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August 2024

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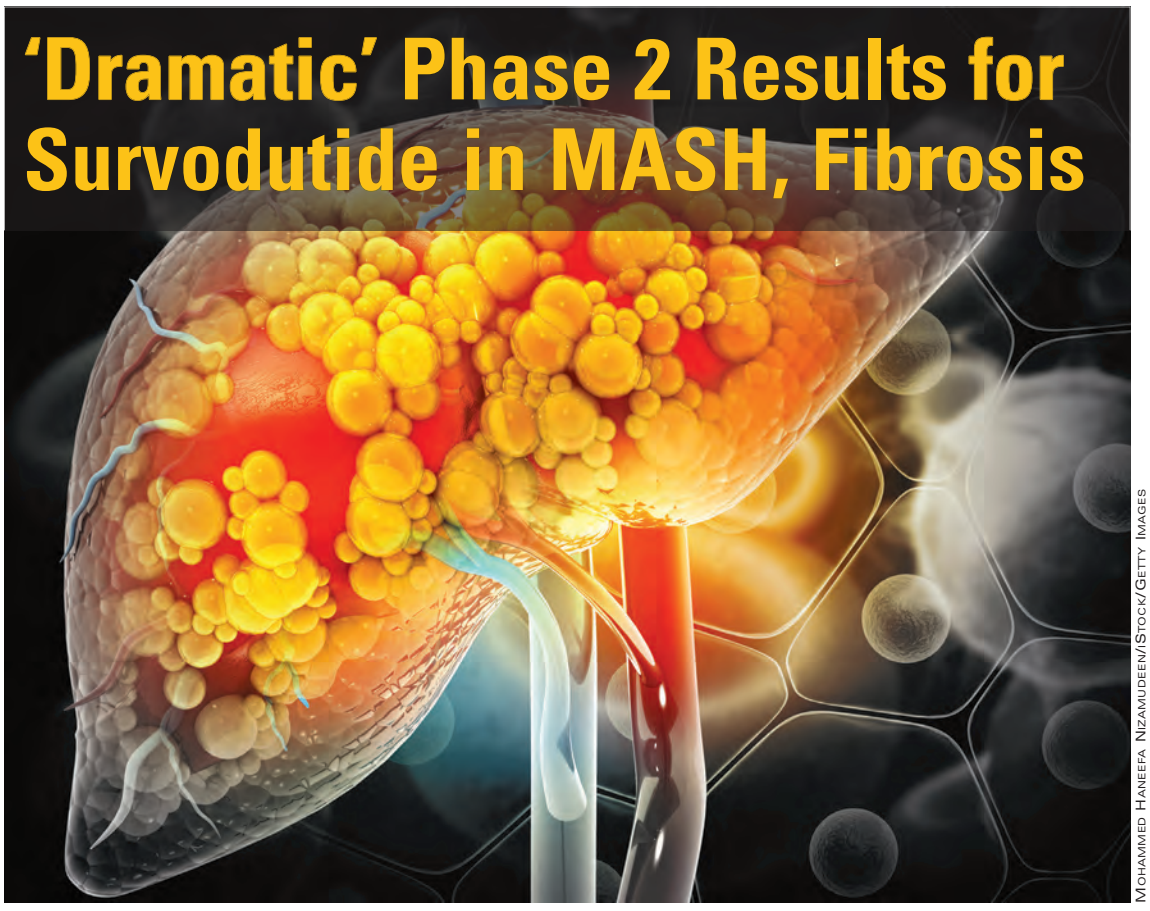
‘Dramatic’ Phase 2 Results for Survodutide in MASH, Fibrosis



MOHAMMED HANEEFA NIZAMUDEEN/ISTOCK/GETTY IMAGES

BY BECKY MCCALL

FROM EASL 2024

MILAN — Survodutide, an investigational dual glucagon-like peptide 1 (GLP-1) and glucagon receptor agonist, led to “exceptional improvement in disease activity and fibrosis” in patients with metabolic dysfunction–associated steatohepatitis (MASH), according to phase 2 results presented at the European Association for the Study of the Liver (EASL) Congress 2024.

The data were simultaneously published in *The New England Journal of Medicine* (2024 Jun 7. doi: 10.1056/NEJMoa2401755).

The primary endpoint data, reported earlier this year in a press release, showed that up to 83% of participants on survodutide showed a statistically significant improvement in MASH compared with those on placebo (18.2%) based on paired biopsy results.

In addition, 75% of patients treated with survodutide experienced resolution of MASH with no worsening of fibrosis compared with 15% of patients on placebo, and in patients with F2/F3 fibrosis, 64.5% achieved improvement in fibrosis without worsening of MASH, reported Arun J. Sanyal, MD, principal study investigator and director of the

See **Survodutide** · *page 23*

Physician-Scientist Taps Into Microbiome to Fight Cancer

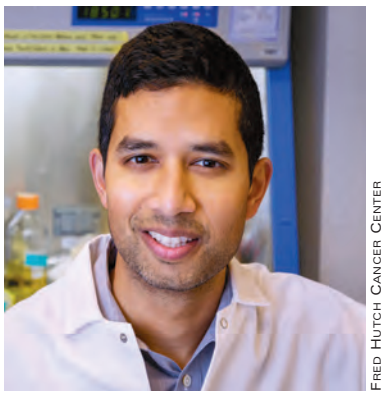
BY JENNIFER LUBELL

MDedge News

The lowest point in the nascent career of Neelendu Dey, MD, helped seal his fate as a physician-scientist.

He had just started his first year as a resident at University of California, San Francisco. One of his patients was a 30-year-old woman who was dying of metastatic colorectal cancer. “I was in my mid-20s interacting with an individual just a few years older than I am, going through one of the most terrible health outcomes one could imagine,” Dr. Dey said.

Member **SPOTLIGHT**



FRED HUTCH CANCER CENTER

Dr. Neelendu Dey

He remembers asking the patient what he could do for her, how he could make her feel more comfortable. “That feeling of helplessness, particularly as we think about young people developing cancer, it really stuck with me through the years,” he said.

See **Scientist** · *page 17*

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LETTER FROM THE EDITOR

Investing in Future Discovery

The field of GI is rapidly evolving, fueled by new scientific discoveries leading to improved understanding of disease mechanisms and more effective treatment approaches for patients with digestive and liver diseases. But there are many challenges confronting the pipeline of early-career investigators essential to future discovery, most notably a constrained funding environment leading to decreased protected time for research during these critical early years.


Dr. Adams

Foundation awards, such as those funded by the AGA Research Foundation, play a pivotal role in supporting the career development of promising young investigators in basic, translational, clinical, and health services research and ensure that we have a strong pipeline of independent investigators to stimulate ongoing discovery and innovation in our field. This year, the AGA Research Foundation distributed $2.6 million in funding to 76 investigators, including 6 coveted Research Scholar Awards awarded to early-career investigators. These promising young researchers represent the best and the brightest in our field — I hope you enjoy learning more about them in the pages of this issue and will join me in continuing to support the Foundation and its work under the leadership of Dr. Michael Camilleri.

Also in our August issue, we bring you continued coverage from DDW and June's EASL Congress, and report on innovative science published in AGA's flagship journals, including a study investigating the impact of *H. pylori* eradication on esophageal cancer risk. We also highlight several important studies relating to eosinophilic esophagitis, including a recent RCT published in *The New England Journal of Medicine* demonstrating the effectiveness of dupilumab in treatment of PPI-refractory pediatric EoE. Our August Member Spotlight features Dr. Neelendu Dey of Fred Hutchinson Cancer Center, who shares his perspectives on pursuing a career as a physician-scientist and chronicles his research focused on harnessing the microbiome for cancer prevention.

Finally, our quarterly In Focus column from *The New Gastroenterologist* provides practical advice regarding how best to evaluate patients with chronic bloating symptoms, a frequent presentation in our GI clinics. As always, thanks for reading and please don't hesitate to reach out with suggestions for future coverage. ■

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

AGA Research Scholar Awards Advance the GI Field

The AGA Research Foundation plays an important role in medical research by providing grants to talented scientists at a critical time in their career. AGA's flagship award is the Research Scholar Award (RSA), which provides career development support for young investigators in gastroenterology and hepatology research.

"The AGA Research Scholar Award will have a significant impact on my career," said Dr. Jason (Yanjia) Zhang, 2024 AGA Research Scholar Award grant recipient, and a gastroenterologist at Boston Children's Hospital. "I aspire to lead a laboratory studying the impact of the microbiome on human gastroenterological diseases. Our lab will focus on the

Continued on following page


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The 2024 AGA Research Scholar Award winners include (L to R, starting top left) Karen Jane Dunbar, Aaron Hecht, Sarah Maxwell, Chung Sang Tse, Jason (Yanjia) Zhang, and Joseph R. Burclaff.

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Announcing Our 2024 AGA Council Chair and Section Leaders

Meet Our New Chair

Douglas J. Robertson, MD, MPH, AGAF
AGA Institute Council Chair
VA Medical Center, White River Junction, Vermont
Geisel School of Medicine at Dartmouth, Hanover, New Hampshire

Dr. Robertson will serve as council chair for 3 years (May 2024-May 2027; DDW 2025, 2026, and 2027).

Section Leadership

We are pleased to announce the results of the elections held recently by the AGA Institute Council, the driving force behind AGA's programming at Digestive Disease Week (DDW). We welcome 8 members into their new roles as section vice chairs, joining the existing 17 Council members. Each new vice chair will serve a 2-year term that began immediately following this year's DDW meeting and extends through DDW 2026. Following their term as vice chair, they will move into the role of section chair for an additional 2 years through DDW 2028.

We are also pleased to announce the members joining nominating committees during the 2026 nomination/election cycle. The chairs of the nominating committee will be the immediate past section chairs, whom we also recognize and thank for their service and dedication to the section and the council.


AGA

The 2024 AGA Council chair and section leaders include (L to R, starting top left) Douglas J. Robertson, Uma Sundaram, Linda Anh Nguyen, Vivek Kaul, Florian Rieder, Don Rockey, Jessica Allegretti, Berkeley M. Limketkai, and Kelli L. VanDussen.

Basic & Clinical Intestinal Disorders (BCID)

Uma Sundaram, MD
Vice Chair
Marshall University School of Medicine, Huntington, West Virginia
Nominating committee members
- Colleen Renee Kelly, MD, AGAF, Chair
- Amy C. Engevik, PhD, Medical University of South Carolina
- Ravinder Gill, PhD, University of Illinois at Chicago
- Madhusudan Grover, MD, Mayo Clinic, Rochester, Minnesota
- Lisa L. Strate, MD, Harborview Medical Center, Seattle

Clinical Practice (CP)

Linda Anh Nguyen, MD
Vice Chair
Stanford (Calif.) University School of Medicine
Nominating committee members
- Gary W. Falk, MD, MS, AGAF, Chair
- Megan Adams, MD, JD, MSc, VA Ann Arbor Healthcare System Endoscopy Unit
- Mohammad Bilal, MD, Minneapolis VA Health Care System
- Carolyn Newberry, MD, Weill Cornell Medical Center, New York
- Adam Weizman, MD, MSc, Mount Sinai Hospital, Toronto

Endoscopy, Technology & Imaging (ETI)

Vivek Kaul, MD, AGAF
Vice Chair
University of Rochester (N.Y.) Medical Center
Nominating committee members
- Irving Waxman, MD, Chair
- Sushovan Guha, MD, PhD, University of Texas at Houston
- Pichamol Jirapinyo, MD, MPH, Brigham and Women's Hospital, Boston
- Vladimir Kushnir, MD, Washington University St. Louis Barnes–Jewish West County Hospital
- Andrew C. Storm, MD, Mayo Clinic, Rochester, Minnesota

Immunology, Microbiology & Inflammatory Bowel Diseases (IMIBD)

Florian Rieder, MD
Vice Chair
Cleveland Clinic Foundation
Nominating committee members
- Fernando S. Velayos, MD, AGAF, Chair
- Brigid S. Boland, MD, University of California, San Diego
- Karen L. Edelblum, PhD, Icahn School of Medicine at Mount Sinai, New York
- Michael Kattah, MD, PhD, UCSF Gastroenterology
- Andres J. Yarur, MD, Cedars Sinai Medical Center, Los Angeles

Continued on following page

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molecular mechanisms underlying how microbes activate gut signaling. The AGA Research Foundation grant will support my transition to independence and build key capacities that will be the foundation of my future lab."

Meet the Recipients

- **Karen Jane Dunbar, PhD,** Columbia University, New York, New York
  Research topic: How local microenvironment signals activate fibroblasts to promote Barrett's esophagus and esophageal adenocarcinoma progression.
- **Aaron Hecht, MD, PhD,** Hospital of the University of Pennsylvania, Philadelphia
  Research topic: The impact of diet on the risk of colonization and dissemination of bacterial pathogens in the gut microbiota.
- **Sarah Maxwell, MD,** University of California, San Francisco
  Research topic: Pediatric metabolic dysfunction–associated steatotic liver disease and food insecurity.
- **Chung Sang Tse, MD,** University of Pennsylvania, Philadelphia
  Research topic: Interventions to improve self-efficacy and reduce disability for adults with inflammatory bowel disease (IBD).
- **Jason (Yanjia) Zhang, MD, PhD,** Boston Children's Hospital, Massachusetts
  Research topic: How the gut microbiome affects what you eat and how much.
- **Joseph R. Burclaff, PhD,** University of North Carolina at Chapel Hill (AGA-Bristol Myers Squibb Research Scholar Award in IBD)
  Research topic: How transcription factors in intestinal epithelial stem cells regulate cell cycle and metabolism.

Funded by the generosity of donors, the AGA Research Foundation's research award program ensures that AGA is building a community of researchers whose work serves the greater community and benefits all our patients.

By joining other AGA members in supporting the AGA Research Foundation, you will ensure that young researchers have opportunities to continue their life-saving work. Your tax-deductible contribution supports the foundation's research award program, including the RSA, which ensures that studies are funded, discoveries are made, and patients are treated.

Learn more or make a contribution at www.foundation.gastro.org. ■

Dupilumab Effective in PPI-Refractory Pediatric EoE

BY DIANA SWIFT

Good news for younger children suffering from the uncommon but debilitating gastrointestinal condition eosinophilic esophagitis (EoE): A randomized placebo-controlled study found the monoclonal antibody dupilumab (Dupixent) led to histologic remission in significantly more affected children than placebo. Data from this trial led to a January US Food and Drug Administration (FDA) approval of the anti-inflammatory biologic for patients aged 1-11 years weighing at least 15 kg.

In addition, the trial, published in *The New England Journal of Medicine* (2024 June. doi: 10.1056/NEJMoa2312282), found that a higher-exposure dupilumab regimen (approximating the trough concentration of a 300-mg dose administered once weekly vs every 2 weeks) improved key secondary endpoints, according to gastroenterologist Mirna Chehade, MD, MPH, AGAF, a professor of pediatrics at Icahn School of Medicine at Mount Sinai and Mount Sinai Kravis Children's Hospital in New York City, and colleagues.

In 2022, the FDA approved the drug for those aged 12 or older weighing at least 40 kg.

"Left untreated or inadequately treated, EoE can progress to esophageal narrowing and strictures, leading to increased risk of food impactions and the need for esophageal dilations," Dr. Chehade said in an interview. "Therefore, it's important that children with EoE have the FDA-approved treatment option based on our study that can address their underlying disease starting at a young age."

She added that dupilumab has the exciting potential to transform the standard of care for many young children living with EoE. "There are, however, factors to consider before switching a child to dupilumab — all related to the child's specific medical history and therefore the perceived potential benefits from the drug."

Commenting on the study but not involved in it, Toni Webster, DO, a pediatric gastroenterologist at Cohen Children's Medical Center in Queens, New York, and an assistant professor at the Zucker School of Medicine at Hofstra/Northwell in Hempstead, New York, said, "Like many allergic diseases, EoE is on the rise and, unfortunately, is affecting our children at alarming rates and at earlier ages. Given its efficacy and side-effect profile, dupilumab will vastly change our ability to treat EoE, especially for families who find diet and daily medication to be a challenge."

IMAGE POINT FR/SHUTTERSTOCK

Dr. Webster noted that an elimination diet is a rigorous choice that is often difficult to navigate. And the oral administration of off-label choices, proton pump inhibitors, and swallowed topical steroids, as well as the newly FDA-approved oral budesonide therapy (Eohilia), may also be challenging because many children have precluding aversions to oral therapy. "Regardless of age, treatment choice for EoE should be a good fit that is a plausible addition to a family's lifestyle," she said.

Blocking interleukin-4 and interleukin-13 inflammatory pathways, dupilumab has shown efficacy in other atopic diseases such as eczema. It broadly inhibits most aspects of type 2 inflammation and that action is reflected in its histologic and transcriptomic effects in affected tissues, Dr. Chehade and associates explained.

The Trial

Conducted at 1 Canadian and 26 US sites, the two-part phase 3 study randomly assigned 102 EoE patients aged 1-11 years who were refractory to proton pump inhibition in a 2:2:1:1 ratio.

Part A enrolled 102 patients and evaluated dupilumab at a weight-tiered higher-dose or lower-dose regimen vs placebo (two groups) for 16 weeks.

Part B was a 36-week extended active–treatment period in which eligible dupilumab recipients from part A maintained their weight-tiered higher- or lower-dose regimen, whereas those in the placebo groups switched to weight-tiered higher- or lower-dose dupilumab.

The primary endpoint was histologic remission (peak esophageal intraepithelial eosinophil count, ≤ 6 per high-power field) at week 16. Continued dupilumab treatment appeared to maintain its effect through week 52.

During part A, histologic remission occurred in 25 of the 37 higher-exposure patients (68%), 18 of the 31 lower-exposure patients (58%), and 1 of the 34 placebo patients (3%).

The difference between the higher-exposure regimen and placebo was 65 percentage points (95% CI, 48-81; $P < .001$), whereas that between the lower-exposure regimen and placebo was 55 percentage points (95% CI, 37-73; $P < .001$).

Higher exposure led to significant improvements in histologic, endoscopic, and transcriptomic measures over placebo. Improvements between baseline and week 52 in all patients were generally similar to those between baseline and week 16 in patients who received dupilumab in part A.

As for adverse events, in part A, the incidence of coronavirus disease, nausea, injection-site pain, and headache was at least 10 percentage points higher among dupilumab recipients at either dose than among placebo recipients. Serious adverse events were reported in three dupilumab patients during part A and in six patients overall during part B.

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Liver & Biliary (LB)

Don Rockey, MD
Vice Chair
Medical University of South Carolina, Charleston
Nominating committee members
- Gyongyi Szabo, MD, PhD, AGAF, Chair
- Brett Fortune, MD, MSc, Montefiore Medical Center, New York City
- Ruben Hernaez, MD, MPH, PhD, Baylor College of Medicine, Houston
- Cynthia Ann Moylan, MD, MHS, MS, Duke University, Durham, North Carolina
- Douglas A. Simonetto, MD, Mayo Clinic, Rochester, Minnesota

Microbiome & Microbial Therapy (MMT)

Jessica Allegretti, MD, MPH
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Nominating committee members
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- Melinda Engevik, PhD, Medical University of South Carolina
- Christian Jobin, PhD, University of Florida
- Vanessa Leone, PhD, The University of Wisconsin–Madison
- Jun Yu, MD, PhD, The Chinese University of Hong Kong

Obesity, Metabolism & Nutrition (OMN)

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University of California Los Angeles
Nominating committee members
- Andres Jose Acosta, MD, PhD, Chair
- Barham K. Abu Dayyeh, MD, MPH, Mayo Clinic, Rochester, Minnesota
- Alan L. Buchman, MD, MSPH, University of Illinois at Chicago
- Octavia Pickett-Blakely, MD, MHS, Hospital of the University of Pennsylvania
- Robert Shulman, MD, Texas Children's Hospital, Baylor College of Medicine, Houston

Pediatric Gastroenterology & Developmental Biology (PGDB)

Kelli L. VanDussen, PhD
Vice Chair
Cincinnati Children's Hospital Medical Center ■

Green Initiative Reduces Endoscopic Waste

BY CAROLYN CRIST
MDedge News

FROM DDW 2024

WASHINGTON — As part of a quality improvement initiative, gastroenterologists at the University of Texas Health Science Center reduced endoscopic waste by using a single tool rather than multiple tools during colonoscopies, according to a study presented at Digestive Disease Week® (DDW).

After discussion of environmentally conscious practices during regular meetings, the odds of gastroenterologists using a single tool — either biopsy forceps or a snare — compared with multiple disposable tools was three times higher.

"The burden of waste is massive, with GI being the third-largest waste generator in healthcare. The number of procedures is increasing, which just means more waste, and we have to look at ways to reduce it," said lead author Prateek Harne, MD, a gastroenterology fellow at the University of Texas Health Science Center, Houston.

Overall, the healthcare industry generates 8.5% of US greenhouse emissions, with more than 70% coming from used instruments and supplies, he said. GI endoscopy generates 85,000 metric tons of carbon dioxide waste annually. That waste stems from high case volumes, patient travel, the decontamination process, and single-use devices.

After seeing the waste at his institution, Dr. Harne wondered how to reduce single-use device and nonrenewable waste, particularly the tools used during polypectomies. He and colleagues decided to focus on single-tool use and collected data about the tools used during screening colonoscopies for 8 weeks before an intervention.

As part of the intervention, Dr. Harne and colleagues discussed green endoscopy initiatives supported by North American gastrointestinal societies during a journal club meeting with gastroenterology faculty. They also discussed potential strategies to reduce waste in day-to-day practice during a monthly business meeting, particularly focused on being mindful of using tools during polypectomies. The meetings occurred 3 days apart.

"The burden of waste is massive, with GI being the third-largest waste generator in healthcare. The number of procedures is increasing, which just means more waste, and we have to look at ways to reduce it."

Then Dr. Harne and colleagues collected data regarding tool use during screening colonoscopies, looking at the number and type of instruments used. Before the meetings, 210 patients underwent colonoscopies, including 34% that required no intervention, 32% that required one tool, and 33% that required multiple tools.

After the meetings, 112 patients underwent colonoscopies, including 34% that required no tools, 49% that used one tool, and 17% that used multiple tools. This represented a 17% increase in the use of one tool ($P < .01$) and a 16% decrease in the use of multiple tools ($P < .01$). The odds of using a single tool compared with multiple tools was 2.98, and there was a statistically significant increase in uptake of snare for polypectomy.

The study was limited by being at a single center, having a small sample size, and using a short-term assessment. At the same time, the findings show potential for a low-cost solution through open discussion with gastroenterologists.

"Sir Isaac Newton had two holes for two different sized cats in his home, but all of his cats ended up using the bigger hole," Dr. Harne said in his conclusion. "Maybe we can do the same for polypectomies and use only the tools that we need."

In an interview, Dr. Harne noted he spoke with the janitorial staff at his institution to learn more about endoscopy unit waste, including how much is recycled, how much is incinerated, and who handles the waste. He recognized the work being done in Europe to understand and reduce endoscopic waste and hopes US groups begin to implement more measures.

"Gastroenterologists and their teams need to be more cognizant of the impact we have on the environment," Dr. Harne said. "As our study shows, if providers are aware that they can and should use fewer tools to get the same results, it can lead to a statistically significant impact, just with a friendly reminder to reduce use."

After the presentation, Dr. Harne discussed other shifts with conference attendees, such as not opening or unwrapping tools until needed during a procedure.

"Small changes could have big impacts. Everything that we do in QI [quality improvement] is meant to help patients and the environment," said Amanda Krouse, MD, a research fellow at the University of California, San Diego, who was a moderator of the DDW session on GI fellow–directed QI projects.

"As our study shows, if providers are aware that they can and should use fewer tools to get the same results, it can lead to a statistically significant impact, just with a friendly reminder to reduce use."

In an interview, Alana Persaud, MD, an endoscopy fellow at Geisinger Medical Center in Danville, Pennsylvania, also a moderator of the session, said: "Ultimately, the medical services we're providing are for the longevity of our patients, but at the same time, we don't want it to be to the detriment of the environment, so paying attention to green endoscopy when we can preserve and use more discretion with our devices is worth it so we can all thrive together."

Dr. Harne did not have any disclosures. ■

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A Balanced Approach

On a cautionary note, Eric H. Chiou, MD, an assistant professor of pediatrics at Baylor College of Medicine and a pediatric gastroenterologist at Texas Children's Hospital in Houston, said that while dupilumab shows great promise, further research is needed on its cost-effectiveness in EoE.

"The cost of treatment will need to be compared relative to potential long-term savings from reduced hospitalizations, fewer complications, and improved quality of life," said Dr. Chiou, who was not involved in the study. "A balanced approach that considers clinical efficacy, patient well-being, cost-effectiveness, and equity is essential."

He added that despite the study's encouraging results, long-term safety and efficacy data are needed to fully understand the impact of dupilumab on pediatric patients with EoE. "Dupilumab will need to be compared with existing treatments for EoE such as dietary management and swallowed topical corticosteroids in terms of efficacy, safety, and quality of life improvements."


Dr. Chiou

Additionally, further research is required to identify which patients are most likely to benefit from this therapy and to explore any potential complications associated with its long-term use. "Understanding the optimal dosing and duration of treatment will also be crucial for maximizing benefits while minimizing risks," Dr. Chiou said.

Dr. Chehade agreed. "While it's great that young children finally have an FDA-approved drug to treat their EoE, more research is needed to learn which patient subsets would derive maximum benefit from dupilumab and at which specific steps in their medical management journey should dupilumab be used."

This study was supported by Sanofi and Regeneron Pharmaceuticals. Dr. Chehade disclosed research funding from and consulting for numerous private-sector companies, among others, Sanofi and Regeneron Pharmaceuticals, AstraZeneca, Shire-Takeda, and Bristol-Myers Squibb. Multiple study coauthors disclosed various relationships with private-sector companies, including Sanofi and Regeneron Pharmaceuticals, for research funding, consulting, travel, employment, and stock or intellectual ownership. Dr. Webster and Dr. Chiou disclosed no competing interests relevant to their comments. ■

In IBD Patients, Statin Use Associated With Lower Risk of Developing PSC

BY CAROLYN CRIST
MDedge News

FROM DDW 2024

WASHINGTON — Statin use may contribute to a significant reduction in the risk of new primary sclerosing cholangitis (PSC) among patients with inflammatory bowel disease (IBD), according to a study presented at Digestive Disease Week® (DDW) 2024.

Statin use was associated with an 86% risk reduction, and only 0.09% of IBD patients who took statins developed PSC.

"We all take care of patients with liver disease, and we know what a significant burden PSC is. These patients have a significantly elevated risk of enhanced fibrosis and cirrhosis, multiple cancers, and cholangitis and sepsis," said lead author Chiraag Kulkarni, MD, a gastroenterology fellow at Stanford (California) University Medical School.

"Despite this, we have to date no proven effective medical care for PSC," he said. "However, over the last decade, there is growing evidence that statins may be beneficial in liver disease, and we see this evidence base stretching from basic science to clinical data."

Dr. Kulkarni pointed to numerous studies that indicate statins may slow disease progression in steatotic liver disease, viral hepatitis, and cirrhosis. But could statins prevent the onset of PSC?

Because PSC incidence is low, Dr. Kulkarni and colleagues focused on a patient population with higher prevalence — those with IBD, who have an overall lifetime risk of 2%-7%. The research team followed patients from the date of IBD diagnosis.

Among 33,813 patients with IBD in a national dataset from 2018 onward, 8813 used statins. Statin users tended to be older than non–statin users.

Overall, 181 patients developed new-onset PSC during a median follow-up of about 45 months after initial IBD diagnosis. Only eight statin users (.09%) developed PSC, compared with 173 patients (.69%) in the control group.

In a propensity score–matched analysis, statin therapy was associated with a significantly lower risk of developing PSC (hazard ratio [HR], 0.14; $P < .001$). The associated E-value was 5.5, which suggested a robust finding and unlikely to be due to nonvisible confounding.

The findings were consistent across secondary and sensitivity analyses, including by age, duration of statin use, and type of statin. For instance, for patients under age 50 where PSC is more likely to occur, statins were associated with a 90% reduction in PSC risk.

"We take away two things from this. First, it's suggested that a protective effect occurs at ages where PSC is most likely to occur," Dr. Kulkarni said. "Second, in combination with our propensity score–matched analysis, the results we are observing are not due to a survival bias, where the patients who survive to an age where statins

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PEARLS from the PROS

The Paradox of Achalasia Symptoms

BY DAVID KATZKA, MD

In contrast to most diseases, as achalasia progresses, the symptoms improve. Specifically, reduction of symptoms of dysphagia lulls the gastroenterologist into thinking their patients are doing well.

This improvement in dysphagia is likely due to two mechanisms. The first is that as the esophagus dilates, there is a greater capacity for food accumulation before sensation occurs.

Whether this is completely a volume issue or whether there is a contribution from increased esophageal body distensibility is unclear. Similarly, as achalasia results from inflammation and destruction of the motor neurons of the myenteric plexus, sensory neurons are also damaged.

As a result, the patient's ability to sense food retention lessens. To some degree, this explains the phenomenon of patients presenting with megaesophagus; after years of initially diminishing or stable symptoms managed with patient accommodation, patients present with end-stage disease manifested by a food-impacted esophagus, nocturnal aspiration, and weight loss.

This aspect of the natural history of achalasia has led esophagologists to follow patients with achalasia after treatment at regular intervals with objective examinations such as timed esophagography to mitigate against this worsening yet symptomatically stable course.


Dr. Katzka

Dr. Katzka is based in the Division of Digestive and Liver Diseases, Columbia University Medical Center, New York. He receives research support from Medtronic and is an associate editor for GI & Hepatology News *(previously published in Gastro Hep Advances. 2024 Jan 19. doi: 10.1016/j.gastha.2024.01.006).*

Maintenance Treatment With Guselkumab for Ulcerative Colitis Meets All Endpoints: QUASAR

BY DAMIAN MCNAMARA, MA

FROM DDW 2024

WASHINGTON — Guselkumab (Tremfya, Janssen/Johnson & Johnson) was superior to placebo for maintenance therapy in people with moderately to severely active ulcerative colitis (UC), according to the results of the phase 3 Quasar Maintenance Study.


Dr. Rubin

The primary outcome of clinical remission at 44 weeks was greater with either of two dose regimens of guselkumab than with placebo, David Rubin, MD, AGAF, reported as part of his presentation (Abstract 759) at the annual Digestive Disease Week® (DDW) 2024.

Guselkumab is not the only biologic approved or in development for UC, but it is unique because of its dual action. It is an interleukin (IL)-23p19 subunit inhibitor that blocks IL-23 and also binds to the CD64 receptor on cells that produce IL-23.

Dr. Rubin, who is chief of the section of gastroenterology, hepatology and nutrition at University of Chicago Medicine, Chicago, Illinois said he was unsure at the beginning of the trial if this dual activity "might have any value."

Targeting both the IL-23 circulating in the tissue and the receptor remains to be proven, "but nonetheless seems reasonable," he said.

The study included 568 people, about 42% of whom had an inadequate response or were intolerant to prior advanced therapy, and 42.5% of whom had failed two or more advanced therapy classes.

Clinical responders from two prior guselkumab induction studies were enrolled in this randomized withdrawal, double-blind maintenance trial. At either 12 weeks or 24 weeks of induction, patients were randomly assigned to subcutaneous 200 mg guselkumab every 4 weeks (n = 190), 100 mg guselkumab every 8 weeks (n = 188), or placebo (n = 190). The placebo group served as a guselkumab withdrawal group.

Participants had a mean age of 41 years and a mean disease duration of 7.8 years. The 40% using oral corticosteroids were tapered off during the study.


Dr. Ananthakrishnan

A total of 45.2% of the 100-mg guselkumab group and 50.0% of the 200-mg guselkumab group met the primary outcome of clinical remission at week 44 compared with 18.9% with placebo.

"It was interesting to note that the 200 mg every 4 weeks was similar in efficacy at week 44 to the 100 mg every 8 weeks. It's much less medicine, but you get similar results," Dr. Rubin said.

Secondary Outcomes Also Superior

"The bottom line is not only did it work, but it worked when you look at some secondary endpoints, including endoscopic remission, where the bowel is completely healed," Dr. Rubin said in an interview.

Overall, 34% of all participants who received guselkumab achieved this outcome, "which is a very high rate," he said. "We haven't seen a Mayo score of zero — meaning endoscopic remission — at that rate with any of our other therapies currently."

Among the participants who achieved clinical remission, 69% of them also showed complete remission on endoscopy.

Other secondary outcomes significantly better at week 44 vs placebo included corticosteroid-free clinical remission, maintenance of clinical remission, clinical response, symptomatic remission, endoscopic improvement, histo-endoscopic mucosal improvement, endoscopic normalization, Inflammatory Bowel Disease Questionnaire remission, and fatigue response.

"It was a great study. I think it's very promising data," said session co-moderator Ashwin N. Ananthakrishnan, MBBS, MPH, AGAF, director of the Crohn's and Colitis Center at Massachusetts General Hospital in Boston.

"As we get more data from these more selective interleukins, we'll get a better sense of how that plays out" vs other similar agents in development, he added.

IL-23 Target Seems Safe

One or more adverse events were reported by 70% of the higher-dose guselkumab group, 65% of the lower-dose guselkumab group, and 68% of the placebo group.

The most common adverse events in a combined 200-mg and 100-mg guselkumab group were lower than in the placebo group: 11.2% vs 14.1% reported COVID-19, 11.2% vs 29.7% reported exacerbation of UC, and 6.1% vs 6.8% experienced arthralgia, respectively.

No cases of active tuberculosis, opportunistic infection, anaphylaxis, serum sickness, Hy's law, or serious hepatic issues were reported. One patient had clear cell renal carcinoma, another had rectal adenocarcinoma, and one hemorrhagic stroke was reported in the treatment groups. No patients died during the trial.

A higher proportion of people in the placebo group (13.7%) discontinued the study than those in the 100-mg guselkumab group (10.6%) and the 200-mg guselkumab group (11.6%).

"In general, we have accepted that the IL-23 target seems to be a very safe one," Dr. Rubin said.

A leading theory is that unlike some interleukins, IL-23 is expressed only where the body has inflammation; therefore, targeting IL-23 does not affect other areas, he explained.

If approved by the Food and Drug Administration, it would expand the official indications for guselkumab, which was approved in 2020 for psoriatic arthritis and in 2017 for plaque psoriasis.

The study was supported by Janssen Research & Development. Dr. Rubin is a consultant for Janssen. Dr. Ananthakrishnan had no relevant disclosures. ■

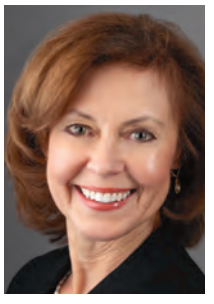
Continued from previous page

are prescribed simply have a biologically different predilection for developing PSC."

Statins also protected against PSC in both ulcerative colitis (HR, 0.21) and Crohn's disease (HR, 0.15), as well as both women (HR, 0.16) and men (HR, 0.22).

Given the uncertainty about the optimal duration of statin therapy for a protective effect, Dr. Kulkarni and colleagues looked at a lag time of 12 months. They found statins were associated with an 84% risk reduction (HR, 0.16), which was similar to the primary analysis.

The study was limited by the inability to capture dosage data or medication adherence. The findings raised several questions, Dr. Kulkarni said, such as the underlying mechanisms and clinical implications. For instance, the underlying mechanisms appear to be related to the pleiotropic effect of statins, modulation of gut inflammation, and alterations in bile acid profiles.


Dr. Szabo

"This is really fascinating and interesting. I wonder about this as a primary prevention strategy in those who have normal cholesterol. Could this work or not?" said Gyongyi Szabo, MD, AGAF, chief academic officer at Beth Israel Deaconess Medical Center, Boston, who was a moderator for the Liver & Biliary Section Distinguished Abstract Plenary Session.

Dr. Kulkarni noted that these findings wouldn't change clinical practice alone, but based on existing literature around statin hesitancy among patients with cardiovascular disease, the risk reduction for PSC could provide another reason to encourage patients to take them.

"To move this to a place where you can actually think about primary prevention, I think the biological mechanisms need to be teased out a little bit more," Dr. Kulkarni said. "Then I think you probably still need to identify a higher-risk group than IBD alone."

Dr. Kulkarni declared no disclosures. ■

Significant Benefit With Liver Transplantation in ACLF: CHANCE Study

BY BECKY MCCALL

FROM EASL 2024

MILAN — Liver transplantation improves survival in patients with acute-on-chronic liver failure (ACLF), according to interim clinical outcomes of the large, international CHANCE study.

To date, the results show that 3-month post–liver transplantation mortality rates in patients with ACLF grades 2 and 3 were only 9%, which is not significantly different than that of patients with decompensated cirrhosis, with a mortality of 7%.

"Treatment of ACLF is an unmet medical need," said Rajiv Jalan, MD, professor of hepatology and honorary consultant in hepatology, University College London Hospitals, London, England.

These findings highlight "the inadequacy of current transplant allocation criteria for patients with ACLF 2 and 3," which is leading to excess mortality on the wait list, he added.

Dr. Jalan presented the interim results at the European Association for the Study of the Liver (EASL) Congress 2024.

If confirmed in the full analysis, these results argue strongly for increasing access to liver transplantation and changing organ allocation for patients with ACLF 2 and 3, he said.

Organ Allocation Principally Based on MELD Scores

ACLF, which occurs in patients with cirrhosis and acutely decompensated liver disease admitted to hospital, carries a high short-term risk for death. The risk for 28-day mortality for ACLF 2 and 3 is between 30% and 90% and characterized by multiorgan failure.

As seen in previous data, even patients on the transplant waiting list with a low Model for End-Stage Liver Disease (MELD) score have a risk for death between 20% and 30% if they are ACLF 2 and 3, Dr. Jalan said.

MELD scores do not consider the risk for death because of failure of extrahepatic organs, he added. Existing worldwide organ allocation systems are principally based on patient MELD scores or its variations; therefore, many patients die on the waiting list.

With this in mind, the CHANCE study aimed to compare 1-year graft and patient survival rates after liver transplantation in patients with ACLF 2 or 3 at the time of transplantation with patients with decompensated cirrhosis without ACLF and transplantation-free survival of patients with ACLF 2 or 3 not listed for liver transplantation.

The multicenter observational study comprised 66 liver transplant centers from 21 countries and over 500 investigators. Recruitment was closed after 1000 patients were enrolled.

Dr. Jalan

Patients were aged 54-56 years, 31%-35% were women, 48%-70% had alcohol-related cirrhosis, and 19%-24% had metabolic dysfunction–associated steatohepatitis. MELD scores ranged from 25 to 36.

For the interim results, Dr. Jalan and colleagues assessed mortality on the waiting list and 3-month post–liver transplantation mortality.

Secondary endpoints included quality of life and cost of care.

Of the 823 patients in the study, they were grouped as follows: 376 patients with ACLF 2 or 3 listed for liver transplantation (group 1), 313 patients with ACLF 0 or 1 and MELD score > 20 listed for liver transplantation (group 2), and 134 patients with ACLF 2 or 3 not listed for liver transplantation (group 3).

Overall, patients in group 1 had very severe ACLF; 177 patients with ACLF 3 had three or more organ failures, Dr. Jalan noted.

"It is interesting to note that, in group 3, there is an overrepresentation of alcohol-related cirrhosis, and this might reflect a bias in transplantation," he added.

Dr. Jalan highlighted geographical points of difference. Patients in the United States were younger, which could be important when interpreting results of post-transplantation outcomes. In Asia, the majority of the patients were men and primarily from India, where living donor transplantation is commonly performed. In Latin America, only 33% of study participants had alcohol-related cirrhosis in contrast to 67% of those in North America.

However, "comorbidities across the world … and MELD scores were also similar," Dr. Jalan said.

Death or Delisting

Between listing and transplantation, 28% of patients in group 1 either died or were delisted, compared with 16% of those in group 2. In group 3, 85% of patients who were not listed for transplantation in the first place died.

Similar to what has been seen in other studies, nearly 50% of patients with ACLF 3 but a MELD score < 25 on the wait list died or were delisted, Dr. Jalan pointed out, suggesting that these patients are disadvantaged under the current system of waiting list priority.

Geographically, deaths on the wait list were significantly higher in Latin America at 40% than in North America, Europe, and Asia at 20%, 18%, and 13%, respectively.

"This is likely due to low donation rates in Latin America," Dr. Jalan said.

Turning to 3-month post-transplantation mortality, the rates in groups 1 and 2 were 9% and 7%, respectively.

"This demonstrates very nicely the clear benefit of transplant," Dr. Jalan said. "The risk of death post transplant, even with ACLF 2 or 3, is not significantly different to those patients with decompensated cirrhosis."

There was a slightly higher risk for death in patients with ACLF 3 than in those with ACLF 2 at 14% vs 7%, but "the risk of death in these patients if they don't have transportation is 70%-80%," he said.

Looking at 3-month post-transplantation mortality by continent, Dr. Jalan highlighted that Latin America showed 16% risk, compared with Asia, Europe, and North America that showed 12%, 7%, and 3% risk, respectively.

"This is probably multifactorial and likely to be influenced by time on the waiting list, quality of organs available, and patient demographics, among other factors," Dr. Jalan said. When very sick people undergo transplantation, "there is a higher risk of death."

The patients in this study have waited a long time, "which worsens their situation," said Dr. Jalan, reinforcing his argument for changing the international organ allocation system to allow earlier access for these patients.

'Organ Allocation Is Extremely Complex'

Comoderator Ana Lleo, MD, PhD, full professor of internal medicine and hepatology, Humanitas University, Milan, Italy, commented that "the number of patients included in this international study is significant," and that the issue of mortality on the wait list is of great clinical interest.

"The landscape of organ allocation is extremely complex," she added.

The system for liver transplantation considers a large number of clinical conditions with very diverse benefit profiles, she explained.

"While we would like to offer liver transplantation for all patients with any range of benefit, the current donations are not sufficient to cover the request," Dr. Lleo said. "Therefore, prioritization remains key."

The findings do illustrate the inadequacy of current transplantation allocation criteria for patients with ACLF 2 and 3, said Debbie Shawcross, MBBS, PhD, professor of hepatology and chronic liver failure, King's College Hospital, London, England, who is also serving as vice-secretary of the EASL Governing Board.

However, "this must be balanced by the recognition that the global donor pool of organs available is a finite resource," she said, echoing Dr. Lleo's comments.

This calls for wider ethical discussions to avoid disadvantaging more stable, often younger patients with cirrhosis who are listed for transplantation, she added.

Dr. Jalan declared he is the inventor of Ornithine Phenylacetate, licensed by UCL to Mallinckrodt Pharma; a speaker and grant reviewer for Grifols Research Collaboration: Yaqrit; and the founder of Yaqrit, Hepyx, CyberLiver, and Gigabiome. Dr. Lleo declared that she does not have any conflicts relevant to this work. Dr. Shawcross declared advisory board/consultancy for EnteroBiotix, Norgine, Satellite Bio, and MRN Health. ■

Emerging Evidence Supports Dietary Management of MASLD Through Gut-Liver Axis

BY CAROLYN CRIST
MDedge News

FROM DDW 2024

WASHINGTON — Microbiota-focused dietary therapy could improve disease outcomes and management of metabolic dysfunction–associated steatotic liver disease (MASLD), according to a study presented at the annual Digestive Disease Week® (DDW) 2024.

For instance, patients with MASLD had lower intake of fiber and omega-3 fatty acids but higher consumption of added sugars and ultra-processed foods, which correlated with the associated bacterial species and functional pathways.

"MASLD is an escalating concern globally, which highlights the need for innovative targets for disease prevention and management," said lead author Georgina Williams, PhD, a postdoctoral researcher in diet and gastroenterology at the University of Newcastle, Australia.

"Therapeutic options often rely on lifestyle modifications, with a focus on weight loss," she said. "Diet is considered a key component of disease management."

Although calorie restriction with a 3%-5% fat loss is associated with hepatic benefits in MASLD, Dr. Williams noted, researchers have considered whole dietary patterns and the best fit for patients. Aspects of the Mediterranean diet may be effective, as reflected in recommendations from the American Association for the Study of Liver Disease (AASLD), which highlight dietary components such as limited carbohydrates and saturated fat, along with high fiber and unsaturated fats. The gut microbiome may be essential to consider as well, she said, given MASLD-associated differences in bile acid metabolism, inflammation, and ethanol production.

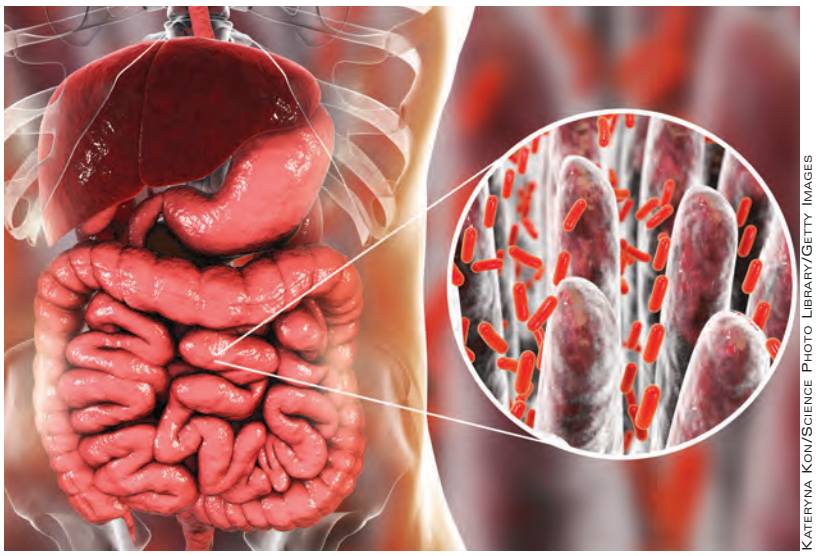
Dr. Williams and colleagues conducted a retrospective case-control study in an outpatient liver clinic to understand diet and dysbiosis in MASLD, looking at differences in diet, gut microbiota composition, and functional pathways in those with and without MASLD. The researchers investigated daily average intake, serum, and stool samples among 50 people (25 per group) matched for age and gender, comparing fibrosis-4, MASLD severity scores, macronutrients, micronutrients, food groups, metagenomic sequencing, and inflammatory markers such as interleukin (IL)-1ß, IL-6, tumor necrosis factor (TNF)-α, cytokeratin (CK)-18, and high-sensitivity C-reactive protein (hsCRP).

Dietary Characteristics

At baseline, the groups differed by ethnicity, prescription medication use, and body mass index (BMI), where the MASLD group had greater ethnic diversity, medication use, and BMI. In addition, the MASLD group had a zero to mild score of fibrosis.

Overall, energy intake didn't differ significantly between the two groups. The control group had higher alcohol intake, likely since the MASLD group was recommended to reduce alcohol intake, though the difference was about 5 grams per day. The MASLD group also had less caffeine intake than the control group, as well as slightly lower protein intake, though the differences weren't statistically significant.

While consumption of total carbohydrates didn't differ significantly between the groups, participants with MASLD consumed more calories from carbohydrates than did the controls. The MASLD group consumed more calories from added and free sugars and didn't meet recommendations for dietary fiber.



KATERYNA KON/SCIENCE PHOTO LIBRARY/GETTY IMAGES

With particular food groups, participants with MASLD ate significantly fewer whole grains, red and orange fruits, and leafy green vegetables. When consuming fruit, those with MASLD were more likely to drink juice than eat whole fruit. These findings could be relevant when considering high sugar intake and low dietary fiber, Dr. Williams said.

With dietary fat, there were no differences in total fat between the groups, but the fat profiles differed. The control group was significantly more likely to consume omega-3 fatty acids, including alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA). The MASLD group was less likely to consume seafood, nuts, seeds, avocado, and olive oil.

With inflammatory markers, hsCRP and CK-18 were increased in MASLD, while IL-1ß was increased in controls, which was consistently associated with higher alcohol intake among the control group. IL-6 and TNF-α didn't differ between the groups.

Notably, dietary fats were most consistently associated with inflammatory markers, Dr. Williams said, with inflammation being positively associated with saturated fats and negatively associated with unsaturated fats.

As for microbiota, the alpha diversity was no different, but the beta diversity was across 162 taxa. Per bacterial species, there was an inverse relationship between MASLD and associations with unsaturated fat, as well as positive indicators of high sugar and fructose intake and low unsaturated fat and dietary fiber intake.

Beyond that, the functional pathways enriched in MASLD were associated with increased sugar and carbohydrates, reduced fiber, and reduced unsaturated fat. Lower butyrate production in MASLD was associated with low intake of nuts, seeds, and unsaturated fat.

In Clinical Practice

Dr. Williams suggested reinforcing AASLD guidelines and looking at diet quality, not just diet quantity. Although an energy deficit remains relevant in MASLD, macronutrient consumption matters across dietary fats, fibers, and sugars.

Future avenues for research include metabolomic pathways related to bile acids and fatty acids, she said, as well as disentangling metabolic syndrome from MASLD outcomes.

Session moderator Olivier Barbier, PhD, professor of pharmacy at Laval University in Quebec City, Canada, asked about microbiome differences across countries. Dr. Williams noted the limitations in this study of looking at differences across geography and ethnicity, particularly in Australia, but said the species identified were consistent with those found in most literature globally.

In response to other questions after the presentation, Dr. Williams said supplements (such as omega-3 fatty acids) were included in total intake, and those taking prebiotics or probiotics were excluded from the study. In an upcoming clinical trial, she and colleagues plan to control for household microbiomes as well.

"The premise is that microbiomes are shared between households, so when you're doing these sorts of large-scale clinical studies, if you're going to look at the microbiome, then you should control for one of the major confounding variables," said Mark Sundrud, PhD, professor of medicine at the Dartmouth Center for Digestive Health in Lebanon, New Hampshire. Dr. Sundrud, who wasn't involved with this study, presented on the role of bile acids in mucosal immune cell function at DDW.

"We've done a collaborative study looking at microbiomes and bile acids in inflammatory bowel disease patients versus controls," which included consideration of households, he said. "We were able to see more intrinsic disease-specific changes."

Dr. Williams declared no relevant disclosures. Dr. Sundrud has served as a scientific adviser to Sage Therapeutics. ■

Combination Therapy Looks Promising for Hepatitis D

BY DIANA SWIFT

The combination of the antiviral bulevirtide (Hepcludex) plus pegylated interferon alfa-2a was superior to bulevirtide monotherapy for chronic hepatitis delta virus (HDV) infection, a multinational phase 2b open-label study in Europe found.

The combination resulted in higher rates of HDV RNA suppression levels at 24 weeks after end of treatment, especially at a higher, 10-mg dose of bulevirtide, according to researchers led by Tarik Asselah, MD, PhD, a professor of medicine and hepatology at Hôpital Beaujon, APHP, Clichy, France, and the University of Paris.

"This response appeared to be maintained from 24-48 weeks after the end of treatment — a finding that supports the concept that sustained undetectable HDV RNA for at least 1 year after treatment is possible in patients with chronic hepatitis D who have been treated with a finite duration of therapy of at least 96 weeks, including 48 weeks of peginterferon alfa-2a therapy," the investigators wrote in *The New England Journal of Medicine* (2024 Jun 6. doi: 10.1056/NEJMoa2314134).

"As of today, there is no approved treatment for chronic HDV infection in the United States. Pegylated interferon alfa-2a, which is not approved for treatment of HDV, is the only option recommended by US treatment guidelines," said study corresponding author Fabien Zoulim, MD, PhD, a hepatologist at the Lyon Hepatology Institute and a professor of medicine at the University of Lyon in France, in comments to *GI & Hepatology News*. "Bulevirtide 2 mg is approved for treating chronic HDV and compensated liver disease, and both bulevirtide and peginterferon are recommended options by the European treatment guidelines."

The study found that most patients with undetectable HDV RNA levels during treatment-free follow-up showed no reduction in HepB surface antigen (HBsAg), suggesting an undetectable HDV RNA level can be achieved and sustained without HBsAg loss, the authors wrote.

While very small numbers in the combo groups and the higher-dose bulevirtide arm cleared HBsAg, "the study was not powered to evaluate the HBsAg response," Dr. Zoulim said.

HDV is a defective virus that requires HBsAg for assembly and propagation, the authors noted. It affects as many as 20 million persons worldwide, and as the most severe form of chronic viral hepatitis, is associated with 2-6 times the risk of hepatocellular carcinoma and 2-3 times the risk of death associated with HBV monoinfection (Hepatol Int. 2023 Oct 3. doi: 10.1007/s12072-023-10575-0).


Dr. Gurakar

Though not common in the United States, it affects an estimated 10-20 million people worldwide (J Hepatol. 2020 Apr. doi: 10.1016/j.jhep.2020.04.008). One US database study found HDV in 4.6% of patients with hepatitis B virus infection (Hepatology. 2024 May. doi: 10.1097/HEP.0000000000000687).

Commenting on the study but not a participant in it, Ahmet O. Gurakar, MD, AGAF, a professor of medicine in the sections of gastroenterology and hepatology at Johns Hopkins School of Medicine in Baltimore, Maryland, said the study findings look promising for the future treatment of HDV, but cautioned that it will be "a slow process to get approval for combination therapy with bulevirtide since the [Food and Drug Administratoin] has previously said it needs to see more studies. The findings need to be confirmed in larger groups, but it's difficult to recruit enough patients in the United States for a trial since hepatitis D is not common in this country — it's more common in the Mediterranean basin Eastern European populations."

The Trial

The investigators randomly assigned 174, largely male, patients ages 18-65 (mean, about 41) years to receive one of four treatments:

- Pegylated interferon alfa-2a alone at 180 µg per week for 48 weeks (n = 24).
- Bulevirtide at a daily dose of 2 mg plus peginterferon alfa-2a at 180 µg per week for 48 weeks, followed by the same daily dose of bulevirtide for 48 weeks (n = 50).
- Bulevirtide at 10 mg plus peginterferon alfa-2a at 180 µg per week for 48 weeks, followed by the same daily dose of bulevirtide for 48 weeks (n = 50).
- Bulevirtide at a daily dose of 10 mg alone for 96 weeks (n = 50).

All were followed for 48 weeks after treatment. The primary comparison was between the 10-mg bulevirtide plus peginterferon alfa-2a group and the 10-mg bulevirtide monotherapy group.

At 24 weeks post treatment, HDV RNA was undetectable in 17% of patients in the peginterferon alfa-2a group. In the other arms, HDV RNA was undetectable in 32% in the 2-mg bulevirtide plus peginterferon alfa-2a group, in 46% of the 10-mg bulevirtide plus peginterferon alfa-2a group, and in 12% of the 10-mg bulevirtide group.

"The findings need to be confirmed in larger groups, but it's difficult to recruit enough patients in the United States for a trial since hepatitis D is not common in this country."

For the primary comparison, the between-group difference was 34 percentage points (95% CI, 15-50; $P < .001$).


Dr. Lok

"Results of this study should prompt reassessment whether bulevirtide should be used in combination with pegylated interferon in patients with no contraindications."

At 48 weeks after the end of treatment, HDV RNA was undetectable in 25% in the peginterferon alfa-2a group, 26% in the 2-mg bulevirtide plus peginterferon alfa-2a group, 46% in the 10-mg bulevirtide plus peginterferon alfa-2a group, and 12% in the 10-mg bulevirtide group.

Also calling the findings promising, Anna Lok, MBBS, MD, AGAF, a gastroenterologist at the University of Michigan, Ann Arbor, said that, "Given that the European Medicines Agency's approval is for bulevirtide alone at 2 mg, results of this study should prompt reassessment whether bulevirtide should be used in combination with pegylated interferon in patients with no contraindications, and if 10 mg is more appropriate than a 2-mg dose."

As to safety, the most frequent adverse events were leukopenia, neutropenia, and thrombocytopenia, with the majority of adverse events being grade 1 or 2.

In comparison with other research, the current trial found that 70% in the 10-mg bulevirtide plus peginterferon alfa-2a group had an undetectable HDV RNA level at the end of treatment versus results of the Hep-Net International Delta Hepatitis Interventional Trial II (HIDIT-II), in which 33%-48% had undetectable levels after 96 weeks of peginterferon alfa-2a therapy, with or without tenofovir disoproxil (Lancet. 2019 Mar. doi: 10.1016/S1473-3099[18]30663-7). And in the phase 3 MYR301 trial, HDV RNA was undetectable in 20%-36% after 96 weeks of bulevirtide monotherapy (N Engl J Med. 2023 Jun. doi: 10.1056/NEJMoa2213429).

The authors acknowledged that in addition to the lack of blinding, the trial was not designed to compare the two doses of bulevirtide and therefore lacked an adequate sample size to allow for formal comparisons. And although it included a peginterferon alfa-2a monotherapy group, it was not sufficiently powered to allow for comparison. They are currently considering plans for further studies in this area.

This study was funded by Gilead Sciences. Dr. Asselah disclosed consulting, safety/data monitoring, or travel for Gilead Sciences, AbbVie, Antio Therapeutics, Eiger Biopharmaceutical, Enyo Pharma, GlaxoSmithKline, Johnson & Johnson Healthcare Systems, and Vir Biotechnology. Dr. Zoulim reported consulting or research for multiple pharmaceutical/biotech companies, including Gilead Sciences. Numerous study coauthors declared financial relationships such as consulting, research, or employment with multiple private-sector companies, including Gilead Sciences. Dr. Lok and Dr. Gurakar disclosed no competing interests relevant to their comments. ■

Researching the Microbiome

Scientist *from page 1*

Dr. Dey, a graduate of the AGA Future Leaders Program, is now a gastroenterologist and researcher at the Fred Hutch Cancer Center in Seattle. In an interview, he talked about his dual role as a physician and scientist, and how those two interests are guiding his research in precancerous conditions of the colon.

Cases like that of the young woman with colon cancer "really help drive the urgency of the work we do, and the research questions we ask, as we try to move the ball forward and help folks at earlier stages," he said.

Q: Why did you choose GI?

When you think about what sorts of chronic diseases really impact your quality of life, gut health is one of the chief contributors among various aspects of health. And that really appealed to me — the ability to take someone who is essentially handicapped by a series of illnesses and symptoms that derive from the GI tract and enable them to return to the person they want to be, to be productive in the way that they want to be, and have a rewarding life.

As I thought about how I wanted to contribute to the future of medicine, one of the ways in which I've always thought that I would do that is through research. When I considered the fields that really appealed to me, both from that clinical standpoint and research standpoint, GI was one that really stood out. There has been a lot of exciting research going on in GI. My lab currently studies the microbiome, and I feel like this is an area in which we can contribute.

Q: What role does digestive health play in overall health?

Obviously, the direct answer is gut health is so critical in something like nutritional intake. Some GI symptoms, if your gut health has gone awry, can really be detrimental in terms of quality of life. But one less obvious role that digestive health plays is its long-term effects. We're starting to appreciate that gut health, the gut microbiome, and gut immune education are probably long-term players. Some experiences in early life might shape our immunity in ways that have consequences for us much later in life. Whether we get early-life antibiotics, for example, may potentially contribute to colorectal cancer down the line. Thinking about the long-term players is more challenging, but it's also an appealing opportunity as we think about how we can shape medicine moving forward.

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

First, being a physician-scientist: It's challenging to be either a physician alone or to be a researcher alone. And trying to do both includes the challenges of both individual worlds. It just takes more time to get all the prerequisite training. And second, there are just challenges with getting the opportunities to contribute in the ways that you want — to get the research funding, to get the papers out, things like that.

Q: Tell me about the work you've been doing in your lab to develop microbiome-based strategies for preventing and treating cancer.

The microbiome presents several opportunities when it comes to cancer prevention. One is identifying markers of cancer risk, or of general good health down the line. Some of those biomarkers could — potentially — feed directly into personalized risk assessment and maybe even inform a future screening strategy. The second opportunity the microbiome presents is if we identify a microbe that influences your cancer risk, can we then understand and exploit, or utilize, that mechanism to mitigate cancer risk in the future? Our lab has done work looking at subspecies levels of microbes that track with health or cancer. We've done some work to identify what these subspecies groupings are and have identified some links to certain precancerous changes in the colon. We think that there's an opportunity here for future interventions.

Q: Have you published other papers?

We recently published another paper (Front Gastroenterol. 2024 Jan. doi: 10.3389/fgstr.2023.1323471) describing how some microbes can interact with a tumor suppressor gene and are influenced in a sex-biased manner to drive tumorigenesis in a mouse model. We think, based on what we're seeing in human data, that there may be some relationships and we're exploring that now as well.

Q: What is your vision for the future in GI, and in your career?

The vision that I have is to create clinical tools that can expand our reach and our effectiveness and cancer prevention. I think that there are opportunities for leveraging microbiome research to accomplish this. And one outcome I could imagine is leveraging some of these insights to expand noninvasive screening at even earlier ages than we do now. I mean, we just dialed back the recommended age for colonoscopy for average-risk individuals to 45. But I could envision a future in which noninvasive screening starts earlier, in which the first stool-based tests that we deploy to assess personalized risk are used in the pediatric clinic. ■

LIGHTNING ROUND

Texting or talking?
Talking

Favorite city in the United States besides the one you live in?
St. Louis

Cat or dog person?
Both

If you weren't a GI, your dream profession?
Musician

Best place you went on vacation?
Borneo

Favorite sport?
Soccer

Favorite ice cream?
Cashew-based salted caramel

Song you have to sing along with when you hear it?
Sweet Child of Mine

Favorite movie or TV show?
25th Hour or Shawshank Redemption

Optimist or Pessimist?
Optimist

EoE Often Persists Despite Treatment

BY WILL PASS
MDedge News

FROM GASTRO HEP ADVANCES

Many patients with eosinophilic esophagitis (EoE) continue to have substantial disease burden despite medical therapy, based on a recent retrospective study.

Challenging patient journeys were common across age groups, with a range of ongoing symptoms and histological abnormalities supporting high unmet need among patients with EoE, lead author Olulade Ayodele, MBBS, MPH,

"Our findings outline the persistent disease activity and difficult therapeutic journeys faced by patients with EoE irrespective of their age, as well as the substantial disease burden."

of Takeda Development Center Americas and colleagues reported.

"Recent studies have found that patients with EoE experience a complicated journey to diagnosis and a substantial disease burden, which requires significant healthcare resource utilization," the investigators wrote in *Gastro Hep Advances* (2024 Mar 1. doi: 10.1016/j.gastha.2024.02.007). "Reasons for this may

EoE *Continued on following page*

In a large, retrospective, real-world cohort study, investigators examined the patient journey in 613 child, adolescent, and adult patients with eosinophilic esophagitis (EoE) via healthcare claims database and electronic medical record data. As we enter into an exciting era in novel biologic therapies in EoE, the article provides comprehensive and reliable information in several critical and actionable areas with respect to EoE diagnosis and management.


Dr. Jain


Dr. Mittal

The study found that 51% of patients had histologic disease activity (defined as eosinophils ≥ 15/high-powered field) 3 years after index endoscopy despite high rates of appropriate first-line medical therapies (proton pump inhibitors in 51%, topical corticosteroids in 10%, combination therapy in 34%) and dietary elimination strategies (some form used in 58%). Nearly one in five patients had an all-cause inpatient hospitalization; and the mean number of emergency department visits was one visit per patient annually. The study also found that only 76% had a follow-up endoscopy after the index procedure, only 57% of patients had follow-up with a gastroenterologist, and 14% of patients saw no relevant EoE specialist.

The study highlights the heterogeneity of the patient experience in EoE and suggests that improvements in the reliability and precision of EoE care models will impact healthcare utilization. In particular, the findings support the need for structured and systematic mechanisms for appropriate follow-up after the index diagnosis and increased use and continued development of novel therapies.

In this era of precision medicine, the take home message from this study is that there is an opportunity to improvement outcomes in EoE by addressing the gap in appropriate medical contact in EoE. This could be achieved by developing systematic care models which address healthcare operational factors, physician tendencies, and patient attitudes.

Anand Jain, MD, is assistant professor in the Division of Digestive Diseases at Emory University School of Medicine, Atlanta, Georgia. Ravinder Mittal, MD, AGAF, is professor in the Division of Gastroenterology at the University of California, San Diego, and staff physician at the San Diego VA Hospital. They report no conflicts of interest.

Esophageal Cancer Risk Unchanged After *H pylori* Eradication

BY WILL PASS
MDedge News

FROM GASTROENTEROLOGY

Decreased prevalence of *Helicobacter pylori* infection is not associated with an increased rate of esophageal cancer, based on a multinational cohort study.

This finding suggests that eradication of *H pylori* is safe with regard to esophageal cancer risk, and eradication campaigns are not contributing to the rising incidence of esophageal adenocarcinoma (EAC) over the past four decades, reported lead author Anna-Klara Wiklund, MD, of Karolinska Institutet, Stockholm, Sweden, and colleagues.

"The decreased risk of esophageal adenocarcinoma seen in individuals with *H pylori* infection is probably explained by the *H pylori*–induced gastric atrophy, which reduces gastric acid production and thus acidic gastroesophageal reflux, the main risk factor for this tumor," the investigators wrote in *Gastroenterology* (2024 Mar 19. doi: 10.1053/j.gastro.2024.03.016). "It seems plausible that eradication of *H pylori* would increase the risk of EAC, although the answer to this question is unknown with the only study on the topic (from our group) having too few cases and too short follow-up."

H pylori *Continued on following page*

Understanding the demographic and biomarker risk predictors of esophageal cancer continues to be a research priority. Many esophageal cancer patients fall outside of current screening guidelines. Updated recommendations have suggested including high-risk women, driven by higher quality datasets, emerging biomarkers, and cost-effective non-endoscopic screening devices.


Dr. Otaki

In this article, Wiklund et al challenge another dogma that *Helicobacter pylori* infection offers protection against esophageal cancer. More specifically that overtreatment of *H pylori* is associated with increased incidence of esophageal adenocarcinoma. Their Nordic data set identified 550 cases of esophageal cancer in the 661,987 patients treated for *H. pylori* from 1995–2018 who were followed >5 million person-years. Interestingly, standardized incidence ratio of esophageal adenocarcinoma decreased over time.

This large dataset continues to encourage us to treat *H pylori* in patients at risk of progressing to gastric cancer. This parallels a growing fund of literature encouraging us to move away from the linear pathophysiologic logic that eliminating *H pylori*–induced gastric atrophy provokes gastroesophageal reflux disease and esophageal cancer. Instead we should factor in other parameters, including the complex interaction between the esophageal microbiome and gastric *H pylori*. Some postulated mechanisms include an extension of the gastric inflammatory milieu into the esophagus, and potential crosstalk with the esophageal microbiome.

Such studies underscore the need to personalize both foregut cancer screening criteria and treatment of inflammatory conditions at a patient and population level, so that we can make meaningful impacts in disease prevalence and cancer survival.

Fouad Otaki, MD, is associate professor in the Division of Gastroenterology & Hepatology at Oregon Health & Science University, Portland.

EoE *Continued from previous page*
include delays in diagnosis owing to nonspecific symptoms, adaptive behaviors, progression of silent disease, lack of adequate follow-up or referral, or suboptimal treatment after diagnosis."

Two medications are currently Food and Drug administration approved for EoE: dupilumab, a biologic for patients aged 1 year and older, and budesonide oral suspension, a topical corticosteroid for patients aged 11 years and older.

The investigators noted that "biologic therapies may not always be selected as first-line treatment, and are often associated with high costs"; however, the effects of real-world treatment decisions like these are poorly documented, prompting the present study.

The final dataset comprised 613 patients with newly diagnosed EoE treated in a rural integrated healthcare system, all of whom had at least 12 months of data before and after a predetermined index date. Individuals were stratified by age, including 182 children, 146 adolescents, 244 adults, and 41 older adults.

Signs and symptoms of EoE frequently worsened after the index date, including dysphagia (34.6% before, 49.9% after), abdominal pain (33.0% before, 48.1% after), and nausea/vomiting (20.1% before, 31.5% after).

At baseline, 80.5% of endoscopies were abnormal and 87.9% of patients had more than 15 eosinophils/high-power field. These parameters improved post index; however, 3 years later, 62.3% of patients still had abnormal endoscopic appearance and 51.2% had abnormal histologic activity.

"Recent studies have found that patients with EoE experience a complicated journey to diagnosis and a substantial disease burden, which requires significant healthcare resource utilization."

Before and after index, the most prescribed treatments were corticosteroids (47.3% before, 87.9% after) and proton pump inhibitors (51.1% before, 96.1% after).

After index, 44.0% of patients discontinued their first-line treatment, and 13.9% experienced disease progression.

"We found that a substantial portion of patients with EoE received variable medical treatments, and did not report undergoing follow-up care, consulting with specialists, or routinely undergoing endoscopy with biopsy after diagnosis; the reasons for this are unknown, but experiences do not appear to be consistent with current guideline recommendations," Dr. Ayodele and colleagues wrote.

They also noted substantial healthcare resource utilization; more than half of the patients visited emergency departments, and nearly one in five were admitted as inpatients.

"Our findings outline the persistent disease activity and difficult therapeutic journeys faced by patients with EoE irrespective of their age, as well as the substantial disease burden," the investigators concluded. "These data highlight the potential unmet medical need of patients with EoE in the United States."

The study was funded by Shire Human Genetic Therapies, a member of the Takeda group of companies. The investigators disclosed additional relationships with RTI Health Solutions and Receptos/Celgene. ■

H pylori *Continued from previous page*

That study involved only 11 cases of EAC (*Helicobacter*. 2020 Jun. doi: 10.1111/hel.12688).

For the present study, Dr. Wiklund and colleagues aggregated data from all individuals who had undergone *H. pylori* eradication in Finland, Denmark, Iceland, Norway, and Sweden from 1995 to 2019. The dataset comprised 661,987 such individuals with more than 5 million person-years after eradication therapy, including 550 cases of EAC. Median follow-up time was approximately 8 years, ranging from 1 to 24 years.

"The results should be generalizable to other high-income countries with low prevalence of *H pylori* and high incidence of EAC, but studies from other regions with different patterns of these conditions are warranted."

Analyzing these data revealed that standardized incidence ratio (SIR) of EAC was not increased after eradication therapy (0.89; 95% CI, 0.82-0.97). In fact, SIR decreased over time after eradication, reaching as low as 0.73 (95% CI, 0.61-0.86) during the follow-up period of 11-24 years. These findings were maintained regardless of age or sex, and within country-by-country analyses.

SIR for esophageal squamous cell carcinoma, which was calculated for comparison, showed no association with eradication therapy (0.99; 95% CI, 0.89-1.11).

"This study found no evidence supporting the hypothesis of a gradually increasing risk of esophageal adenocarcinoma over time after *H pylori* eradication treatment," the investigators wrote.

Other risks were detected, including an overall increased SIR of EAC observed among participants with gastroesophageal reflux disease (GERD) and those using long-term proton pump inhibitors (PPIs). These were expected, however, "considering the strong and well-established association with EAC."

Dr. Wiklund and colleagues suggested that more studies are needed to confirm their findings, although the present data provide confidence that *H pylori* eradication does not raise risk of EAC.

"This is valuable knowledge when considering eradication treatment for individual patients and eradication programs in high-risk populations of gastric cancer," they wrote. "The results should be generalizable to other high-income countries with low prevalence of *H pylori* and high incidence of EAC, but studies from other regions with different patterns of these conditions are warranted."

They also called for more basic research to understand why eradicating *H pylori* does not lead to an increased risk of EAC.

The study was supported by Sjoberg Foundation, Nordic Cancer Union, Stockholm County Council, Stockholm Cancer Society. Investigators disclosed no conflicts of interest. ■

A Paradigm Shift in Evaluating and Investigating the Etiology of Bloating

In Focus
Brought To You By The New Gastroenterologist

BY RAJAN SINGH, PHD, AND BAHARAK MOSHIREE, MD, AGAF

Dr. Singh is assistant professor (research) at the University of Nevada, Reno, School of Medicine. **Dr. Moshiree** is director of motility at Atrium Health, and clinical professor of medicine, Wake Forest Medical University, Charlotte, North Carolina.

Introduction

Abdominal bloating is a common condition affecting up to 3.5% of people globally (4.6% in women and 2.4% in men),[1] with 13.9% of the US population reporting bloating in the past 7 days.[2] The prevalence of bloating and distention exceeds 50% when linked to disorders of gut-brain interaction (DGBIs) such as irritable bowel syndrome (IBS), constipation, gastroparesis, and functional dyspepsia (FD).[3,4] According to the Rome IV criteria, functional abdominal bloating and distention (FABD) patients are characterized by recurrent symptoms of abdominal fullness or pressure (bloating), or a visible increase in abdominal girth (distention) occurring at least 1 day per week for 3 consecutive months with an onset of 6 months and without predominant pain or altered bowel habits.[5]

Multiple pathophysiological mechanisms are involved in ABD that complicate clinical management. There is an unmet need to understand the underlying mechanisms that lead to the development of ABD.

Prolonged abdominal bloating and distention (ABD) can significantly impact quality of life and work productivity and can lead to increased medical consultations.[2] Multiple pathophysiological mechanisms are involved in ABD that complicate clinical management.[4] There is an unmet need to understand the underlying mechanisms that lead to the development of ABD, such as food intolerance, abnormal viscerosomatic reflex, visceral hypersensitivity, and gut microbial dysbiosis. Recent advancements and acceptance of a multidisciplinary management of ABD have shifted the paradigm from merely treating symptoms to subtyping the condition and identifying overlaps with other DGBIs in order to individualize treatment that addresses the underlying pathophysiological mechanism. The recent AGA clinical update provided insights into the best practice advice for evaluating and managing ABD based on a review of current literature and on expert opinion of coauthors.[6] This article aims to deliberate a practical approach to diagnostic strategies and treatment options based on etiology to refine clinical care of patients with ABD.

Pathophysiological Mechanisms

ABD can result from various pathophysiological mechanisms. This section highlights the major causes (illustrated in Figure 1).

Food intolerances

Understanding food intolerances is crucial for diagnosing and managing patients with ABD. Disaccharidase deficiency is common (eg, lactase deficiency is found in 35%-40% of adults).[7] It can be undiagnosed in patients presenting with IBS symptoms, given the overlap in presentation with a prevalence of 9% of pan-disaccharidase deficiency. Sucrase-deficient patients must often adjust sugar and carbohydrate/starch intake to relieve symptoms.[7] Deficiencies in lactase and sucrase activity, along with the consumption of some artificial sweeteners (eg, sugar alcohols and sorbitol) and fructans can lead to bloating and distention. These substances increase osmotic load, fluid retention, microbial fermentation, and visceral hypersensitivity, leading to gas production and abdominal distention. One prospective study of symptomatic patients with various DGBIs (n = 1372) reported a prevalence of lactose intolerance and malabsorption at 51% and 32%, respectively.[8] Furthermore, fructose intolerance and malabsorption prevalence were 60% and 45%, respectively.[8] Notably, lactase deficiency does not always cause ABD, as not all individuals with lactase deficiency experience these symptoms after consuming lactose. Patients with celiac disease (CD), non-celiac gluten sensitivity (NCGS), and gluten intolerance can also experience bloating and distention, with or without changes in bowel habits.[9] In some patients with self-reported NCGS, symptoms may be due to fructans in gluten-rich foods rather than gluten itself, thus recommending the elimination of fructans may help improve symptoms.[9]

Visceral hypersensitivity

Visceral hypersensitivity is explained by an increased perception of gut mechano-chemical stimulation, which typically manifests in an aggravated feeling of pain, nausea, distension, and ABD.[10] In the gut, food particles and gut bacteria and their derived molecules interact with neuroimmune and enteroendocrine cells causing visceral sensitivity by the proximity of gut's neurons to immune cells activated by them and leading to inflammatory reactions (Figure 1). Interestingly, patients with IBS who experience bloating without distention exhibit heightened visceral hypersensitivity compared to those who experience both bloating and distention and those with actual increase in intraluminal gas, such as those with intestinal pseudo-obstruction, experience less pain than those without.[11] The conscious perception of intraluminal content and abdominal distention contributes to bloating. Altered gut-brain interactions amplify this conscious perception of abdominal wall tension and can be further influenced by psychological factors such as anxiety, depression, somatization, and hypervigilance. Thus, outlining a detailed understanding of visceral hypersensitivity and its role in gut-brain interactions is essential for

Abdominal bloating and distension (ABD) are common gastrointestinal complaints seen by providers in clinic. These symptoms can also be very difficult to manage. Dr. Rajan Singh and Dr. Baharak Moshiree review the pathophysiological mechanisms that can cause ABD, including food intolerances, visceral hypersensitivity, pelvic floor dysfunction, abdominophrenic dyssynergia, gut dysmotility, and small intestinal bacterial overgrowth. They further discuss a practical approach to diagnostic testing.

Based on presumed etiology, Dr. Singh and Dr. Moshiree further explain the different modalities of management of ABD, including dietary interventions, prokinetics and laxative, probiotics, antibiotics, biofeedback therapy, central neuromodulators, and brain-gut behavioral therapies.

Judy Trieu, MD, MPH
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The New Gastroenterologist

diagnosing and managing ABD.

Pelvic floor dysfunction

Patients with anorectal motor dysfunction often experience difficulty in effectively evacuating both gas and stool, leading to ABD.[12] Impaired ability to expel gas and stool results in prolonged balloon expulsion times, which correlates with symptoms of distention in patients with constipation.

Abdominophrenic dyssynergia

Abdominophrenic dyssynergia is characterized as a paradoxical viscerosomatic reflex response to minimal gaseous distention in individuals with FABD.[13] In this condition, the diaphragm contracts (descends), and the anterior abdominal wall muscles relax in response to the presence of gas. This response is opposite to the normal physiological response to increased intraluminal gas, where the diaphragm relaxes and the anterior abdominal muscles contract to increase the craniocaudal capacity of the abdominal cavity without causing abdominal protrusion.[13] Patients with FABD exhibit significant abdominal wall protrusion and diaphragmatic descent even with relatively small increases in intraluminal gas.[11] Understanding the role of abdominophrenic dyssynergia in abdominal bloating and distention is essential for effective diagnosis and management of the patients.

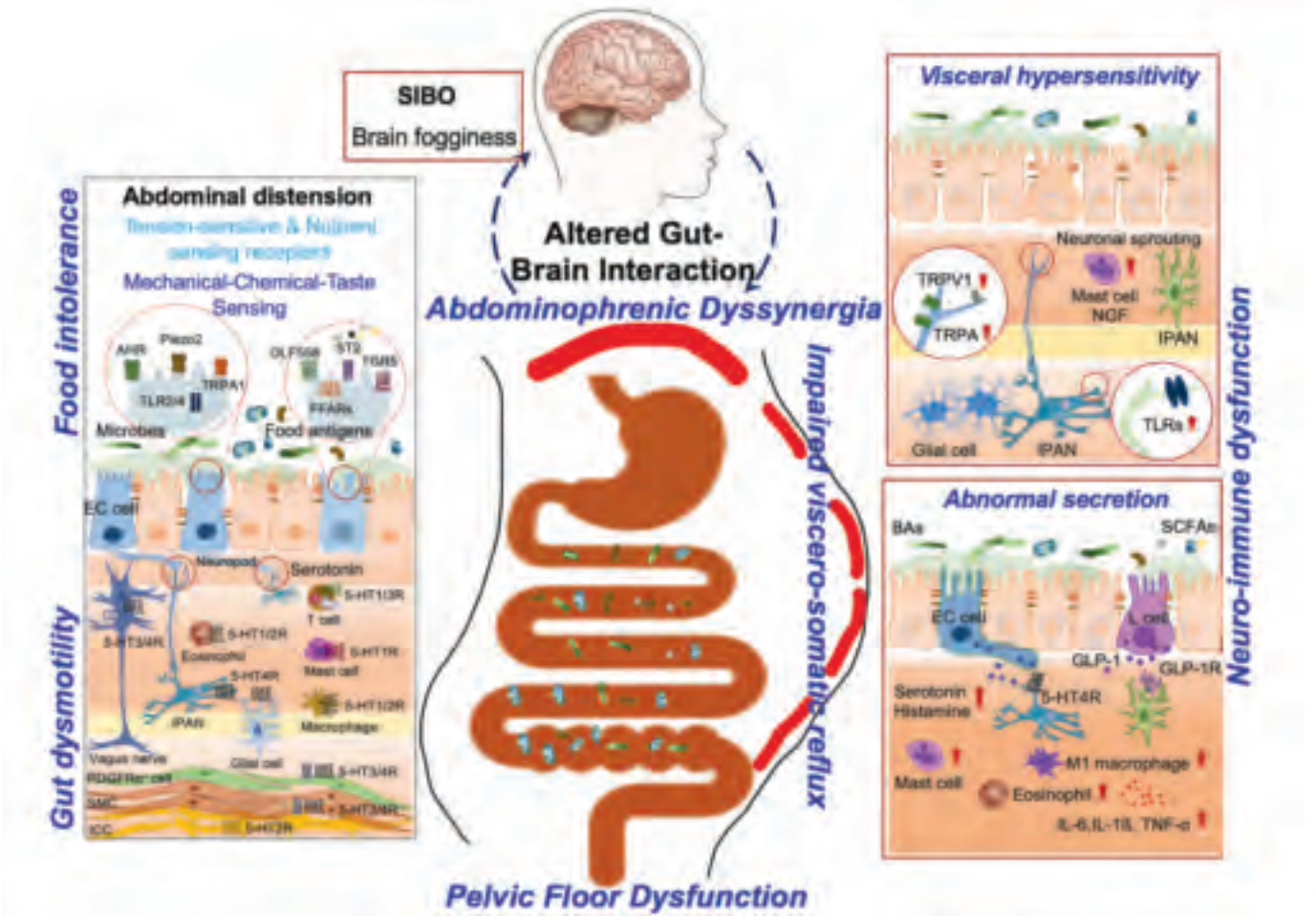

Figure 1. Proposed pathophysiological mechanisms underlying abdominal bloating/distension are illustrated.

Dr. Singh and Dr. Moshiree

Small intestinal bacterial overgrowth (SIBO)

SIBO is overrepresented in various conditions, including IBS, FD, diabetes, gastrointestinal (GI) surgery patients and obesity, and can play an important role in generating ABD. Excess bacteria in the small intestine ferment carbohydrates, producing gas that stretches and distends the small intestine, leading to these symptoms. Additionally, altered sensation and abnormal viscerosomatic reflexes may contribute to SIBO-related bloating.[4] One recent study noted decreased duodenal phylogenetic diversity in individuals who developed postprandial bloating.[15] Increased methane levels caused by intestinal methanogen overgrowth, primarily the archaea *Methanobrevibacter smithii*, is possibly responsible for ABD in patients with IBS-C.[16] Testing for SIBO in patients with ABD is generally recommended only if there are clear risk factors or severe symptoms warranting a test-and-treat approach.

Practical Diagnosis

Diagnosing ABD typically does not require extensive laboratory testing, imaging, or endoscopy unless there are alarm features or significant changes in symptoms. Here is the AGA clinical update on best practice advice[6] for when to conduct further testing:

Diagnostic tests should be considered if patients exhibit:

- Recent onset or worsening of dyspepsia or abdominal pain
- Vomiting
- GI bleeding
- Unintentional weight loss exceeding 10% of body weight
- Chronic diarrhea
- Family history of GI malignancy, celiac disease, or inflammatory bowel disease

Physical examination

If visible abdominal distention is present, a thorough abdominal examination can help identify potential issues:

- Tympany to percussion suggests bowel dilation.
- Abnormal bowel sounds may indicate obstruction or ileus.
- A succussion splash could indicate the presence of ascites and obstruction.
- Any abnormalities discovered during the physical exam should prompt further investigation with imaging, such as a computed tomography (CT) scan or ultrasound, to evaluate for ascites, masses, or increased bowel gas due to ileus, obstruction, or pseudo-obstruction.

Radiologic imaging, laboratory testing, and endoscopy

- An abdominal x-ray may reveal an increased stool burden, suggesting the need for further evaluation of slow transit constipation or a pelvic floor disorder, particularly in patients with functional constipation, IBS-mixed, or IBS-C.
- Hyperglycemia, weight gain, and bloating can be a presenting sign of ovarian cancer therefore all women should continue pelvic exams as dictated by the gynecologic societies. The need for an annual pelvic exam should be discussed with healthcare professionals especially in those with family history of ovarian cancer.
- An upper endoscopy may be warranted for patients over 40 years old with dyspeptic symptoms and abdominal bloating or distention, especially in regions with a high prevalence of *Helicobacter pylori*.
- Chronic pancreatitis, indicated by bloating and pain, may necessitate fecal elastase testing to assess pancreatic function.

The expert review in the AGA clinical update provides step-by-step advice regarding the best practices[6] for diagnosis and identifying who to test for ABD.

Treatment Options

The following sections highlight recent best practice advice on therapeutic approaches for treating ABD.

Dietary interventions

Specific foods may trigger bloating and abdominal distention, especially in patients with overlapping DGBIs. However, only a few studies have evaluated dietary restriction specifically for patients with primary ABD. Restricting nonabsorbable sugars led to symptomatic improvement in 81% of patients with FABD who had documented sugar

Continued on following page

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malabsorption.[17] Two studies have shown that IBS patients treated with a low-fermentable, oligo-, di-, and monosaccharides (FODMAP) diet noted improvement in ABD and that restricting fructans initially may be the most optimal.[18] A recent study showed that the Mediterranean diet improved IBS symptoms, including abdominal pain and bloating.[19] It should be noted restrictive diets are efficacious but come with short- and long-term challenges. If empiric treatment and/or therapeutic testing do not resolve symptoms, a referral to a dietitian can be useful. Dietitians can provide tailored dietary advice, ensuring patients avoid trigger foods while maintaining a balanced and nutritious diet.

Prokinetics and laxatives

Prokinetic agents are used to treat symptoms of FD, gastroparesis, chronic idiopathic constipation (CIC), and IBS. A meta-analysis of 13 trials found all constipation medications superior to placebo for treating abdominal bloating in patients with IBS-C.[20]

Probiotics

Treatment with probiotics is recommended for bloating or distention. One double-blind placebo-controlled trial with two separate probiotics, *Bifidobacterium lactis* and *Lactobacillus acidophilus*, showed improvements in global GI symptoms of patients with DGBI at 8 weeks versus placebo, with improvements in bloating symptoms.[21]

Antibiotics

The most commonly studied antibiotic for treating bloating is rifaximin.[22] Global symptomatic improvement in IBS patients treated with antibiotics has correlated with the normalization of hydrogen levels in lactulose hydrogen breath tests.[22] Patients with nonconstipation IBS randomized to rifaximin 550 mg three times daily for 14 days had a greater proportion of relief of IBS-related bloating compared to placebo for at least 2 of the first 4 weeks after treatment.[22] Future research warrants use of narrow-spectrum antibiotics study for FABD as the use of broad-spectrum antibiotics may deplete commensals forever, resulting in metabolic disorders.

As bloating results from multiple disturbed mechanisms, including altered gut-brain interaction, these symptoms can be amplified by psychological states such as anxiety, depression, or somatization.

Biofeedback therapy

Anorectal biofeedback therapy may help with ABD, particularly in patients with IBS-C and chronic constipation. One study noted that post–biofeedback therapy, myoelectric activity of the intercostals and diaphragm decreased, and internal oblique myoelectric activity increased.[23] This study also showed ascent of the diaphragm and decreased girth, improving distention.

Central neuromodulators

As bloating results from multiple disturbed mechanisms, including altered gut-brain interaction, these symptoms can be amplified by psychological states such as anxiety, depression, or somatization. Central neuromodulators reduce the perception of visceral signals, re-regulate brain-gut control mechanisms, and improve psychological comorbidities.[6] A large study of FD patients demonstrated that both amitriptyline (50 mg daily) and escitalopram (10 mg daily) significantly improved postprandial bloating compared to placebo.[24] Antidepressants that activate noradrenergic and serotonergic pathways, including tricyclic antidepressants (eg, amitriptyline) and serotonin-norepinephrine reuptake inhibitors (eg, duloxetine and venlafaxine), show the greatest benefit in reducing visceral sensations.[6]

Brain-gut behavioral therapies

A recent multidisciplinary consensus report supports a myriad of potential brain-gut behavioral therapies (BGBTs) for treating DGBI.[25] These therapies, including hypnotherapy, cognitive-behavioral therapy (CBT), and other modalities, may be combined with central neuromodulators and other GI treatments in a safe, noninvasive, and complementary fashion. BGBTs do not need to be symptom-specific, as they improve overall quality of life, anxiety, stress, and the burden associated with DGBIs. To date, none of the BGBTs have focused exclusively on FABD; however, prescription-based psychological therapies are now Food and Drug Administration approved for use on smart apps, improving global symptoms that include bloating in IBS and FD.

Recent AGA clinical update best practices should be considered for the clinical care of patients with ABD.[6]

Conclusion and Future Perspectives

ABD are highly prevalent and significantly impact patients with various GI and metabolic disorders. Although our understanding of these symptoms is still evolving, evidence increasingly points to the dysregulation of the gut-brain axis and supports the application of the biopsychosocial model in treatment. This model addresses diet, motility, visceral sensitivity, pelvic floor disorders, and psychosocial factors, providing a comprehensive approach to patient care.

Physician-scientists around the globe face numerous challenges when evaluating patients with these symptoms. However, the recent AGA clinical update on the best practice guidelines offers step-by-step diagnostic tests and treatment options to assist physicians in making informed decisions. A multidisciplinary approach and a patient-centered model are essential for effectively managing treatment in patients with ABD. More comprehensive, large-scale, and longitudinal studies using metabolomics, capsule technologies for discovery of dysbiosis, mass spectrometry, and imaging data are needed to identify the exact contributors to disease pathogenesis, particularly those that can be targeted with pharmacologic agents. Collaborative work between gastroenterologists, dietitians, gut-brain behavioral therapists, and endocrinologists is crucial for clinical care of patients with ABD.

Careful attention to the patient's primary symptoms and physical examination, combined with advancements in targeted diagnostics like the analysis of microbial markers, metabolites, and molecular signals, can significantly enhance patient clinical outcomes. Additionally, education and effective communication using a patient-centered care model are essential for guiding practical evaluation and individualized treatment. ■

References available online at MDedge.com/gihepnews

‘Exceptional Improvement’

Survodutide *from page 1*

Virginia Commonwealth University (VCU) Stravitz-Sanyal Institute for Liver Disease and Metabolic Health, VCU School of Medicine, Richmond, Virginia.

What’s so amazing is that this “exceptional improvement” is after 48 weeks of therapy with a class of molecule that is already known to also have cardiometabolic benefits, Dr. Sanyal said in an interview with *GI & Hepatology News*.

Dr. Sanyal

“At the highest dose of survodutide [6.0 mg], two thirds of patients in whom we have biopsy data, at both the beginning and the end, actually showed fibrosis regression within 48 weeks. This is pretty dramatic.”

“At the highest dose of survodutide [6.0 mg], two thirds of patients in whom we have biopsy data, at both the beginning and the end, actually showed fibrosis regression within 48 weeks,” he said. “This is pretty dramatic.”

Efficacy and Safety of Survodutide

A total of 293 participants with biopsy-confirmed MASH and fibrosis stages F1-F3 were randomly assigned (1:1:1:1) to receive once-weekly subcutaneous injections of survodutide 2.4 mg (n = 73), 4.8 mg (n = 72), or 6.0 mg (n = 74) or placebo (n = 74).

Around half of study participants were women, with mean age around 50 years and a body mass index around 35 kg/m^2. Overall, 26%-30% had type 2 diabetes, 24%-36% had F2 fibrosis, and 23%-30% had F3 fibrosis. The total Nonalcoholic Fatty Liver Disease Activity Score was 5.2.

After completing a 24-week rapid dose-escalation phase, participants followed a 24-week maintenance phase. Histologic improvement (reduction) in MASH without worsening of fibrosis after 48 weeks of treatment comprised the primary endpoint, whereas a reduction in liver fat content by at least 30% and biopsy-assessed reduction in fibrosis by at least one stage were among the secondary endpoints.

The main analyses of the trial were based on two treatment sets: Actual treatment (the actual dose received at the start of the maintenance phase; per protocol) and planned treatment (the maintenance dose assigned to participants at randomization). Dr. Sanyal mainly reported results based on actual treatment, which were used for the primary analysis.

The overall primary endpoint data, including nonresponders, showed a 47% improvement in MASH in the 2.4-mg treatment group, 62% in the 4.8-mg group, and 43% in the 6.0-mg group compared with 13.5% in the placebo group ($P < .001$).

In addition, 50% of patients on 2.4- and 6-mg doses experienced a statistically significant improvement in fibrosis (F1-F3) without worsening of MASH.

In patients with F2/F3 fibrosis, 64.5% of participants in the 6-mg survodutide group showed improvement vs 25.9% in the placebo group.

Reduction in liver fat by at least 30% was achieved by up to 87% in the 6-mg group according to MRI-estimated proton density fat fraction; when nonresponders were included, the percentage was 76.9% of the 6-mg group. Other outcomes included weight loss and reductions in A1c.

The results did not differ markedly between doses, which “is really exciting news,” Dr. Sanyal said.

Patients who are intolerant of the highest dose can switch to a lower dose without a big loss of efficacy, he said, adding that even the low dose was sufficient to get near maximal glucagon effect.

Adverse events were similar between survodutide and placebo, except for gastrointestinal events, including nausea, diarrhea, and vomiting. The occurrence of serious adverse events also was similar between survodutide and placebo.

Discontinuation due to adverse events was 20% across all the survodutide groups (with 16% due to gastrointestinal events) vs 3% in the placebo group.

Dual-Agonist vs Monoagonist Therapy

The dual-agonist approach may confer clinical advantages over GLP-1 receptor monoagonist pharmacotherapies for MASH.

“GLP has no receptors in the liver, so all its effects are mediated outside the liver, particularly for weight loss and improvement in metabolic status, increase in insulin secretion and sensitivity, and overall systemic glycemia,” Dr. Sanyal explained.

“People with established fibrosis take longer to respond in terms of downstream liver scarring with extrahepatic changes alone,” he added.

With “glucagon directly targeting the liver, we believe this reduces oxidative stress and possibly stimulates FGF-21 secretion [liver-derived factor that regulates lipid and glucose metabolism] in the liver, so there are likely multiple mechanisms driving the antifibrogenic benefits,” Dr. Sanyal said.

In comparison, the study authors highlighted that data on the GLP-1 receptor monoagonist semaglutide suggest a significantly higher proportion of patients on semaglutide achieve MASH resolution than those on placebo but that it does not result in “a significantly higher percentage of patients with improvement in fibrosis stage.

“It might be that it takes longer to get an effect in the liver with semaglutide,” Dr. Sanyal said.

By year-end, we will know how the GLP-1 alone approach (eg, semaglutide) and the dual-agonist approach work, and we will eventually have data on triple agonists, Dr. Sanyal added.

Reducing the Burden of Steatotic Liver Disease

Comoderator Debbie Shawcross, MBBS, PhD, professor of hepatology and chronic liver failure, King’s College, London, England, remarked on the importance of new drugs, including survodutide, in reducing the burden of steatotic liver disease.

Approximately one third of the world’s population and between 7% and 9% of children have steatotic liver disease, she noted. The buildup of fat causes inflammation and scarring of the liver, which may then progress to liver cirrhosis and primary liver cancers.

Survodutide offers much hope “as a drug that will reduce both liver inflammation and scarring, while also providing the benefit of improved diabetic control,” Dr. Shawcross said.

Reflecting on the dual agonism, she said that both the glucagon and GLP-1 receptors are critical to controlling metabolic functions.

Survodutide is currently being investigated in five phase 3 studies for people living with overweight and obesity, both of which are associated with MASH.

“GLP has no receptors in the liver, so all its effects are mediated outside the liver, particularly for weight loss and improvement in metabolic status, increase in insulin secretion and sensitivity, and overall systemic glycemia.”

There is also a trial looking at people with overweight/obesity with confirmed or presumed diagnosis of MASH, according to a company press release.

Dr. Sanyal reported grants, consultancy fees, and speaker fees from a wide range of companies working in the field of liver medicine. Dr. Shawcross reported no conflicts of interest in relation to this drug, but disclosed advisory board membership/consultancy for EnteroBiotix, Norgine, Satellite Bio, and MRN Health. ■

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