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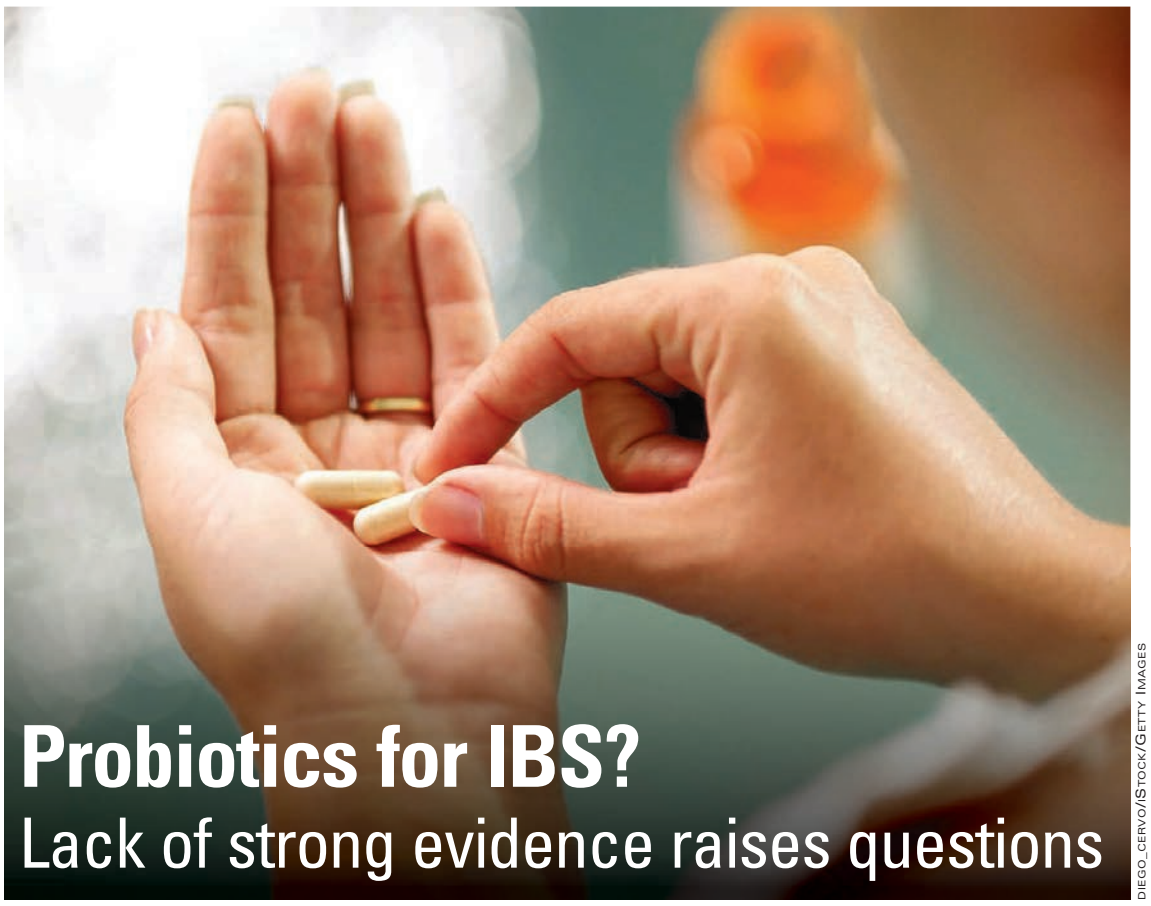

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Probiotics for IBS?

Lack of strong evidence raises questions

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

A variety of probiotics may relieve symptoms in patients with irritable bowel syndrome (IBS), but most evidence from randomized controlled trials remains low certainty or very low certainty, with many studies suffering from bias, according to a recent review and meta-analysis.

These shortcomings in the probiotic research landscape should be kept in mind when making treatment recommendations, reported researchers who were led by Alexander C. Ford, MBChB, of the Leeds Gastroenterology Institute, University of Leeds (England). They suggested these issues need to be addressed in the methodology of future clinical trials.

"Although multiple probiotics have been tested in IBS in randomized controlled trials, understanding of which probiotics may be beneficial is limited," the investigators wrote in Gastroenterology (2023 Aug 2. doi: 10.1053/j.gastro.2023.07.018).

They noted that previous efforts – including their own – to meta-analyze these findings have been hindered by a scarcity of trial

See **IBS** · *page 9*

FDA OKs two new treatments for UC

BY MEGAN BROOKS

The Food and Drug Administration has approved two new treatments for patients with ulcerative colitis (UC).

In October, the FDA approved etrasimod (Velsipity, Pfizer) for moderate to severe active UC in adults. Etrasimod, an oral sphingosine-1-phosphate (S1P) receptor, binds with high affinity to receptors 1, 4, and 5. It is the second agent in the S1P class approved for UC. The other agent, ozanimod (Zeposia, Bristol-Myers Squibb), which was approved for moderate to severe active UC in May 2021, is an S1P receptor modulator that is selective for the S1P1 and S1P5 receptors located on endothelial cells and oligodendrocytes, respectively.

Etrasimod's approval was based on safety and efficacy data from two randomized, double-blind, placebo-controlled phase 3 trials — ELEVATE UC 52 trial, and ELEVATE UC 12 trial. The Lancet published full results from the two trials on March 2. Both trials enrolled patients with UC who had previously failed or were intolerant of at least one conventional, biologic, or Janus kinase (JAK) inhibitor therapy.

In ELEVATE UC 52, clinical remission at 12 weeks occurred in 27% of patients taking etrasimod, vs 7% of patients taking a placebo (20% difference; $P < .001$). At week 52, remission rates were 32% with active treatment, vs. 7% with placebo (26% difference; $P < .001$).

In ELEVATE UC 12, clinical remission was achieved among 26% of patients who received etrasimod, vs 15.0% of patients who received placebo (11% difference; $P < .05$).

Statistically significant improvements were also observed with etrasimod (vs. placebo) on all key secondary endpoints, including endoscopic

See **FDA** · *page 9*

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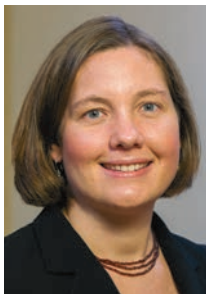
LETTER FROM THE EDITOR

The supply-demand mismatch in GI

Among the many healthcare system vulnerabilities exposed by the COVID-19 pandemic is the growing mismatch between the supply of healthcare providers and the growing population-level demand for care.

We feel the impact of this supply-demand mismatch daily in our GI practices as we strive to expand access in our clinics and endoscopy suites, particularly in rural and urban underserved communities. In gastroenterology, increased demand for care has been driven by a perfect storm of population growth, increased patient awareness of GI health, and rising incidence of digestive diseases.


Dr. Adams

Between 2019 and 2034, the U.S. population is expected to grow by 10.6%, and the population aged 65 and older by over 42%. Recent increases in the CRC screening–eligible population also have contributed to unprecedented demand for GI care. Furthermore, care delivery has become more complex and time-consuming with the evolution of personalized medicine and high prevalence of comorbid conditions. At the same time, we are faced with a dwindling supply of gastroenterology providers. In 2021, there were 15,678 practicing gastroenterologists in the U.S., over half of whom were 55 years or older. This translates to one gastroenterologist per 20,830 people captured in the U.S. Census.

Addressing this supply-demand mismatch in GI requires a multipronged approach that addresses its complex drivers. First and foremost, we must expand the number of GI fellowship training slots to boost our pipeline. There are approximately 1,840 GI fellows currently in training, one-third of whom enter the workforce each year. While the number of fellowship slots in the GI fellowship match has slowly increased over time (from 525 available slots across 199 programs in 2019 to 657 slots across 230 programs in 2023), this incremental growth is dwarfed by overall need. Continued advocacy for increased funding to support the expansion of training slots is necessary to move the needle. Such lobbying recently led to the addition of 1,000 new Medicare-supported graduate medical education positions across specialties over a 5-year period starting in 2020, illustrating that change is possible. At the same time, we must address the factors that are causing gastroenterologists to leave the workforce prematurely through early retirement or part-time work by investing in innovative solutions to address burnout, reduce administrative burdens, enhance the efficiency of care delivery, and maintain financial viability. By investing in our physician workforce and its sustainability, we can ensure that our profession is better prepared to meet the needs of our growing and increasingly complex patient population now and in the future.

We hope you enjoy the November issue of GI & Hepatology News and have a wonderful Thanksgiving. ■

Megan A. Adams, MD, JD, MSc
Editor-in-Chief

Talking to your patients about CRC screening

Patients may be confused by conflicting guidance about when to start colorectal cancer screening. AGA stands firmly behind recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer (MSTF), the American Cancer Society, and other national medical societies and advocacy organizations, that colorectal cancer screening for average risk individuals should start at age 45.

What should you say to your patients who may be confused by conflicting news reports?

Consider these talking points:

1) Colorectal cancer will be the leading cause of cancer-related death among 20- to 49-year-olds by 2030. Putting off screening until age 50 may be a grave mistake.

2) Screening for colorectal cancer can help find polyps early, sometimes even before they become cancer.

3) There are several tests for colorectal cancer screening, including colonoscopy, but there are also tests that are noninvasive.

For more resources to share with your patients, visit the AGA GI Patient Center at https://patient.gastro.org/. ■

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High interest in probiotics for IBS

IBS *from page 1*

data coupled with heterogeneity across probiotic strains, combinations, and doses, resulting in clinical uncertainty.

"... making recommendations concerning which probiotics, or combinations of probiotics, are beneficial according to IBS subtype or individual symptom has been difficult to date," they wrote.

To narrow this knowledge gap, the researchers conducted an updated systematic review and meta-analysis with newly identified trials.

"There is continued interest in the role of probiotics in the management of IBS, as evidenced by the publication of more than 20 new randomized clinical trials since the prior version of this meta-analysis in 2018."

"There is continued interest in the role of probiotics in the management of IBS, as evidenced by the publication of more than 20 new randomized controlled trials since the prior version of this meta-analysis in 2018," they wrote.

The new dataset included 82 RCTs comprising 10,332 patients with IBS. Along with safety, three separate efficacy endpoints were evaluated: global symptoms, abdominal pain, and abdominal bloating or distension.

For global symptoms, moderate certainty evidence supported the efficacy of *Escherichia coli* strains; low certainty data supported *Lactobacillus plantarum* 299V and other *Lactobacillus* strains; and very low certainty evidence supported *Bacillus, LacClean Gold S*, and *Duolac 7s* strains, and combination probiotics.

For abdominal pain, low certainty evidence supported *Bifidobacterium* strains and *Saccharomyces cerevisiae* I-3856. Very low certainty data supported *Lactobacillus*, *Saccharomyces*, and *Bacillus* strains, and combination probiotics.

Very low certainty evidence supported the benefits of *Bacillus* strains and combination probiotics for alleviating abdominal bloating or distension.

In a safety analysis of 55 trials involving more than 7,000 patients, risk of adverse events was no higher for probiotics than placebo.

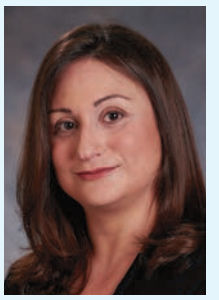
"Our analyses provide some support for the use of certain probiotics in IBS, and also for particular strains for specific symptoms," the investigators wrote. "However, there is a paucity of data for their use in patients with IBS-C [IBS with constipation], with only 7 RCTs reporting efficacy in this subtype, and no evidence of efficacy in any of these analyses. Their use in patients with IBS-C is, therefore, not supported by current evidence."

A broader discussion in the publication called out the general lack of high certainty evidence in this area of clinical research.

"Only 24 of 82 eligible RCTs were low risk of bias across all domains, and there was significant heterogeneity between trials in many of our analyses, as well as evidence of publication bias, or other small study effects, in some of our analyses," the researchers wrote. "The fact that few of the included studies were low risk of bias across all domains should be borne in mind when making treatment recommendations."

The investigators disclosed relationships with Salix, Biocodex, 4D Pharma, and others. ■

IBS patients frequently inquire about probiotics. As a clinician, this can be difficult to address. A search of the literature yields numerous small trials. Turning to the guidelines does not help, as the AGA Clinical Practice Guidelines on Probiotics offer no recommendations for IBS due to the low quality of evidence. Nevertheless, we have patients who want to try probiotics. Some of these patients have had inadequate responses to first-line therapies and/or prefer a nonpharmacological approach.



Dr. Videlock

What should we recommend? This updated systematic review and meta-analysis by Goodoory and colleagues includes 82 trials with data from over 10,000 patients. The authors use new methodology to impute dichotomous outcomes which incorporates 46 additional trials in pooled analyses. While the overall conclusions are similar to prior "low" or "very low" certainty of evidence across the board, strain-specific analyses highlight several probiotics that appear efficacious. The manuscript in combination with the extensive supplement can serve as a roadmap for clinicians to make informed recommendations about probiotics to IBS patients.

For example, the strain with the most trials was *Lactobacillus plantarum* 299V. The dose used (10 billion CFU once daily) is commercially available (Jarrow Formulas Ideal Bowel Support® LP299V®). *Bacillus* strains were also promising for global symptoms, abdominal pain and bloating. Two trials used the same strain and dose, *Bacillus coagulans* MTCC 5856, 2 billion CFU once daily, also commercially available (LactoSpore). Both can be purchased via major online retailers for $10-13 for a 30-day supply. I am glad to have something to recommend however conditionally.

Elizabeth (Beth) Videlock, MD, PhD, is assistant professor of medicine in the Vatche and Tamar Manoukian Division of Digestive Diseases at the University of California Los Angeles (UCLA) and a staff physician in Gastroenterology in the Greater Los Angeles Veterans Affairs (VA) Healthcare System. She is co-lead of the Neurodevelopmental and Neurodegenerative Diseases Research Program of the Goodman-Luskin Microbiome Center at UCLA. She has no relevant disclosures.

New treatments for ulcerative colitis

FDA *from page 1*

improvement and mucosal healing at weeks 12 and 52, and corticosteroid-free remission and sustained clinical remission at week 52.

The approved recommended dose is 2 mg once daily.

The most common side effects of etrasimod are headache, elevated values on liver tests, worsening of UC, SARS-CoV-2 infection, dizziness, pyrexia, arthralgia, abdominal pain, and nausea. Full prescribing information is available online.

FDA approves subcutaneous vedolizumab for maintenance therapy

In September, the FDA approved the subcutaneous administration of vedolizumab (Entyvio SC, Takeda) for maintenance therapy in adults with moderately to severely active UC after induction therapy with intravenous administration of vedolizumab. It may be available this fall as a single-dose prefilled pen (Entyvio Pen).

The approval of subcutaneous (SC) vedolizumab was based on results from the phase 3, randomized, double-blind, placebo-controlled VISIBLE 1 trial. The trial assessed the safety and efficacy of maintenance therapy with SC vedolizumab in adult patients with moderately to severely active UC who achieved clinical response at week 6 following two doses of intravenous vedolizumab.

At week 6, 162 patients were randomly allocated (2:1) to vedolizumab or placebo by subcutaneous injection every 2 weeks. The primary endpoint was clinical remission at week 52, defined as a total Mayo score of 2 or less and no individual subscore greater than 1.

At week 52, nearly half (46%) of patients who received vedolizumab SC maintenance therapy achieved clinical remission, compared with 14% of those who received placebo SC ($P < .001$).

The safety profile of SC vedolizumab was "generally consistent" with that of intravenous vedolizumab, with the addition of injection-site reactions, the drugmaker, Takeda, said in a news release.

The most common adverse reactions are nasopharyngitis, headache, arthralgia, nausea, pyrexia (fever), upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in the extremities. ■

The role of neutrophils in Wilson's disease

Research focuses on inhibiting their function

BY WILL PASS
MDedge News

FROM CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

Modulating N2-neutrophil activity could offer a new therapeutic approach to Wilson's disease, according to a preclinical study.

Inhibiting neutrophil function via transforming growth factor (TGF-beta-1) inhibition or methylation inhibition reduced parenchymal liver fibrosis and injury while improving liver function in a mouse model of Wilson's disease, shows new research published in Cellular and Molecular Gastroenterology and Hepatology (2023 Jul 2. doi: 10.1016/j.jcmgh.2023.06.012).

Also called progressive hepatolenticular degeneration, Wilson's disease is an inherited nervous system disorder that can lead to liver disease.

It is caused by variants in the ATP7B gene which can lead to abnormalities in copper metabolism that lead to accumulation of the heavy metal in the liver and brain, resulting in damage to both organs. Approximately 60% of patients with Wilson's disease present with hepatic syndromes, and of those 50%-60% go on to develop liver cirrhosis.

Current treatments aim to address metal deposition, but this approach is poorly tolerated by many patients, wrote investigators who were led by Junping Shi, MD, PhD, of the Institute of Hepatology and Metabolic Diseases, The Affiliated Hospital of Hangzhou (China) Normal University.

"Drug interventions (such as copper chelators and zinc salts) reduce pathologic copper deposition, but side effects can be observed in up to 40% of patients during treatment and even after years of treatment, particularly nephropathy, autoimmune conditions, and skin changes," the investigators wrote. "Liver transplantation is an effective treatment for Wilson's disease, particularly for patients with end-stage liver disease, but donor shortages and lifelong immunosuppression limit its use. Therefore, alternative treatments with higher specificity in Wilson's disease patients are urgently needed."

"Neutrophil heterogeneity shows therapeutic potential, and pharmacologic modulation of N2-neutrophil activity should be explored as an alternative therapeutic to improve liver function in Wilson's disease."

The present study explored the underlying metabolic abnormalities in Wilson's disease that result in liver injury and fibrosis, and related therapeutic approaches. Based on previous studies that have shown a relationship between persistent neutrophil infiltration and chronic tissue inflammation and damage, the investigators sought to explore the role of neutrophils in Wilson's disease, with a focus on the N2 subtype.

First, they analyzed neutrophil populations in the livers of Atp7b–/– mice and atp7b–/– zebrafish, both of which are established animal models of Wilson's disease. Compared with the wild-type comparison animals, the livers of disease model animals showed increased neutrophil infiltration, in terms of both count and density.

In one of several related experiments, administering a neutrophil agonist in the presence of copper led to significantly greater neutrophil infiltration in mutant versus wild-type fish, as well as greater increases in lipid droplets and disorganized tissue structure, which serve as markers of disease activity.

"Collectively, these data suggested that neutrophils infiltrated the liver and accelerated liver defects in Wilson's disease," the investigators wrote.

Additional experiments with the mouse model showed that pharmacologic ablation of N2 neutrophils via two approaches led to reduced liver fibrosis, offering a glimpse at therapeutic potential. These findings were further supported by experiments involving a cellular model of Wilson's disease with isolated bone marrow neutrophils. "Neutrophil heterogeneity shows therapeutic potential, and pharmacologic modulation of N2-neutrophil activity should be explored as an alternative therapeutic to improve liver function in Wilson's disease," the investigators concluded, noting that TGFβ1, DNMT3A, or STAT3 could all serve as rational therapeutic targets.

The authors disclosed no conflicts of interest. ■

The treatment of Wilson disease relies on use of chelators (D-pencilliamine; trientine) that promote urinary copper excretion and zinc, which blocks intestinal absorption.

These drugs, which must be taken continuously, are effective but are associated with significant side effects.

Another chelator, bis-choline-tetrathiomolybdate (TTM), promotes biliary, rather than urinary copper excretion.

Dr. Pack

TTM improved neurological function in clinical trials; however, dose-dependent transaminase elevations were noted.

Thus, there is a need to identify new therapeutic approaches to reduce impact of copper toxicity in hepatocytes.

In the current issue of CMGH, Mi and colleagues utilize zebrafish and mouse models of Wilson disease to generate novel insights into the pathogenesis and molecular basis of liver injury and fibrosis caused by ATP7B mutations.

"...it will be important to determine whether this pharmacologically modifiable signaling pathway is activated in patients with Wilson's disease..."

In the zebrafish model, they first showed that fluorescently labeled neutrophils accumulate in the livers of live, mutant animals, which are transparent, and thus, uniquely suited to these studies.

Gene expression analyses showed that the liver neutrophils are metabolically active and sensitize hepatocytes to copper-induced injury, thus providing a therapeutic rational for neutrophil inhibition.

Next, the authors confirmed these findings in the mouse model, showing specifically that the N2-neutrophil subtype predominated and correlated with the degree of liver injury.

Subsequent gene expression studies in the mouse, combined with in vitro analysis of bone marrow–derived neutrophils, identified a molecular signaling pathway originating in hepatocytes that triggered N2 differentiation.

This pathway, which was previously shown to drive N2 differentiation in cancer models, involves TGF-beta induced methylation (and hence repression) of a gene (SOCS3) that itself, blocks expression of STAT3, a gene that drives N2 differentiation.

Importantly, liver injury and fibrosis were reduced in the mouse model by drugs that inhibit TGF-beta or DNA methylation, and hence N2 differentiation, or by directly blocking the activity of N2 neutrophils.

In summary, this new study not only provides novel insights into the pathogenesis and potential treatment of Wilson disease, but also demonstrates how signaling pathways, such as the one involving TGF-beta-SOCS3-STAT3, are reiteratively used in a variety of pathologic contexts.

In future, it will be important to determine whether this pharmacologically modifiable signaling pathway is activated in patients with Wilson's disease, and whether it impacts the pathogenesis of more common liver disorders.

Michael Pack, MD, is professor of medicine at Perelman School of Medicine, University of Pennsylvania, Philadelphia. He has no conflicts.

Findings support BAS for microscopic colitis

Bile acid sequestrants have not yet been tested in clinical trials for the condition

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Approximately two out of three patients with microscopic colitis respond to bile acid sequestrants (BAS), and therapy is generally well tolerated, based on a recent retrospective study.

The findings support BAS treatment in patients with microscopic colitis who fail first-line therapy, or have intolerance to those agents, wrote researchers who were led by Darrell S. Pardi, MD, AGAF, a gastroenterologist with Mayo Clinic, Rochester, Minn. The American Gastroenterological Association has refrained from issuing recommendations for BAS monotherapy in microscopic colitis (MC) due to lack of evidence. The AGA recommends budesonide as first-line therapy for patients with moderate to severe symptoms of MC. However, the treatment is associated with a high rate of relapse (40%-81%) once the patient stops taking the drug. Its long-term use is associated with a risk of side effects.

"At present, there are no randomized controlled trials that have evaluated the efficacy of BAS monotherapy for MC," investigators wrote in Clinical Gastroenterology and Hepatology (2023 May 10. doi: 10.1016/j.cgh.2023.04.031).

The study analyzed data from 282 patients (88.3% women) with microscopic colitis treated between 2010 to 2020. Bile acid malabsorption was defined by elevated serum 7α-hydroxy-4-cholesten-3-one or by fecal testing. After a median follow-up of 4.5 years, cholestyramine was the most prescribed BAS (64.9%), followed by colesevelam (21.6%) and colestipol (13.5%). Approximately half of the patients achieved a complete response (49.3%), while 16.3% had a partial response. Nonresponders accounted for 24.8% of the population, and 9.6% of patients did not tolerate BAS therapy. These outcomes were not significantly impacted by BAS dose or combination with other agents.

After discontinuing BAS, 41.6% of patients had recurrence in a median of 21 weeks. The findings suggest that BAS is a valid second-line option with a favorable risk-benefit profile, and an elevated dose appears unnecessary to achieve clinical response.

The authors suggested that BAS may be particularly useful as long-term maintenance therapy for patients wishing to avoid prolonged corticosteroid exposure.

Dr. Pardi has recevied grant funding from Pfizer, Vedanta, Seres, Finch, among others. And, consulted for Vedanta, Seres, and others. ■

Despite being increasingly recognized and diagnosed, there remains a scantiness of studies addressing therapeutic options in microscopic colitis (MC). Oral budesonide is recommended as first-line option; however, there is a high relapse rate after budesonide discontinuation, some patients are intolerant, and there is concern for steroid toxicity associated with long-term exposure.


Dr. Torres

While the cause of MC remains elusive, there is a rationale to suggest that bile acids may play a role in disease pathogenesis. Not only are BA important signaling molecules, acting in inflammation and metabolism, but also prior small studies reported on BA malabsorption co-existing in MC, with variable response rates to BA sequestrants.

This retrospective large study of 282 patients with MC showed that almost two-thirds of patients will present a complete or partial response to BA sequestrant therapy (cholestyramine, colesevelam, and colestipol).

For those that relapsed following BA therapy discontinuation, re-treatment was successful in the majority of cases.

Therapy was well tolerated, however caution is needed, as it can interfere with absorption of other medications, and in the long-term also with fat-soluble vitamins. It remains to be determined which patients could benefit the most from BA therapy, since no predictors of response were identified, nor was response associated with BA malabsorption. Nonetheless, this study shows that BA therapy could be an attractive option for steroid-dependent, steroid refractory or intolerant MC patients potentially worth trying before embarking on immunosuppressive or biological therapy. It also highlights the need for carefully conducted clinical trials exploring other options beyond budesonide for this chronic and debilitating condition.

Joana Torres, MD, PhD, is a consultant gastroenterologist at Hospital Beatriz Angelo and Hospital da Luz in Portugal and assistant professor in Uniersidade de Lisboa, Portugal. She has no conflicts.

Nano drug delivery could overcome toxicity in HCC

The treatment could enable safer, more effective therapy in hepatocellular carcinoma

BY WILL PASS
MDedge News

FROM GASTRO HEP ADVANCES

Employing a targeted nano drug delivery system for patients with hepatocellular carcinoma (HCC) could overcome issues with liver toxicity, leading to safer treatment and better outcomes, according to a recent review.

Nanomedicines homing in on the Wnt/beta-catenin signaling pathway could be particularly impactful, Mamatha Bhat, MD, PhD, a hepatologist and clinician-scientist at Toronto General Hospital Research Institute, and colleagues reported, as this is one of the most up-regulated pathways in HCC.

To date, however, agents addressing this pathway have been hindered by off-target toxicity, suggesting that more work is needed to develop the right payload for nanoparticle delivery, the investigators wrote in Gastro Hep Advances (2023 Jul 20. doi: 10.1016/j.gastha.2023.07.012).

"Although nanotherapeutics offers an unmatched improvement in drug delivery, due to the limited impact and treatment-resistance demonstrated by the current systemic therapies, there is currently no approved nanomedicine for the treatment of HCC," the investigators wrote. "Therefore, it is of utmost importance to dig deeper into understanding the signaling pathways that govern hepatocarcinogenesis and identify novel targets that can be used to develop more specific and targeted nanotherapies."

Their review focused on the Wnt/beta-catenin signaling pathway, but first, Dr. Bhat and colleagues discussed the characteristics of inorganic versus lipid nanoparticles, as these differences can determine liver uptake.

Inorganic nanoparticles have a high surface-to-volume ratio, leading to increased surface charges that enhance cellular uptake. However, they are prone to oxidation, requiring surface modifications or short circulation times to prevent degradation. These nanoparticles are limited in delivering chemotherapeutic drugs and peptides, and are not suitable for encapsulating nucleic acids.

In contrast, lipid nanoparticles are preferred for targeted delivery in HCC, according to the investigators. They have a natural affinity for apolipoprotein E (apo E), resembling lipoproteins, which aids in specific liver cell targeting. When lipid nanoparticles enter the bloodstream, they interact with apo E–rich lipoproteins like HDL cholesterol and LDL cholesterol, leading to

Continued on following page

AGA issues CPU for CRC screening and surveillance

Consider age, family history, hereditary syndromes, prior screening, predisposing conditions

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

The American Gastroenterological Association has published a Clinical Practice Update with new best practice advice for colorectal cancer (CRC) screening and postpolypectomy surveillance.

Led by Rachel B. Issaka, MD, of Fred Hutchinson Cancer Center, Seattle, the Clinical Practice Update focuses primarily on time frames for surveillance based on known risk factors, plus a caution against widespread use of emerging risk-stratification tools that need more real-world evidence among diverse populations.

"Based on current evidence, risk stratification for initiating CRC screening or surveillance should be based on age, family history, predisposing hereditary CRC syndromes, prior screening, or other CRC predisposing conditions," the authors wrote in Gastroenterology (2023 Sep 21. doi: 10.1053/j.gastro.2023.06.033).

With these parameters in mind, Dr. Issaka and colleagues issued nine best practice advice statements, noting that systematic reviews were not conducted, so statements are not rated based on quality of evidence or strength of presented considerations.

Authors characterized two risk strata for CRC. Individuals with a first-degree relative who was diagnosed with CRC, should be considered at increased risk of CRC, particularly if that relative was diagnosed before age 50. In contrast, people with no such family history, or a personal history of CRC, hereditary CRC syndromes, inflammatory bowel disease, or other predisposing conditions, should be considered average risk for CRC.

Those with average risk should start CRC screening at age 45, while those with increased risk should start screening at age 40, or 10 years before the age of diagnosis of their youngest affected relative, whichever is sooner.

"The age to initiate screening according to family history of CRC could be optimized based on the number of affected family members, age at diagnosis of the affected relatives, as well as the 10-year cumulative incidence of CRC according to age within a specific source population (e.g., country)," the investigators wrote. "However, in the absence of widely available risk calculators developed for such risk-adapted screenings, a simplified approach to consider is initiating screening approximately 10 years before the age of diagnosis of the youngest affected relative or at age 40 years."

The decision to screen and conduct postpolypectomy surveillance beyond age 75 should factor in risks, benefits, screening history, and comorbidities. Individuals with average risk can choose between several options for screening based on preference and availability, including fecal immunochemical test, colonoscopy, flexible sigmoidoscopy plus fecal immunochemical test, multitarget stool DNA fecal immunochemical test, and computed tomography colonography, authors wrote. Those with high risk, however, should undergo colonoscopy.

The final best practice advice statement offers a word of caution against widespread use of new risk-stratification tools for CRC and postpolypectomy surveillance that have yet to demonstrate real-world effectiveness and cost-effectiveness in diverse populations.

Investigators disclosed relationships with Geneoscopy, CellMax Life, and Universal Diagnostics, among others. ■

Continued from previous page

formation of complexes recognized by LDL cholesterol receptors on liver cells. This triggers receptor-mediated endocytosis, internalizing apo E–lipid nanoparticle complexes into HCC cells.

The other major variable is the selected treatment target. Dr. Bhat and colleagues made the case for the Wnt/beta-catenin signaling pathway based on alterations found in approximately two-thirds of patients with HCC.

"Aberrant activation of this pathway and mutations in genes encoding key components are characteristic to hepatocarcinogenesis and promote tumor growth and dedifferentiation," they wrote.

Although beta-catenin itself makes for an obvious molecular target, especially considering known associations with drug resistance, its flat structure lacks deep binding pockets that would be suitable for small-molecule inhibitors, and any available pockets may be altered by numerous posttranscriptional modifications. Instead, beta-catenin could be indirectly modulated by nanoparticle-mediated siRNA therapy, as this would allow for precise delivery of siRNA to cancer cells, minimizing off-target toxicity.

Alternative approaches could involve targeting proteasomal degradation of beta-catenin, transcriptional coactivators of beta-catenin, or different oncogenes in HCC, all of which are described in further detail in the review, along with promising preclinical findings.

"With ongoing advancements in nanotechnology, there is optimism that it will continue to play a vital role in overcoming the challenges associated with HCC management and contribute to further advancements in therapeutic outcomes for patients," the authors concluded.

One coauthor disclosed external funding by a Mitacs Elevate postdoctoral fellowship in collaboration with Highland Therapeutics. The remaining authors disclosed no conflicts of interest. ■

Hepatocellular carcinoma remains a major health problem associate with increasing prevalence and mortality rates worldwide. Around 50%-60% of HCC patients are exposed to systemic therapies during their natural history. Atezolizumab plus bevacizumab (median OS; 19.2 mo, ORR, 30%), and durvalumab plus tremelimumab (median OS, 16.4 mo; ORR, 20%) are considered first line treatment options for advanced HCC, and sorafenib or lenvatinib are recommended for patients with any contraindication for immune checkpoint inhibitors. These therapies are indicated for "all comers" and no molecular markers /personalize medicine are currently available for this cancer. The lack of precision oncology relates to the fact that the most common mutations (i.e., TERT, TP53, CTNNB1) are unactionable targets. In this scenario, advances in precision oncology are an unmet medical need.


Dr. Llovet

The Wnt/B-catenin signaling pathway is a master regulator of oncogenesis in HCC and defines one of the molecular subclasses characterized by CTNNB1 mutations (~25%-30%) or AXIN1 mutations (~5%-10%). Most of these tumors have an immune excluded/desert phenotype. Thus, targeting this pathway is expected to provide a primary antitumoral effect along with an immune-modulatory effect rescuing cases with an immune-excluded phenotype.

In this review, the authors discuss the applicability of precision oncology in HCC targeting the WNT/B-catenin pathway by inhibiting the interaction with transcriptional coactivators of B-catenin such as CBP and TCF or by enhancing the proteasomal degradation of B-catenin, reducing pathway activation, with drugs like Tankyrase inhibitors and casein kinase 1a activators. These approaches are challenging due to its associated off-target toxicity and its complexity. To overcome these caveats, the author propose to utilize nanotechnology to deliver Wnt inhibitors, an approach that currently requires further research to refine the most promising strategies and drugs suitable for clinical implementation.

Josep M. Llovet, MD, PhD, FAASLD, director, Mount Sinai Liver Cancer Program in New York, and head of translational research in the Liver Cancer Group, Liver Unit, IDIBAPS, Hospital Clínic Barcelona. Dr. Llovet receives research support from Bayer Pharmaceuticals, Eisai Inc, Bristol-Myers Squibb, and Ipsen.

Member SPOTLIGHT

Advancing personalized medicine in IBD

BY JENNIFER LUBELL
MDedge News

Ask Joanna Melia, MD, what her biggest practice challenge is, and she'd say the need for more precision medicine in inflammatory bowel disease.

Gastroenterologists have more treatments at their disposal today than ever before, particularly in the last decade. "We have had tremendous advances in many areas of understanding contributors to disease," said Dr. Melia, an assistant professor of medicine at Johns Hopkins Medicine in Baltimore who specializes in inflammatory bowel disease (IBD). But the hurdle is in translating the science to clinical care that is individualized to each patient based on condition and stage of the condition.

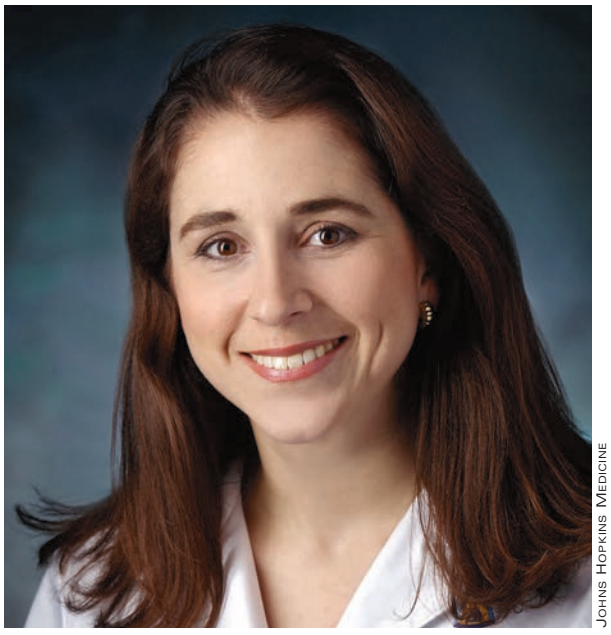
"That still remains a bit of a dream," she said. Much of her career has been devoted to chasing down a particular genetic variant that contributes to IBD, with the goal of reaching more precise treatments for patients.

In an interview, she shared how she entered this line of work, and what her research has revealed about Crohn's disease, manganese, and a common genetic variant known as ZIP8.

Q: Your expertise is in inflammatory bowel disease and manganese deficiency. Why these two areas?

Dr. Melia: In talking to many patients with IBD, I was always struck by the questions around nutritional factors related to disease. As a fellow, I was embedded in a lab that focused on genetics of IBD. A micronutrient transporter, ZIP8, has a mutation in it that increases the risk of Crohn's disease.

I've dedicated the last 8 years to understanding how this mutation can increase risk. It initially started out as a project focused on zinc, because that's what the transporter was thought to regulate. However, it's evolved as we've learned more about it, underscoring the importance of manganese, another micronutrient that we derive from food.



Johns Hopkins Medicine

Dr. Joanna Melia

We have established that having this mutation changes how the body handles manganese and affects downstream processes that involve manganese. What I'm doing now is trying to connect those dots on why those processes are important in Crohn's disease and whether we can target them for treatment.

Q: How does manganese deficiency lead to IBD?

Dr. Melia: In individuals with this mutation, their blood manganese levels are lower than people who don't have this mutation. When we talk about manganese deficiency or insufficiency, what we're really talking about is lower blood levels. But it's more complicated than that at the tissue level.

What we and other groups are working on right now is trying to understand if the manganese levels change in the gut and what happens in inflammation. The gut is a particularly interesting area for manganese, in that much of the manganese that we eat is excreted. We only absorb a small amount of it. And so, manganese levels within the gut lumen may actually be quite high – and may be even higher in inflammation. But there are things we don't understand about that and how it relates to mucosal levels of manganese and Crohn's disease. The ileum, the site of the Crohn's disease that's specifically associated with this mutation, might be particularly sensitive to changes in the manganese levels or the downstream processes that changing manganese availability affects.

One of those processes is glycosylation. Manganese is important to properly glycosylate your proteins. Many enzymes help cells put sugars on proteins, and many of those enzymes need manganese to do it. Glycosylation of proteins is important so cells know where those proteins should go, and the sugars help them stay where they need to be. When you change protein glycosylation, you can stress the cells. We know individuals who carry this mutation have changes in the glycosylation of their proteins. What we're working on right now is understanding which key proteins might change when that happens, and why that's a potential problem, especially in the ileum.

Q: How might your research inform practice?

Dr. Melia: We've seen significant progress in new medications and new pathways that have emerged. We still have this fundamental problem that our immune-targeting medicines are only helping about 50% of the patients.

It's critical that we begin to identify new pathways. And my hope is that in studying genes like the ZIP8 (SLC39A8), which is associated with the dysregulation of manganese, we can understand different pathways and mechanisms to target.

If we could help correct the glycosylation problem, that would help to boost the barrier function of the gut and perhaps decrease the activation of those immune cells, because you're just reinforcing the barrier integrity of the gut.

We want to target that glycosylation problem as we would treat patients with congenital disorders of glycosylation by giving supplemental sugars. We think this problem of glycosylation extends beyond patients with the ZIP8 mutation, but it is also really important for patients with the mutation. So, the goal would be to use ZIP8 genetics to help prioritize patients for therapy targeting this problem.

Q: You're involved in the American Gastroenterological Association Future Leaders Program. What is your role in this program? Why is it important?

Dr. Melia: I was very grateful for the opportunity to participate in the AGA's Future Leaders Program. I think it was exceedingly valuable for two main reasons.

One, it really offered an insight into the role of the AGA and the important role that the AGA plays in the careers of gastroenterologists. Two, it was such a unique opportunity to work with colleagues nationwide and to build a network of individuals who are all at a similar stage in their careers. It was a very inspiring group to meet and to have the opportunity to work with as part of that program, and I thank the AGA for supporting such an initiative. ■

Lightning round

Do you prefer texting or talking?
Texting

If you weren't a gastroenterologist, what would you be?
Teacher

What was the last movie you watched?
Great Bear Rainforest

What is your favorite city in the U.S.?
Surry, Maine

What song do you absolutely have to sing along with when you hear it?
Any song by Whitney Houston

Are you an introvert or extrovert?
Introvert

How many cups of coffee do you drink per day?
One

Call for Nominations

Member SPOTLIGHT

Nominate your colleagues to be featured in Member Spotlight. Email GIHepNews@gastro.org

AGA patient and physician advocates visit Capitol Hill to push for prior authorization reform

Five patients and nearly 50 physician members of the American Gastroenterological Association recently traveled to Washington, D.C., to meet with lawmakers on Capitol Hill and urge them to advance legislation reforming prior authorization and other health insurance barriers.

In our first in-person Advocacy Day on Capitol Hill since 2019, AGA leaders and patient advocates from 22 total states met with House and Senate offices to educate members of Congress and their staff about policies affecting GI patient care such as prior authorization and step therapy. Federal research funding and Medicare reimbursement were also on the agenda.

In the meetings, the patients shared their stories of living with various gastrointestinal diseases, including ulcerative colitis and Crohn's disease, and the struggles they've gone through to get treatments approved by their insurers.

AGA

AGA members ready to advocate on behalf of GI, left to right: Dr. Rachel Issaka, AGA President Barbara Jung, AGA Government Affairs Committee Chair Rotonya Carr, Dr. Omeed Alipour, and Dr. Carol Murakami.

AGA physicians shared the provider perspective of how policies like prior authorization negatively impact practices. According to a 2023 AGA member survey, 95% of respondents say that prior authorization restrictions have impacted patient access to clinically appropriate treatments and patient clinical outcomes and 84% described that the burden associated with prior authorization policies have increased "significantly" or "somewhat" over the last 5 years.

AGA's advocacy day came not long after UnitedHealthcare's announcement of a new "Gold Card" prior authorization policy to be implemented in 2024, which will impact most colonoscopies and endoscopies for its 27 million commercial beneficiaries. The group expressed serious concerns about the proposed policy to lawmakers.

"It was a wonderful and empowering experience to share my personal story with my Representative/Senator and know that they were really listening to my concerns about insurer overreach," said Aaron Blocker, a Crohn's disease patient and advocate. "I hope Congress acts swiftly on passing prior authorization reform, so no more patients are forced to live in pain while they wait for treatments to be approved."

As gastroenterologists, we spend too much administrative time submitting onerous prior authorization requests on a near daily basis. We hope Congress takes our concerns seriously and comes together to rein in prior authorization.

AGA thanks the patient and physician advocates who participated in this year's Advocacy Day and looks forward to continuing our work to ensure timely access to care. ■

New AGA podcast series explores the latest in *C. difficile*

Staying up to date on the latest in *Clostridioides difficile* is critical for providing the best possible care for your patients, as it is one of the most commonly reported bacterial infections. AGA's new on-demand program, "*C. difficile*: Preparing the Field for Change," is a six-part podcast series that outlines effective approaches to patient-centered care that will transform your practice.

Each 30-minute episode delves into a different topic – from microbiome therapy and fecal microbiota transplantation to documenting patient history – that will help you improve patient outcomes and reduce the risk of complications.

Tune in and subscribe to our channel Inside Scope wherever you listen to podcasts (Apple or Google). To claim CME credit for listening, visit AGA University (agau.gastro.org).

This series is supported by educational grants from Aimmune Therapeutics, Seres Therapeutics, and Ferring Pharmaceuticals. ■

Honor a loved one and support the AGA Research Awards Program

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Did you know that you can honor a family member, friend, or colleague through a gift to the AGA Research Foundation? A simple, flexible, and versatile way to ensure the AGA Research Foundation can continue our work for years to come is a gift in your will or living trust, known as a charitable bequest. To make a charitable gift in a will, you need a current will or living trust. You can include a gift in your will or living trust stating that a specific asset, certain dollar amount, or, more commonly, a percentage of your estate will pass to the AGA in honor of your loved one.

We hope you'll consider including a gift to the AGA Research Foundation in your will or living trust. It's simple, just a few sentences in your will or trust are all that is needed.

The official bequest language for the AGA Research Foundation is: "I, [name], of [city, state, ZIP], give, devise, and bequeath to the AGA Research Foundation [written amount or percentage of the estate or description of property] for its unrestricted use and purpose."

For more information on how to give and recognize your loved one, visit http://gastro.planmylegacy.org/.

Consider joining the AGA Legacy Society to support GI research

The AGA Legacy Society honors individuals who have chosen to benefit the AGA Research Foundation through a significant current or planned gift.

"The AGA Research Foundation is focused on all research, including basic, clinical, and translational. This means their research is the underpinning of future patient care," said Lawrence S. Kim, MD, AGAF, vice president of the AGA Institute and a member of the AGA Legacy Society.

Members can pledge to contribute $25,000 or more in cash or securities within a 5-year period. Or, members can provide a contribution of $50,000 or more through a deferred gift (planned gift) such as a bequest, a charitable trust, a gift of life insurance, or others.

For more information, see https://shorturl.at/fmPR8.

Selecting therapies for moderate to severe inflammatory bowel disease

Key factors in decision-making

In Focus
Brought To You By The New Gastroenterologist

BY ARIELA K. HOLMER, MD, SHANNON CHANG, MD, MBA, AND LISA MALTER, MD

With an expanding armamentarium of biologics and small molecules, selecting therapies in the treatment of inflammatory bowel disease (IBD) has become increasingly complex. Despite new advances in treatment, head-to-head clinical trials, which are considered the gold standard when comparing therapies, remain limited. Other comparative effectiveness studies and network meta-analyses are the currently available substitutes to guide decision-making.[1]

While efficacy is often considered first when choosing a drug, other critical factors play a role in tailoring a treatment plan. This article focuses on key considerations to help guide clinical decision-making when treating patients with moderate to severe IBD (Figure 1).

Disease activity versus severity

Both disease activity and disease severity should be considered when evaluating a patient for treatment. Disease activity is a cross-sectional view of one's signs and symptoms which can vary visit to visit. Standardized indices measure disease activity in both Crohn's disease (CD) and ulcerative colitis (UC).[2,3] Disease severity encompasses the overall prognosis of disease over time and includes factors such as the presence or absence of high-risk features, prior medication exposure, history of surgery, hospitalizations and the impact on quality of life.[4]

For prevention of disease complications, the goals of treatment should be aimed at both reducing active symptoms (disease activity) and healing mucosal inflammation, preventing disease progression (disease severity) and downstream sequelae including cancer, hospitalization, or surgery.[5] Determining the best treatment option takes disease activity and severity into account, in addition to the other key factors listed (Figure 2).

Extraintestinal manifestations

Inflammation of organs outside of the gastrointestinal tract is common and can occur in up to 50% of patients with IBD.[6] The most prevalent extraintestinal manifestations (EIMs) involve the skin and joints, which will be the primary focus in this article. We will also focus on treatment options with the most evidence supporting their use. Peripheral arthritis is often associated with intestinal inflammation, and treatment of underlying IBD can simultaneously improve joint symptoms. Conversely, axial spondyloarthritis does not commonly parallel intestinal inflammation. Anti–tumor necrosis factor (TNF) agents including infliximab and adalimumab are effective for the treatment of both peripheral and axial disease.[6]

Ustekinumab, an interleukin (IL)-12/23 inhibitor, may be effective for peripheral arthritis; however, it is ineffective for the treatment of axial spondyloarthritis.[6] Janus kinase (JAK) inhibitors which include tofacitinib and upadacitinib are oral small molecules used to treat peripheral and axial spondyloarthritis and have more recently been approved for moderate to severe IBD.[6,7]

Erythema nodosum and pyoderma gangrenosum are skin manifestations seen in patients with IBD. EN appears as subcutaneous nodules and parallels intestinal inflammation, while PG consists of violaceous, ulcerated plaques, and presents with more significant pain. Anti-TNFs are effective for both EN and PG, with infliximab being the only biologic studied in a randomized control trial of patients with PG.[8] In addition, small case reports have described some benefit from ustekinumab and upadacitinib in the treatment of PG.[9,10]

Dr. Holmer is a gastroenterologist with NYU Langone Health specializing in inflammatory bowel disease. **Dr. Chang** is director of clinical operations for the NYU Langone Health Inflammatory Bowel Disease Center. **Dr. Malter** is director of education for the Inflammatory Bowel Disease Center at NYU Langone Health and director of the inflammatory bowel disease program at Bellevue Hospital Center, New York.

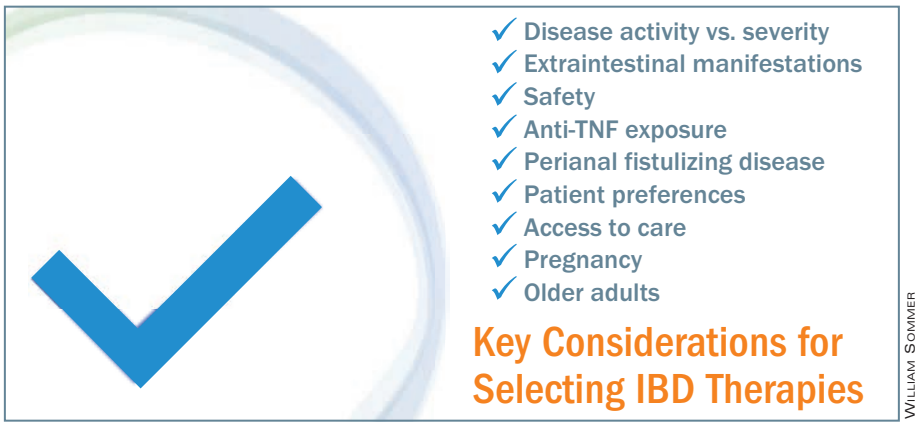

Figure 1

Safety

The safety of IBD therapies is a key consideration and often the most important factor to patients when choosing a treatment option. It is important to note that untreated disease is associated with significant morbidity, and should be weighed when discussing risks of medications with patients. In general, anti-TNFs and JAK inhibitors may be associated with an increased risk of infection and malignancy,

With increasing options for the treatment of inflammatory bowel disease, choosing the "right" medication can be overwhelming. There are several factors beyond drug efficacy that should be considered, which contribute to the complexity of managing IBD.

In this issue of The New Gastroenterologist, Ariela K. Holmer, MD, Shannon Chang, MD, MBA, and Lisa Malter, MD, break down the factors guiding medication decision-making in moderate to severe IBD, such as disease activity and severity, extraintestinal manifestations, safety, prior drug exposure, perianal fistulizing disease, patient preference, and treatment access. This comprehensive yet digestible review will assist in individualizing IBD therapy in the inpatient and outpatient practice.

Judy A. Trieu, MD, MPH
Editor-in-Chief
The New Gastroenterologist

while ustekinumab, vedolizumab, risankizumab, and ozanimod offer a more favorable safety profile.[11] In large registries and observational studies, infliximab was associated with up to a two times greater risk of serious infection, compared with nonbiologic medications, with the most common infections being pneumonia, sepsis, and herpes zoster.[12] JAK inhibitors are associated with an increased risk of herpes zoster infection, with a dose-dependent effect seen in the maintenance clinical trials with tofacitinib.[7]

Ozanimod may be associated with atrioventricular conduction delays and bradycardia; however, long-term safety data have reported a low incidence of serious cardiac-related adverse events.[13] Overall, though risks of infection may vary with different therapies, other consistent risk factors associated with greater rates of serious infection include prolonged corticosteroid use, combination therapy with thiopurines, and disease severity. Anti-TNFs have also been associated with an increased risk of lymphoma, especially when used in combination with thiopurines. Reassuringly, however, in patients with a prior history of cancer, anti-TNFs and non-TNF biologics have not been found to increase the risk of new or recurrent cancer.[14] Ultimately, in patients with a prior history of cancer, the choice of biologic or small molecule should be made in collaboration with a patient's oncologist.

Anti-TNF exposure

Anti-TNFs were the first available biologics for the treatment of IBD. After the approval of vedolizumab in 2014, the first non-TNF biologic, many patients enrolled in clinical trials thereafter had already tried and failed anti-TNFs. Exposure to anti-TNFs may reduce the efficacy of a future biologic. In patients treated with vedolizumab, endoscopic and clinical outcomes were negatively impacted by prior anti-TNF exposure.[15] However, in VARSITY, a head-to-head clinical trial where 20% of patients with UC were previously exposed to anti-TNFs other than adalimumab, vedolizumab had significantly higher rates of clinical remission and endoscopic improvement, compared with adalimumab.[16] Clinical remission rates with tofacitinib were not impacted by exposure to anti-TNF treatment, and similar findings were observed with ustekinumab.[7,17] Risankizumab, a newly approved selective anti-IL23, also does not appear to be impacted by prior anti-TNF exposure by demonstrating similar rates of clinical remission regardless of biologic exposure status.[18] Therefore, in patients with prior history of anti-TNF use, consideration of ustekinumab, risankizumab, or JAK inhibitors as second-line agents may be more favorable, compared with vedolizumab.

Figure 2 – Treatment options for moderate to severe IBD

	Crohn's Disease		Ulcerative Colitis	
	Drug Class	Therapy	Drug Class	Therapy
Outpatient	Anti-TNF	Infliximab Adalimumab Certolizumab	Anti-TNF	Infliximab Adalimumab Golimumab
	Anti-integrin	Vedolizumab	Anti-integrin	Vedolizumab
	Anti-IL 12/23	Ustekinumab	Anti-IL 12/23	Ustekinumab
	Anti-IL 23	Risankizumab	–––	–––
	JAKi*	Upadacitinib	JAKi*	Tofacitinib Upadacitinib
	–––	–––	S1P	Ozanimod
Hospitalized Patients	–––	–––	Anti-TNF	Infliximab
	–––	–––	JAKi	Tofacitinib [32] Upadacitinib [33]
Perianal Fistulizing Disease	Anti-TNF	Infliximab Adalimumab	–––	–––
	Anti-IL 12/23	Ustekinumab	–––	–––
	JAKi*	Upadacitinib	–––	–––

*Patient must have failed or demonstrated intolerance to anti-TNF first

Source: Dr. Ariela K. Holmer, Dr. Shannon Chang, and Dr. Lisa Malter

MDEDGE NEWS

Perianal fistulizing disease

Perianal fistulizing disease can affect up to one-third of patients with CD and significantly impact a patient's quality of life.[19] The most robust data for the treatment of perianal fistulizing disease include the use of infliximab with up to one-third of patients on maintenance therapy achieving complete resolution of fistula drainage. While no head-to-head trials compare combination therapy with infliximab plus immunomodulators versus infliximab alone for this indication specifically, one observational study demonstrated higher rates of fistula closure with combination therapy, compared with infliximab monotherapy.[19] In a post hoc analysis, higher infliximab concentrations at week 14 were associated with greater fistula response and remission rates.[20] In patients with perianal disease, ustekinumab and vedolizumab may also be an effective treatment option by promoting resolution of fistula drainage.[21]

More recently, emerging data demonstrate that upadacitinib may be an excellent option as a second-line treatment for perianal disease in patients who have failed anti-TNF therapy. Use of upadacitinib was associated with greater rates of complete resolution of fistula drainage and higher rates of external fistula closure (Figure 2).[22] Lastly, as an alternative to medical therapy, mesenchymal stem cell therapy has also shown to improve fistula drainage and improve external fistula openings in patients with CD.[23] Stem cell therapy is available only through clinical trials in the United States at this time.

Patient preferences

Overall, data are lacking for evaluating patient preferences in treatment options for IBD especially with the recent increase in therapeutic options. One survey demonstrated that patient preferences were most impacted by the possibility of improving abdominal pain, with patients accepting additional risk of treatment side effects in order to reduce their abdominal pain.[24] An oral route of administration and improving fatigue and bowel urgency were similarly important to patients. Patient preferences can also be highly variable with some valuing avoidance of corticosteroid use while others valuing avoidance of symptoms or risks of medication side effects and surgery. It is important to tailor the discussion on treatment strategies to each individual patient and inquire about the patient's lifestyle, medical history, and value system, which may impact their treatment preferences utilizing shared decision-making.

Access to treatment including the role of social determinants of health

The expanded therapeutic armamentarium has the potential to help patients achieve the current goals of care in IBD. However, these medications are not available to all patients because of numerous barriers including step therapy payer policies, prohibitive costs, insurance prior authorizations, the role of social determinants of health, and proximity to IBD expertise.[25] While clinicians work with patients to determine the best treatment option, more often than not, the decision lies with the insurance payer. Step therapy is the protocol used by insurance companies that requires patients to try a lower-cost medication and fail to respond before they approve the originally requested treatment. This can lead to treatment delays, progression of disease, and disease complications. The option to incorporate the use of biosimilars, currently available for anti-TNFs, and other

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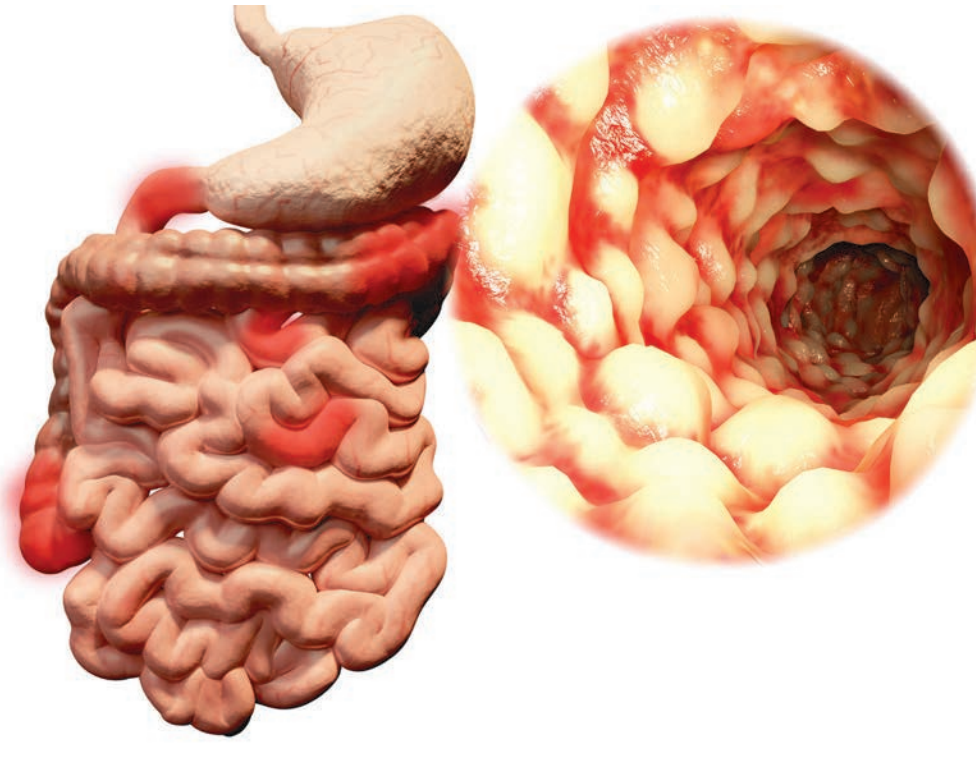

SELVANEGRA/ISTOCK/GETTY IMAGES

In Crohn's disease, specific areas of the gastrointestinal tract – highlighted here in red – tend to be more affected than other areas.

Continued from previous page

biologics in the near future, will reduce cost and potentially increase access.[26] Additionally, working with a clinical pharmacist to navigate access and utilize patient assistance programs may help overcome cost-related barriers to treatment and prevent delays in care.

Socioeconomic status has been shown to impact IBD disease outcomes, and compliance rates in treatment vary depending on race and ethnicity.[27] Certain racial and ethnic groups remain vulnerable and may require additional support to achieve treatment goals. For example, disparities in health literacy in patients with IBD have been demonstrated with older Black men at risk.[28] Additionally, the patient's proximity to their health care facility may impact treatment options. Most IBD centers are located in metropolitan areas and numerous "IBD deserts" exist, potentially limiting therapies for patients from more remote/rural settings.[29] Access to treatment and the interplay of social determinants of health can have a large role in therapy selection.

Special considerations: Pregnancy and older adults

Certain patient populations warrant special consideration when approaching treatment strategies. Pregnancy in IBD will not be addressed in full depth in this article; however, a key takeaway is that planning is critical and providers should emphasize the importance of steroid-free clinical remission for at least 3 months before conception.[30] Additionally, biologic use during pregnancy has not been shown to increase adverse fetal outcomes, thus it should be continued to minimize disease flare. Newer novel small molecules are generally avoided during pregnancy because of limited available safety data.

In discussions of treatment options with patients with IBD, it's important to individualize care and share the decision-making process with patients. Goals include healing intestinal inflammation and improving symptoms and quality of life.

Older adults are the largest growing patient population with IBD. Frailty, or a state of decreased reserve, is more commonly observed in older patients and has been shown to increase adverse events including hospitalization and mortality.[31] Ultimately reducing polypharmacy, ensuring adequate nutrition, minimizing corticosteroid exposure, and avoiding undertreatment of active IBD are all key in optimizing outcomes in an older patient with IBD.

Conclusion

When discussing treatment options with patients with IBD, it's important to individualize care and share the decision-making process with patients. Goals include improving symptoms and quality of life while working to achieve the goal of healing intestinal inflammation. In summary, this article can serve as a guide to clinicians for key factors in decision-making when selecting therapies in moderate to severe IBD. ■

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U.S. MSTF responds to ACP CRC guidance statement

The American College of Physicians published an updated colorectal cancer screening guidance statement in August in Annals of Internal Medicine (2023. doi: 10.7326/M23-0779) for asymptomatic average-risk adults. The guidance states that clinicians should start screening for CRC in asymptomatic average-risk adults at age 50 years, despite recommendations from the U.S. Multi-Society Task Force (MSTF) which recommends screening start at age 45. (The task force consists of representatives from the American Gastroenterological Association, the American College of Gastroenterology, and the American Society for Gastrointestinal Endoscopy.)

The ACP cited "the uncertainty around benefits and harms of screening in this population," yet, CRC is increasing among people 50 years old and younger. Cases are growing at such a pace that CRC is expected to be the leading cause of cancer-related death among 20- to 49-year-olds by 2030.

The MSTF followed-up with the following comment published in Annals of Internal Medicine:

"We are disappointed that the American College of Physicians (ACP) guides clinicians to consider not screening asymptomatic average-risk adults between the ages of 45 to 49 years for colorectal cancer (CRC). This contrasts with recommendations from multiple respected organizations, including the US-MSTF, the USPSTF, the ACG and the ACS. We are concerned that this statement may undermine efforts to increase CRC screening in the face of significant increases in the incidence of CRC in those under age 50, and emerging data showing the benefit of screening in this population.

"Accordingly, we ask your readers to consider the following. While epidemiologic trends in this age group are described as a 'small increase in CRC incidence,' this does not capture the actual magnitude of the public health burden of CRC in 45-49–year-olds. A recent study of CRC incidence rates from 2000-2015 demonstrated a 46% increase in CRC incidence between ages 49 and 50..."

Read the complete statement at https://shorturl.at/acltQ. ■

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