Clinical Roundtable Monograph

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The Guide to Guidelines in Ulcerative Colitis: Interpretation and Appropriate Use in Clinical Practice

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Target Audience

This CME monograph will target gastroenterologists, primary care physicians, nurse practitioners, physician assistants, and nurses.

Goal Statement

The primary goal of this CME monograph is to encourage the application of the latest advances in evidence-based medicine to improve the quality of care and improve outcomes for the patients affected by ulcerative colitis (UC).

Educational Objectives

Upon completion of this educational activity, participants should be able to:

- Critically appraise the scientific evidence and methodologies used to develop clinical practice guidelines in inflammatory bowel disease (IBD)
- Describe how clinical guideline recommendations can be integrated with real-world and clinical trial data to inform clinical decision-making in IBD
- Apply current treatment goals and paradigms to the care of individual patients with UC

Accreditation Statement and Credit Designation

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the New Mexico Medical Society (NMMS) through the joint providership of Rehoboth McKinley Christian Health Care Services (RMCHCS) and GI Health Foundation. RMCHCS is accredited by the NMMS to provide continuing medical education for physicians.

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Introduction

In October 2020 and January 2021, a group of clinical experts in the field of inflammatory bowel disease (IBD) convened virtually to discuss current ulcerative colitis (UC) guidelines and how to interpret them in the context of the evolving treatment paradigms and targets for UC. After reviewing the evolution of guideline development, key recommendations and differences between the current UC guidelines published by the American College of Gastroenterology (ACG) and American Gastroenterological Association (AGA) were evaluated. In addition, the faculty offered practical advice for incorporating the guideline recommendations into clinical practice. This monograph, which summarizes discussions from these meetings, is intended to provide clinicians with practical context for understanding and applying UC guidelines into patient care.

> If you look across the country, you would find that there's a twofold variance in length of stay. And when you plug in all the factors that are associated with how long a patient might be in the hospital for severe UC, you would only explain about 15% of the variance, and the biggest variance would be physician behavior. So if you're running a health care system, even if you do not get it perfect, it's better to have consistency than just have everybody doing whatever they want. That's a fundamental reason why we need guidelines.
> –Gary R. Lichtenstein, MD

Overview of Clinical Practice Guidelines

Why Do We Have Guidelines?

Clinical practice guidelines, now ubiquitous in our health care system, were developed in an effort to translate the complexity of scientific data into recommendations for clinical practice with the hope of improving health care quality and outcomes.[1] Guidelines aim to improve patient care by encouraging the use of interventions of proven benefit and by reducing unnecessary variation in practice.[2] Recognizing the large variation in how

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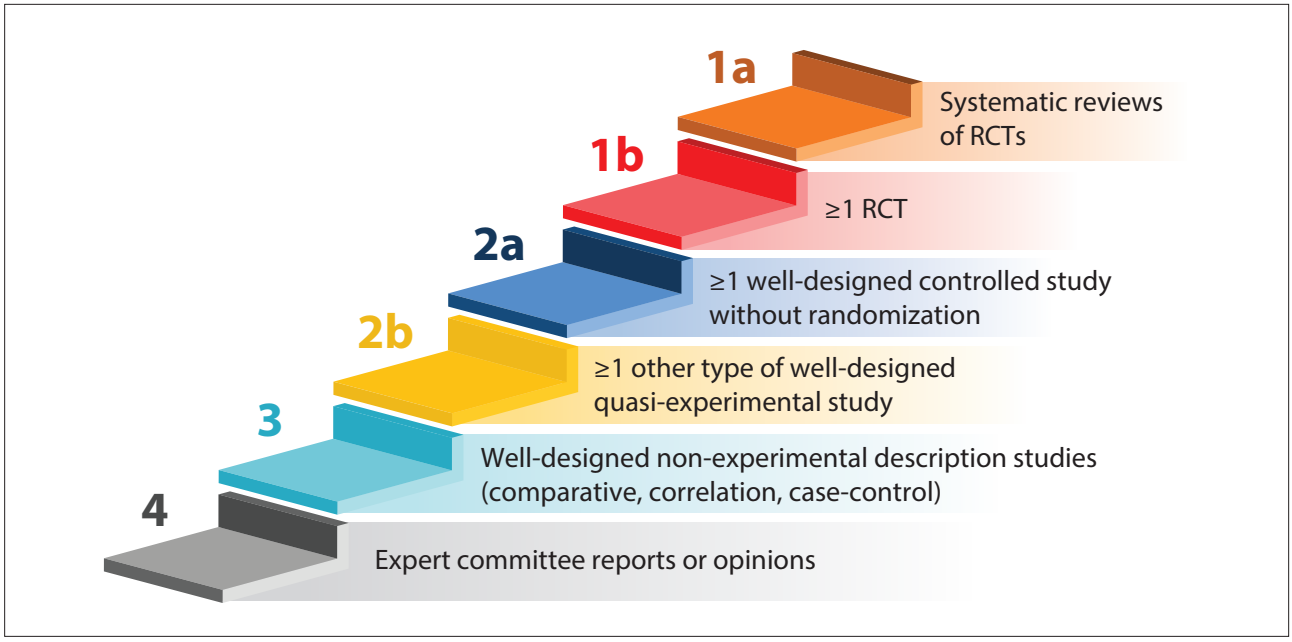

Figure 1. Levels of evidence.[8] RCT, randomized controlled trial.

IBD is managed, Dr Feagan noted that "if you accept the idea that there's a right way to do things, then excess variation leads to poor outcomes. So, guidelines try to standardize outcomes by achieving consensus on the best way to do things." Dr Sandborn added that guidelines provide a useful reference for busy clinicians, "a place to easily go and see the data and become familiar with it." Additionally, guidelines influence policy, with strong recommendations having the potential for incorporation into quality improvement initiatives or affecting insurance reimbursement.[2]

Guideline Development Process

The process for guideline development has evolved throughout the past decades. Before the advent of evidence-based medicine,[1] clinical practice guidelines were developed through an informal consensus of experts. Beginning with the Delphi method in the 1960s, several formal consensus methods were introduced that aimed to obtain the most reliable consensus of a group of experts and minimize bias.[3,4] With the emergence of evidence-based medicine in the 1980s as a foundation for decision-making,[2] the emphasis on clinical practice guidelines has increasingly shifted towards *how* they are developed, with a focus on multidisciplinary input that is based on a systematic review of published research and that explicitly links the recommendations to the supporting evidence.[5] As Dr Feagan explained, "the process met up with evidence-based medicine, applying epidemiological principles to ranking evidence and looking at clinical evidence in a new way to form the modern guidelines process."

Today, the process of developing clinical practice guidelines begins with identifying and refining the topic, determining the clinical questions that will be addressed, and defining the composition of the guidelines panel.[5-7] Achieving a balance of disciplines in the guidelines panel is essential for ensuring that the guidelines will be valued by all the members of the multidisciplinary team and incorporated successfully into practice.[5] "Getting the right blend between methodologists and practicing clinicians who treat patients and understand the practical issues is critical," noted Dr Feagan.

The next key step is conducting a systematic review of the evidence, with the literature identified according to an explicit search strategy and then evaluated against consistent methodologic standards.[5] Appraising the quality of evidence is critical to determining the degree to which studies are susceptible to bias and thus the degree of support they provide for the strength of recommendations. In addition to bias, other factors that can decrease the quality of evidence include inconsistency, indi-

> Meta-analysis of high-quality RCTs is as good as it gets. Meta-analysis trumps a single trial because it can generate more precise estimates of effects. However, that does not mean that a meta-analysis of poor studies trumps a large high-quality RCT; that's a common misconception.
> –Brian G. Feagan, MD

rectness, and imprecision.[6] Many classification schemes exist for assessing levels of evidence, with most employing a hierarchical approach based on the type of data generated (Figure 1).[8] Dr Feagan noted that misconceptions regarding meta-analyses or systematic reviews are common, emphasizing that the quality of such evidence depends on the quality of trials included in the analysis.

> Network meta-analyses don't draw the same conclusions as a single large comparative study and should be considered hypothesis-generating.
> –Brian G. Feagan, MD

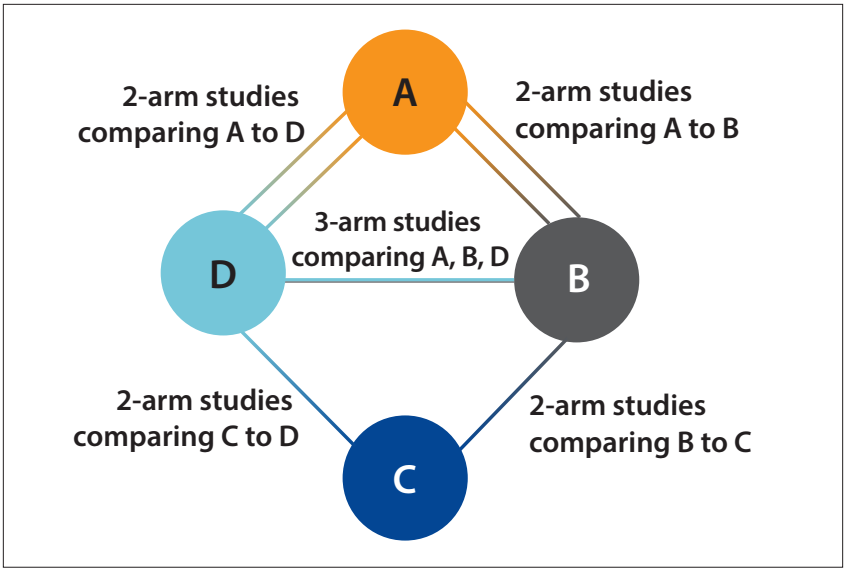

Figure 2. Principles of network meta-analysis.[9]

What About Network Meta-Analyses?

Network meta-analyses have increasingly been used over the past several years as a technique for indirectly comparing clinical trial data. A relatively recent development, network meta-analysis is used to extend the principles of meta-analysis to evaluate multiple treatments within a single analysis.[9,10] With this technique, 3 or more interventions can be compared simultaneously in a single analysis by combining both direct and indirect evidence across a network of studies (Figure 2).[9] In this context, direct evidence is derived from comparative efficacy trials, whereas indirect evidence refers to the evidence obtained through one or more common comparators.[10] By combining this mixed evidence in a single analysis, network meta-analysis produces estimates of the relative effects between any pair of interventions in the network, as well as the ranking and hierarchy of interventions.[9] Importantly, the validity of network meta-analysis relies on the assumption that the studies included are similar with regard to all factors that can affect the relative results. Dr Feagan explained that "the big caveat with these analyses is that they should be viewed as hypothesis-generating since the studies are inherently different, and you're relying on the assumption that the placebo effects across studies conducted over the past 10 years are similar." He continued, "When you think about the patient types in IBD over the past decade, it's a leap of faith to believe that assumption is correct." Dr Sandborn added that although "network meta-analyses can play a useful role in the absence of head-to-head trials, they should be considered to be another piece of evidence and not necessarily confused with the truth."

After the quality of the evidence is assessed, recommendations are developed and graded to differentiate those based on strong evidence from those based on weak evidence.[5] This information is intended to provide the user with an estimate of the group's confidence that following the recommendation will produce the desired health outcome.[7] As with levels of evidence, many classification schemes have been developed for grading recommendations. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach is commonly used to grade the strength of recommendations and has been adopted as the standard by many guideline developers and organizations, including the AGA and the ACG.[4,11,12] The GRADE approach typically scores the strength of recommendations as either strong or weak, also known as conditional or discretionary.[2,6] While the GRADE approach acknowledges that expertise is required to interpret any form of evidence, it considers that opinion is an interpretation of—rather than a form of—evidence.[6]

Once recommendations are developed and graded, the guidelines are then made available for public policy evaluation. This step is critical, Dr Feagan pointed out, "because there is no point in having guidelines if they can't be implemented." Lastly, the guidelines are submitted for peer review and published.

Does the Guidelines Process Matter?

Given the different methods used to develop clinical practice guidelines, the quality and agreement across 8 breast cancer guidelines were explored using 5 different instruments.[13] Although no major disagreement was detected among the guidelines, the 3 guidelines that were classified as evidence-based were found to be of higher quality

than guidelines that were consensus-based. Importantly, up to 94% of the variation in the quality score among the guidelines examined could be explained by the quality of evidence used for their development. Commenting on these findings, Dr Feagan noted that "this is the bottom line: if you have poor-quality evidence, you get poor-quality guidelines and disagreement. And if you have high-quality evidence, you get quality guidelines with high concordance."

Incorporating UC Clinical Guidelines Into Practice

Multiple international and national clinical practice guidelines are available to guide clinicians in various aspects of UC management.[11,14-16] In the United States, guidelines for UC management have been updated recently by both the ACG[16] and the AGA.[11] Although both guidelines were developed using GRADE methodology, they differ in several key areas. Published in 2019, the ACG guidelines cover a broad scope of UC management, addressing diagnosis, treatment, and overall management of adults across varying severities of UC, including hospitalized patients.[16] In contrast, the AGA published 2 guidelines, one in 2019 and the other in 2020, focusing on the medical management of mild-to-moderate[17] and moderate-to-severe UC,[11] respectively. Whereas the ACG guidelines include recommendations for the use of conventional therapies (ie, 5-aminosalicylic acid [5-ASA] drugs, budesonide, oral and intravenous corticosteroids),[16] the AGA restricts recommendations for moderate-to-severe UC to the use of immunosuppressive agents, biologics, and small molecules for the induction and maintenance of remission.[11] Furthermore, the AGA bases its recommendations for these therapies on a technical review of the evidence that included a network meta-analysis to inform the comparative efficacy of different pharmacologic therapies.[11,18]

> With ulcerative colitis, there's a very high correlation between rectal bleeding and what you find at endoscopy. The correlation of diarrhea to endoscopy is a little less so, but it's pretty good. And our clinical trials reflect our clinical practice in that sense. By contrast, the correlation between symptoms and endoscopy in Crohn's disease is terrible, it's a coin toss.
> –William J. Sandborn, MD

Evolving Management Strategies in UC

An obligate first step in assimilating UC guidelines into clinical practice is to interpret their recommendations in the context of the broader management landscape. With that in mind, it is important to recognize that the goals of therapy in IBD have evolved from merely controlling symptoms to preventing disease progression, surgery, and disability.[16,19-21] Central to this shift is the recognition that treating only to symptom resolution in IBD can leave active disease (ie, mucosal inflammation) and is insufficient to alter long-term remission or complication rates.[21] While the disconnect between symptoms and mucosal inflammation is particularly striking in Crohn's disease, a considerable proportion of patients with UC have been shown to have mucosal inflammation without clinical symptoms.[16,22]

In light of the progressive nature of IBD and evolving treatment goals, early intervention and a treat-to-target approach have emerged as pillars of optimal care in UC.[19,21,23] A number of studies have found that early intervention with biologics can slow disease progression and improve long-term outcomes in Crohn's disease.[24-29] Although the evidence is more limited in UC, preliminary data indicate that there is benefit to early intervention in these patients as well.[30-33] To that end, the management of UC is increasingly driven by identifying patients who are candidates for early intervention by assessing their prognostic factors for aggressive disease.[34-36] With this approach, patients with risk factors for an unfavorable disease course are treated earlier after initial diagnosis with highly effective therapies than those with fewer risk factors, who may be managed with a conventional "step-up" approach.[11,34,36] In patients with limited anatomic involvement and mild endoscopic disease who are believed to have a low risk for colectomy, treatment with oral and/or rectal 5-aminosalicylates with or without oral budesonide is recommended.[16,37] In contrast, more effective therapies are recommended for those with poor prognostic factors, such as extensive colitis, deep ulcers, previous requirement for corticosteroids, and failure to respond to conventional treatments.

An additional paradigm shift in IBD care over the past decade is the incorporation of a treat-to-target approach. Although used in rheumatoid arthritis and type 2 diabetes for many years, the first major step in promoting this strategy in IBD was the publication of the STRIDE (Selecting Therapeutic Targets in IBD) recommendations in 2015.[23] The treat-to-target approach aims to achieve disease remission by regular monitoring and adjusting therapy according to the achievement of treatment response targets (Figure 3).[20,21,23] A key element of a successful treat-to-target approach is collaboration between the physician and the patient to discuss treatment targets and to work together to achieve

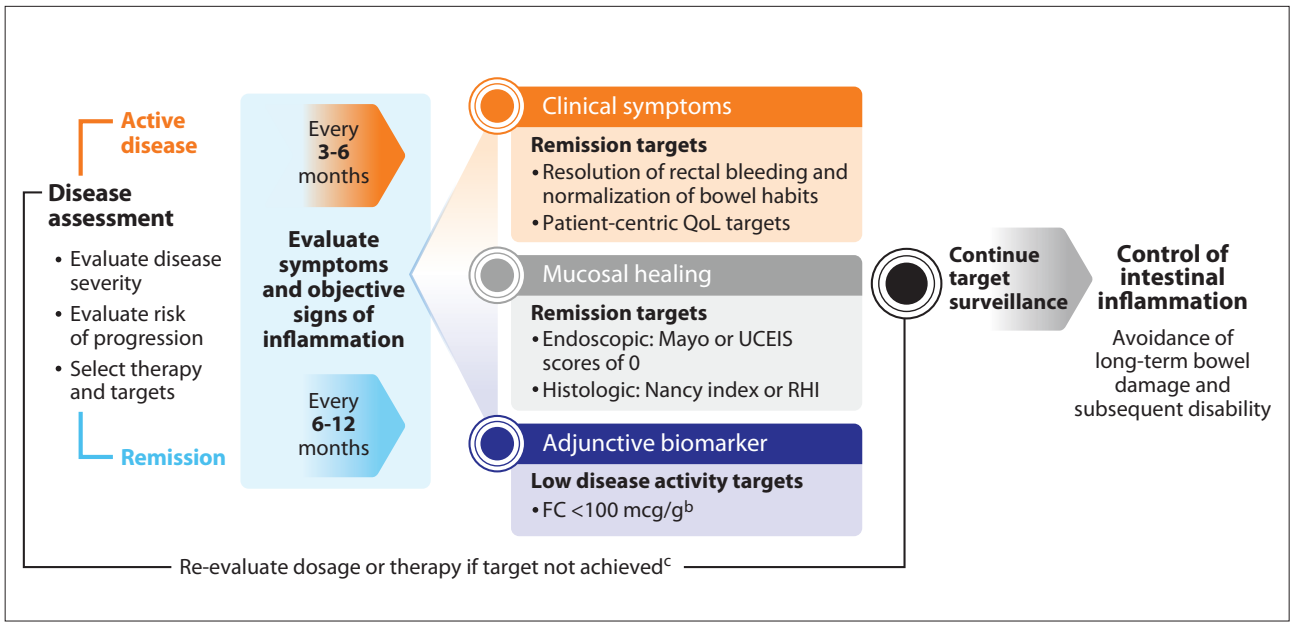

Figure 3. Proposed ulcerative colitis treat-to-target strategy.[21] FC, fecal calprotectin; QoL, quality of life; RHI, Robarts' Histological index; UCEIS, Ulcerative Colitis Endoscopic Index of Severity.

them through regular monitoring and therapy adjustment.[20,23]

Treatment Targets in UC

An integral part of a successful treat-to-target approach is identifying the appropriate treatment targets. Consistent with the traditional focus on achieving clinical remission, the initial treatment of UC continues to target clinical endpoints such as restoring normal bowel frequency and resolving bleeding and urgency.[16,21,23] However, with growing data demonstrating the correlation between mucosal healing with improved outcomes in UC (lower relapse rate and colectomy risk),[38,39] treatment goals have evolved to include sustained control of inflammation.[16,21,23] Accordingly, mucosal healing, or endoscopic remission, is now widely recognized as an important goal of therapy and is acknowledged as such in the current ACG guidelines for UC.[16,21,23]

In contrast to the endoscopic aspects of mucosal healing, the role of histologic healing as a treatment target is still somewhat uncertain.[16,21,40-43] Histologic healing, defined as microscopic normalization of the colonic mucosa, is a distinct target from endoscopic healing, a measure of endoscopically visible disease activity.[21] A growing number of studies demonstrate that histologic remission in UC is predictive of steroid-free remission, clinical relapse, hospitalization, and steroid use,[16,44] while others have associated the degree of histologic inflammation with dysplasia and colorectal cancer.[16,45,46] Dr Lichtenstein noted that "histologic healing is not yet part of our standard approach because in the past it wasn't measured and assessed, which leaves some evidence gaps; however, we recognize now that it portends a better outcome in ulcerative colitis." Nevertheless, histologic healing is not currently recommended as a target, as it has not yet been prospectively validated as an endpoint of treatment.[16]

Recognizing the need for less invasive markers of inflammation, the value of several adjunctive biomarkers in monitoring has been explored.[16] Fecal calprotectin is the most extensively studied of these biomarkers, and its role has grown, with accumulating data demonstrating correlations of low concentrations with the absence of mucosal inflammation and of rising concentrations with relapse in UC.[16,21] Dr Feagan commented that "although endoscopy is the benchmark for monitoring, fecal calprotectin is pragmatic when there are problems with access to endoscopy." Although not addressed

> It seems logical that ustekinumab and golimumab should have also been included as options for first-line therapy for induction in the most recent ulcerative colitis guidelines, as both were as effective as infliximab and vedolizumab in the network meta-analysis and both are available in subcutaneous formulations.
>
> –Gary R. Lichtenstein, MD

Table 1. Key UC Guideline Recommendations for Moderate-to-Severe Ulcerative Colitis[11,16]

	ACG	AGA
Induction of remission in bio-naive patients	• Recommended therapies include oral budesonide MMX, oral systemic corticosteroids, anti-TNF therapy (adalimumab, golimumab, or infliximab), vedolizumab, or tofacitinib[a] • Recommend against thiopurine monotherapy or methotrexate	• Infliximab, adalimumab, golimumab, vedolizumab, tofacitinib,[a] or ustekinumab are recommended over no treatment • Suggest using infliximab or vedolizumab rather than adalimumab in bio-naive patients, although adalimumab is a reasonable alternative in those who place higher value on the convenience of self-administered subcutaneous injection • Recommend against thiopurine monotherapy or methotrexate
Induction of remission in TNF-α antagonist-experienced patients	• Vedolizumab or tofacitinib • Recommendation applies to all anti-TNF therapies, but recommends reactive drug level measurement to assess the reason for loss of response and, if the level is therapeutic, switch out of class	• Ustekinumab or tofacitinib • Recommendation just for scenario of previous exposure and loss of response or no response to infliximab • No recommendation for loss of response to golimumab or adalimumab since no reliable data
Maintenance of remission	• After steroid induction of remission, maintenance with thiopurines is better than no treatment • Recommendation against steroids or methotrexate as maintenance therapy	• No recommendation in favor of, or against, using biologic monotherapy (TNF-α antagonists or vedolizumab) or tofacitinib, rather than thiopurine monotherapy, for maintenance of remission • Due to different design of maintenance trials, no comparative effectiveness meta-analysis of different agents possible • Methotrexate should not be used for maintenance of remission
Combination therapy	• Combine infliximab therapy with a thiopurine during induction	• Suggest combining TNF-α antagonists, vedolizumab, or ustekinumab with thiopurines or methotrexate, rather than biologic monotherapy

ACG, American College of Gastroenterology; AGA, American Gastroenterological Association; FDA, US Food and Drug Administration; TNF, tumor necrosis factor.

[a]FDA recommendation in July 2019 on tofacitinib labeling restricts its use to patients who have failed or are intolerant to anti-TNF therapies.

in the AGA guidelines, the ACG suggests the use of fecal calprotectin as a surrogate for endoscopy to assess for mucosal healing when endoscopy is not feasible or available.[16]

Inducing and Maintaining Remission in UC: Do the Guidelines Agree?

Despite the many similarities, there are a number of inconsistencies in the recommendations regarding the management of moderate-to-severe UC between the ACG and AGA guidelines (Table 1).[11,16] Whereas the ACG recommends the use of prednisone or oral budesonide MMX for induction of remission,[16] the AGA does not address these therapies given its focus on immunosuppressives, biologics, and small-molecule therapies. However, despite being "the drugs that everyone loves to hate," Dr Feagan commented that "steroids are excellent induction drugs and good therapies to add on to biologics to get rapid symptomatic remission." He continued, "It is imperative to get patients to symptomatic remission, and if you have to use steroids to get there—using cessation of bleeding as a marker—you should use them."

Several inconsistencies regarding recommendations for induction therapy exist between the ACG and AGA guidelines. Dr Sandborn commented that "there are a number of ambiguities in the recommendations for moderate-to-severe UC that require discussion and context to apply them in practice." While both guidelines consider tumor necrosis factor alpha (TNF-α) antagonists, vedolizumab, tofacitinib, and ustekinumab as options for biologic-naive patients, the AGA suggests the use of infliximab or vedolizumab over adalimumab for induction in this setting, a conditional recommendation based on results of a network meta-analysis and the landmark VARSITY trial.[11,18,47] Given that the only significant difference noted between therapies in the network meta-analysis in this population was between adalimumab and infliximab (Figure 4),[18] the absence of ustekinumab and golimumab in this recommendation has been questioned, particularly as both agents can be considered for subcutaneous convenience. Similar discrepancies exist in the recommendations for TNF-α antagonist–experienced patients, with ustekinumab or tofacitinib recommended by the AGA and tofacitinib or vedolizumab recommended by the ACG. Commenting on this, Dr Sandborn noted that "the absence of ustekinumab for bio-experienced induction in the ACG guidelines means those guidelines are out of date."

Incorporating Combination Therapy Into Practice

The TNF-α antagonists are relatively

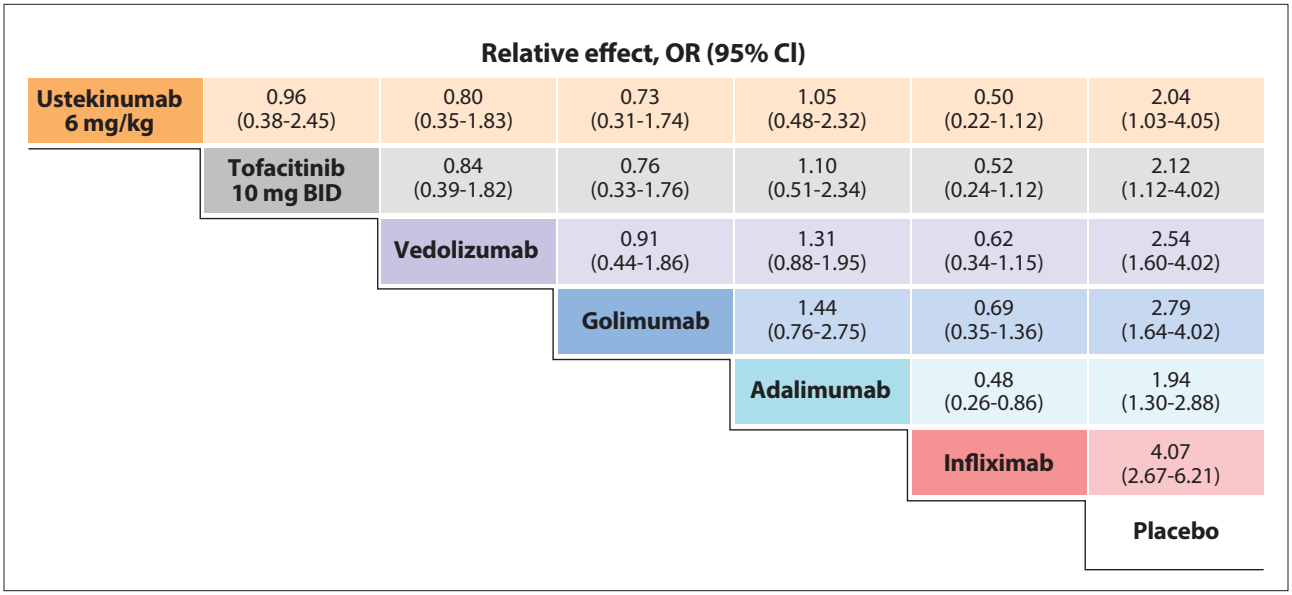

Figure 4. AGA technical review network meta-analysis: GRADE summary of findings reporting the comparative efficacy of different pharmacologic agents for inducing clinical remission in biologic-naive patients with moderate-to-severe ulcerative colitis.[18] AGA, American Gastroenterological Association; BID, twice daily; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio.

immunogenic, and combination therapy is essential, if tolerated, to prevent immunogenicity and loss of efficacy. Analyses of data from large pivotal trials have demonstrated reduced antibody formation, higher serum concentrations of TNF-α antagonists, and greater clinical benefit when immunosuppressive therapies are combined with these agents.[48-50] Most notably, the landmark prospective UC-SUCCESS trial clearly demonstrated the superiority of combination infliximab/thiopurine therapy compared with either agent as monotherapy.[31] Accordingly, the ACG and AGA guidelines agree that TNF-α antagonists should be combined with immunosuppressives during induction.[11,16]

In contrast, the benefit of combination therapy for the newer monoclonal antibodies has not been studied in prospective controlled trials. Post hoc subanalysis of data from the GEMINI trial found reduced immunogenicity of vedolizumab when combined with immunomodulators; however, only 3.7% of patients had samples that were positive for anti-vedolizumab antibodies at any time.[51] Similarly, the immunogenicity of ustekinumab appears to be minimal. A recent analysis of 680 patients treated with ustekinumab demonstrated a reduction in antibody formation with concomitant immunosuppressives from 6.8% (33 of 487 patients) to 3.1% (6 of 193 patients), a difference that did not influence the median serum ustekinumab concentration.[52] A recent retrospective study of 912 patients with IBD (263 with UC, 286 with Crohn's disease) found no difference in clinical response or remission with combination therapy compared with either vedolizumab or ustekinumab as monotherapy (Figure 5).[53] Of interest, the AGA guidelines suggest that vedolizumab or ustekinumab can also benefit from combination with immunosuppressives, a recommendation based on post hoc analyses.[11] Given the minimal immunogenicity of these agents and the lack of prospective, controlled trials evaluating combination therapy with these therapies, this recommendation has not been met with universal agreement.

> Combination therapy is essential with anti-TNF therapies, but in my opinion, there is not enough evidence to suggest that combination therapy is necessary to optimize efficacy with ustekinumab or vedolizumab.
> –William J. Sandborn, MD

Is Combination Therapy for a Lifetime?

The optimal duration of combination therapy is an important area of uncertainty, as there are currently very limited prospective data to guide decision-making.[54-56] However, Dr Feagan noted that "there is a large randomized controlled trial fully recruited in Europe that should help answer this question." Although he speculates that combination therapy will prove to be superior over time, he added that given the risks of thiopurines, his practice

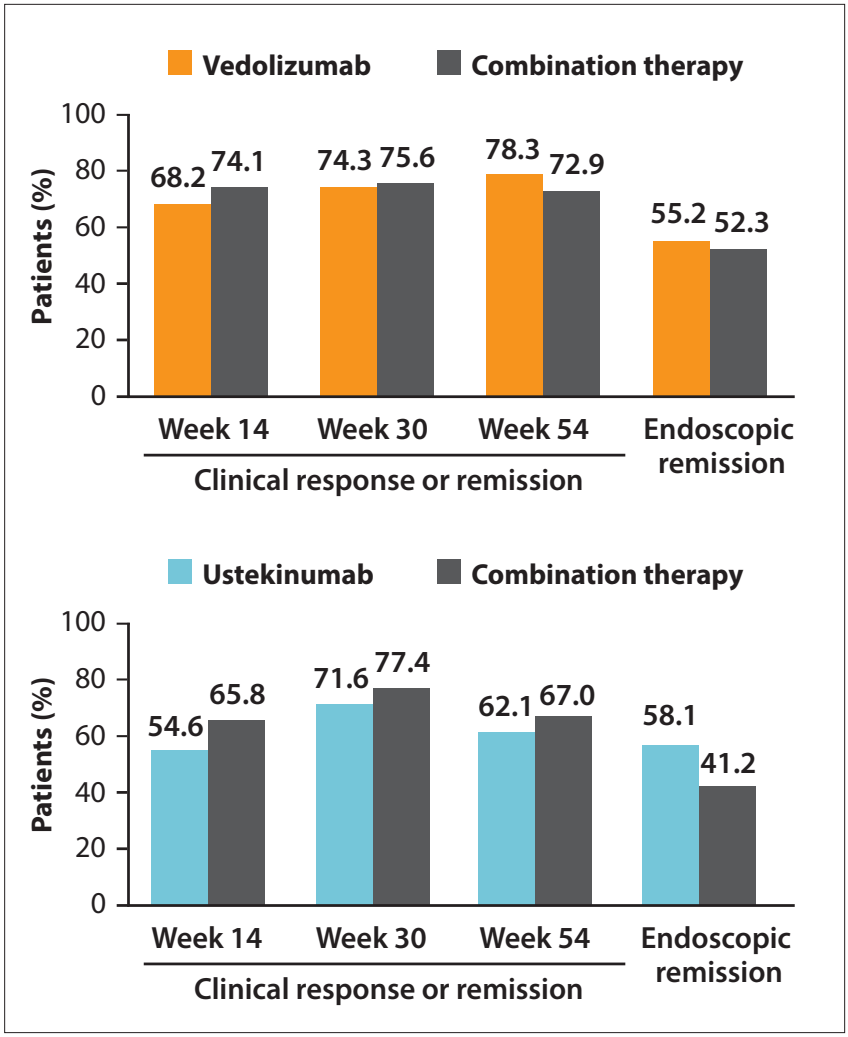

Figure 5. Outcome with combination therapy compared with monotherapy for vedolizumab and ustekinumab in patients with inflammatory bowel disease.[53]

is to discontinue azathioprine in his patients who are older than 60 years. Dr Sandborn agreed that his practice is to discontinue thiopurines and switch to monotherapy in patients after they reach 60 to 65 years of age.

Positioning Therapies in UC

With the availability of several classes of biologics and targeted therapies with demonstrated efficacy in UC, positioning different agents in the treatment course of patients can be challenging.[57] Although clinical practice guidelines effectively synthesize the evidence regarding efficacy and safety of these therapies, they offer limited guidance on choosing the optimal first- and second-line therapies for individual patients. Commenting on this, Dr Sandborn noted that "All the tightening of the guideline process and adding other stakeholders doesn't solve the underlying problem, which is a lack of data to help distinguish what is similarly effective and what drugs you should use in what order." Such decisions require consideration of the advantages and limitations of each therapy in the context of patients' values, preferences, and clinical circumstances. Beyond efficacy, key factors that may inform clinical decision-making include the rapidity of action, safety, safety in pregnancy, route of administration, effect on extraintestinal manifestations (EIMs), and cost/access (Table 2).[58,59]

The TNF-α antagonists have been the mainstay of treatment for IBD for more than 20 years, and robust data support their efficacy in achieving and maintaining clinical and endoscopic remission, improving quality of life, reducing hospitalizations and surgeries, and managing EIMs in UC.[16,58,60-65] These therapies are also effective in managing postoperative patients at high risk for recurrence.[58] However, as previously mentioned, these agents are considerably immunogenic and require concomitant immunosuppression to maintain response.[11,16,59] The most important safety concern with TNF-α antagonists is the risk for serious infection, which may be reduced by screening for hepatitis B and tuberculosis and ensuring appropriate immunization before initiating treatment.[59]

Vedolizumab has emerged as a first-line agent for moderate-to-severe UC due to its efficacy, favorable safety profile, and low rate of immunogenicity.[58,59,66] Ustekinumab, recently approved for use in UC,[67] also offers excellent safety with low immunogenicity.[59] Given their safety profile, these agents may be preferred over less targeted therapies, such as TNF-α antagonists, in elderly patients or those with a history of malignancy or infectious complications.[58]

Unlike the biologics, tofacitinib is an oral small-molecule inhibitor that has demonstrated a notably rapid onset of action, with some patients in phase 3 trials achieving meaningful improvement in the partial Mayo score in as early as 2 weeks.[68] Key safety concerns with tofacitinib include the risk for infection, particularly reactivation of herpes zoster; hyperlipidemia; and thromboembolic risks.[16,68,69] Data indicating an increased risk for deep venous thromboembolism and pulmonary embolism associated with tofacitinib in patients with rheumatoid arthritis recently prompted the addition of a warning to the product labeling.[69] In light of this risk, the indication for tofacitinib has been designated a

Table 2. Key UC Guideline Recommendations for Moderate to Severe Ulcerative Colitis[58,59,67,69-72]

	TNF-α Antagonist Therapies	Vedolizumab	Ustekinumab	Tofacitinib
Benefits	• Speed of onset (infliximab) • Subcutaneous convenience (adalimumab, golimumab) • TDM-based dose adjustments • Treats EIMs • Excellent data in pregnancy • No increased risk for solid malignancies	• Gut-specific • Excellent safety profile • Low immunogenicity • Live vaccines	• Excellent safety profile • Subcutaneous convenience (q8w) • Low immunogenicity • Treats associated conditions (eg, psoriasis)	• Oral • Rapid onset • No immunogenicity • Stable pharmacokinetics
Limitations	• Increased risk for infections • Increased risk for skin cancer (if co-administered with thiopurines) and non-Hodgkin lymphoma • High immunogenicity and need for concomitant immunosuppression	• Initially thought to have slower onset of action • May not be effective for EIMs	• Limited data on treating EIMs	• Not approved for biologic-naive patients[a] • DVT/PE risk to be defined • Herpes zoster • Cytopenias • No experience in pregnancy

DVT, deep venous thrombosis; EIMs, extraintestinal manifestations; FDA, US Food and Drug Administration; PE, pulmonary embolism; TDM, therapeutic drug monitoring; TNF tumor necrosis factor.

[a]FDA recommendation in July 2019 on tofacitinib labeling restricts its use to patients who have failed or are intolerant to anti-TNF therapies.

second-line therapy after failure or intolerance to TNF-α antagonists.[69]

Putting It All Together: From Guideline to Bedside

Although both the ACG and AGA clinical practice guidelines effectively summarize the science to inform clinical decisions, it is incumbent on the practicing clinician to successfully translate the science to patient care. To that end, it is important to interpret the guidelines in the context of how they are developed and the data used for their development. Although current UC guidelines are based on the highest quality evidence available, clinical trials are not always reflective of clinical practice. For example, some of the most common symptoms experienced by patients with UC (eg, fatigue/low energy, abdominal bloating/fullness, nausea, loss of appetite) are not routinely captured by clinical trials.[73] Dr Sandborn added that the current guideline recommendations are to some degree based on symptomatic data rather than composite clinical and endoscopic data consistent with a treat-to-target strategy.

Transforming guideline recommendations into a clinical decision for individual patients requires interpretation of the guidelines in the context of an individual patient's clinical circumstances, values, and preferences.[2] As Dr Sandborn explained, "you have to realize that guidelines are guidelines. They're not the *Bible*. You have to use common sense and judgment, and you should be familiar with the high points of the primary literature and decide for yourself in the context of an individual patient because the patient in front of you may not exactly represent the patients that were studied in the clinical trials." The need to tailor clinical decisions may be greater in the face of conditional recommendations and uncertain evidence.[2] Shared decision-making is also important in such situations, and clinicians are encouraged to discuss the risk and benefits of various options in the context of patient preferences.[2]

> Our guidelines are largely based on symptom data, which are somewhat divorced from STRIDE-1 and -2 guidelines about treat-to-target. There's a big disconnect between what we're doing in clinical practice and what was done in the clinical trials.
> –William J. Sandborn, MD

> You have to put the pros and cons in aggregate and see what this means for the patient. Look at the guidelines and put them in context of how they're written.
> –Gary R. Lichtenstein, MD

Conclusions

The process for developing guidelines has improved dramatically over the past decades, evolving from an informal, consensus-based method to a multidisciplinary approach focused on linking graded recommendations to the supporting evidence. Accordingly, the current guidelines for UC management developed by the ACG and AGA provide a shortcut to the evidence for practicing clinicians to facilitate clinical decision-making. However, translating guideline recommendations effectively into practice requires that they be interpreted in the context of how they were written, as well as in the evolving treatment landscape of UC. Notably, with the growing emphasis on altering the natural history of the disease, early intervention for high-risk patients and a treat-to-target strategy in UC are becoming foundations of optimal therapy. Finally, clinicians are encouraged to utilize the UC guidelines to help them combine the best clinical science with their best clinical judgment tailored to their individual patients' clinical circumstances, values, and preferences.

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Post Test & Evaluation