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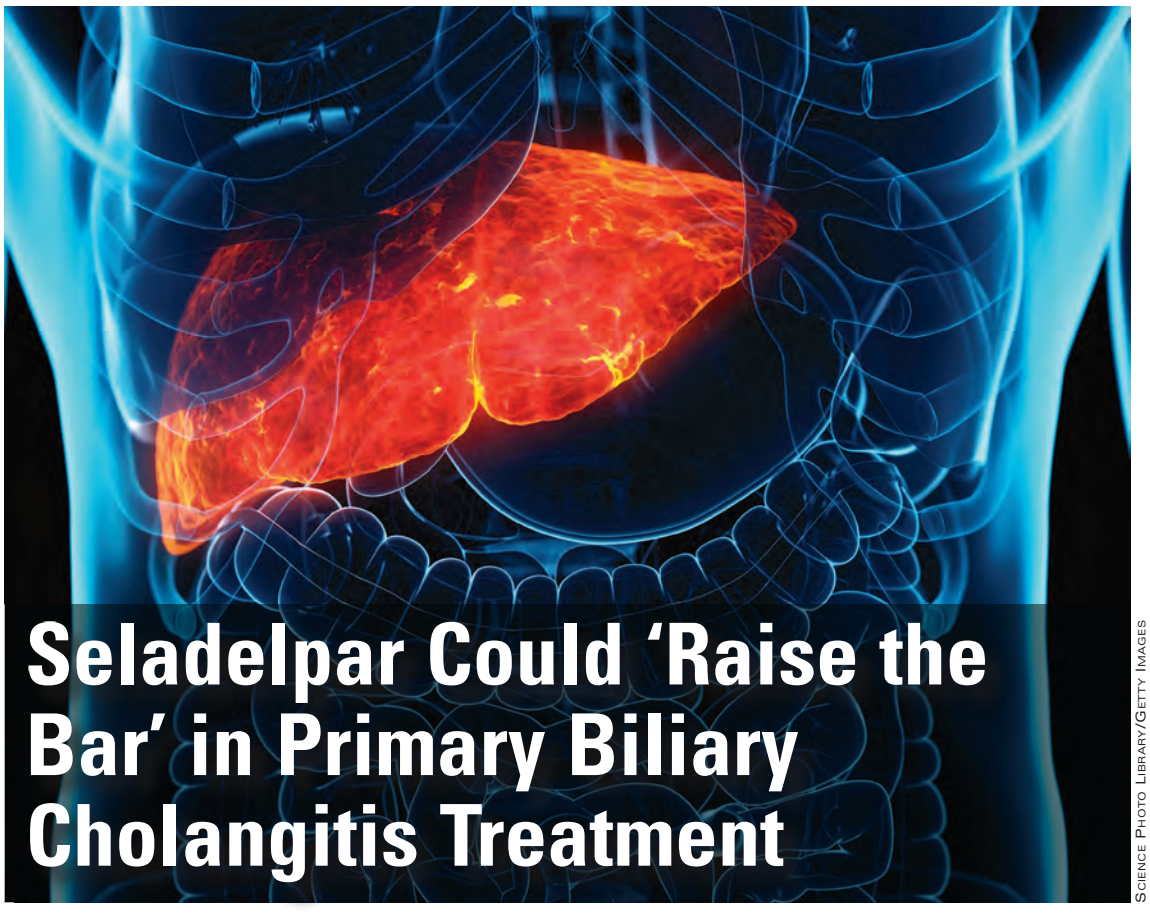

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Seladelpar Could 'Raise the Bar' in Primary Biliary Cholangitis Treatment

BY MEGAN BROOKS

Seladelpar, an investigational selective agonist of peroxisome proliferator–activated receptor-delta (PPAR-delta), significantly improves liver biomarkers of disease activity and bothersome symptoms of pruritus in adults with primary biliary cholangitis (PBC), according to the full results of the RESPONSE phase 3 study.

"At a dose of 10 mg daily, 1 in 4 patients normalize their alkaline phosphatase level," chief investigator Gideon Hirschfield, PhD, BM BChir, with the Toronto Center for Liver Disease at Toronto General Hospital, Toronto, Ontario, Canada, said in an interview.

The study data are "genuinely exciting ... and support the potential for seladelpar to raise the bar in PBC treatment," Dr. Hirschfield added in a news release.

Seladelpar is being developed by CymaBay Therapeutics, which funded the study.

The results were published online in *The New England Journal of Medicine* (2024 Feb 29. doi: 10.1056/NEJMoa2312100).

Topline data from the studywere presented in November at The Liver Meeting 2023: American Association for the Study of Liver Diseases.

See **Cholangitis** · *page 22*

Real-World Dupilumab Highly Effective in Refractory EoE

Symptoms improved in 91%

BY DIANA SWIFT
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Severe, refractory, and fibrostenotic eosinophilic esophagitis (EoE) responded well in the everyday clinical setting to the monoclonal antibody dupilumab (Dupixent). Most patients achieved histologic, endoscopic, and symptom improvement with a median of 6 months' treatment with the interleukin 4 and 13 blocker, and esophageal stricture diameter improved as well, according to a single-center retrospective study in *Clinical Gastroenterology and Hepatology* (2024 Feb. doi: 10.1016/j.cgh.2023.08.015).

"Dupilumab has real-world efficacy for a severe EoE population, most of whom would not have qualified for prior clinical trials," concluded gastroenterologists Christopher J. Lee, MD (lead author), and Evan S. Dellon, MD, MPH, AGAF, of the Center for Esophageal Diseases and Swallowing, at the University of North Carolina School of Medicine in Chapel Hill.

These real-world findings aligned with data from the group's phase 3 clinical trial (N Engl J Med. 2022 Dec 22. doi: 10.1056/NEJMoa2205982).

In addition, several case reports or series have highlighted the real-world efficacy of dupilumab, with a particular focus on pediatric patients (JPGN Reports. 2022 May. doi: 10.1097/PG9.0000000000000180) and those with other atopic diseases.

See **Dupilumab** · *page 21*

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LETTER FROM THE EDITOR

Congratulations to AGA's New Leaders

Each January, the AGA Nominating Committee meets to complete a very important task — namely, selection of new members of AGA's Governing Board, pending approval by the membership.

Having served on this committee in the past, I can attest to how challenging a task it is to select these leaders from such a talented and committed pool of candidates, each of whom has served the organization in numerous impactful roles over the course of many years.

This year's recently announced additions to the Governing Board, who will assume their roles this summer, include Dr. Byron Cryer (incoming Vice President), Dr. Shahnaz Sultan (Clinical Research Councillor), and Dr. Jonathan Rosenberg (Practice Councillor).

I have had the pleasure of working with each of them over the years from my very early days at AGA and am confident that AGA will continue to thrive under their leadership. Please join me in congratulating Byron, Shahnaz, and Jonathan on their new roles!

In this month's issue of *GIHN*, we highlight a phase 3 RCT from *NEJM* demonstrating the efficacy of seladelpar, an alternative to ursodeoxycholic acid in patients with PBC with refractory pruritus.

Dr. Adams

In this month's issue of *GIHN*, we highlight a phase 3 RCT from *NEJM* demonstrating the efficacy of seladelpar, an alternative to ursodeoxycholic acid in patients with PBC with refractory pruritus.

From the CGH Practice Management section, Dr. Michelle Kim (Cleveland Clinic) and colleagues provide helpful tips on how to optimize EHR use in GI practice, including by incorporating novel tools based on artificial intelligence, natural language processing, and speech recognition.

In our April *Member Spotlight*, we are excited to feature gastroenterologist and stand-up comedienne Dr. Shida Haghighat of UCLA, who shares her passion for addressing health disparities and highlights how humor helped her cope with the demands of medical training. We hope you enjoy these, and all the stories included in our April issue.

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

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FDA Emphasizes Alternative Device Sterilization

BY HEIDI SPLETE
MDedge News

The US Food and Drug Administration (FDA) has expanded its guidance on medical device sterilization to include vaporized hydrogen peroxide, according to an agency press release issued on January 8.

The update is intended to promote wider use of vaporized hydrogen peroxide (VHP) as a viable alternative to ethylene oxide (EtO). The FDA guidance on sterile devices has been revised to include VHP.

The acceptance of VHP as an Established Category A method of sterilization is another step toward the FDA's larger goal of reducing EtO use, according to the release.

Sterilization is essential for certain medical devices, but the use of EtO, currently the most common method, involves the release of emissions that are potentially harmful to health, and the FDA seeks to identify safe and effective alternatives to reduce risk to the environment and communities where device sterilization occurs. Current Established Category A sterilization methods include moist heat, dry heat, EtO, and radiation.

"Vaporized hydrogen peroxide's addition as an established sterilization method helps us build a more resilient supply chain for sterilized devices that can help prevent medical device shortages," Suzanne Schwartz, MD, director of the Office of Strategic Partnerships and Technology Innovation in the FDA's Center for Devices and Radiological Health, said in the press release.


Dr. Schwartz

"As innovations in sterilization advance, the FDA will continue to seek additional modalities that deliver safe and effective sterilization methods that best protect public health," she said.

The FDA has supported the development of EtO alternatives since 2019, and remains committed to reducing EtO emissions and also to avoiding potential device shortages, according to the release.

VHP Offers Welcome Alternative

"Ethylene oxide is highly flammable and carcinogenic and poses exposure-related safety concerns for reprocessing staff, as well as environmental risks," said Venkataraman R. Muthusamy, MD, AGAF, of the University of California, Los Angeles, in an interview. "These risks have led some states or regions to ban or limit its use, but despite these risks, it is currently the most commonly used sterilization technique for medical devices in the United States," he said. Therefore, coming up with alternatives has been a high priority for the FDA, he added.


Dr. Muthusamy

VHP has several advantages over EtO, Dr. Muthusamy said. VHP breaks down safely into water and oxygen, with low residual levels after exposure, and has no known oxidation or discoloration effects. In addition, VHP has a low temperature, and should theoretically be safe to use with endoscopes, although data are lacking.

Dr. Muthusamy said that he was not yet too familiar with VHP as a technique, in part because most accessories in GI are single-use.

Primary issues with expanding the use of vaporized hydrogen peroxide as a sterilizing agent in GI clinical practice include availability and the cost of acquiring the devices needed, Dr. Muthusamy told *GI & Hepatology News*. "Also, the comparative efficacy of this technique in sterilizing GI endoscopes to ethylene oxide and the impact of VHP on scope durability and performance will need to be assessed, and the impact of VHP on the health and safety of reprocessing staff will need to be assessed and monitored," he said.

There is an interest in the GI community in "green" endoscopy and reducing waste, Dr. Muthusamy said. If an inexpensive, safe, and cost-effective option for sterilization of other devices beyond endoscopes exists, "perhaps we could reduce our use of some disposables as well," he said.

Dr. Muthusamy had no financial conflicts to disclose. ■

How to Optimize EHR Use in Gastroenterology Practices

BY MARILYNN LARKIN

Implementing strategies to optimize electronic health record (EHR) use can save time, improve the doctor-patient relationship, and reduce burnout, a new practice management article suggests.

Michelle Kang Kim, MD, PhD, AGAF, chair of gastroenterology at Cleveland Clinic, Ohio, and colleagues provide EHR improvement strategies and examples that can be adapted for use in a variety of gastroenterology clinic settings.


Dr. Kim

Their article, which was published online in *Clinical Gastroenterology and Hepatology* (2023 Dec. doi: 10.1016/j.cgh.2023.12.002), includes the following suggestions, among others:

- Develop optimization teams. An example is SPRINT, a short, intensive team-based intervention at the University of Colorado Health, Aurora, Colorado, that developed specialty-specific tools, provided EHR efficiency training, and helped streamline workflows. The optimization project increased EHR satisfaction scores and reduced documentation time.
- Reroute low-acuity messages. Low-risk medication refills or appointment requests can be handled by nurses and medical assistants. This strategy has helped reduce the inbox burden.
- Create order sets for complex treatment dosing. One example is Cleveland Clinic's *Helicobacter pylori* order set, which enables clinicians to quickly place orders with built-in dosages.
- Personalize EHR drop-down menus. Incorporate inflammatory bowel disease (IBD) severity scores, biopsy sampling, resection protocols, specimen container numbering, and other workflow-specific documentation into the EHR.
- Employ medical scribes. These professionals can serve as personal assistants, supporting care teams and reducing clinician documentation time. Alternatively, clinical support staff, such as nurses, can assist with documentation and messages, helping to reduce physician burnout. "These models could be particularly useful in GI specialties that require a multidisciplinary approach, for example, IBD and hepatology," the authors write.
- Provide real-time training on best practices. There is no widely accepted EHR training curriculum for students, and experienced physicians face time constraints in learning new practices. Real-time training can help clinicians at all levels optimize their time outside the clinic.

In addition, the authors addressed novel tools and strategies that have been recently deployed and/or are in development, which are based largely on artificial intelligence (AI), natural language processing, and speech recognition. For now, these tools are digitizing data to help automate some EHR tasks, supporting communications with patients, and assisting in clinical decision-making.

Reroute low-acuity messages. Low-risk medication refills or appointment requests can be handled by nurses and medical assistants. This strategy has helped reduce the inbox burden.

However, the authors note that, although current optimization tools are promising, "there is still a lack of knowledge about their usability and effects on provider and patient well-being. More research is needed to evaluate current methodologies and design intelligent tools for the future that will help GI providers overcome the EHR-related obstacles specific to our field and harness the enormous potential of AI in optimizing the busy GI practice."

This work received no external funding, and the authors disclosed no conflicts. ■

Kris V. Kowdley, MD, AGAF, FAASLD, FACP, FACG

Director, Liver Institute Northwest
Seattle, Washington

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2/2024 NON-US-003675

Primary Biliary Cholangitis: Managing a Progressive Liver Disease

Primary biliary cholangitis (PBC) is a progressive autoimmune liver disease that specifically targets biliary epithelial cells (BECs). Characteristic findings in PBC are bile duct injury, features of cholestasis, and hepatic fibrosis, usually accompanied by the presence of antimitochondrial antibody (AMA) in 90% to 95% of patients.[1,2] Disease course and progression rates are highly variable among individual patients.[3] PBC develops due to epigenetic or environmental triggers in genetically susceptible individuals **(Figure 1)**.[3,4]

In PBC, an aberrant immune response to PDC-E2–expressing BECs damages bile ducts. Further evidence supports a direct pathogenic effect of AMA on hepatobiliary tissues that may stimulate additional autoimmune responses.[3,5] Several genetic loci, particularly in genes associated with human leukocyte antigen, have been identified as associated with PBC.[5] Environmental triggers may include certain urinary tract infections, hormone replacement therapy, nail polish and hair dyes, cigarette smoking, and industrial toxins. Socioeconomic factors also may play a role in PBC development.[3,5]

PBC is a rare disease, with an estimated global prevalence of 14.6/100,000 people[6]; 9 in 10 patients are women.[2] Typical patients are women aged 40 to 60 years, and it is exceptionally rare under age 25. Diagnosis of asymptomatic PBC has increased with AMA testing, allowing early intervention and improving outcomes with medical therapy. Among patients asymptomatic at diagnosis, median time to symptom development is 2 to 4.2 years.[3] Without treatment, the long-term consequences of PBC can include shorter survival times compared with healthy people; symptomatic patients, in comparison to asymptomatic patients at diagnosis, can have shorter median survival.[3] Untreated PBC typically progresses to fibrosis, cirrhosis, and may lead to potential liver failure within 10 to 20 years.[6] The availability of successful treatments for PBC has the potential to prolong time to progression, reducing need for transplant, and underscoring the importance of early diagnosis.[3]

Symptoms

Many patients are asymptomatic when abnormal routine liver function tests (LFTs) trigger further evaluation. PBC should be considered in patients with chronic cholestasis, which may be suspected if there is an unexplained elevation in alkaline phosphatase (ALP) level.[3] Diagnosis may not be apparent due to the nature of symptoms such as fatigue and pruritus of varying severity. In my experience, symptomatic patients occasionally have been referred to other specialties, which delays accurate diagnosis because pruritus or sicca syndrome may not suggest liver disease. Other symptoms, although less common, include xanthomas, abdominal pain, sleep disturbance or mood disorders, and some autoimmune disorders **(Table 1)**.[3,5] Severe pruritus is typically the most bothersome symptom for patients, limiting daily activities, disrupting sleep, and undermining quality of life (QoL).

Comorbid extrahepatic autoimmune diseases (EAIDs) are another challenge; Sjögren syndrome prevalence of (47.4% in a US outpatient study), followed by autoimmune thyroid disease (9% to13%), and systemic sclerosis (2% to 4%).[3,7,8] Fortunately, comorbid EAIDs do not impact PBC outcomes.[8] Other extrahepatic complications include sicca complex (dry eye/dry mouth; 34%), hyperlipidemia (75%-96%), and osteoporosis (20% to 40%).[9]

Figure 1. Risk factors associated with PBC[4]

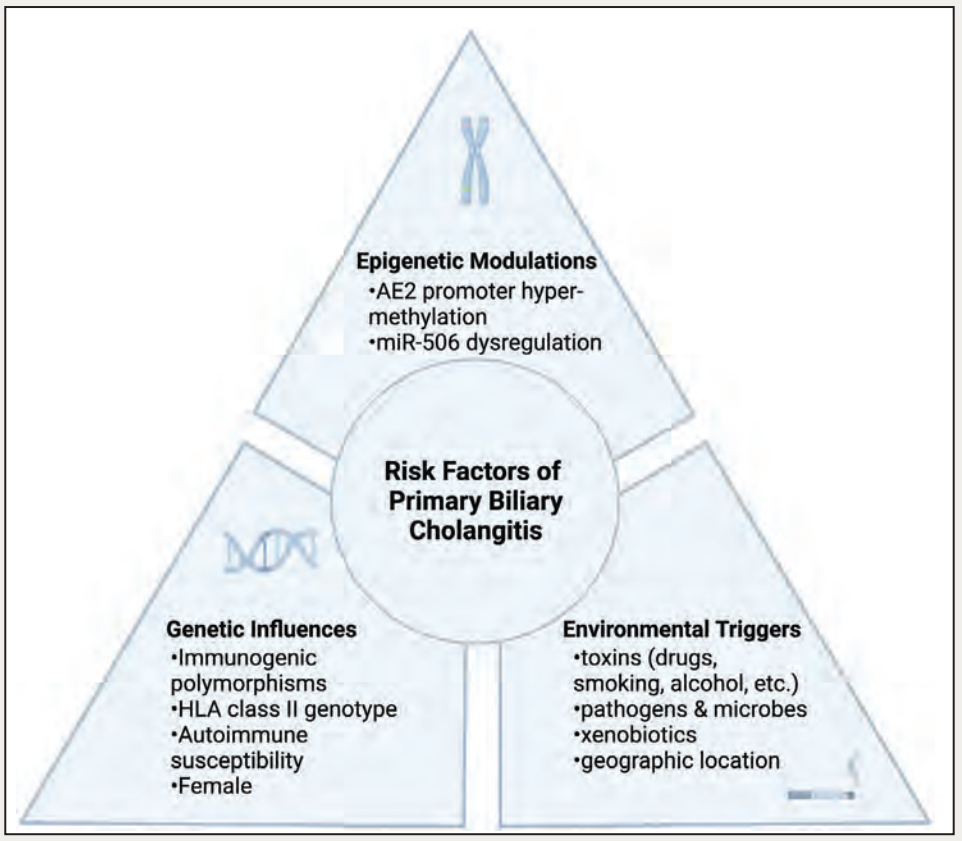

Fig. 1. Risk factors of primary biliary cholangitis. It is hypothesized that genetic factors and autoimmune susceptibility combined with certain environmental factors may trigger PBC. It is difficult to assess an individual's risk, but several factors have been correlated with an increased risk of developing PBC. Such factors include sex, age, geographic location, lifestyle choices, and inflammation. PBC, primary biliary cholangitis.

Modified from Medford 2023.

Diagnostic Pathway

Diagnosis of PBC can be confirmed if 2 of these 3 criteria are met: (1) elevated ALP level indicating a biliary source; (2) presence of AMA (or disease-specific antinuclear antibodies mentioned below) on validated assays; or (3) histopathologic evidence of nonsuppurative cholangitis.[3] The ALP level in noncirrhotic patients is a good indicator of inflammation and biliary damage severity.[3] A biopsy is rarely needed with a positive AMA test, but may be considered for AMA-negative patients or if autoimmune hepatitis (AIH) is suspected.[5] A small percentage of diagnoses are made using anti-gp210 and anti-sp100, which are PBC-specific antinuclear antibodies found in about 50% of AMA-negative patients.[1] Serum cholesterol is elevated in PBC—predominantly due to high-density vs low-density cholesterol— is not thought to increase cardiovascular risk.[3,5]

Differential diagnoses include biliary obstruction or stricture, primary sclerosis cholangitis, hepatitis, and drug- or toxin-induced hepatotoxicity.[10] AIH/PBC overlap typically refers to simultaneous AIH in people with a diagnosis of AMA-positive PBC.[3] Between 8% to 19% of patients with PBC may develop AIH/PBC overlap syndrome. AIH/PBC may be

Table 1. Clinical features of primary biliary cirrhosis[11]

Clinical features	Prevalence	Potential mechanism
Fatigue	20%-85%	Excessive manganese deposits in globus pallidum, elevated inflammatory cytokines
Pruritus	20%-75%	Cholestasis, increased opiodergic tone
Jaundice	10%-60%	Cholestasis
Xanthomas	15%-50%	Hypercholesterolemia and hyperlipidemia
Osteoporosis	35%	Disturbances in bone remodeling due to metabolic changes in PBC
Dyslipidemia	> 75%	Reduction in biliary secretion of cholesterol. Toxic effects of unconjugated bilirubin

Modified from Purohit 2015.

Table 2. Validated continuous scores using first-line therapy response at 12 months[14,15]

Score	Outcomes	Variables
UK-PBC[2]	Risk of liver transplant or liver-related death at 5, 10, or 15 years	**At baseline:** albumin, platelet count **At 12 months:** ALP, AST, ALT, bilirubin
GLOBE[15]	Liver transplant-free survival at 3, 5, and 10 years	Age at diagnosis **At 12 months:** ALP, bilirubin, albumin, platelet count

Modified from Martini 2023, Carbone 2016, and GLOBE.

Note: Both scores were validated in European and North American populations.

AST = aspartate aminotransferase.

suspected when there is a high alanine transaminase (ALT):ALP ratio or very high ALT levels (>5 times upper limit of normal [ULN]).[3] Diagnosis requires confirmed PBC plus highly elevated ALT and serum immunoglobulin G; biopsy is required for histologic evidence of hepatitis.[5]

Treatment and Management of PBC

Over time, there has been a decrease in liver transplants needed for people living with PBC. To that end, a patient's response to medical therapy is the best predictor of transplant-free survival. ALP and bilirubin levels at diagnosis are reliable surrogate markers for prognosis and response to therapy.[3,5] Response to first-line therapy also has been validated as a predictor of risk for progression or transplant **(Table 2)**. AMA-positive patients with normal ALP levels are considered at low risk for PBC development and potentially can be followed up with periodic LFTs.[3] Symptomatic disease, elevated bilirubin, and ALP level ≥2 ULN are factors associated with worse prognosis.[2]

The goals of medical therapy are to slow progression of disease and address cholestatic symptoms. I always include patients in treatment decision-making and take into account their concerns and goals. It is imperative to empower patients to participate in their care and long-term health.

Monitoring for treatment response can begin as early as 6 months after initiation of first-line therapy and must be done at 12 months.[1] Recent research suggests that inadequate response (ALP 1.9 times ULN) at 6 months of treatment identifies patients who could benefit from second-line therapies.[13] Additional investigational therapies are being evaluated for patients with PBC

We are recognizing that routine monitoring of laboratory tests in PBC often is not done. Timely monitoring is crucial for identifying those who can benefit from second-line therapy. Follow-up blood tests are necessary at least every 6 months to identify changes in liver biochemical tests. We know that modest changes in serum ALP and bilirubin levels may make a difference in long-term outcomes.

Equally important from the patient's perspective is symptom management, as symptoms negatively impact daily life.[1,3] Chief among these is pruritus, which occurs in 20% to 70% of patients and may not respond to typically used first-line treatment options. Depending on severity, pruritus—which is worse at night—disrupts sleep, impairs QoL, and can lead to damaged skin surfaces due to scratching. A stepwise approach to pruritus management is recommended.[1] Although antihistamines are mentioned in guidelines, my preference is to avoid these drugs when treating cholestatic pruritus, since they may not be effective and exacerbate sicca syndrome and fatigue. Failing to recognize that pruritus may be related to liver disease sometimes delays diagnosis.

Fatigue impact is unrelated to the severity of underlying biliary disease and generally is unresponsive to medical therapies; however, it is important that patients be evaluated for secondary causes (eg, medications, anemia).[5] Patients with sicca symptoms may achieve some relief with artificial tears or medications that stimulate tear production and should review oral hygiene after Sjögren syndrome or other EAIDs have been ruled out.[5]

Patients with PBC have a lifelong disease, but it can be managed medically over the long term with preventive care and appropriate follow-up. Patients should be advised to abstain from alcohol and smoking and to avoid or manage obesity. Long-term follow-up is summarized in **Table 3**. Oral contraceptives, hormone replacement, and pregnancy may worsen pruritus due to the effects of estrogen on cholestasis.[3] About 20.7% of sisters and 7.8% of brothers of patients with PBC will be AMA positive, and ALP screening is recommended for first-degree female family members starting at age 30.[3]

Comprehensive care of patients with PBC often requires physicians to interact with other healthcare providers to ensure optimal pruritus management and accurate metabolic test result interpretation. In my practice, we tend to function as the medical home or coordinator for patients. We also know we can attempt to achieve normalization of ALP and bilirubin levels to maximize favorable long-term outcomes. This is particularly important now that we have several promising new investigational medications in clinical trials.

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Table 3. Recommended long-term follow-up for patients with PBC[3]

Action	Frequency
All Patients	
Liver function tests	Every 3 to 6 months
Bone mineral density	Every 2 years
Special Situations	
Assess vitamins A, D, E, and prothrombin time	Annually if bilirubin >2.0 mg/dL
Upper endoscopy	Every 1 to 3 years if: • Cirrhotic • Mayo risk >4.1 • Transient elastography ≥17 kPa
Ultrasound with or without alpha fetoprotein	Every 6 months if: • Suspected cirrhosis • Male patient

Modified from Lindor 2019.

Member SPOTLIGHT

GI Physician Channels Humor to Incentivize Cancer Screenings

BY JENNIFER LUBELL

MDedge News

Growing up in a household where GI issues dominated conversations, it's no surprise that Shida Haghighat, MD, chose gastroenterology as her area of study in medicine.

She watched her father suffer from the complications of Crohn's disease and her brother struggle with irritable bowel syndrome. "We always needed to know where the nearest bathroom was. I grew up with that around me, and I was always just fascinated by the gut and the digestive system," said Dr. Haghighat, who just finished up her fellowship at the University of Miami and is now a gastroenterologist at University of California, Los Angeles. She also serves as social media editor for AGA's *Gastro Hep Advances*.

As she got to know the personalities of the GI department in the first year of medical school, "I realized that our senses of humor and personalities kind of aligned, and I was like, 'Oh yeah, this is where I'm supposed to be,' " said Dr. Haghighat, who can be found on X @DoctorShida.

Humor is something Dr. Haghighat has reached for throughout her life and career. She eventually channeled her gift for satire onto the stage and the internet, as a stand-up comedian. In an interview with *GI & Hepatology News*, she spoke about the connection between GI medicine and humor, and the creative ways she has helped promote cancer screening in underserved populations.

Q: What practice challenges have you faced in your career?

Dr. Haghighat: I trained in a county hospital, so I've always worked with underserved and vulnerable populations. One of the challenges hasbeen just navigation of care, especially as it pertains to cancer diagnoses or cancer screening. A lot of the time, patients don't understand why they have to do a test or something invasive like a colonoscopy for symptoms they don't have.

COURTESY DR. SHIDA HAGHIGHAT

Dr. Shida Haghighat

Lightning round

Texting or talking?
Text

Favorite city in US besides the one you live in?
Denver

Cat or dog person?
Dog

Best place you went on vacation?
Patagonia

Favorite sport?
Basketball

Favorite ice cream?
Rocky Road

Song you have to sing along with when you hear it?
Celine Dion's My Heart Will Go On

Q: A focus of yours has been improving uptake of screening in underserved communities. Please talk about the work you've done in this area.

Dr. Haghighat: I was at Los Angeles General Medical Center — a county hospital in Los Angeles — for residency, where we treated underserved, uninsured patients. I noticed in our primary care clinics a very low uptake of colon cancer screening. Patients didn't want to bring the stool tests back or get colonoscopies. I surveyed a bunch of the patients and asked: How can we make colon cancer screening easier for you? About a third of the patients said, "If I can do it in the clinic before I go home, that would be great."

So, I started this initiative called "Go Before You Go." We would ask patients, "Hey, do you need to go to the bathroom right now, if you can?" Our nurses handed them the stool test to do in the bathroom before they left the clinic after their doctor visits.

We saw really good results with that. Surprisingly, a lot of people can go on demand. We saw increased screening rates, and that quality improvement project went on to win multiple first place awards in research competitions. So that's what got me interested, and that's where I had my beginnings of increasing preventative services in underserved communities on the ground.

Q: Can you discuss some health disparity studies you've done in this area?

Dr. Haghighat: As a GI at Jackson Memorial Hospital in Miami, I was seeing cancer disparities firsthand every day. I wanted to approach these disparities from a research funding standpoint on a federal level. I was particularly interested in gastric cancer because it's not common enough in the United States to warrant universal screening, but it's very common among certain racial and ethnic minorities, which would warrant targeted screening.

I evaluated cancer funding allocation from the National Cancer Institute (J Natl Cancer Inst. 2023 June. doi: 10.1093/jnci/djad097) among the most common cancers in the United States and found that cancer afflicting a higher proportion of racial and ethnic minorities was receiving lower funding. One of those cancers was stomach cancer. This study basically highlighted that, to decrease these disparities, a top-down policy approach is necessary to distribute cancer research funding equitably across these groups.

A lot of stomach cancer comes from a bacteria called *Helicobacter pylori*, which can be more prevalent in certain countries. In another study, I looked at country of birth as a risk factor for stomach cancer, specifically for gastric intestinal metaplasia, which is a precursor for gastric cancer (Lancet Reg Health Am. 2023 Nov 28. doi: 10.1016/j.lana.2023.100635).

We found that country of birth is a key risk factor for gastric intestinal metaplasia and that it should be incorporated into risk stratification for targeted screening.

Q: Outside of medicine, you perform as a stand-up comedian. You have a popular satirical alias on social media. How did you get interested in stand-up comedy?

Dr. Haghighat: I gave my medical school's commencement speech, and I had sprinkled a few jokes in there. Afterward, multiple people approached me and said, "You should really consider stand-up comedy. Your timing and delivery are great." A few months later, I started my intern year in Los Angeles and simultaneously took stand-up comedy classes. I started performing at local clubs around town throughout residency, and I had two or three good sets that I could rely on. And so that's how I got into stand-up comedy.

My intern year is also when I started this social media satire account. It was a way to cope with the anxieties and stress of residency. Before I knew it, the account gained multitudes of followers, doctors, and other medical professionals. And I joke that the more hours I work in a week, the more memes I make, the more posts I make. It's kind of a creative outlet for me after a long day.

Q: What types of things do you talk about during your stand-up act?

Dr. Haghighat: A lot of it is about growing up in an immigrant household as a first-generation Iranian American. One of my favorite jokes is, my parents gave me so many options for a career. They said I could be a family doctor, a surgeon, a plastic surgeon, and if I worked hard, even a wife of a surgeon. But I talk a lot about being a woman in medicine. That always gets a lot of laughs. And now that I've graduated GI fellowship, I'm excited to incorporate some GI jokes because it turns out people love poop jokes. ■

AGA Outlines a Plan to Improve the Care of All Patients with IBD

A new AGA white paper, published in *Clinical Gastroenterology and Hepatology* (2024 Feb 28. doi: 10.1016/j.cgh.2024.01.050), highlights barriers to care and calls for collaboration among our healthcare community, insurers, pharmaceutical companies, and legislators to improve and optimize care for more than 3 million Americans living with inflammatory bowel disease (IBD).


Dr. Sofia

Over the last two decades, there has been a revolution in therapeutics fueled by exciting research and development that continues to expand the treatment options for IBD, offering tools for better disease control. However, the most effective therapies are cost prohibitive and have largely become inaccessible due to insurer-mandated barriers to care, such as prior authorization and step therapy.

AGA has created a plan that addresses these barriers and proposes tangible solutions to provide patients with high quality, high value care.

1. The lived experiences and valuable insights from both patients and expert clinicians should be reflected in the data and research represented in the field.
2. AGA recognizes the powerful benefit of individually tailoring IBD therapy based on risk, comorbidities, and response, and encourages all stakeholders to do the same.
3. As a field, we need to move beyond insurer-mandated step therapy and fail first policies.
4. AGA urges insurers to cover all necessary disease activity and drug level monitoring, which will ensure patients are able to achieve treat-to-target-driven outcomes.
5. Streamlined and expedited expert reviews should be guaranteed to all providers when they are mandated by an insurer.
6. To ensure transparency and accountability, AGA wants to require that payors publish their denial and appeals data.
7. AGA believes that holistic patient-centered multidisciplinary care, including psychosocial and dietary support, should be covered by insurance. Having access to such care contributes to improved patient resilience and well-being, which will lead to decreased health care utilization and better health outcomes.
8. AGA supports the creation and continuation of a variety of patient education programs to improve health literacy and awareness of complex healthcare systems.
9. AGA is committed to improving patients' access to expert specialized clinical IBD care. This includes flexible delivery models to ensure that underserved populations are being reached. In addition, AGA supports training and educating specialty providers across the spectrum of medical care (advanced practice providers, nurse educators, etc.) to increase the number of qualified IBD providers.
10. Piloting innovative shared incentive partnerships between high value subspecialty care practices and payors will be a new shared goal.
11. AGA wants to engage pharmaceutical partners in developing equitable programs to address prohibitive drug costs while also expanding patient access and support.

'Every day, we see people that have been harmed by delayed and inadequate care. … We must work together to collaborate on solutions to strengthen and advance the care for all people with IBD.'

12. AGA plans to continue to advocate for legislation to make access to therapy equitable for Medicare and Medicaid patients.

"Unaffordable drug costs, step therapy, and other insurer-mandated barriers are fixable problems," said M. Anthony Sofia, MD, a coauthor of the AGA white paper and an IBD specialist at Oregon Health & Science University, Portland. "Every day, we see people that have been harmed by delayed and inadequate care. Solving these barriers would lift an unimaginable weight off our patient's shoulders and allow them to lead healthier lives. We must work together to collaborate on solutions to strengthen and advance the care for all people with IBD."

View the full white paper at www.cghjournal.org/article/S1542-3565(24)00204-0/abstract. ■

AGA Research Foundation Memorial and Honorary Gifts: A Special Tribute to a Family Member, Friend, or Colleague

Did you know you can honor a family member, friend, or colleague whose life has been touched by GI research through a gift to the AGA Research Foundation? Your gift will honor a loved one or yourself and support the AGA Research Awards Program, while giving you a tax benefit.

- **Giving now or later.** Any charitable gift can be made in honor or memory of someone.

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- **A gift through your will or living trust.** You can include a bequest 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 Research Foundation in honor of your loved one. A gift in your will of $50,000 or more qualifies for membership in the AGA Legacy Society, which recognizes the foundation's most generous individual donors.

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IBS Placebo Responses Predicted by Patient Beliefs

BY WILL PASS
MDedge News

FROM GASTRO HEP ADVANCES

Placebo responses in patients with irritable bowel syndrome (IBS) may be altered by baseline beliefs and the patient-provider relationship, according to investigators.

These findings may improve prediction of placebo responses in IBS, and may help avoid patient-provider "mismatch," both of which can alter treatment outcomes and confound clinical trial findings, reported lead author Jeffrey M. Lackner, PsyD, chief of the division of behavioral medicine at the University of Buffalo, New York, and colleagues.


Dr. Lackner

"A relatively large (40%) placebo response in IBS trials obscures potentially useful, mechanistic, and pharmacodynamically induced symptom changes among agents that do reach market," the investigators wrote in *Gastro Hep Advances* (2023 Oct 14. doi: 10.1016/j.gastha.2023.10.003). "This begs the question of what individual difference factors distinguish placebo responders."

While previous studies have explored placebo patient predictors in IBS, most focused on study design and baseline personal characteristics such as age and sex, with none yielding prognostically reliable findings, according to Dr. Lackner and colleagues. Mid-treatment factors such as patient-provider dynamics have not been featured in published meta-analyses, they noted, despite their potential importance.

"This limitation partly reflects the demands of efficacy trials that prioritize pre- and post-treatment data over that collected during acute phase, when the putative mechanisms underpinning placebo effects play out," the investigators wrote. "The expectation that one can benefit from a treatment, for example, is optimally assessed after its rationale is delivered but before a clinically thorough regimen is provided, meaning that it cannot be fruitfully assessed at baseline along with other personal characteristics when treatment rationale is not fully disclosed. The same applies to relational factors such as patient-physician interactions that define the context where treatment is delivered, and placebo response presumably incubates."

To explore the above factors, Dr. Lackner and colleagues conducted a secondary analysis of 145 patients with Rome III-diagnosed IBS from the Irritable Bowel Syndrome Outcome Study.

During the study, patients were randomized to receive either 10 sessions of clinic-based cognitive-behavioral therapy (CBT), 4 sessions of minimal-contact CBT, or 4 sessions of supportive counseling and education without any prescribed behavior changes. Responses were measured by the IBS version of the Clinical Global Improvement Scale, with evaluations conducted at the treatment midpoint and 2 weeks after treatment.

Candidate predictors at baseline included pain catastrophizing, somatization, emotion regulation, neuroticism, stress, and others, while clinical factors included treatment expectancy/credibility and patient-provider relationship.

Responses during treatment were significantly associated with lower somatization and stress level at baseline, as well as greater patient-provider agreement on treatment tasks (*P* less than .001).

Posttreatment responses were significantly associated with baseline gastroenterologist-rated IBS severity, anxiety, agreement that the patient and the provider shared goals from a provider perspective, and ability to reframe stressful events in a positive light (*P* less than .001). That ability to reconsider emotions was also associated with a faster placebo response (*P* = .011).

"The strength of placebo responsiveness is subject to the influence of patient factors that precede treatment delivery (rethinking or reinterpreting stressful situations in everyday life in a way that reduces their subsequent impact) and specific elements of provider-patient interactions that occur while treatment is delivered, particularly practitioners' estimation that patients agree on their goals and tasks to achieve them," Dr. Lackner and colleagues concluded. "We believe this line of research can help identify factors that drive placebo response and narrow the patient-provider 'mismatch' that undermines the quality, satisfaction, and efficiency of IBS care."

The study was supported by NIH. The investigators disclosed no conflicts of interest.

Irritable bowel syndrome (IBS) is associated with impaired functioning and work or school absenteeism. Current treatments are suboptimal and there is a need for improved management strategies. A challenge in designing trials can be placebo response. Placebo can also be a treatment modality with approximately 40% response in adults and children with IBS. The study by Lackner et al. provides predictors of the magnitude, and timing of placebo response. Accordingly, certain behaviors and strategies adopted by patients and clinicians in addition to pharmacotherapy can harness greater clinical improvements.


Dr. Santucci

While patient factors such as stress levels, somatization, and anxiety played a role in predicting placebo response, an interesting domain was "cognitive reappraisal," the ability to alter the impact of stressful events by reframing unpleasantness toward them. This was associated with greater global improvement post treatment and differed between rapid and delayed responders. Cognitive reappraisal has shown changes in the limbic system such as activation of the prefrontal cortex like placebo analgesia. Thus, optimal introduction of treatments to patients may be important to maximize the cognitive appraisal abilities, enhance expectation effects, and improve treatment outcomes. Minimizing nocebo effects may be equally important to decrease side effects.

The agreement between patients and clinicians on treatment goals and tasks also predicted response. Thus, developing thorough treatment goals beforehand could be crucial to sustain treatment responses. For example, improved functioning may be a goal to agree upon rather than symptom reduction alone before commencement of treatment. Similarly, shared decision-making during treatment may have a tremendous influence on favorable outcomes.

Neha Santucci, MD, MBBS, is director of the Disorders of Gut-Brain Interaction Program at the Neurogastroenterology and Motility Center, Pediatric Gastroenterology, Hepatology and Nutrition, Cincinnati Children's Hospital Medical Center, and associate professor of pediatrics, University of Cincinnati College of Medicine in Ohio. She has no relevant conflicts.

Global Rates of *H. pylori*, Gastric Cancer, Dropping Together

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

The global prevalence of *Helicobacter pylori* (*H. pylori*) infection in adults has fallen more than 15% over the past three decades, and gastric cancer incidence appears to be falling in turn, according to investigators.

These findings suggest that decreasing *H. pylori* prevalence does indeed reduce rates of gastric cancer, although large-scale clinical trials are needed to solidify confidence in this apparent relationship, reported lead author Yi Chun Chen, PhD, of National Taiwan University, Taipei, and colleagues.

"Eradication of *H. pylori* infection heals chronic active gastritis and peptic ulcer disease and reduces the risk of peptic ulcer bleeding in aspirin users and the risk of gastric cancer in infected individuals," the investigators wrote in *Gastroenterology* (2024 Jan 2. doi: 10.1053/j.gastro.2023.12.022). "However, whether reduction of the prevalence of *H. pylori* is associated with

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Global Meta-Analysis Reveals that 1 in 12 Adults May Have Fecal Incontinence

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Approximately 1 in 12 adults worldwide has fecal incontinence (FI), according to a recent meta-analysis.

FI is more common among individuals 60 years and older, yet a considerable portion of younger people — almost 5% — may also suffer from FI, reported Isabelle Mack, PhD, of University Medical Hospital, Tübingen, Germany, and colleagues.

"Clinicians' understanding of the prevalence and risk factors for FI have evolved with time," the investigators wrote in *Clinical Gastroenterology and Hepatology* (2023 Sep 19. doi: 10.1016/j.cgh.2023.09.004). "Initially, FI was regarded as a symptom that predominantly affected older people, especially nursing home residents. Its prevalence among community-dwelling adults was underrecognized, possibly because persons with FI were hesitant to even disclose that they were symptomatic. Now, we recognize that FI is common in the community."


Dr. Mack

The only previous meta-analysis of FI, published in 2006, included both community and noncommunity studies, and reported an FI prevalence of 4.3%. Two subsequent reviews put the median prevalence at 7.7%, yet neither offered geographic insights.

To address this knowledge gap, Dr. Mack and colleagues conducted a meta-analysis of 80 studies involving 548,316 community-dwelling teenagers and adults. The median response rate across the studies was 66%.

Evaluating these data revealed a pooled global prevalence of FI was 8.0%, with a lower rate of 5.4% when FI was confined to Rome criteria.

"Placed in perspective, the 8.0% prevalence of FI is lower than or similar to the global prevalence of IBS, as assessed by a meta-regression (11.2%) and by a systematic review (8.8%) using pre–Rome IV criteria, and it is twofold greater than the IBS prevalence assessed with Rome IV criteria," the investigators wrote.

Among individuals aged 60 years and older, the FI prevalence was 9.3%, compared with 4.9% for younger people (odds ratio [OR], 1.75; 95% CI, 1.39-2.20).

"These differences are at least partly explained by age-associated declines in anorectal function (e.g., lower anal resting pressure and rectal distensibility, denervation of the external anal sphincter)," the investigators wrote.

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a reduction of the incidence of gastric cancer at the population level remains uncertain."

According to several previous meta-analyses, the global rate of *H. pylori* infection has been in a downtrend, but Dr. Chen and colleagues pointed out several limitations of these publications, including scarcity of recent data, insufficiently representative data, inconsistent diagnostic methods, and lack of adjustment for socioeconomic status.

"We therefore conducted this comprehensive systematic review and meta-analysis, including healthy individuals recruited in hospital-based studies, to provide an updated global prevalence and the secular trend of *H. pylori* infection," the investigators wrote, noting that they leveraged meta-regression analysis to "identify factors affecting heterogeneity of the prevalence," and concurrently evaluated the corresponding global incidence of gastric cancer.

Their dataset, which included 1,748 articles from 111 countries, suggested that the global rate of *H. pylori* is indeed in a downtrend.

From a crude global prevalence of 52.6% prior to 1990, the rate of *H. pylori* decreased to 43.9% among adults in 2015-2022, but was "still as high as" 35.1% among children and adolescents in the same 2015-2022 period. Multivariate regression analysis showed that prevalence decreased significantly, by 15.9%, among adults, but not in children and adolescents.

"The significant reduction of *H. pylori* prevalence in adults can be explained by the improvement of socioeconomic status, cleaner water supply, better sanitation and hygiene status, and widening of indication for eradication therapy," Dr. Chen and colleagues wrote. "The higher prevalence in adults than in children/adolescents is explained by the cohort effect because most *H. pylori* infection is acquired in childhood."

Global incidence of gastric cancer among both male and female individuals declined approximately in parallel with decreasing prevalence of *H. pylori*. Rates of gastric cancer decreased most in high-incidence countries such as Brazil, Japan, and China.

"These studies collectively provide evidence for the causal association of *H. pylori* infection and gastric cancer and that elimination of this bacterium can prevent the development of gastric cancer," the investigators wrote.

Still, more work is needed.

"Future prospective studies should be conducted to confirm whether public health interventions or mass screening and eradication of *H. pylori* infection to reduce its prevalence may reduce the incidence of gastric cancer at population level," Dr. Chen and colleagues concluded. "Besides, it is also important to consider the potential adverse consequences of *H. pylori* eradication, such as emergence of antibiotic resistance. The benefit-to-harm ratio and cost-effectiveness should also be taken into account."

The study was funded by the National Taiwan University Hospital, the Taiwan Ministry of Science and Technology, the Taiwan Ministry of Health and Welfare, and others. The investigators disclosed no conflicts of interest. ■

Chen et al.'s study establishes a connection between the global decline in *H. pylori* infection rates and the decrease in gastric cancer cases, analyzing data from 1,748 articles across 111 countries. It highlights a significant drop in adult *H. pylori* prevalence from 52.6% before 1990 to 43.9% between 2015 and 2022, crediting improvements in socioeconomic conditions, water quality, and sanitation, along with targeted eradication efforts. This emphasizes the critical role of public health measures in reducing *H. pylori* infections and, consequently, gastric cancer risks, showcasing the success of eradication campaigns and widespread screening.


Dr. Chen

Nevertheless, the research advises caution regarding the widespread elimination of *H. pylori* due to the risk of antibiotic resistance. It advocates for a measured evaluation of the pros and cons, as well as the cost-effectiveness of such interventions. The authors call for additional large-scale clinical trials to verify these results and improve public health tactics.

The findings indicate that precise public health actions can greatly influence disease prevention, underlining the necessity of well-informed policies backed by ongoing clinical research and trials. Such an informed approach is essential to confirm that the advantages of eradication surpass the potential dangers, particularly considering the growing concern over antibiotic resistance. This study lays the groundwork for effective gastric cancer prevention strategies and emphasizes the ongoing need for research to shape sound public health policies and actions.

Li-Ju Chen, PhD, is a postdoctoral researcher in the Division of Clinical Epidemiology and Aging Research at the German Cancer Research Center, Heidelberg, Germany. She declared no conflicts of interest in regard to this review.

AGA Clinical Practice Update Guides Usage of GLP-1 Receptor Agonists Before Endoscopy

BY WILL PASS
MDedge News

FROM CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

The American Gastroenterological Association (AGA) has issued a rapid clinical practice update on the use of glucagon-like peptide 1 (GLP-1) receptor agonists prior to endoscopy.

The update was partly prompted by consensus-based perioperative guidance issued by the American Society of Anesthesiologists in June 2023, which advises withholding GLP-1 receptor agonists before endoscopy. This recommendation has caused some anesthesia providers to cancel or postpone endoscopic procedures, or even elect general endotracheal intubation over standard sedation.

"Many facilities and medical centers are now struggling to revise preprocedural protocols for patients taking this class of medications despite the lack of high-level evidence regarding how to proceed," the panelists wrote in *Clinical Gastroenterology and Hepatology* (2023 Nov 7. doi: 10.1016/j.cgh.2023.11.002). "Important questions include whether these preprocedural changes are necessary, if they truly mitigate periprocedural aspiration, or if the delays instituted by following this guidance might further compound the major problem currently faced nationwide: that of large numbers of patients awaiting endoscopic procedures because of delays from the COVID-19 pandemic, reduction in the recommended age threshold to start colorectal cancer screening in 2018, and workforce challenges."

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FI was also significantly more common among women than men (9.1% vs 7.4%; OR, 1.17; 95% CI, 1.06-1.28).

"Although these differences in FI prevalence between men and women seem relatively small, most patients with FI who seek medical attention are women (unpublished data)," the investigators wrote. "We suspect that men less commonly seek medical attention for FI because they may be secretly resigned to having FI, because FI may have less of an emotional impact on men, and because health literacy with regard to FI is lower for men."

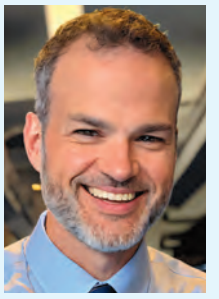
Geographically, prevalence of FI was highest in Australia and Oceania, followed by North America, Asia, and Europe. Data were insufficient to estimate rates in the Middle East and Africa.

Dr. Mack and colleagues concluded by noting how bothersome FI is for so many individuals worldwide, which should warrant closer attention from the medical community.

"Because nearly one in four community-dwelling women with FI report that the symptom has a moderate or severe impact on one or more domains of quality of life, more resources should be devoted to research in this area," they wrote. "Future epidemiologic studies of FI should also assess the severity of FI, risk factors for FI, and the impact of FI on quality of life. In addition, because some patients are reluctant to acknowledge or discuss FI during an in-person interview, written or internet-based surveys may be preferable."

This study was supported by the National Institute of Diabetes and Digestive and Kidney Diseases. The investigators disclosed no conflicts of interest. ■

Fecal incontinence (FI) is the GI disease that remains invisible to many except its sufferers. Even in the seemingly safe confines of a physician's office, many patients won't admit to providers that they suffer from this socially isolating condition. This systematic review and meta-analysis by Mack et al. — like other prevalence studies before it — serves as a useful reminder just how common this hidden disease remains. While FI is common in institutionalized persons, this study importantly found that 1 in 12 community-dwelling individuals worldwide suffer from FI as well.



Dr. Staller

Some of the study's key findings will come as little surprise to those who have taken an incontinence history from a reticent patient: People are more likely to report incontinence in mailed surveys than face-to-face or telephone interviews. Additionally, older individuals and women were more likely to experience incontinence than younger people. While women have always been more likely to seek care for FI, the current study suggests that women have an increased prevalence of FI as well, fitting with known additional risk factors such as obstetric trauma.

What should the practicing clinician take away from this study? Simply put, when it comes to FI, you need to ask: how often, how much, how urgent (or passive), and what type (solid or liquid). This disease is far too common to remain in the shadows, yet most GI fellows do not receive sufficient training on a condition that is so widespread.

Kyle Staller, MD, MPH, is director, GI Motility Laboratory at Massachusetts General Hospital and Harvard Medical School, both in Boston. He has served as a consultant for Anji, Ardelyx, GI Supply, Mahana, and Restalsis, and received research support from Ardelyx.

Study Characterizes Pathologic B-Cell Maturation in Crohn's Disease

BY WILL PASS
MDedge News

FROM CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

Crohn's disease (CD) involves altered B-cell expansion and maturation in draining mesenteric lymph nodes, according to investigators.

These findings begin to address a knowledge gap in Crohn's disease that has been more thoroughly explored in ulcerative colitis, reported lead author Sonja Kappel-Latif, MD, PhD, of Medical University of Vienna, Vienna, Austria, and colleagues.

"Recent studies have investigated the role of B-cell responses in ulcerative colitis, which exclusively affects the colon, whereas data in CD, which mainly affects the terminal ileum, are insufficient," the investigators wrote in wrote in *Cellular and Molecular Gastroenterology and Hepatology* (2023 Dec 24.

Continued on following page

The pathophysiology of inflammatory bowel disease (IBD) is complex and involves multiple mechanisms. Among these mechanisms, dysfunction and overactivation of the intestinal immune system are widely implicated. Dysfunctions in both the innate and adaptive immune systems have been demonstrated. However, mucosal immunology research related to IBD has long been particularly focused on T lymphocytes because of the failure of the rituximab clinical trial (anti-CD20) in ulcerative colitis (UC). Recent data have indicated modifications in the landscape of B-lymphocyte subpopulations within the inflamed mucosa of patients with UC or ileal Crohn's disease (CD).

Dr. Uzzan

At the intestinal level, the gut-associated lymphoid tissues (GALT), which include the mesenteric lymph nodes (MLN), is a particularly key site for B-lymphocyte biology. This study is notable for its analysis of lymphoid structures accessible only during surgery. They showed that CD19 B cells were expanded in affected MLNs. Germinal centers (GCs) in affected areas were significantly larger and presented a more mature anatomical structure. The more "active" state of GCs was confirmed by key markers of GC activation such as BCL6 and the proliferating marker KI67. Plasmablasts were also increased. Overall this suggests ongoing antigenic stimulation within affected MLNs of patients with CD.

Similarly, to what was previously shown in the inflamed colonic and ileal mucosa of IBD patients, isotype usage showed a skewing from IgA to IgG1. Further analysis of the B-cell receptor showed a very diverse repertoire of B cells, reflecting a large panel of antigenic stimulation. As we know, IBD are complex diseases that may not be explained by a single or a limited set of antigenic drivers.

Whether these changes in the B-cell compartment are a triggering event of inflammation or a bystander, reflecting the increased intestinal permeability and exposure to microbiota antigens during inflammation, remains to be explored and further studied.

Mathieu Uzzan, MD, PhD, is based in the gastroenterology department, Hopital Henri Mondor, APHP, Créteil, France. He has no relevant disclosures.

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The rapid clinical practice update, commissioned and approved by the AGA, includes background on the relationship between GLP-1 receptor agonists and endoscopic procedures, followed by clinical strategies for patients taking these medications.

Lead panelist Jana G. Al Hashash, MD, MSc, AGAF, of Mayo Clinic, Jacksonville, Florida, and colleagues began by noting that GLP-1 receptor agonists have been associated with increased gastric residue in patients with diabetes, and among nondiabetic patients, increased gastric retention of solids but not liquids. Delayed gastric emptying and increased residual gastric contents may be more common among patients on GLP-1 agonists who have vomiting, nausea, dyspepsia, or abdominal bloating, they added.

The above findings "imply an increased risk of aspiration in patients receiving GLP-1 receptor agonist medications who present for procedures that require sedation," the panelists wrote, but more data are needed to support this hypothesis.

iStock/Getty Images

Yet the implications for endoscopic risk are still unclear.

Dr. Al Hashash

'There is clearly insufficient published evidence for a robust systematic review and guideline. … the AGA's suggestions are expert opinions, *which may inform but should not replace clinical judgment.*'

Residual liquid in the stomach, at least, is "less of an issue," according to the update, since "it is easily removed during an esophagogastroduodenoscopy, and this is the first maneuver performed by endoscopists on entering the stomach."

While residual solids in the stomach could theoretically increase risk of aspiration, other patients with gastroparesis, such as those taking opioids, are not routinely given "special dietary precautions or medication adjustments" prior to endoscopy, Dr. Al Hashash and colleagues wrote. Even patients with severe gastroparesis who are undergoing gastric peroral endoscopic myotomy (which depends upon an empty stomach), are only required to stop ingesting solid foods the day before the procedure, they noted.

"It is appropriate that the AGA's perioperative suggestions for patients on GLP-1 [receptor agonists] are labeled 'consensus-based guidance on perioperative management,' because there is clearly insufficient published evidence for a robust systematic review and guideline," they wrote. "As such, the AGA's suggestions are expert opinions, *which may inform but should not replace clinical judgment.*"

The panelists therefore called for an individualized approach when managing GLP-1 receptor agonists prior to endoscopy, particularly in patients with diabetes, for whom withholding these medications "might provide more risk than benefit."

Withholding GLP-1 receptor agonists may be safe and reasonable for patients taking them solely for weight loss, but "this should not be considered mandatory or evidence-based," as it remains unclear whether withholding one dose is enough to restore normal gastric motility.

"Generally, in patients on GLP-1 receptor agonists who have followed standard perioperative procedures (typically an 8-hour solid-food fast and a 2-hour liquid fast) and who do not have symptoms of nausea, vomiting, dyspepsia, or abdominal distention, we advise proceeding with upper and/or lower endoscopy," the panelists concluded.

The rapid clinical practice update was commissioned and approved by the AGA. The update panelists disclosed relationships with Apollo Endosurgery, Medtronic, Boston Scientific, and others. ■

AGA Offers Practical Advice on IBD Diets

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

The American Gastroenterological Association (AGA) has released a clinical practice update on the role of diet and nutritional therapies in patients with inflammatory bowel disease (IBD).

The new guidance, authored by Jana G. Al Hashash, MD, MSc, AGAF, of Mayo Clinic, Jacksonville, Florida, and colleagues, includes 12 best practices that address dietary options, enteral and parenteral nutrition, patient monitoring, and the need for multidisciplinary care.

"There is growing recognition of the role of diet in the care of patients with IBD, as both an etiopathogenic risk factor and, more recently, as a disease-modifying modality," the update panelists wrote in *Gastroenterology* (2024 Mar. doi: 10.1053/j.gastro.2023.11.303).

Historically, they noted, patients with IBD had been advised to avoid many different foods including fiber, but this strategy may result in unintended consequences.

"[T]hese approaches frequently led patients with IBD to avoid what are traditionally considered healthy foods, even after achieving clinical remission," Dr. Al Hashash and colleagues wrote.

With an increasing body of data available for dietary interventions in both Crohn's disease and ulcerative colitis, they wrote the present clinical practice update to offer some needed clarity.

OKSANAKIAN/GETTY IMAGES

A Starting Point

First, the panelists advise that, unless contraindicated, all patients with IBD follow a Mediterranean diet while minimizing salt, sugar, and ultraprocessed foods.

Patients with symptomatic intestinal strictures may struggle to digest raw fruits and vegetables because of their fibrous nature, they added, so these patients should first soften these foods through cooking, steaming, or "careful chewing" before consumption.

"No diet has consistently been found to decrease the rate of flares in adults with IBD," the update panelists noted. "A diet low in red and processed meat may reduce ulcerative colitis flares, but has not been found to reduce relapse in Crohn's disease."

Beyond these dietary suggestions for adults, the update advises breastfeeding for newborns and a Mediterranean diet for children, as both may reduce risk of developing IBD.

The update suggests that exclusive enteral nutrition is a reasonable option to induce clinical remission and endoscopic response, or as a steroid-sparing bridge, in Crohn's disease, although this may be more effective in children than adults.

Malnourished patients may also benefit from exclusive enteral nutrition prior to elective surgery for Crohn's disease, Dr. Al Hashash and colleagues added, as this strategy can "optimize nutritional status and reduce postoperative complications."

A Crohn's disease exclusion diet, which involves partial enteral nutrition therapy, may be

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doi: 10.1016/j.jcmgh.2023.12.006).

"Granuloma formation within the thickened, inflamed mesentery of patients with CD, however, is associated with significantly worse outcome, and microstructural analysis has suggested increased numbers of B cells in CD mesentery."

Dr. Kappel-Latif

Previous studies have shown that abnormal B-cell development in patients with CD leads to development of IgG-targeting commensal — instead of pathogenic — gut bacteria. Yet B-cell receptor sequencing in CD has been conducted on only peripheral blood, despite awareness that anticommensal IgG antibodies can be transported across mucosal barriers in patients with ulcerative colitis, sustaining intestinal inflammation.

To better characterize local B-cell responses in CD, the investigators evaluated paired samples of draining mesenteric lymph nodes (MLNs) from both healthy and adjacently affected intestinal tissue, yielding a range of findings.

First, the investigators noted that CD19+ B cells and CD45+ leukocytes were expanded in affected MLNs, while T cells were reduced. A closer look showed that IgD-CD27- B cells were more abundant among CD19+CD45+ B cells in affected MLNs. Within this CD45+C-D19+CD27+IgD- B-cell fraction, CD38- memory B cells were reduced.

The above findings suggest "ongoing antigenic stimulation within affected MLNs," the investigators wrote.

Further comparison of paired samples showed that germinal centers (within which B cells mature) were significantly larger in affected MLNs, and contained dark and light zones. In contrast, healthy MLNs had smaller, more immature germinal centers.

Because of T-cell dependence during B-cell isotype switching within these germinal centers, the investigators next conducted immunohistochemistry staining for Bcl6, a "master regulator" of T-follicular helper cells expressed in class-switching B cells, and Ki67, which indicates cell proliferation. These analyses shows that both markers were "highly positive" within the germinal centers of affected MLNs.

Next, Dr. Kappel-Latif and colleagues conducted B-cell receptor (BCR) sequencing to characterize differences in class switching. Compared with healthy MLNs, affected MLNs showed decreased use of IGHA and IGHE alongside a significant uptick in IGHG1/2.

Further analyses showed that somatic hypermutation (SHM) frequency was significantly higher in IGHM and IGHA B cells, which was driven by mutations in complementary determining regions (CDRs) and framework regions of IGHA B cells, and mutations in the CDRs of IGHM B cells.

BCR diversity increased in the IGHG1/2 B cells, but remained unchanged in the IGHM or IGHA B cells.

"Overall, our results indicate ongoing class switching within draining MLNs of affected intestinal segments, with a shift toward IGHG1/2 BCRs," the investigators concluded. "The lack of high SHM rates within IGHG1/2 BCRs, the difference between IGHA and IGHG1/2 BCRs in single MLNs, and increased diversity in IGHG1/2 BCRs suggests that many antigens do not result in long-lasting immunologic stimulation, and IGHA and IGHG1/2 responses may target different pathogens/commensals."

'Granuloma formation within the thickened, inflamed mesentery of patients with [Crohn's disease] … is associated with significantly worse outcome, and microstructural analysis has suggested increased numbers of B cells in CD mesentery.'

The study was supported by the Austrian Science Fund and the Major of Vienna. The investigators disclosed no conflicts of interest. ■

AGA Guideline Supports Fecal Microbiota Therapies for CDI but Not IBD or IBS

BY DIANA SWIFT
MDedge News

FROM GASTROENTEROLOGY

Based on a synthesis of best available evidence, the American Gastroenterological Association (AGA) has released clinical recommendations on fecal microbiota–based therapies (FMT) in adults with gastrointestinal diseases.

Addressing *Clostridium difficile* infection (CDI), Crohn's disease (CD), ulcerative colitis (UC), pouchitis, and irritable bowel syndrome (IBS), the guidance supports FMT for the prevention of recurrent CDI but not for inflammatory bowel disease (IBD) or IBS — outside of clinical trials.

The AGA's recommendations were published in *Gastroenterology* (2024 Mar. doi: 10.1053/j.gastro.2024.01.008).

"Fecal microbiota–based therapies are effective therapy to prevent recurrent *C. difficile* in select patients," the AGA guideline states. "Conventional fecal microbiota transplant is an adjuvant treatment for select adults hospitalized with severe or fulminant *C. difficile* infection not responding to standard-of-care antibiotics. Fecal microbiota transplant cannot yet be recommended in other gastrointestinal conditions."

"We thought it was important to write this guideline because of the growing number of trials of FMT in IBD and IBS populations. It was also important with the new FDA-approved treatments on the market," the guideline's first author, Anne F. Peery, MD, MSCR, AGAF, told this news organization, noting that the recently approved products did not yield better results than those of conventional rectal FMT. "The guidelines will help clinicians understand the available therapies and how to use these treatments," added Dr. Peery, associate professor in the Division of Gastroenterology and Hepatology at the University of North Carolina School of Medicine in Chapel Hill.

Although the existing evidence is of low or very low certainty, Dr. Peery acknowledged, gastroenterologists "should be comfortable with conventional FMT and also the new FDA-approved products. We spent a considerable amount of time developing implementation considerations, which is practical advice to help clinicians use the guideline recommendations."

THIERRY ZOCCOLAN/AFP/GETTY IMAGES

Syringes are filled with stool to treat patients with serious infections of the colon with FMT.

Designed to counteract intestinal dysbiosis and restore protective gut flora, the FMT approach includes conventional, colonoscopically delivered donor stool transplants as well as two newly approved options: rectally given fecal microbiota (live-jslm/Rebyota) and most recently, orally delivered fecal microbiota spores (live-brpk/ Vowst).

The AGA urges careful pretreatment consideration for patients who require frequent antibiotics or long-term antibiotic prophylaxis since ongoing antibiotics may diminish the efficacy of FMT.

The guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation framework to prioritize clinical questions, identify patient-centered outcomes, and conduct an evidence synthesis, followed by the Evidence-to-Decision framework to develop recommendations for these therapies and algorithms for their implementation into clinical practice.

Recommendations

The eight-member panel suggested the following practices on behalf of the AGA Clinical Guidelines Committee:

- In immunocompetent adults with recurrent CDI, select use of FMT can be used after completion of standard-of-care antibiotics to prevent recurrence. It can be considered after the second recurrence (episode 3) of CDI or in select patients at high risk for either recurrent CDI or a morbid CDI recurrence. Recurrent CDI is defined as clinically significant diarrhea ≥ 3 unformed stools in 24 hours with a confirmatory positive test within 8 weeks of completing antibiotics. Select use includes patients who have recovered from severe, fulminant, or particularly treatment-refractory CDI and patients with significant comorbidities. Severe CDI involves a leukocyte count of ≥15 × 10^9 cells/L and/or creatinine ≥1.5 mg/dL, while fulminant CDI involves shock, ileus, or megacolon and can be fatal.
- In mildly or moderately immunocompromised adults with recurrent CDI, the guidance recommends select use of conventional fecal microbiota transplant.
- In severely immunocompromised adults or those undergoing cytotoxic treatment, the AGA advises against the use of any fecal microbiota-based therapies to prevent recurrent CDI.
- Conventional FMT is not advised in patients who have bowel perforation or obstruction or are severely immunocompromised.
- For CDI patients not interested in FMT, reasonable alternatives to prevent recurrence are a vancomycin taper, tapered-pulsed fidaxomicin, or bezlotoxumab.
- In adults hospitalized with severe or fulminant CDI not responding to standard-of-care antibiotics, the AGA recommends select use of conventional FM transplant.
- In the current absence of evidence, the guidance advises against the use of conventional fecal microbiota transplant as treatment for IBD or IBS except in the context of clinical trials.

"We felt the data for using FMT in the treatment of UC was promising, but there is still a lot more work to be done in IBD and IBS," Dr. Peery said. For each disease section the guideline outlined directions for future research. It will be updated in 3-5 years as more evidence becomes available.

This guideline was fully funded by the AGA Institute. Dr. Peery and fellow panel member Benjamin Lebwohl, MD, are supported by grants the National Institute of Diabetes and Digestive and Kidney Diseases. Panel member Colleen R. Kelly, MD, is supported by the National Institute of Allergy and Infectious Diseases.

None of the panel members had any conflicts of interest to report. ■

Continued from previous page

considered in mild or moderate cases, according to the update.

"Data on the use of enteral nutrition in the treatment of active ulcerative colitis are limited," the panelists wrote, although early data suggest it is safe and well tolerated, and can improve prealbumin levels.

Parenteral Nutrition

The update recommends short-term parenteral nutrition for patients with phlegmonous inflammation and/or an intra-abdominal abscess, as this can act as a bridge to surgical intervention.

Patients with prolonged ileus, short bowel syndrome, or high-output gastrointestinal fistula may also be candidates for parenteral nutrition, as well as those who have tried and failed both oral and enteral nutrition.

Lastly, the update encourages transition from long-term parenteral nutrition to oral intake and customized hydration management "whenever possible."

Multidisciplinary Care

Dr. Al Hashash and colleagues concluded by advising that all patients with complicated IBD be comanaged by a gastroenterologist and a registered dietitian, both of whom should remain watchful for signs of malnutrition.

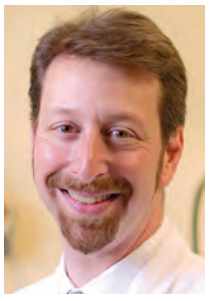
Using serum protein as a surrogate marker of malnutrition is no longer recommended and there are different criteria that should be utilized to identify malnutrition. Routine iron and vitamin D testing are warranted, as well as B12 testing for patients with extensive ileal disease or a history of ileal surgery.

This clinical practice update was commissioned and approved by the AGA. The update panelists disclosed relationships with Merck, Celgene, Janssen, and others. ■

‘Real-world efficacy’

Dupilumab *from page 1*

“Despite nonresponse to prior treatments, these patients can likely expect to see results similar to what was seen in the clinical trial,” Dr. Dellon said in an interview. “However, it would be good to have similar confirmatory data from other centers, and I’m sure those data will be forthcoming as more EoE patients are treated with dupilumab.”


Dr. Dellon

The placement of dupilumab in the EoE treatment algorithm is still actively being investigated. “While the phase 3 study led to [Food and Drug Administration] approval, it had strict inclusion and exclusion criteria, and some populations were ineligible,” he added. “In particular, the very severe EoE patients who either had a very narrow esophagus where the scope wouldn’t pass, or who had severe strictures and symptoms requiring esophageal dilation and who couldn’t go 6-12 months without dilation, couldn’t be enrolled. So the efficacy of dupilumab in this more severe group was not known.”

The group hypothesized that dupilumab would be effective in this population but did not know if the efficacy would be similar to that in the clinical trial. “The overall response rates, which were very similar to what were seen in the phase 3 trial, were surprising,“ Dr. Dellon said. ”The other surprising finding was the increase in esophageal caliber, as measured by the size achieved with esophageal dilation.”

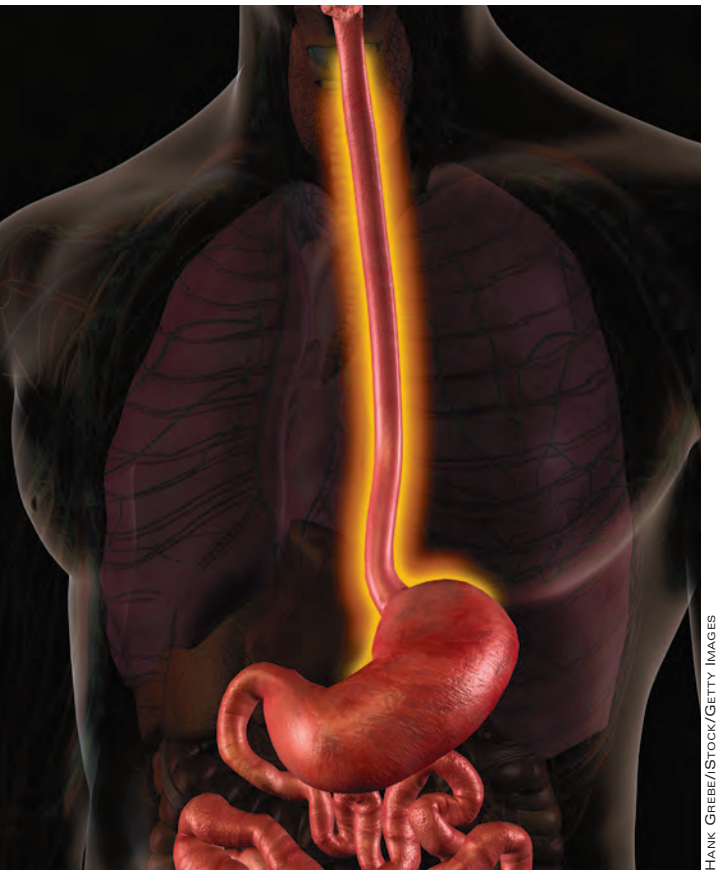
The Study

The investigators identified 46 patients treated with dupilumab for refractory fibrostenotic EoE at the university’s medical center. All had failed or lost response to one or more standard therapies such as proton pump inhibitors, topical glucocorticosteroids, and a food elimination diet.

Previous treatments also included systemic steroids, cromolyn, ketotifen, montelukast, and 6-mercaptopurine, all with minimal response. Some 85% of patients had undergone an average of 9.0+ 7.0 pre-dupilumab dilations.

The biologic was initially prescribed off-label before FDA approval. Patients received it at a dose of 300 mg subcutaneously either fortnightly (n = 16) or weekly (n = 30), depending on insurance approval and timing of prescription. Length of treatment varied based on the time from prescription to first post-treatment evaluative endoscopy.

Patients showed endoscopic, histologic, and symptomatic improvement on dupilumab compared with both the worst and the pre-dupilumab esophagogastroduodenoscopies.


Hank Grebe/iStock/Getty Images

Among the specific findings:

- Peak eosinophil counts significantly decreased.
- Post-dupilumab histologic response rates were 80% and 57% for fewer than 15 eosinophils per high-power field, and 6 or fewer eosinophils per high-power field, respectively.
- The Endoscopic Reference Score decreased from 5.01 to 1.89 ($P < .001$ for all).
- Pre-dilation esophageal diameter increased from 13.9 to 16.0 mm ($P < .001$), although the proportion of strictures was stable.
- Global symptom improvement was reported in 91% of patients ($P < .001$).

Commenting on the study but not involved in it, David Katzka, MD, professor of medicine at Columbia University in New York City, said the findings would be of immediate use to practicing gastroenterologists.


Dr. Katzka

“It’s necessary to do clinical trials, but real-world data make the clinician feel more comfortable in prescribing. Interestingly, I am seeing dupilumab being recommended not just for refractory disease but also as first-line therapy,” he said.

Dr. Dellon noted that the incidence and prevalence of EoE are rising rapidly in the US and around the world (Curr Allergy Asthma Rep. 2022 Oct 3. doi: 10.1007/s11882-022-01042-1). “This increase is outpacing growing recognition of the disease,” he said. “Most likely, environmental factors are driving this change.” He called for studies to determine the long-term efficacy of dupilumab for this severe subgroup — and the potential benefit of moving dupilumab earlier into the treatment algorithm.

The latter is a controversial question, noted Dr. Katzka. “For patients with other indications such as asthma or eczema, dupilumab is the ideal medication,” he said. And it can be a first-line therapy if there are contraindications to alternatives or if compliance will be better with a once-weekly injection as opposed to a twice-daily medication or a food elimination diet. But overall, our more established therapies should be considered first.”

Dr. Katzka emphasized the need to further define EoE phenotypes in order to personalize therapy. “There’s likely a group of patients who should go straight to dupilumab, perhaps those marked by factors such as severity, progression, young age, or other atopic disorders. But we have yet to definitively identify this group.”

The authors reported no specific funding for this analysis. Dr. Dellon reported research funding and/or consulting fees from multiple pharmaceutical companies, including Regeneron/Sanofi, the developers of dupilumab. Dr. Lee had no competing interests to disclose. Dr. Katzka reported consulting for Medtronic, and is an associate editor for *GI & Hepatology News*. ■

‘Unequivocal sign of progress’

Cholangitis *from page 1*

‘Unequivocal’ Progress

Up to 40% of patients with PBC have an inadequate response to first-line therapy with ursodeoxycholic acid (UDCA) and are at a high risk for disease progression. More than half of patients with the disease fail to respond to second-line therapy with obeticholic acid.


Dr. Hirschfield

Seladelpar, and the dual PPAR-alpha and PPAR-delta agonist elafibranor, are an “unequivocal sign of progress, marking the arrival of a new era in which PBC treatment is expected to provide both biochemical benefits and amelioration of symptoms for patients,” David N. Assis, MD, with the Section of Digestive Diseases, Yale School of Medicine, New Haven, Connecticut, wrote in a linked editorial.

In the RESPONSE study, 193 patients with PBC who had an inadequate response to or a history of unacceptable side effects with UDCA were randomly allocated to either oral seladelpar 10 mg daily or placebo for 12 months. The vast majority (93.8%) continued UDCA as standard-of-care background therapy.

The primary endpoint was a biochemical response, which was defined as an alkaline phosphatase (ALP) level < 1.67 times the upper limit of the normal range, with a decrease of 15% or more from baseline, and a normal total bilirubin level at 12 months.

After 12 months, 61.7% of patients taking seladelpar met the primary endpoint vs 20% of patients taking placebo.

In addition, significantly more patients taking seladelpar than placebo had normalization of the ALP level (25% vs 0%). The average decrease in ALP from baseline was 42.4% in the seladelpar group vs 4.3% in the placebo group.

At 12 months, alanine aminotransferase and gamma-glutamyl transferase levels were reduced by 23.5% and 39.1%, respectively, in the seladelpar group compared with 6.5% and 11.4%, respectively, in the placebo group.

“In PBC, we use target endpoints, so the trial was not powered or able to show yet clinical outcomes because the pace of the disease is quite slow. But we believe that the normalization of liver tests and improvement in quality of life will change the disease trajectory over time,” Dr. Hirschfield said.

Significant Reduction in Pruritus

A key secondary endpoint was change in patient-reported pruritus.

At baseline, 38.3% of patients in the seladelpar group and 35.4% of those in the placebo group had moderate to severe pruritus, with a daily numerical rating scale (NRS) score of 4 or higher out of 10.

Among these patients, the reduction from baseline in the pruritus NRS score at month 6 was significantly greater with seladelpar than with placebo (change from baseline, −3.2 points vs −1.7 points). These improvements were sustained through 12 months.


Dr. Assis

Improvements on the 5-D Itch Scale in both the moderate to severe pruritus population and the overall population also favored seladelpar over placebo for itch relief, which had a positive impact on sleep. Similar results demonstrating reductions in itch and improvements in sleep were observed using the PBC-40 questionnaire.

Adverse events that led to discontinuation of seladelpar or placebo were rare, and there was no between-group difference in the incidence of serious adverse events.

“No worrisome adverse events affecting the muscles were observed, including among patients receiving statins. Certain gastrointestinal events — abdominal pain, abdominal distention, and nausea — were reported more frequently in the seladelpar group than in the placebo group,” the study authors wrote.

The most common adverse events that occurred in ≥ 5% of patients in either group were COVID-19 and pruritus. A greater percentage of patients treated with placebo reported pruritus (15.4% vs 4.7%) as an adverse event — a finding consistent with the positive effect of seladelpar on reducing pruritus.

The researchers noted that 96.4% of patients who participated in the RESPONSE trial chose to enroll in the extension trial to evaluate long-term safety and the side-effect profile of seladelpar.

Potential First-Line Treatment?

In Dr. Assis’ view, the RESPONSE trial, coupled with the recently reported ELATIVE trial of the dual PPAR-alpha and PPAR-delta agonist elafibranor in PBC, “cement the role of PPAR agonists as the preferred second-line treatment in primary biliary cholangitis.”

“The reduction in serum cholestatic markers and the safety profiles of elafibranor and seladelpar offer clear advantages beyond what was previously shown with obeticholic acid. These trials also cement a new treatment goal for primary biliary cholangitis in which a reduction in pruritus should be expected as part of anticholestatic treatment,” Dr. Assis wrote.

“The results of these trials suggest that the use of PPAR agonists in primary biliary cholangitis could improve treatment outcomes while also improving quality of life, which is a highly desirable alignment of clinician and patient goals,” Dr. Assis added.

Looking ahead, Dr. Hirschfield sees a potential role for seladelpar earlier in the course of PBC treatment, he said in an interview.

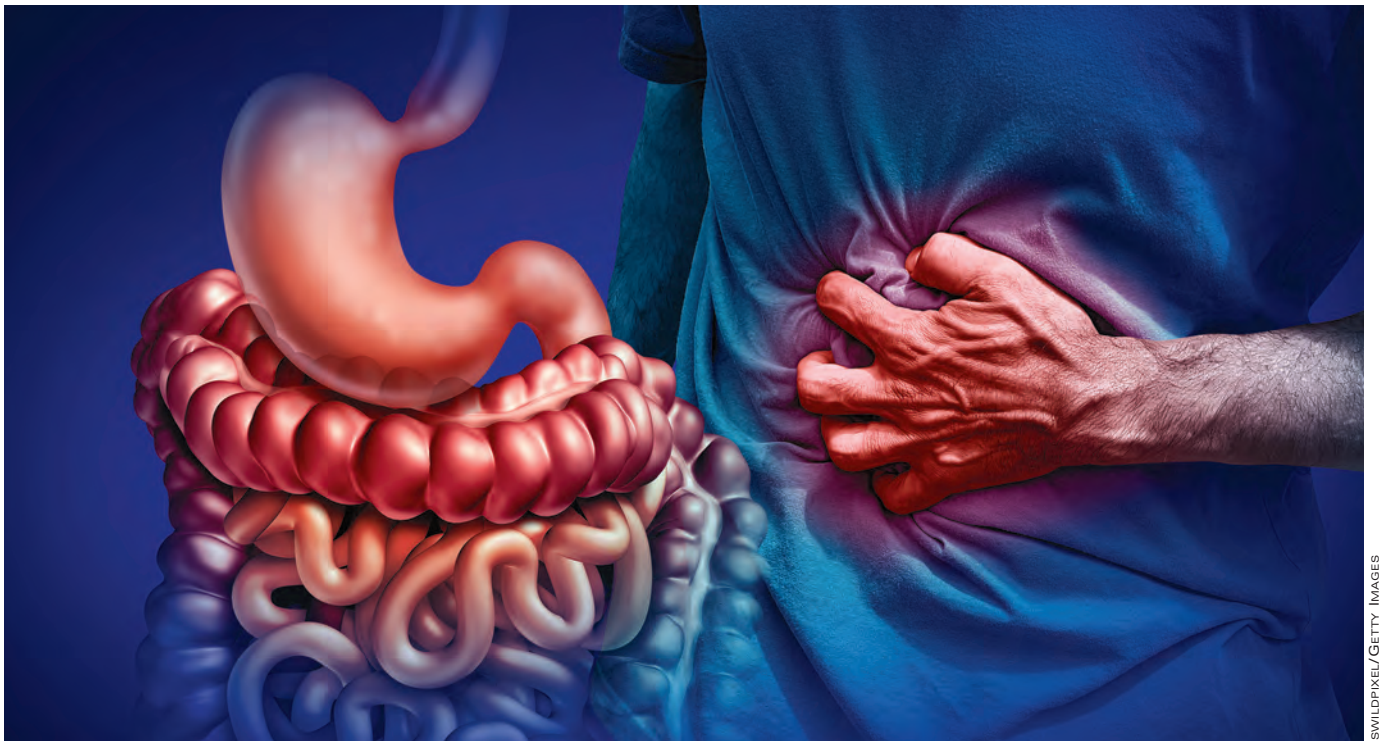
“Over time, the way we treat patients will not be to wait to fail. It will be treat to target and treat to success,” Dr. Hirschfield said.

Earlier this month, the US Food and Drug Administration accepted CymaBay Therapeutics’ new drug application for seladelpar for the treatment of PBC, including pruritus in adults without cirrhosis or with compensated cirrhosis (Child Pugh A) who fail to respond adequately or cannot tolerate UDCA. Seladelpar for PBC was granted breakthrough designation in October 2023.

The study was funded by CymaBay Therapeutics. Disclosures for authors and editorialist are available at NEJM.org. ■

Risankizumab in Crohn's Disease: Clinical, Endoscopic Outcomes Remain Stable for up to 3 Years

BY BECKY MCCALL



SWILDPIXEL/GETTY IMAGES

STOCKHOLM — Long-term data on risankizumab (Skyrizi) in moderate to severe Crohn's disease (CD) show that clinical remission and endoscopic response rates remain stable for up to 3 years, according to results of the FORTIFY extension study.

"For me, most striking are the endoscopic endpoints," Marc Ferrante, MD, PhD, AGAF, said in an interview. In the most conservative analysis, "you see a benefit the longer you follow the patients ... We haven't seen this with many — if any — other compounds before."

Dr. Ferrante

Dr. Ferrante, from University Hospitals Leuven in Belgium, added that patients showed less antibody formation in response to risankizumab, an anti-interleukin (IL)–23 p19 inhibitor, compared with anti–tumor necrosis factor agents.

"Most patients seemed to continue on treatment without the formation of antibodies to risankizumab becoming a problem," he said. Also, for patients who achieve a good response to risankizumab, the effects were the same whether "they received this biologic first line, or only after failing other compounds."

Generally, "I think we all have the impression that the IL-23 inhibitors have good efficacy, probably even better than other compounds available," said Dr. Ferrante. "And, importantly, this is true without any increased adverse effects."

"Now, with these new long-term data in risankizumab, we see the benefit-risk ratio continues to be favorable," he added.

Dr. Ferrante presented the data (Abstract DOP 53) on February 23 at the annual congress of the European Crohn's and Colitis Organisation.

Open-Label Extension up to 152 Weeks

The ongoing FORTIFY maintenance open-label extension study is evaluating the long-term efficacy and safety of risankizumab in patients with moderate to severe CD.

These data follow the initial 52-week study published in 2022 showing that subcutaneous risankizumab was a safe and efficacious treatment for maintenance of remission in patients with moderately to severely active CD. Dr. Ferrante also led that study.

Participants in this open-label extension study who had already completed 52 weeks of maintenance dosing received 180-mg subcutaneous risankizumab every 8 weeks (n = 872) at week 56. Those who had received prior rescue therapy, a single 1200-mg intravenous risankizumab dose followed by 360 mg subcutaneously every 8 weeks, continued with this latter regimen (n = 275). Data for analysis were pooled from both treatment groups (risankizumab 180 mg and 360 mg), and clinical outcomes were evaluated every 6 months.

Data for the population, after patients who received rescue treatment were imputed as nonresponders, showed Clinical Disease Activity Index (CDAI) response of 84.9% at week 56 and 52.7% at week 152. CDAI remission was 66.7% at week 56 and 47.2% at week 152 for this population.

For endoscopic outcomes, additional benefit was seen over time. Endoscopic response, considered to be the best available predictor of long-term outcomes, was 50.8% at week 56 and 52.5% at week 152. Endoscopic remission was 35.8% at week 56 and 41.8% at week 152, and ulcer-free endoscopy was seen in 28.6% patients at week 56 and 35.5% at week 152.

The safety profile of risankizumab is consistent and supports long-term treatment, Dr. Ferrante said.

Treatment emergent adverse events included major adverse cardiovascular events in five patients on risankizumab and 50 serious infections.

'Effective and Durable Option'

Providing comment, Tim Raine, MD, a consultant gastroenterologist & IBD lead at Cambridge University Hospitals, United Kingdom, remarked on the value of long-term extension studies for understanding the impact of continued drug administration beyond the typical 1-year time horizon of registrational clinical trials given that CD is currently incurable.

"However, there are limitations with long-term extension studies," he said in an interview. In particular, the patients who remain in the study tend to be "those who have had a good experience with the drug and remain motivated to take part in ongoing monitoring."

But "patients will drop out of a long-term extension study for reasons that may or may not reflect loss of benefit from the drug, and this can be problematic with handling of missing data," he explained.

In light of this issue, "the investigators have used the most stringent way of handling these patients, regarding all who drop out as instances of failure of the drug. This offers the most robust assessment of durability of response that may slightly underestimate the true long-term efficacy," said Dr. Raine.

"Nevertheless, the response and remission rates for clinical endpoints suggest good durability of effect out to 3 years of follow-up. The endoscopic data are also encouraging," he asserted.

"Taken together, these data suggest that risankizumab can offer an effective and durable option for some patients with Crohn's disease and is associated with a favorable safety profile."

Dr. Ferrante disclosed ties with AbbVie, Agomab Therapeutics, Amgen, Biogen, Boehringer Ingelheim, Celgene, Celltrion, EG, Eli Lilly, Falk, Ferring, Janssen, Janssen-Cilag, Lamepro, Medtronic, MRM, MSD, Pfizer, Regeneron, Samsung Bioepis, Sandoz, Takeda, ThermoFisher, Truvion Healthcare, and Viatris. Dr. Raine disclosed ties with AbbVie, Arena, Aslan, AstraZeneca, Boehringer-Ingelheim, BMS, Celgene, Ferring, Galapagos, Gilead, GSK, Heptares, LabGenius, Janssen, Mylan, MSD, Novartis, Pfizer, Sandoz, Takeda, and UCB. ■

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