A Practical Review on When and How to Select First-Line Biologic Therapy in Patients with Inflammatory Bowel Disease

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The role of biologic therapy in inflammatory bowel disease is well-established. However, the decision to start biologic therapy is complex and involves important consideration of patient and disease related factors. Early biologic therapy is increasingly favored, especially in patients with Crohn's disease and ulcerative colitis with high-risk features. Once the decision is made to start biologic therapy, the selection of therapy is even more complex given the paucity of available head-to-head studies. Most indirect comparative effectiveness studies have demonstrated favorable results for anti-tumor necrosis factor (TNF) alpha therapy (especially infliximab) in Crohn's disease and infliximab and vedolizumab in ulcerative colitis. Selection of biologic therapy also involves consideration of other factors, including medication safety, additional patient factors (e.g. age, comorbidity, history of malignancy), cost, insurance, patient preference, and provider preference. Once biologic therapy is selected, optimization of therapy should be strongly considered.

INTRODUCTION

With the increasing amount of biologic therapies available for patients with both Crohn's disease (CD) and ulcerative colitis (UC), it is important to select the most appropriate first-line biologic therapy. It similarly can be

unclear when to initiate biologic therapy in a given patient in relation to their disease course. We will review the available data on when to select biologic therapy for a given patient with inflammatory bowel disease (IBD) and attempt to provide some practical guidance on how to select the most appropriate agent. Specifically, we will discuss important considerations when making treatment decisions, including medication efficacy and safety, patient-specific factors, insurance, cost, patient preference, and provider preference. Lastly, the importance of drug optimization will be discussed with an emphasis on proactive therapeutic drug monitoring (TDM).

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When Should Biologic Therapy Be Initiated?

Prior to selecting the appropriate first-line biologic therapy for any given patient with IBD, it is important to consider when to start biologic therapy. There is increasing evidence for the benefit of early biologic therapy, but this may not apply to all patients with IBD. Therefore, the decision on when to start biologic therapy is complex and involves consideration of patient and disease-specific factors. This section will review the best available evidence to guide the timing of biologic therapy for patients with IBD. We will also include a summary of how biologic therapy is positioned within recent guidelines.

When to Initiate Biologic Therapy in Crohn's Disease

The traditional, or "step-up," approach to biologic therapy for CD requires that a patient first fail conventional therapy, such as corticosteroids or immunomodulators, prior to proceeding with biologic therapy. Unfortunately, many patients are exposed to many courses of corticosteroids prior to initiation of an immunomodulator, let alone a biologic.[1] This approach has been challenged over time by emerging evidence that early biologic therapy, or a "top-down," approach is more effective.[2] The concept is to treat the disease while it is still inflammatory, before complications arise and patients require surgery. The benefit of a "top-down" approach was first demonstrated in a landmark open-label randomized controlled trial (RCT) by D'Haens et al. that demonstrated higher remission rates at week 52 in patients treated early with infliximab and azathioprine compared to conventional therapy (61.5% vs. 42.2%, p=0.0287).[3] There were also higher rates of complete endoscopic remission at 2 years in the top-down group (73.1% vs. 30.4%, p=0.0028), which led to greater rates of sustained clinical remission during years 3-4 (70.8% vs. 27.3%, p=0.036).[4] Since this landmark trial, several other studies have demonstrated the benefits of early biologic therapy in CD.[5-9]

Despite the evidence supporting early biologic therapy and a "top-down" approach to the treatment of CD, it is important to note that this paradigm has not been validated and is not explicitly advocated in recent guidelines for CD.[10-12] Instead, current guidelines recommend using disease severity and initial risk assessment to guide the timing of biologic therapy. Furthermore, there is also a push to distinguish disease severity and disease risk from disease activity, where activity represents inflammation at a cross-sectional moment in time, and severity and risk take into account the past history of the disease and the global, longitudinal disease burden.[13-16] In initially assessing a patient's risk, the factors that have been associated with moderate-high-risk include age <30 years at time of diagnosis, extensive anatomic involvement, perianal disease, deep ulceration, history of surgery, stricturing or penetrating disease, and visceral adiposity.[17-20] If a patient is deemed moderate-high-risk based on these factors, the American Gastroenterological Association (AGA)

Table 1. Summary of Comparative Effectiveness Studies in CD

Study	Study Type	Outcome(s)	Summary of Findings
Singh et al.[35]	Retrospective analysis of administrative claims database	CD-related hospitalization Abdominal surgery Corticosteroid use All-cause hospitalization	**Infliximab** superior to adalimumab (CD-related hospitalization, abdominal surgery, corticosteroid use) **Infliximab** superior to certolizumab pegol (CD-related hospitalization, all-cause hospitalization)
Singh et al.[36]	Network meta-analysis	Induction and maintenance of clinical remission	**Infliximab** and **adalimumab** superior to ustekinumab and vedolizumab
Cholapranee et al.[37]	Meta-analysis	Induction of mucosal healing	**Infliximab** and **adalimumab** favored over placebo

recommends biologic therapy with anti-TNF therapy.[10,11] While newer biologic therapies, such as ustekinumab and vedolizumab, are not currently included in AGA guidelines, these agents are likely to be incorporated in future guideline documents. Similarly, guidelines from the American College of Gastroenterology (ACG) recommend anti-TNF therapy in patients who are deemed moderate to high risk with moderate to severe Crohn's disease, in addition to patients who are refractory to steroids or immunomodulators and patients with severe fulminant disease.[12] While newer agents, such as ustekinumab and vedolizumab, are included in ACG guidelines,[12] there is little guidance on the early use of these agents. There is also little guidance and even fewer recommendations on how to position these drugs.

When to Initiate Biologic Therapy in Ulcerative Colitis

The role for biologic therapy in UC is well-established, but the timing of initiation in the disease course is less clear than for CD. Also, as opposed to CD, 5-aminosalicylates (5-ASA) therapy is extremely effective and plays a major role in the treatment of mild to moderate UC.[21,22] Early initiation of biologic therapy in UC may help prevent disease-related complications, such as colon cancer, hospitalizations, and surgery.[2] Also, it has been shown that ongoing inflammation is a risk factor for colorectal cancer in patients with UC,[23] and controlling this inflammation may decrease the risk of developing cancer.[24] With that said, studies evaluating the timing of biologic therapy in UC have not demonstrated a clear benefit for early initiation, as has been demonstrated in CD, but these studies are likely confounded by disease severity.[25-28] Therefore, it is difficult to make any strong conclusions regarding the use of early biologic therapy in UC based on such studies.

Based on current guidelines for UC from the ACG[22] and AGA,[29] the role biologic therapy is well-established for induction and maintenance of remission in moderate to severe disease and in acute severe UC (ASUC). However, similar to CD, the definition of severity for UC is evolving, and there is an increasing emphasis on disease risk and prognosis, especially pertaining to colectomy risk. This notion was previously incorporated into

the AGA Institute Ulcerative Colitis Clinical Care Pathway,[30] which suggested that early therapy with a biologic agent should be considered in patients who have factors associated with high colectomy risk or worse prognosis. These factors include extensive colitis, deep ulcers, age <40, elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), steroid-requiring disease, history of hospitalization, *Clostridium difficile* infection, and cytomegalovirus (CMV) infection.[30] However, more recent guidelines from both the ACG[22] and AGA,[29] primarily used disease severity to guide when biologic therapy is used, which was largely defined by the traditional Truelove-Witts criteria[31] and Mayo score.[32] Guidelines from the ACG include biologic therapy in patients with initial moderately to severely active ulcerative colitis and recommend the use of anti-TNF therapy (infliximab, adalimumab, and golimumab), vedolizumab, and tofacitinib in patients who respond to induction with any of these agents.[22] Infliximab is also included in the management of ASUC (discussed later). However, the ACG provides little guidance on how to position these therapies against each other. Also, these guidelines predate the approval of ustekinumab for UC[33] and the recent Food and Drug Administration (FDA) recommendation for using tofacitinib only in patients who have had anti-TNF failure or intolerance.[34] On the other hand, the recently published guidelines from the AGA do provide some guidance on how to position different biologic therapies in patients with moderate-severe UC.[29] Briefly, infliximab and vedolizumab are favored over adalimumab in biologic-naïve patients, and vedolizumab or adalimumab are favored over ustekinumab or tofacitinib in patients previously exposed to infliximab. While this updated document provides some practical guidance, it does not take into account other important factors in deciding biologic therapy, such as safety, patient-specific factors, cost, insurance, patient preference, and provider comfort.

Drug Selection – Which Biologic Therapy is Best?

Once the decision is made to start biologic therapy, the next decision involves selecting the optimal biologic agent for a given patient. Anti-TNF

therapy is the most established biologic for the treatment of IBD. However, whether anti-TNF therapy is the best first-line biologic therapy has been called into question with the emergence of newer biologic therapies, such as vedolizumab and ustekinumab. Furthermore, there are multiple practical considerations when making this decision, including disease-related factors, patient-specific factors, cost, insurance, medication-specific factors, patient preference, and provider comfort and experience. How to best position these therapies remains a question, especially with limited head-to-head randomized controlled trials (RCTs). This section will review the available data including indirect comparative effectiveness studies.

Table 2. Summary of Comparative Effectiveness Studies in UC

Study	Study Type	Outcome(s)	Summary of Findings
Singh et al.[38]	Network meta-analysis	Induction of remission Mucosal healing	**Infliximab** and **vedolizumab** superior to adalimumab and golibumab
Singh et al.[39]	Network meta-analysis	Induction of remission Endoscopic improvement	**Infliximab** superior to vedolizumab, tofacitinib and ustekinumab
Bonovas et al.[40]	Network meta-analysis	Clinical response Clinical remission Mucosal healing	**Infliximab** superior to adalimumab (clinical response, clinical remission, mucosal healing) **Infliximab** superior to golibumab (clinical response, mucosal healing)
Singh et al.[41]	Propensity score-matched retrospective analysis of administrative claims database	Corticosteroid use	**Infliximab** superior to adalimumab
Singh et al.[42]	Propensity score-matched retrospective analysis of nationwide cohort	All-cause hospitalization	**Infliximab** superior to adalimumab
Cholapranee et al.[37]	Meta-analysis	Induction of mucosal healing	**Infliximab** superior to adalimumab
Faleck et al.[43]	Propensity score-matched analysis of VICTORY Consortium	Clinical remission	**Vedolizumab** superior to anti-TNF agents
Sands et al.[44]	Prospective RCT (VARSITY Trial)	Clinical remission (Week 52) Endoscopic improvement Corticosteroid-free remission (Week 52)	**Vedolizumab** superior to adalimumab (clinical remission at week 52, endoscopic improvement) No difference between vedolizumab and adalimumab for corticosteroid-free remission at week 52

Studies on Comparative Efficacy – Crohn's Disease

With the limited availability of head-to-head comparisons, most of the studies evaluating the comparative efficacy of different biologic therapies for CD and UC have involved indirect comparison, namely through large retrospective analyses, meta-analyses, or propensity score matched-cohort studies.[35-43] A recent network meta-analysis by Singh et al. showed that infliximab and adalimumab were ranked highest for induction of clinical remission in biologic-naïve patients using surface area under the cumulative ranking (SUCRA) probabilities compared to ustekinumab and vedolizumab (SUCRA 0.93 for infliximab; SUCRA 0.75 for adalimumab).[36] Adalimumab (SUCRA 0.97) and infliximab (SUCRA 0.68) also ranked highest in the outcome of maintenance of remission. An additional study by Cholapranee et al. indirectly compared biologic therapies using a meta-analysis of RCTs for CD and found that anti-TNF therapy with infliximab or adalimumab was favored over placebo for maintenance of mucosal healing (28% vs. 1%, OR 19.71, 95% CI 3.51-110.84), but there were similar rates of mucosal healing when comparing infliximab and adalimumab.[37] These and other comparative effectiveness studies in CD patients support the benefit of anti-TNF therapy over other biologic therapies, and there is arguably a benefit for infliximab over other anti-TNF agents based on pharmacokinetics and onset of action. A summary of the comparative efficacy data for CD is included in Table 1.

Studies on Comparative Efficacy – Ulcerative Colitis

In UC, a network meta-analysis involving biologic-naïve patients from 12 RCTs compared the approved anti-TNF agents (infliximab, adalimumab, and golimumab), vedolizumab, and tofacitinib using SUCRA probabilities.[38] In this study, all agents were found to be more effective than placebo, and infliximab and vedolizumab ranked higher than adalimumab and golimumab for induction of remission and mucosal healing. Furthermore, an updated network meta-analysis by Singh et al. showed that infliximab ranked higher than vedolizumab, tofacitinib, and ustekinumab in biologic-naïve patients for induction of clinical remission (OR 4.07, 95% CI 2.67-6.21; SUCRA 0.95) and endoscopic improvement (SUCRA

0.95).[39] Another study by Singh et al. using a propensity-score matched cohort of patients from a large Danish cohort also showed favorable results for infliximab over adalimumab with higher rates of all-cause hospitalization in patients treated with adalimumab (HR 1.84, 95% CI 1.18-2.85).[42] Lastly, the aforementioned study by Cholapranee et al. found that for induction of mucosal healing, adalimumab was inferior to infliximab (OR 0.45, 95% credible interval [CrI] 0.25-0.82).[37]

Recently, a phase 3b, randomized, double-blind, double-dummy, active-controlled superiority trial to detect treatment differences between vedolizumab and adalimumab (VARSITY trial) has gained much attention as it is the first head-to-head study to directly compare two biologic therapies in IBD.[44] This study demonstrated a higher rate of clinical remission (primary endpoint) and endoscopic improvement (39.7% vs. 27.7%, 95% CI 5.3-18.5, p<0.0001) at week 52 in patients on vedolizumab compared to adalimumab. However, there was no difference between each group in corticosteroid-free remission at week 52 (12.6% in vedolizumab group vs. 21.8% in adalimumab group, 95% CI 18.9-0.4). It is important to note that dosing was fixed in both treatment groups, which is an important consideration since the benefit of dose intensification and optimization has been established for both therapies.[45-49] A summary of the comparative efficacy data for UC is included in Table 2.

Specific Clinical Scenarios
Fistulizing Crohn's Disease

Fistulizing CD is recognized as a unique phenotype that is associated with more severe outcomes/higher disease risk.[11,12] Infliximab is the only biologic agent that has prospectively demonstrated benefit with fistula closure as the primary outcome in RCTs[50,51] and is, therefore, recommended by current guidelines.[11,12] Other biologic agents, including adalimumab, certolizumab, ustekinumab, and vedolizumab are not well-studied in this setting.[52-56]

Acute Severe UC

The benefit of infliximab and non-inferiority to cyclosporine in ASUC has been well-demonstrated.[57-61] Therefore, infliximab is the only

biologic therapy that is considered an effective rescue therapy in ASUC and is included in recent guidelines.[22,29] With this said, the phenomenon of fecal drug loss may be a limitation,[62] and studies on accelerated dosing have shown mixed results.[63-65] However, disease severity is likely a significant confounder in these studies.

Associated or Co-Existing Systemic Conditions

It is well-known that several systemic conditions and extraintestinal manifestations (EIMs) are associated with both CD and UC, including rheumatologic conditions, dermatologic conditions, and ocular conditions.[66-69] Furthermore, other systemic conditions, such as rheumatoid arthritis, plaque psoriasis, and psoriatic arthritis, may co-exist in a patient with IBD. In this setting, selection of a therapy that may offer dual-benefit in concomitantly treating both the IBD and the co-existing condition makes the most sense.[66] Also, the benefit of anti-TNF therapy in treating EIMs has been demonstrated in several studies.[70-71] Furthermore, infliximab, adalimumab, ustekinumab, and tofacitinib are also FDA-approved for rheumatologic indications that may co-exist with IBD.[72-75] Conversely, vedolizumab may be less ideal in this setting based on its presumed "gut-selective" mechanism of action.[76]

Safety –Risk and Benefit

Safety Data for Anti-TNF Therapy

The potential risk of biologic therapy is a common concern for both patients and providers and often plays an integral role when selecting biologic therapy. The risks of anti-TNF therapy have been especially recognized and will be discussed, but it should be emphasized that these risks are relatively low and much less than the risks of disease complications and surgery. [77,78] Lemaitre *et al.* specifically examined the risk of lymphoma with anti-TNF therapy using a large nationwide French database and showed a higher risk of lymphoma in patients on combination therapy compared those on thiopurine monotherapy (adjusted HR 2.35, 95% CI 1.31-4.22, p<0.001) or anti-TNF monotherapy (adjusted HR 2.53, 95%CI, 1.35-4.77, p<0.001).[78] These findings translated to very low annual incidence rates for

Table 3. Factors to Consider in Selecting First-Line Biologic Therapy

Disease-Specific Factors	Patient-Specific Factors
Disease severity Perianal disease Presence of extraintestinal manifestations Co-existing conditions (e.g. rheumatoid arthritis, psoriasis)	Age Medical comorbidities (e.g. congestive heart failure, renal disease) History of malignancy Pregnancy
	Insurance and Cost Individual policy restrictions Out-ofpocket costs
Medication-Specific Factors Efficacy Safety Immunogenicity Route of administration Rapidity of onset Durability of remission Availability and Data on TDM Time on Market	**Patient Preference** Individual patient goals and values Adherence and engagement in care Shared decision making
	Provider Comfort and Experience Familiarity with a given agent Experience with optimizing, monitoring, and assessing response to therapy

lymphoma of 0.041% for anti-TNF monotherapy and 0.095% for combination therapy. In addition, several large studies have shown an increased risk of opportunistic and serious infections associated with anti-TNF therapy.[79-82] Notably, another large population-based French study evaluated the risk of opportunistic and serious infections with thiopurine monotherapy, anti-TNF monotherapy, and combination therapy, and demonstrated an annual incidence rate of serious infection of 1.89% for anti-TNF monotherapy and 2.24% for combination therapy.[78,83-84]

Other notable risks that have been associated with anti-TNF therapy include melanoma, dermatologic reactions, and immunogenicity.[85-90] Notably, immunogenicity with resultant anti-drug antibody formation is arguably under recognized and remains the most common risk anti-TNF

therapy with rates of anti-drug antibodies of up to 65.3% for infliximab and 38.0% for adalimumab.[90] Since the development of anti-drug antibodies can lead to loss-of-response and resultant disease worsening, this matter should be addressed with patients when addressing other risks of anti-TNF therapy. Also, this risk can be mitigated by proactive TDM, emphasizing the importance of this practice (discussed later).

Safety Data for Newer Therapies

There are less available safety data for vedolizumab and ustekinumab due to shorter duration on the market, but the available follow-up data for these agents has been highly favorable with low risk of serious adverse events, serious infections, and immunogenicity.[91-93] With this said, vedolizumab and ustekinumab have been recognized for their strong safety profile and may not only be selected as first-line therapy in some cases for their demonstrated efficacy, but also for their well-recognized safety based on available data. On the other hand, several risks of tofacitinib have been recognized, including lymphopenia, hypercholesterolemia, and infection, namely herpes zoster.[94] In addition, an interim analysis of an FDA post-marketing trial in patients with rheumatoid arthritis over age 50 with at least one cardiovascular risk factor demonstrated an increased occurrence of pulmonary embolism (PE) and mortality in patients taking tofacitinib 10 mg twice daily.[34] This has led to a black box warning from the FDA and a recommendation to only use tofacitinib at the lowest effective dose in patients with UC who have failed or not tolerated anti-TNF therapy.[34]

The Importance of Balancing Other Risks

While medication risk is an important consideration that is well-recognized, it is important to recognize the higher risks of complications from poorly-controlled disease activity, including fistula, stricture, and surgery. Notably, Osterman et al. showed that higher disease activity and corticosteroid use (by day 120) were associated with an increased risk of infection.[95] Furthermore, the increased mortality risk associated with corticosteroids and narcotics has been well demonstrated.[96-98] Lastly, recent studies have shown

the 10-year risk of surgery is around 40% for CD[99] and around 15% for UC.[100] In patients with CD, the risk of developing an intestinal complication, such as fistula or stricture, is 50% within 20 years after diagnosis.[101] Thus it is important to put the risks of medications into perspective with the high risks of poorly-controlled IBD.

Other Factors to Consider

There are several other factors that impact selection of biologic therapy, including additional patient-specific factors (e.g. age, comorbidity), cost, insurance, patient preference, and provider preference and comfort.[102-110] These factors are outlined in Table 3.

Drug Optimization – How Do You Optimize the Drug You Choose?

For any selected biologic therapy in any given patient, the importance of drug optimization is becoming increasingly recognized, especially with anti-TNF therapy. It has been demonstrated that there is a high rate of loss-of-response with anti-TNF therapy, even within the first year.[111,112] The benefit of optimization using combination therapy with an immunomodulator has been previously demonstrated in both CD and UC by The Study of Biologic and Immunomodulator Naïve Patients in Crohn's Disease (SONIC)[113] and UC-SUCCESS Trials,[114] respectively. However, a *post hoc* analysis of the SONIC trial demonstrated that combination therapy benefited a greater number of patients at higher quartiles of infliximab drug concentration at week 30, and the benefit diminished in patients at the highest quartile of infliximab drug concentration (>5.02 µg/mL).[115] While this was a *post hoc* analysis, these findings support that the benefit of combination therapy is likely due to the effect on increasing infliximab drug concentrations, supporting the approach of optimized monotherapy. Proactive TDM has gained increasing recognition as a preferred method of biologic drug optimization in patients with IBD. There are several retrospective studies demonstrating the benefit of proactive TDM over reactive TDM or empiric dose escalation.[116,48] Notably, a retrospective study of 264 patients with CD (n=167) and UC (n=97) from multiple centers showed less treatment failure (HR 0.16, 95% CI 0.09-0.27), fewer IBD-related surgeries (HR 0.30,

Figure 1. A Practical Approach Towards Selecting First-Line Biologic Therapy in IBD
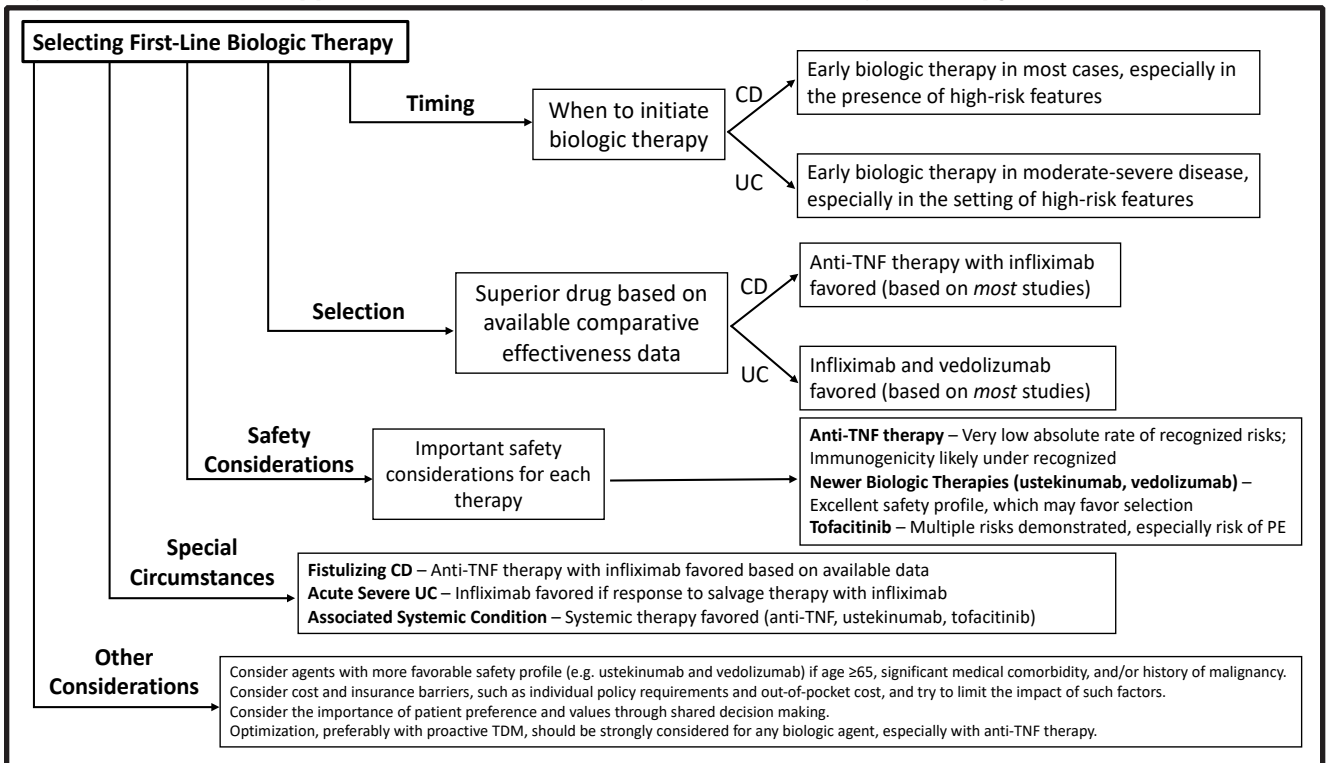
95% CI 0.07-0.33), less antibodies to infliximab (HR 0.25, 95% CI 0.07-0.84), and fewer serious infusion reactions (HR 0.17, 95% CI 0.04-0.78) in patients treated with proactive vs. reactive TDM of infliximab.[116]

Despite these data, proactive TDM has not been recommended by a recent guideline document by the AGA,[117] largely due to the results of a prospective study with methodologic flaws. The Trough Level Adapted Infliximab Treatment (TAXIT) Trial is often touted as a "negative" study for not meeting its primary endpoint.[118] However, one-time dose optimization in patients with CD with low drug concentrations resulted in improved remission rates and CRP. Furthermore, several secondary outcomes including less disease flares favored continued proactive dose optimization despite issues with study design (all patients were optimized prior to randomization, follow-up period of 1 year was too short, and the target drug concentration of infliximab was low at 3-7 µg/mL).

More recently, the Pediatric Crohn's Disease Adalimumab Level-based Optimization Treatment (PAILOT) Trial was a well-designed prospective RCT by Assa et al. that showed improved corticosteroid-free clinical remission from week

8 to week 72 (82% vs. 48%, P=0.002) in pediatric patients with CD who underwent proactive TDM compared with reactive TDM.[49] Furthermore, more patients in the proactive TDM group also achieved normalization of CRP and fecal calprotectin compared to the reactive TDM group (42% vs. 12%, p=0.003). This study represents the first prospective study to achieve its primary endpoint and demonstrate benefit for proactive TDM of an anti-TNF agent. This study, among others, hopefully will lead to a shift in practice in favor of proactive TDM of biologic therapy, especially for anti-TNF therapy, which has been advocated by several groups.[119,120] If one is not going to use optimized monotherapy with an anti-TNF, combination therapy with an immunomodulator should be considered for all patients.

CONCLUSION

The timing and selection of biologic therapy for patients with IBD can be difficult, and this matter has been complicated further by the introduction of newer biologic therapies for CD and UC. There are several factors to consider when deciding on the timing of biologic therapy and on how to select which biologic therapy is best for a given patient.

Current guidelines do provide some guidance on when to select biologic therapy with an emphasis on assessing disease risk or prognosis to guide this decision, for both CD and UC. However, there is limited guidance for which agent to select for a given patient. There are available comparative effectiveness data for both CD and UC that may inform this decision, but this does not take into account other important factors, such as safety, additional patient-specific factors, cost, insurance, patient preference, and provider preference. We propose a practical approach towards making this decision with consideration of all these factors (Figure 1). Nonetheless, once a biologic therapy is selected, it is important to optimize whichever therapy is chosen, preferably with proactive TDM. ∎

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