a long-term safety study in RA patients on tofacitinib 5 mg or 10 mg twice daily or anti-TNFs, interim analysis reported higher rates of pulmonary embolism with tofacitinib 10 mg compared with anti-TNFs (19 cases in 3884 patient-years versus 3 cases in 3982 patient-years, respectively) and all-cause mortality (45 cases in 3884 patient-years versus 25 cases in 3982 patient-years, respectively) [50••]. In July 2019, the FDA placed a black box warning on tofacitinib for pulmonary embolism and mortality and changed the label moving tofacitinib to a second-line therapy after anti-TNFs for UC patients. The dose should be decreased to 5 mg twice a day as early as 8 weeks if there is a response to therapy [32].

In patients with past history of malignancy, elderly patients, or multiple past infectious complications, we usually

recommend starting with a more targeted biologic therapy like vedolizumab or ustekinumab depending on severity of disease.

Comparative Effectiveness Data

Comparative effectiveness studies and network meta-analyses have recently been used to compare positioning of biologic therapies. These studies give us some insights; however, it should be noted that these studies are limited by inherent biases in their study designs.

In the VARSITY trial comparing vedolizumab to adalimumab in UC, week 52 clinical remission rates (31.4% versus 22.5%; $p = 0.006$) and endoscopic improvement (39.7% versus 27.7%, $p < 0.001$) were higher in vedolizumab versus adalimumab patients, respectively [23••]. Approximately, 20% of the 771 patients included were previously exposed to anti-TNF agents. Higher clinical response rates in the vedolizumab group were seen as early as week 6, suggesting that dose optimization during the trial would not have impacted results. The results of this study cannot be extrapolated to other anti-TNF agents, including infliximab.

A network meta-analysis of randomized controlled trials in moderate-to-severe UC compared the efficacy and safety first- (biologic naïve) and second-line therapies [51]. Infliximab and vedolizumab were ranked the highest for induction of clinical remission and mucosal healing when used as first-line therapies. Tofacitinib performed best as a second-line therapy behind anti-TNF agents for induction of clinical remission and mucosal healing. Due to the variability of trial design, maintenance data could not be analyzed. Vedolizumab was found to be the safest agent when evaluating infections and serious adverse events.

In another network meta-analysis comparing immunomodulators, anti-TNF, vedolizumab, and combination therapies for induction and maintenance of remission in CD, adalimumab and infliximab with azathioprine were superior to certolizumab for induction of remission [52]. Adalimumab and infliximab with azathioprine were superior to certolizumab and thiopurines for maintenance of remission. Adalimumab was found to be superior to vedolizumab for maintenance of remission. There was no data included on ustekinumab at the time this meta-analysis was performed.

We look forward to the results of another head-to-head trial, the SEAVUE trial, evaluating the safety and efficacy of ustekinumab versus adalimumab in CD (NCT03464136). This among other trials will give key insights into positioning biologic therapy.

Postoperative Crohn's Disease

After an intestinal resection in Crohn's disease, prophylactic treatment is recommended over expectant endoscopic monitoring in patients with risk factors for postoperative recurrence (POR) such as multiple resections, active smokers, or penetrating phenotypes [53]. The risk of a second intestinal resection in Crohn's disease has been reported to be 29% [54]. In individuals who are high risk for Crohn's recurrence, early initiation of anti-TNFs is recommended within 4 to 8 weeks after surgery [53, 55]. In a network meta-analysis, anti-TNF monotherapy was the most effective treatment in preventing clinical and endoscopic POR as compared with placebo, antibiotics, immunomodulators, mesalamines, and budesonide [56]. No high-quality trials exist to support combination therapy for prevention of POR [53].

The majority of postoperative studies to date support infliximab as a first-line biologic for prevention of POR. Infliximab (5 mg/kg every 8 weeks) has been shown in a worldwide, randomized control trial of nearly 300 patients with Crohn's disease after ileocolonic resection to be superior to placebo in preventing endoscopic POR with an absolute risk reduction of 29% [57••]. In a smaller, prospective, open-label study of 24 patients after ileocolonic resection, the time to endoscopic recurrence was significantly longer in patients receiving infliximab as compared with placebo (1231 days versus 460 days, respectively; $p = 0.003$) [58].

Adalimumab may also be considered first line for prevention of POR. In the multinational, randomized POCER study, postoperative Crohn's patients at high risk of recurrence were treated with either thiopurines or adalimumab [59, 60]. In a post hoc, per-protocol analysis, endoscopic recurrence was more common in the thiopurine cohort compared with the adalimumab cohort (39% versus 13%, respectively; $p = 0.02$) [60]. In a Spanish multicenter, randomized trial of 91 patients randomized to either adalimumab (160 mg, 80 mg, then 40-mg maintenance) or azathioprine (2.5 mg/kg), endoscopic recurrence at 1 year was similar between adalimumab versus azathioprine (30% versus 33%, respectively; $p = 0.76$) [61]. However, adalimumab was better tolerated than azathioprine with discontinuation rates of 4% versus 23%, respectively ($p = 0.011$).

There is limited data regarding newer biologics in the postoperative Crohn's patient for prevention of POR. In a retrospective cohort of postoperative Crohn's patients on vedolizumab to prevent POR, 25% were found to be in endoscopic remission at 6 to 12 months postoperatively. In the same retrospective cohort, 66% of those patients receiving anti-TNFs to prevent POR were in endoscopic remission ($p = 0.01$) [62]. A randomized, placebo-controlled pilot study is underway at the University of Pittsburgh to evaluate endoscopic recurrence at 1 year with vedolizumab (NCT02834754). Based on the currently available evidence, it is our practice to initiate anti-TNFs first line for prevention of POR unless there is a contraindication or if there are strong patient preferences to avoid anti-TNFs.

Fertility and Pregnancy

Fertility, conception, and pregnancy are major concerns for women with IBD during their childbearing years. Gastroenterologists

are frequently at the forefront coordinating treatment plans with obstetrics, colorectal surgery, maternal-fetal specialists, and reproductive endocrinologists. Aside from methotrexate, medications used to treat IBD are not believed to have an effect on egg freezing or assisted reproductive technology (ART) [63]. Patients should be dissuaded from conception with active disease given the increased likelihood of flare during pregnancy [64].

The anti-TNFs (infliximab, adalimumab, golimumab, certolizumab pegol) are all safe in pregnancy and can be confidently used first line in women with moderate-to-severe IBD hoping to conceive. Though all anti-TNFs except for certolizumab pegol are known to cross the placenta, it is recommended that all anti-TNFs be maintained throughout pregnancy with pre-pregnancy dosing regimens with timing of the first postpartum dose to be given several days postpartum to minimize trough levels at delivery [63, 65]. No increased risk of infection has been found in children born to mothers exposed to anti-TNFs during pregnancy [66]. However, anti-TNF monotherapy is suggested given possible concerns regarding increased infectious risk in children born to mothers exposed to combination immunomodulator and anti-TNFs during pregnancy [67].

Limited pregnancy data and birth outcomes exist for vedolizumab and ustekinumab. Preliminary data from retrospective cohorts shows low risk for children exposed to vedolizumab during pregnancy [68, 69]. A prospective ustekinumab exposure registry comprised of Crohn's, psoriasis, and psoriatic arthritis patients has been ongoing since 2013 with an expected completion date of July 2020 (NCT02103361). Currently, the use of vedolizumab and ustekinumab during pregnancy is supported by current clinical care pathways, though authors acknowledge the limited available data [63].

At present time, tofacitinib should not be used first line in women with IBD who are planning to conceive. Tofacitinib is not recommended for use in the first trimester due to a risk of fetal malformation at supratherapeutic doses in animal studies [63].

Extraintestinal Manifestations

Extraintestinal manifestations (EIMs) occur in up to 47% of IBD patients, with arthralgias being the most commonly reported [70, 71]. Certain EIMs parallel disease activity, while others do not. Therapies that heal the mucosa, from oral mesalamine to any biologic therapy, should improve EIMs that parallel disease activity. In a post hoc analysis of the GEMINI trials, UC and placebo patients had similar rates of arthritis or arthralgia, whereas CD patients on vedolizumab had lower rates of arthralgias when compared with placebo (HR 0.63; 95% CI 0.44–0.89) [72]. Details on whether the arthralgias and arthritis correlated with disease activity is not known. However, in EIMs that are typically independent of intestinal disease activity, such as central spondyloarthropathy, pyoderma gangrenosum, and uveitis, choosing a more systemic therapy such as an anti-TNF, ustekinumab, or tofacitinib is preferred.

A Practical Approach to Choosing First-Line Therapy

Based on the data reviewed in this article along with our patient experience, we will now discuss how we typically manage a variety of IBD patient types in practice. When choosing therapy for a patient, efficacy is the first factor that should be addressed. Following efficacy, we discuss rapidity of action, safety, pregnancy, route of administration, and among many other considerations.

In the moderate-to-severe UC patient, vedolizumab and infliximab are our preferred first-line options. Given the low safety risk and improved outcomes in the TNF antagonist-naïve patients, we are starting vedolizumab first line more often. Ustekinumab may be a first-line option for UC in the near future once it is FDA-approved and real-world data is reported. In the moderate-to-severe CD patient, infliximab, adalimumab, vedolizumab, and ustekinumab are all reasonable first-line options. If a patient has evidence of complicated CD; for example, perianal disease, penetrating or stricturing disease, or multiple EIMs, we start either infliximab or adalimumab. If the CD patient has an inflammatory phenotype, we are using either vedolizumab or ustekinumab more frequently first line, given the low rate of adverse events.

Table 1 First-line therapy recommendations

	Infliximab	SQ anti-TNF	Vedolizumab	Ustekinumab	Tofacitinib
Moderate-to-severe UC	++	++	++	Pending approval	-
Moderate-to-severe CD	++	++	++	++	-
Severe steroid refractory UC	++	-	-	-	+
Pregnancy	++	++	++	++	-
Postoperative CD	++	++	+	+	-
History of malignancy	-	-	++	++	-
Recurrent infection	-	-	++	++	-

(++ = strong choice for first-line therapy, + = good choice for first line therapy, - = not a good choice for first line therapy)

In IBD patients with a recent history of malignancy or history of multiple infections, vedolizumab or ustekinumab are our treatments of choice. In a young female expecting to become pregnant in the near future or flaring during pregnancy, any of the biologics are reasonable first-line options. We would not use tofacitinib in this population. In the postoperative patient with a high risk of recurrence, we will start either infliximab or adalimumab since there is a paucity of evidence with the newer biologics. In the severe steroid refractory UC patient, either in the hospital or about to be admitted, we use infliximab first line with an accelerated induction schedule. If a patient does not respond to infliximab or failed infliximab in the past, we would use tofacitinib (Table 1).

Conclusion

This is an exciting time to be caring for IBD patients. However, choosing the optimal first-line biologic can be a challenging task given the numerous medications and assortment of mechanisms of action available. Upcoming changes are expected. Ustekinumab is expected to be approved for UC shortly. Several JAK inhibitors, including filgotinib and upadacitinib, and selective IL-23 inhibitors are in the pipeline. The conversation regarding positioning of anti-TNFs, anti-integrins, IL12/23 inhibitors, and JAK inhibitors will continue to evolve.

Compliance with Ethical Standards

Conflict of Interest David Hudesman is a consultant for Abbvie, Janssen, Salix, Takeda, and Pfizer.

Shannon Chang is a consultant for Takeda, Oshi Health, and Pfizer.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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