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Official newspaper of the AGA Institute

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March 2022

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Courtesy Dr. Siew Ng

Dr. Siew Ng says microbiota modulation should be considered to support "timely recovery" in those with post–acute COVID-19 syndrome.

Gut bacteria linked with long COVID

BY THOMAS R. COLLINS
MDedge News

Disruption of the bacteria in the gut is linked with susceptibility to long COVID-19 syndrome, according to new findings.

While links have been found between the gut's microbiome and COVID-19, as well as other diseases, this is the first published research to show a link specifically to COVID's long-term effects, the investigators, based at the Chinese University of Hong Kong, wrote in Gut (2022 Jan 25. doi: 10.1136/gutjnl-2021-325989).

"To our knowledge, this is the first study to show that altered gut microbiome composition is strongly associated with persistent symptoms in patients with COVID-19 up to 6 months after clearance of SARS-CoV-2 virus," said Siew Ng, MBBS, PhD, AGAF, associate director at the university's Center for Gut Microbiota Research.

At three hospitals, the researchers enrolled 106 patients with COVID-19 from February to August 2020 with stool samples at admission and at 1 month and 6 months after discharge, and compared them with people who did not have

See **COVID** · *page 26*

Spanish-speaking patient navigator ups CRC screening

BY HOWARD WOLINSKY

A Spanish-speaking patient navigator dramatically increased the percentage of Hispanics undergoing colorectal screening with colonoscopies in Providence, R.I.

Screening colonoscopies are a well-established approach to reducing colorectal cancer mortality by identifying and removing polyps. However, Hispanics in the United States lag behind the general population in completion rates for screening colonoscopies.

"Starting colorectal cancer colonoscopy screening at age 45 saves lives. But this life-saving procedure is underutilized by certain populations, not only because of limited access to care but because of cultural, language, and educational barriers that exist," Abdul Saied Calvino, MD, MPH, program director of the Complex General Surgical Oncology Fellowship at Roger Williams Medical Center, Providence, told this news organization.

Tailored patient navigation is effective but has not been widely adopted. The new study is one of the first to look at the "real-life" impact of these types of programs in the

See **Spanish** · *page 19*

ARFID: Food intake disorder seen in patients with GI disease

BY NEIL OSTERWEIL
MDedge News

FROM CROHN'S & COLITIS CONGRESS

Problems with eating and nutrition are common among patients with inflammatory bowel disease (IBD) and other gastrointestinal disorders, but clinicians who treat them should be careful not to automatically assume that patients have eating disorders, according to a psychologist who specializes in the psychological and social aspects of chronic digestive diseases.

On the other hand, clinicians must also be aware of the possibility that patients could have a recently identified syndrome cluster called avoidant

See **ARFID** · *page 24*

INSIDE

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LETTER FROM THE EDITOR

Dressing in blue

On the first Friday in March, it has become an annual tradition to dress in blue to promote colorectal cancer awareness. Twitter feeds are filled with photos of members of our gastroenterology community (sometimes entire endoscopy units!) swathed in various shades of blue. This tradition was started in the mid-2000's by a patient diagnosed with early-onset colorectal cancer who planned a fund raiser at her daughter's elementary school where students were encouraged to wear a blue outfit and make a $1 donation to support awareness of this deadly but preventable cancer.

Dr. Adams

What was once a local effort has now grown into a national phenomenon, and a powerful opportunity for the medical community to educate patients, friends, and family regarding risk factors for colorectal cancer.

What was once a local effort has now grown into a national phenomenon, and a powerful opportunity for the medical community to educate patients, friends, and family regarding risk factors for colorectal cancer and the importance of timely and effective screening. But while raising awareness is vital, it is only an initial step in the complex process of optimizing delivery of screening services and improving cancer outcomes through prevention and early detection.

In this month's issue of GIHN, we report on a study from Cancer demonstrating the effectiveness of Spanish-speaking patient navigators in boosting colorectal cancer screening rates among Hispanic patients.

We also highlight a quality improvement initiative at a large academic medical center demonstrating the impact of an electronic "primer" message delivered through the patient portal on screening completion rates in a mailed fecal immunochemical test outreach program. Finally, in this month's Practice Management Toolbox column, Dr. Brill and Dr. Lieberman advise us on how to prepare for upcoming coverage changes impacting screening colonoscopy – a result of AGA's tireless efforts to eliminate financial barriers impeding access to colorectal cancer screening.

As always, thank you for being a dedicated reader and please stay safe out there. Better days are ahead.

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

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RECAM vs. RUCAM: Finding a better way to diagnose drug-induced liver injury

BY MARCIA FRELLICK
MDedge News

Researchers looking for a better way to diagnose drug-induced liver injury (DILI) have found evidence to support the use of the Revised Electronic Causality Assessment Method (RECAM).

The broadly used Roussel Uclaf Causality Assessment Method (RUCAM), introduced in 1993, "has been a valuable clinical framework for DILI diagnosis," but it has been clouded by subjectivity and poor reliability, wrote the authors, led by Paul H. Hayashi, MD, MPH, with the Food and Drug Administration, in Hepatology (2022 Jan 11. doi: 10.1002/hep.32327). Citing a review from the Journal of Hepatology (2011 Feb 23. doi: 0.1016/j.jhep.2011.02.007, Dr. Hayashi and colleagues noted three major problems: "(1) unclear operating instructions and subjectivity leading to poor reliability and usability, (2) unclear validity due to lack of an accepted gold standard and (3) domain criteria that are not evidence-based."

The lack of an evidence-based and reliable diagnostic tool is a significant obstacle in clinical care and research.

Reaching a new method

The researchers used classification tree analysis to set diagnostic cut-offs for RECAM and then compared RECAM with RUCAM for correlation with expert opinion diagnostic categories in 194 DILI cases (98 from the Drug-Induced Liver Injury Network, 96 from the Spanish DILI Registry).

The area under receiver operator curves for identifying at least probable DILI were the same at 0.89 for both RECAM and RUCAM.

The authors wrote, "However, RECAM diagnostic categories have better observed overall agreement with expert opinion (0.62 vs. 0.56 weighted kappa, $P = .14$), and had better sensitivity to detect extreme diagnostic categories (73 vs. 54 for highly likely or high probable, $P = .02$; 65 vs. 48 for unlikely/excluded, $P = .08$) than RUCAM diagnostic categories."

They concluded that RECAM "is at least as capable as RUCAM in diagnosing DILI compared to expert opinion but is better than RUCAM at the diagnostic extremes."


Dr. Martin

RECAM appears to add objectivity and clarity that can improve precision and reliability when diagnosing DILI and improve diagnostic standardization, according to authors. It has automated scoring, which reduces subjective input and should lead to better reliability among raters, something that has limited RUCAM's adaptation in clinical practice and research. RECAM has automatic warnings for data inconsistencies, which RUCAM does not. In RUCAM, a different diagnosis or other data could rule out DILI, but the case would still gain points in other criteria.

The authors explained, "Even when data clearly diagnose acute viral hepatitis or autoimmune hepatitis by simplified autoimmune hepatitis score, points are still given for latency, dechallenge, or underlying hepatotoxicity risk of the drug. ... One can over-ride these warnings, if one believes DILI may be concurrent with the non-DILI diagnosis. However, –6 points are still assessed."

Diagnosis of exclusion

Paul Martin, MD, chief, division of digestive health and liver diseases, Mandel Chair in Gastroenterology, and professor of medicine at the University of Miami, said in an interview that he hopes RECAM will become widely used and better address a condition that sometimes doesn't get enough attention. DILI remains underappreciated, he said, despite it being a major cause of morbidity and mortality in some patients.

"Any algorithm or criteria that can improve diagnostic accuracy is useful because typically it is a diagnosis of exclusion," Dr. Martin said. "This new system seems to be as good as any other prior algorithms to diagnose drug-induced liver injury."

He added, "This should help clinicians with individual patients with unexplained liver disease."

The authors noted some limitations. RECAM was developed in U.S. and Spanish cohorts, so its performance in other regions is unclear. It is not known how effective RECAM is in less severe cases. It also needs to be tested by other clinicians, including nonhepatologists.

The authors also added, "It is currently limited to single-agent medication cases leaving the user to score each medication individually in multidrug cases. However, any competing medication causing loss of points in the RUCAM, probably deserves its own RECAM score."

The DILIN is structured as a cooperative agreement with funds provided by the National Institute of Diabetes and Digestive and Kidney Diseases. Dr. Hayashi is employed by the FDA, but the conclusions of this paper do not reflect any opinion of the FDA. One coauthor has advised Pfizer, GSK, and NuCANA through Nottingham University Consultants, and another has received support from Gilead and AbbVie and consulted for Sanofi. The remaining authors have no conflicts. Dr. Martin reports no relevant financial relationships. ■

CLINICAL CHALLENGES AND IMAGES

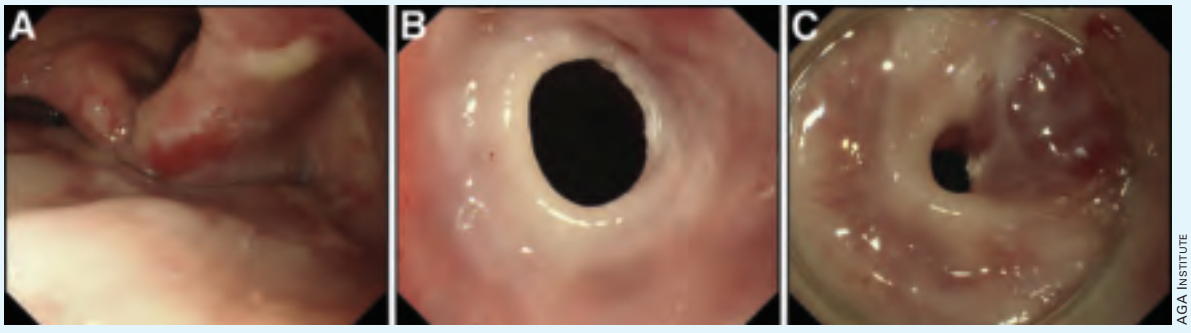
What's your diagnosis?

BY YUHEI UMEDA, MD; KYOSUKE TANAKA, MD, PHD; AND REIKO YAMADA, MD, PHD
Previously published in Gastroenterology (2020 Jan;158[1]:54-5).

A 70-year-old man with a history of rectal cancer was referred to our clinic for chronic dysphagia and odynophagia. He did not have fevers or an allergic history. Physical examination was unremarkable except for multiple erosions in the oral cavity. Upper gastrointestinal endoscopy revealed multiple erosions in the palate and laryngopharynx (Figure A), a web stricture in the cervical esophagus (Figure B), and multiple scars in the thoracic esophagus. Laboratory examination showed normal results including a normal white blood cell count (8,010/mcL; eosinophils 360/mcL), hemoglobin level (14.0 g/dL), mean corpuscular volume (97.8 fL), serum iron level (140 mcg/dL), and ferritin level (50.5 mg/L). His dysphagia gradually worsened and he finally could not take pills nor solid food. Two weeks after the first endoscopy, a second endoscopic examination was performed and it showed exacerbation of esophageal stricture and appearance of a bloody blister (Figure C).

What is the diagnosis?

The answer is on page 19.



AGA Clinical Practice Update: Expert Review

Managing refractory gastroparesis

BY JIM KLING
MDedge News

Gastroparesis can be tricky to diagnose and treat, in part because its symptoms can be difficult to distinguish from functional dyspepsia. A new clinical practice update from the American Gastroenterological Association aims to help physicians treat medically refractory gastroparesis with practical advice stemming from expert opinion and a literature review.

Although gastroparesis can be caused by known factors such as diabetes and medications, the largest group is idiopathic. The authors define medically refractory gastroparesis as symptoms that are not due to medication use, that continue despite dietary changes and first-line treatment with metoclopramide.

Although the authors outline several best practice advice statements on symptom identification and management, they acknowledge that much uncertainty still exists. "Our knowledge gap remains vast, and areas for future research include study of pathophysiology and etiology, as well as identification of clinical and investigation-based predictors of response to each management approach," the authors wrote. Their report is in Clinical Gastroenterology and Hepatology (2021 Oct. doi: 10.1016/j.cgh.2021.10.038).

They also called for research to identify gastroparesis phenotypes that are most likely to respond to individual management approaches.

Common gastroparesis symptoms include nausea, vomiting, early satiety, bloating, postprandial fullness, abdominal pain, and weight loss. Many of these overlap with functional dyspepsia (FD). In fact, one study found that 42% of gastroparesis could be reclassified as having functional dyspepsia, and 37% of FD patients as having gastroparesis (Gastroenterology. 2021 May;160[6]:2006-17).

About 5 million adults in the United States (Gastrointest Endosc Clin N Am. 2019 Jan;29[1]:1-14), and 7.2% of the world population (Gastroenterology. 2021 Jan;160[1]:99-114.e3), report gastroparesis-like symptoms. The similarities between the two groups poses a significant diagnostic challenge. However, a careful history, physical exam, and appropriate diagnostic tests should allow the physician to rule out other conditions that may mimic gastroparesis. Repeating scintigraphy may change diagnosis from gastroparesis to FD or vice versa, but the authors note that this technique is often performed incorrectly and so should be conducted at centers that closely follow guidelines. They suggest a 4-hour meal-based test of gastric emptying over the wireless motility capsule because it provides a better physiological assessment.

They also suggest that treatment should focus on the most bothersome symptom, along with reducing the potential for complications such as esophagitis, malnutrition, and weight loss, as well as improving quality of life.

There are medications available for nausea and vomiting, although most have not been studied in large randomized controlled trials. These agents include domperidone, 5-hydroxytryptamine$_3$ receptor antagonists, neurokinin receptor antagonists, and phenothiazine antipsychotics.

There are also medications available to increase the rate of gastric emptying. Erythromycin can be used intravenously or orally ahead of meals, while the 5-HT4 receptor agonist velusetrag improved gastric emptying in healthy volunteers with no sign of cardiac side effects. The commonly available 5-HT4 agonist prucalopride has also shown promise in improving gastric emptying.

"Our knowledge gap remains vast, and areas for future research include study of pathophysiology and etiology, as well as identification of clinical and investigation-based predictors of response to each management approach."

For visceral pain, the authors suggest not using opioids because they may slow gastric emptying and increase pain perception. It is believed that neuromodulators such as tricyclic antidepressants and serotonin norepinephrine reuptake inhibitors may reduce perception of pain, but there is limited high-quality evidence available for these therapies. The authors suggest that higher potency tertiary tricyclic amines such as amitriptyline or imipramine may be effective, particularly in diabetic gastroparesis since they provide relief in FD.

Nonpharmaceutical options include gastric electrical stimulation, which improves refractory nausea and vomiting in some patients with gastroparesis, but does not accelerate gastric emptying. It may also improve glycemic control, nutritional status, and quality of life. The treatment may be well suited to opioid-free patients with refractory or intractable nausea and vomiting whose predominant symptom is not abdominal pain.

Other therapies focus on the pylorus and its role in gastric emptying, which can be impaired as a result of abnormalities of pyloric tone and pressure. Functional lumen imaging probe can be used to probe pyloric tone and pressure, but it is expensive, invasive, and not widely available.

Outside of clinical trial settings, the authors advise against the use of intrapyloric botulinum toxic injection and transpyloric stent placement. Per oral endoscopic myotomy has shown some efficacy at improving symptoms and reducing gastric emptying times, but it has not been studied in sham-controlled trials. The authors call the technique intriguing, but say it should not be considered a first-line therapy, and should be performed only at tertiary centers with expert motility specialists and endoscopists.

In extreme cases, enteral nutrition may be necessary, and a transjejunal tube or combined gastrojejunostomy tube should be emplaced beyond the pylorus. In a retrospective case series, patients experienced weight recovery with acceptable morbidity and mortality, and the implant was removed at an average of 20 months (Am J Gastroenterol. 1996 Oct;91[10]:2174-8).

The authors have consulted or been on scientific advisory boards for Salix, Ironwood, Allergan, Arena, Allakos, Medtronic, Diversatek, Takeda, Quintiles, and IsoThrive. ■

HEIKO119/THINKSTOCK

AGA helps break down barriers to CRC screening

BY JOEL V. BRILL, MD, AGAF; AND DAVID A. LIEBERMAN, MD, AGAF

The new year has already marked major progress for colorectal cancer (CRC) screening with the implementation of the Removing Barriers to Colorectal Cancer Screening Act by the Centers for Medicare & Medicaid Services, which will protect Medicare beneficiaries from an unexpected bill if a polyp is detected and removed during a screening colonoscopy, as well as new guidance from the federal government requiring private insurers to cover colonoscopy as a follow-up to a noninvasive CRC screening test without imposing cost sharing for patients.

The American Gastroenterological Association is strongly committed to reducing the incidence of and mortality from colorectal cancer. There is strong evidence that CRC screening is effective, but only 65% of eligible individuals have been screened. A. Mark Fendrick, MD, and colleagues recently found that cost sharing for CRC screening occurred in 48.2% of patients with commercial insurance and 77.9% of patients with Medicare coverage (JAMA Netw Open. 2021 Dec. doi: 10.1001/jamanetworkopen.2021.36798). The elimination of these barriers to CRC screening should improve adherence and reduce the burden of CRC.

As one of AGA President John M. Inadomi's initiatives, the AGA created the CRC Screening Continuum Executive Committee in 2021 to develop AGA Position Statements that highlight the continuum of CRC screening and identify barriers, as well as work with stakeholders to eliminate known barriers. Chaired by former AGA President, David Lieberman, MD, AGAF, and with public policy guidance from Kathleen Teixeira, Vice President of Public Policy and Government Affairs at the AGA, the committee identified that, at that time, colonoscopies after positive stool tests had often been considered "diagnostic" and, therefore, were not covered in full the way a preventive screening is required to be covered by the Affordable Care Act. The committee recognized that copays and deductibles are barriers to CRC screening and contribute to health inequity and socioeconomic disparities. Noninvasive screening should be considered a part of programs with multiple steps, all of which – including follow-up colonoscopy if the test is positive – should be covered by payers without cost sharing as part of the screening continuum. Further, screening with high-quality colonoscopy should be covered by payers without cost sharing, consistent with the aims of the ACA. The committee recommended that the full cost of screening, including the bowel prep, facility and professional fees, anesthesia, and pathology, should be covered by payers without cost sharing.

The committee recognized that copays and deductibles are barriers to CRC screening and contribute to health inequity and socioeconomic disparities.

Dr. Lieberman

Over the past decade, the AGA and other organizations have spent countless hours advocating for closing the gap. In September 2021, Dr. Inadomi and Dr. Lieberman, along with the American Cancer Society Cancer Action Network and Fight CRC, met with Assistant Secretary of Labor, Ali Khawar, and representatives from the U.S. Department of Health & Human Services and U.S. Department of Treasury to request they direct private health plans to cover colonoscopy after a positive noninvasive CRC screening. In January 2022, guidance from the U.S. Department of Labor, HHS, and the Treasury clarified that private insurance plans must cover follow-up colonoscopies after a positive noninvasive stool test. In the Frequently Asked Questions (FAQs) about the Affordable Care Act Implementation, Part 51 (https://www.dol.gov/sites/dolgov/files/EBSA/about-ebsa/our-activities/resource-center/faqs/aca-part-51.pdf), the departments affirmed that a plan or issuer must cover and may not impose cost sharing with respect to a colonoscopy conducted after a positive noninvasive stool-based screening test or direct visualization screening test for colorectal cancer for individuals described in a U.S. Preventive Services Task Force recommendation from May 18, 2021. As stated in that USPSTF recommendation, the follow-up colonoscopy is an integral part of the preventive screening without which the screening would not be complete (https://www.uspreventiveservicestaskforce.org/uspstf/recommendation/colorectal-cancer-screening). The follow-up colonoscopy after a positive noninvasive stool-based screening test or direct visualization screening test is therefore required to be covered without cost sharing in accordance with the requirements of Public Health Service Act section 2713 and its implementing regulations.

Dr. Brill

Over the past decade, the AGA and other organizations have spent countless hours advocating for closing the gap.

Plans and issuers must provide coverage without cost sharing for plan or policy years beginning on or after May 31, 2022. While this new guidance will expand coverage of follow-up colonoscopies to many more individuals nationwide, including individuals who have coverage through Medicaid expansion, it does not apply to traditional Medicaid and Medicare plans.

The members of the CRC Screening Continuum Executive Committee include Dr. Brill and Dr. Lieberman, as well as Uri Ladabaum, MD; Larry Kim, MD; Folasade May, MD, PhD, MPhil; Caitlin Murphy, MD; and Richard Wender, MD. Disclosures are on file with the AGA National Office. ■

Dr. Brill is chief medical officer, Predictive Health, Phoenix. Dr. Lieberman is professor of medicine, division of gastroenterology and hepatology, Oregon Health & Science University, Portland, as well as a past president of the AGA. Dr. Brill discloses consulting for Accomplish Health, Alimetry, Allara Health, AnX Robotica, Arch Therapeutics, Biotax, Boomerang Medical, Brightline, Calyx, Capsovision, Check Cap, Clexio, Curology, Docbot, Echosens, Endogastric Solutions, evoEndo, Family First, FDNA, Food Marble, Freespira, Gala Therapeutics, Glaukos, gTech Medical, Gynesonics, Hbox, Hello Heart, HyGIeaCare, Innovative Health Solutions, IronRod Health, Johnson & Johnson, Lantheus, Le-Minou, Lumen, Mainstay Medical, MaternaMed, Medtronic, Mightier, Motus GI, OncoSil Medical, Palette Life Sciences, Perry Health, Perspectum, Red Ventures, Reflexion, Respira Labs, Salaso, Smith+Nephew, SonarMD, Stage Zero Life Sciences, Steris, Sword Health, Tabula Rosa Health Care, Ultrasight, Vertos Medical, WL Gore, and holds options/warrants in Accomplish Health, AnX Robotica, Capsovision, Donsini Health, Hbox, Hello Heart, HyGIeaCare, Perry Health, Restech, StageZero Life Sciences, SonarMD. Dr. Lieberman is a consultant to Geneoscopy.

How to prepare for CRC coverage changes

Contact your payor's provider relations representative now to confirm that the payor will implement coverage of colonoscopy after a positive noninvasive CRC screening test without imposing cost sharing for their members effective June 1, 2022, or whether coverage is effective only for plan years beginning on or after May 31, 2022.
Ask if the waiver of financial responsibility applies if the patient has a positive noninvasive CRC test in the first half of 2022 but the colonoscopy cannot be scheduled until June.
Find out if the patient has a grandfathered plan, one that was in existence on March 23, 2010 and has stayed basically the same. Grandfathered plans are not required to provide all of the benefits and consumer protections required by the Affordable Care Act and, therefore, would not be required to cover the colonoscopy after a positive noninvasive CRC screening test without imposing cost sharing for the member.
Educate office staff that the new guidance affects only private plans. Traditional Medicaid and Medicare still impose cost sharing for beneficiaries who undergo colonoscopy as a follow-up to a noninvasive CRC screening test.

Source: AGA Institute

Introducing the new AGA FORWARD Scholars

We're proud to announce the 10 early-career physician-scientists selected as "Scholars" for the 2021-2023 AGA FORWARD Program: Fostering Opportunities Resulting in Workforce and Research Diversity, supported by the National Institutes of Health (1R25DK118761-01). This new cohort of Scholars will participate in a training and mentorship program designed to provide concrete and applicable skills to promote physician-scientists from underrepresented populations in the pursuit of successful careers.

"AGA is excited to announce our second cohort of FORWARD Program Scholars as we continue in our promise to inspire and cultivate the next generation of prominent, diverse leaders in gastroenterology and hepatology," said Byron Cryer, MD, FORWARD Program cochair, AGA Equity Project cochair, and associate dean for the Office of Faculty Diversity & Development at UT Southwestern Medical Center, Dallas. "This class includes gastroenterology and hepatology's most gifted leaders who are trailblazers for the future of academic medicine."

- Muyiwa Awoniyi, MD, PhD
- Bubu Banini, MD, PhD
- Jihane Benhammou, MD, PhD
- Manuel Braga Neto, MD, PhD
- Cassandra Fritz, MD
- Joel Gabre, MD
- Rachel Issaka, MD, MAS
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- Vivian Ortiz, MD
- Nicolette Rodriguez, MD, MPH

Each Scholar has been paired with a top GI investigator for the duration of the program who will provide mentorship and help in developing the Scholar's leadership skills and strengthening their research and management skills to ensure continued success in their careers. In addition to the GI mentors, the program will be introducing five "near-peer" mentors from the inaugural FORWARD cohort who will each serve as program guides for the current cohort Scholars.

Learn more about this program at https://www.gastro.org/aga-leadership/initiatives-and-programs/forward-program.

Simple ways to create a legacy

Creating a legacy of giving is easier than you think. Take some time to start creating your legacy while supporting the AGA Research Foundation. Gifts to charitable organizations, such as the AGA Research Foundation, in your plans ensure your support for our mission continues for years to come.

Here are two ideas to help you get started.

- **Name the AGA Research Foundation as a beneficiary.** This arrangement is one of the most tax-smart ways to support the AGA Research Foundation after your lifetime. When you leave retirement plan assets to us, we bypass any taxes and receive the full amount.
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Want to learn more about including a gift to the AGA Research Foundation in your plans? Visit our website at https://gastro.planmylegacy.org.

Register for the 2022 AGA Tech Summit

Innovative technologies for obesity management, emerging noninvasive diagnostic tools, and the AI revolution in health care are just some of the topics featured at the 2022 AGA Tech Summit, April 14-15, in San Francisco. Registration is now open (http://agau.gastro.org/diweb/catalog/item/id/6308511).

This year's Summit features a keynote lecture from Rajni Natesan, MD, MBA, chief medical officer for Braid Health, on how the power of data connectivity is being used in the transformation of health care.

The 2022 Summit continues to feature ancillary programs for physician innovators and trainees interested in innovation.

See the next big idea in gastroenterology. The Shark Tank competition is where GI innovators pitch their concepts to a panel of judges.

Dr. Rajni Natesan

Have an idea you think has potential?

Get an exclusive behind-the-scenes tour of the MedTech world through the AGA Innovation Fellows Program. The program connects GI fellows in their third and fourth year, as well as those in advanced endoscopy fellowship programs, with successful physician innovators and industry thought leaders with the goals of sharpening their entrepreneurial talents and introducing careers in GI innovation.

Join the GI innovation community at the AGA Tech Summit and be part of it yourself.

Is proactive drug monitoring the way to go for IBD?

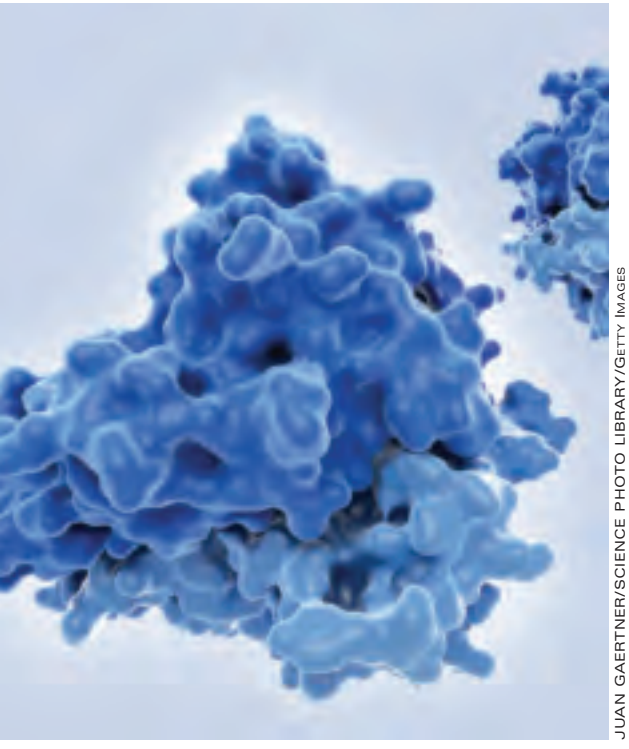
Dear colleagues,

We shift gears from discussing GI hospitalists to focusing on the treatment of inflammatory bowel disease.

Dr. Ketwaroo

The introduction of anti-TNFs brought about a paradigm shift in IBD management. With the ability to measure drug and antibody levels, we are also able to alter dose and timing to increase the efficacy of these medications. Some experts have extended this *reactive* drug monitoring approach to a more *proactive* method with the expectation that this may prevent loss of efficacy and development of adverse events. Dr. Loren G. Rabinowitz and colleagues and Dr. Hans Herfarth describe these two approaches to anti-TNF management in IBD, drawing from the current data and their own experiences. I look forward to hearing your thoughts and experiences by email (ginews@gastro.org). ■

Gyanprakash A. Ketwaroo, MD, MSc, is an assistant professor of medicine at Baylor College of Medicine, Houston. He is an associate editor for GI & Hepatology News.



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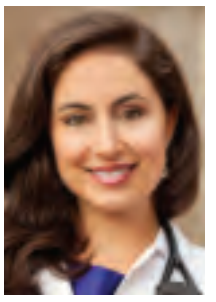
Many of these medications inhibit tumor necrosis factor (illustrated above).

Better outcomes than reactive TDM

Reactive therapeutic drug monitoring (TDM) refers to a strategy of assessing drug concentration and presence of antidrug antibodies (ADAs) in the setting of primary nonresponse (PNR) and loss of response (LOR) to a biologic agent. In this context, TDM informs possible reasons for loss or lack of response to treatment, for example, insufficient drug concentration or the development of high-titer ADAs (immunogenicity), thus better directing the management of these unwanted outcomes. Insufficient anti-TNF concentrations have been associated with PNR and lack of clinical remission at 1 year in patients with IBD, underscoring the need for a durable strategy to ensure appropriate drug concentrations from the induction through maintenance phases of biologic administration. For a significant number of patients, reactive TDM identifies at-risk patients too late, when ADAs have already formed. Because the number of medications to treat IBD remains limited, waiting for a patient to lose response to an agent, particularly anti-TNF, increases the likelihood of immunogenicity, thus rendering an agent unusable. Proactive TDM or checking drug trough concentrations preemptively and at predetermined intervals and dosing to an appropriate concentration, can improve patient outcomes. If drug concentration is determined to be not "at target," dosage and timing of administration can be increased with or without the addition of an immunomodulator (thiopurines or methotrexate) in order to optimize the biologic's efficacy and prevent immunogenicity. This approach allows the provider to anticipate and proactively guard against PNR and future LOR. ■



Dr. Rabinowitz

Dr. Papamichael

Dr. Cheifetz

Loren G. Rabinowitz, MD; Konstantinos Papamichael, PhD, MD; and Adam S. Cheifetz, MD, AGAF, are with the department of medicine and division of gastroenterology at Beth Israel Deaconess Medical Center and Harvard Medical School, both in Boston. Dr. Rabinowitz reports no conflicts of interest. Dr. Papamichael reports lecture fees from Mitsubishi Tanabe Pharma and Physicians Education Resource; consultancy fees from Prometheus Laboratories; and scientific advisory board fees from ProciseDx and Scipher Medicine Corporation. Dr. Cheifetz reports consulting for Janssen, AbbVie, Samsung, Arena, Grifols, Prometheus, Bristol Myers Squibb, Artizan, Artugan, and Equllium.

Taking a look at existing evidence

The debate of therapeutic drug monitoring (TDM) in the setting of anti–tumor necrosis factor therapy has been ongoing for over a decade. Reactive TDM, the measurement of drug concentrations in the context of loss of treatment response, is now generally accepted and recommended in multiple national and international inflammatory bowel diseases (IBD) guidelines. Proactive TDM, defined as the systematic measurement of drug trough concentrations and antidrug antibodies with dose adaptions to a predefined target drug concentration, seems to offer a possibility to stabilize drug levels and prevent antidrug antibody formation due to low systemic drug levels, thus potentially preventing the well-known loss of response to anti-TNF therapy, which occurs in more than 50% of patients over time.

Dr. Herfarth

However, proactive TDM is not endorsed by evidence-based guidelines, dividing IBD physicians into believers and nonbelievers and limiting uptake into clinical practice. As with reactive TDM, one should assume that the framework for proactive TDM should have been reliably established based on factual data derived from prospective controlled studies and not rely on retrospective cohorts or "Expert Panel" consensus statements. And indeed, several prospective controlled studies with sizable IBD patient cohorts have been published. Of note, all TDM studies were conducted in patients on anti-TNF maintenance therapy, and currently no prospective studies in larger IBD populations are available for proactive TDM during induction therapy. In the comparison of proactive TDM vs. reactive TDM, three studies have demonstrated no significant differences in drug persistence or overall maintenance of clinical remission. ■

Hans Herfarth, MD, PhD, AGAF, is a professor of medicine and codirector of the UNC Multidisciplinary IBD Center at University of North Carolina, Durham. He reports serving as a consultant to Alivio, AMAG, BMS, Boehringer, ExeGi Pharma, Finch, Gilead, Janssen, Lycera, Merck, Otsuka, Pfizer, PureTech, and Seres and receiving research support from Allakos, Artizan, and Pfizer.

Read more!
Please find full-length versions of these debates online at MDedge.com/gihepnews/perspectives.

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Tailored program has high success

Spanish *from page 1*

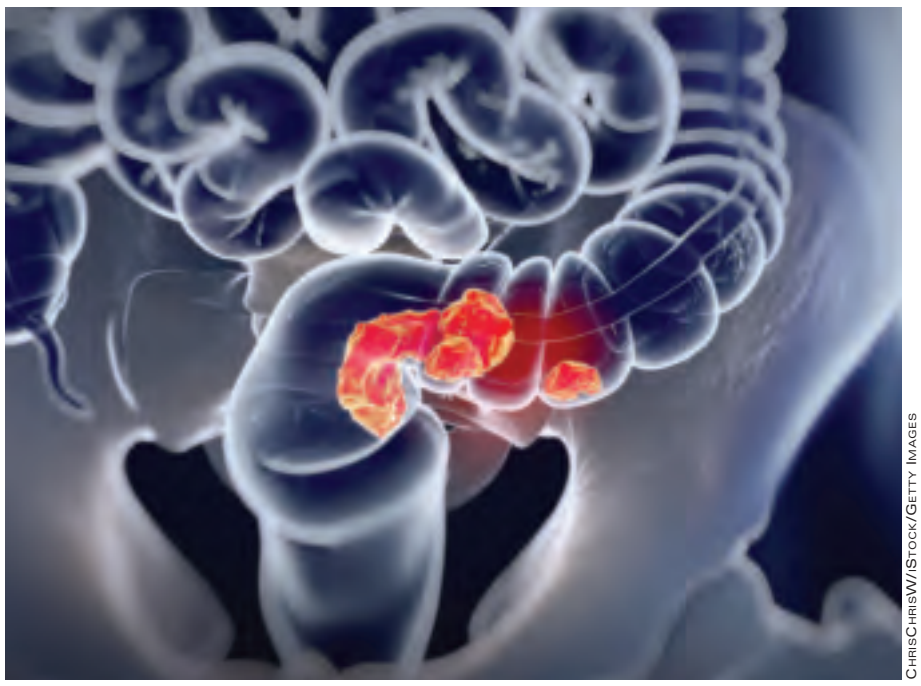
Hispanic population, Dr. Calvino and his colleagues reported in the journal Cancer (2022 Feb 7. doi: 10.1002/cncr.34112).

Colorectal cancer is the second-leading cause of cancer-related death in the United States overall and the third–most diagnosed cancer site, according to the American Cancer Society. Among Hispanics, colorectal cancer is the second-leading cause of cancer mortality and the second–most diagnosed site of malignancy.

Dr. Calvino and his colleagues sought to learn if a culturally tailored patient navigation program could improve rates of screening colonoscopies among Hispanic residents in Providence.

The hospital hired a dedicated Spanish-speaking navigator/coordinator and enrolled 698 men and women into the program.

The navigator sent introductory letters in Spanish to study participants, made phone calls to educate patients about the importance of cancer screening, and called again to ensure that all potential barriers to colonoscopy were overcome, Dr. Calvino said. Colonoscopy completion, cancellations, and no-shows were recorded. Participants were followed for 28 months.



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The program proved highly successful, according to the researchers. At the end of the study period, 85% of patients – exceeding the national goal of 80% set by the National Colorectal Cancer Roundtable – had completed testing, with no differences between men and women; the cancellation rate was 9%, and only 6% of patients failed to show up for endoscopy.

Among the group that underwent colonoscopy, 254 (43%) had polyps removed and 8 (1.3%) required colectomy, the researchers reported. Five patients (0.8%) were diagnosed with malignancy.

Dr. Calvino attributed the 15% combined rate of no-shows and cancellations to the cost of the procedure (copayment, out-of-pocket expense, and loss of wages) and the inability to follow up with those patients. He added that 90% of those who completed the procedure said that, without the patient navigation program, they would not have completed the screening colonoscopies.

Aimee Afable, PhD, MPH, an expert on health disparities and immigrant health at Downstate Health Science University, New York, called the new study small but "important."

Dr. Afable said strong evidence supports the ability of patient navigation programs to improve the reach and impact of screening programs aimed at the underserved. However, hospitals typically do not adequately fund such initiatives. (Dr. Calvino said the program at Roger Williams started with a grant from the OLDCO Foundation and is now supported by his institution.)

90% of those who completed the procedure said that, without the patient navigation program, they would not have completed the screening colonoscopies.

"In 2022, post COVID, it is common to see health care support staff leaving institutions, hospitals because they're not being paid well, and they are overburdened," Dr. Afable told this news organization. "Patient navigation is not, unfortunately, a routine part of health care in the U.S. despite its central role in ensuring continuity of care."

Funding for the study was provided by a grant from the OLDCO Foundation. Coauthor John C. Hardaway, MD, PhD, reports being a cancer liaison physician for the American College of Surgeons. The other authors have disclosed no relevant financial relationships. Dr. Afable has no disclosures. ■

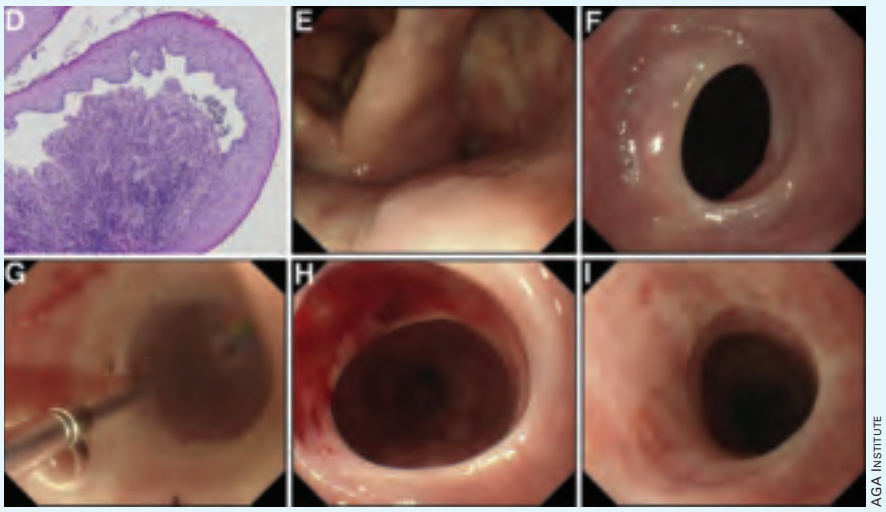
CLINICAL CHALLENGES AND IMAGES

The diagnosis

Answer to "What's your diagnosis?" from page 7: Mucous membrane pemphigoid with esophageal web stricture.

Additional laboratory examination showed that his serum anti-BP180 antibody level was high (11.7 U/mL; normal range, <9.0 U/mL). Biopsy specimens taken from the laryngopharyngeal erosion showed subepithelial blister formation and it was consistent with pemphigoid pathologically (Figure D). He did not have cutaneous lesions and was diagnosed with mucous membrane pemphigoid (MMP). After endoscopic dilation, prednisolone (20 mg/d) was administered orally. Three months after the start of the prednisolone treatment, follow-up endoscopy showed improvements of the laryngopharyngeal erosions (Figure E) and esophageal blister on the web. However, esophageal narrowing remained, and thus endoscopic balloon dilation was performed (Figure F–H). Three months after the dilation, the narrowing improved (Figure I).

MMP is an autoimmune blistering disease that induces the formation of mucous membrane subepithelial bullae. Basement membrane zone components such as collagen XVII (also known as BP180) are targets of autoantibodies in MMP. Symptomatic esophageal involvement affects 5.4% of patients with MMP and dysphagia is the most frequent symptom.[1] Endoscopic findings include erosion, web stricture, subepithelial hematomas, and scars.[2,3] Endoscopic dilation is sometimes necessary for the treatment of severe esophageal strictures.[1]



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Improved follow-up needed for pancreatic cancers

BY BRANDON MAY
MDedge News

A relatively large number of late-stage pancreatic ductal adenocarcinomas (PDACs) are detected during follow-up surveillance, yet no single patient- or protocol-specific factor appears to be significantly associated with detecting late-stage disease during this period, according to a new systematic literature review and meta-analysis.

Impact of interval progression

The researchers, led by Ankit Chhoda, MD, of Yale University, New Haven, Conn., wrote in Gastroenterology (2021 Nov. doi: 10.1053/j.gastro.2021.11.021) that interval progression in high-risk individuals "highlights the need for improved follow-up methodology with higher accuracy to detect prognostically significant and treatable lesions."

Individuals at high risk for PDAC are encouraged to undergo routine surveillance for the disease because early detection and resection of T1N0M0 PDAC and high-grade precursors may improve survival outcomes. According to Dr. Chhoda and colleagues, challenges of interval progression of cancers during the surveillance period for gastrointestinal malignancies have been well described in the general and at-risk patient populations. Previous studies, the authors explained, have not scrutinized the issues associated with late-stage PDACs detected during follow-up surveillance.

The diagnosis of late-stage PDACs during follow-up emphasizes the need for implementing "quality measures to avoid preventable causes."

"Late-stage PDACs necessitate critical appraisal of current follow-up strategies to detect successful targets and perform timely resections," the authors wrote. The researchers added that the diagnosis of late-stage PDACs during follow-up emphasizes the need for implementing "quality measures to avoid preventable causes, including surveillance adherence and diagnostic errors."

Outcomes of interest

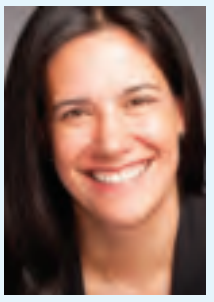
To understand the incidence rates of late-stage PDACs during follow-up in high-risk individuals, Dr. Chhoda and researchers performed a systematic literature review and meta-analysis of data that included follow-up strategies for early PDAC detection among a high-risk population.

Outcomes of interest for the analysis included the overall diagnosis of advanced neoplasia as well as surveillance-detected/interval late-stage PDACs (T2–4N0M0/metastatic stage PDAC) during follow-up. The investigators defined surveillance-detected and interval late-stage PDACs as late-stage PDACs that were detected during surveillance and as those presenting symptomatically between visits, respectively.

The researchers also performed metaregression of the incidence rates of late-stage PDACs to examine the relationship with clini-

Surveillance of individuals at increased risk of pancreatic ductal adenocarcinoma (PDAC) offers an opportunity to improve disease mortality through detection of premalignant lesions and earlier-stage PDAC. Emerging data suggest that outcomes in surveillance-detected PDAC are superior to those diagnosed after onset of signs and symptoms. This study by Chhoda et al. highlights a potential quality gap in current surveillance programs, namely the diagnosis of interval cancers and late-stage metastatic PDAC.

Investigators report a cumulative incidence of late-stage PDAC of 1.7 per 1,000 patient-years in surveillance, while the incidence of any advanced neoplasia (high-grade PanIN, high-grade IPMN, NET > 1 cm, and any stage PDAC) was 3.3 per 1,000 patient-years. Importantly, late-stage PDAC was defined as T2-4N0-1M0-1 in this study. This is based on the 2013 International Cancer of the Pancreas Screening definition of "success of a screening program" as treatment of T1N0M0 PDAC, which was later updated to include a resected PDAC confined to the pancreas.



Dr. Lucas

The cumulative incidence of resectable lesions was 2.2 per 1,000 patient-years, while the incidence of unresectable PDAC was 0.6 per 1,000 patient-years in surveillance. Unfortunately, clinical features were unable to predict the onset of these 11 unresectable PDACs.

Given data-reporting limitations, it is uncertain how many advanced PDACs were a result of delayed surveillance, diagnostic errors, or other preventable factors. Addressing these contributing factors as well identifying clinical indicators that may improve the efficacy of existing regimens (such as new onset diabetes, worsening in glycemic control in a person with diabetes, weight loss, and incorporation of novel biomarkers) will be critical to optimizing PDAC surveillance outcomes in in high-risk individuals.

Aimee Lucas, MD, AGAF, is associate professor of medicine, division of gastroenterology, Icahn School of Medicine at Mount Sinai, New York. She reports receiving research support and consulting from Immunovia, who developed a blood-based biomarker for early PDAC detection.

coradiologic features in high-risk individuals.

A total of 13 studies on surveillance in 2,169 high-risk individuals were included in the systematic review, while 12 studies were included in the meta-analysis. Across studies, high-risk individuals were followed for over 7,302.72 patient-years for the purposes of detecting incident lesions or progression of preexisting pancreatic abnormalities.

The impact of these quality measures "on surveillance outcomes will not only improve quality of surveillance practices, but also enrich our communication with patients."

In all high-risk individuals who underwent follow-up, the investigators identified a total yield of advanced neoplasia of 53. This total yield consisted of 7 high-grade pancreatic intraepithelial neoplasms, 7 high-grade intraductal papillary mucinous neoplasms, and 39 PDACs. According to the meta-analysis, the cumulative incidence of advanced neoplasia was 3.3 (95% confidence interval, 0.6-7.4; $P <$ .001) per 1,000 patient-years. During follow-up, the cumulative incidence of surveillance-detected/interval late-stage PDACs was 1.7 per 1,000 patient-years (95% CI, 0.2-4.0; $P = .03$).

Further analysis explores other factors

In a separate analysis, the investigators sought to identify the relationship between the modality of follow-up imaging and late-stage PDAC incidence. Imaging modalities used during follow-up were mostly cross-sectional imaging, such as computed tomography or magnetic resonance imaging with cholangiopancreatography (n = 4) or endoscopic ultrasound, and cross-sectional modalities (n = 8).

The investigators found no significant associations between late-stage PDACs and surveillance imaging, baseline pancreatic morphology, study location, genetic background, gender, or age. Incidence of late-stage PDACs in studies with mostly cross-sectional imaging was 0.7 per 1,000 patient-years (95% CI, 0.0-8.0). This incidence rate was lower than that reported with EUS and cross-sectional modalities (2.5 per 1,000 patient-years; 95% CI, 0.6-5.4), but this difference was not statistically significant ($P = .2$).

No significant difference was found during follow-up in the incidence of late-stage PDACs between high-risk individuals with baseline pancreatic abnormalities (0.0 no significant difference; 95% CI, 0.0-0.3) vs. high-risk individuals with normal baseline (0.9 per 1,000 patient-years; 95% CI, 0.0-2.8) ($P = .9$).

Most studies included in the analysis did not report on diagnostic errors and surveillance adherence, the researchers wrote.

Nonadherence to surveillance as well as delays in surveillance accounted for four late-stage PDACs, and surveillance cessation and/or delays were reported in 4 out of 19 high-risk individuals. There was limited information on symptoms, presentation timing, site of lesion, and surveillance adherence, which the investigators indicated prevented a formal meta-analysis.

In their summary, the study authors noted that in clinical practice there is a need for improved quality measures and adherence to surveillance programs to reduce the risk of diagnostic errors. The authors stated that evidence on the impact of these quality measures "on surveillance outcomes will not only improve quality of surveillance practices, but also enrich our communication with patients who undergo surveillance."

The researchers reported no conflicts of interest with the pharmaceutical industry, and the study did not receive any funding. ■

A deep dive on tofacitinib's mode of action

BY JIM KLING
MDedge News

A new study has revealed potential cell-specific effects of the human Janus kinase (JAK) inhibitor tofacitinib, including possible targets – such as intestinal inflammation – for future research and even for increasing the drug's effects.

The work used both mice and human cell models to explore the drug's effect in inflammatory bowel disease (IBD). The mouse models suggested that the drug's pharmacokinetics may be affected by intestinal inflammation. The human cell models seem to identify equilibrative nucleoside transporters as the likely route of cellular uptake of tofacitinib; this mechanism appears to be upregulated during inflammation and could present a therapeutic target to bolster the drug's effects.

"Finally, we decipher an important membrane transport mechanism that regulates cellular uptake of tofacitinib into activated immune cells."

"We identify intestinal inflammation as a decisive modulator of the systemic pharmacokinetics of tofacitinib in mice, which needs to be studied and confirmed in humans. Finally, we decipher an important membrane transport mechanism that regulates cellular uptake of tofacitinib into activated immune cells, suggesting a model that explains a preferred uptake of tofacitinib into activated immune cells and a potential starting point to interfere with and channel such an uptake," wrote the authors, led by Bernhard Texler and Andreas Zollner, both with the Christian Doppler Laboratory for Mucosal Immunology at the Johannes Kepler University in Linz, Austria, who published the results in Cellular and Molecular Gastroenterology and Hepatology (2021 Oct. doi: 10.1016/j.jcmgh.2021.09.004).

IBD-related inflammation likely involves multiple cytokine pathways. The JAK-signal transducers and activator of transcription (JAK-STAT) pathway is downstream to more than 50 cytokines and growth factors, so disruption of their activity by JAK-STAT inhibitors like tofacitinib could counter the effects of more than one cytokine at a time.

Tofacitinib received Food and Drug Administration approval for the treatment of ulcerative colitis in 2018, but the details of its mechanism of action against intestinal inflammation remain poorly understood. For example, despite its efficacy against ulcerative colitis, the drug doesn't work for Crohn's disease patients. That may be because the drug affects specific cell populations involved only in UC pathogenesis.

To better understand the drug's pharmacokinetics, the researchers examined the effects of tofacitinib in cells isolated from human peripheral blood, as well as an experimental mouse model of colitis.

The drug inhibited proliferation of both naive and memory cytotoxic and helper T cells. At higher concentrations, it had strong effects on innate immune system cells, including monocytes, macrophages, and human intestinal epithelial organoids. It promotes the anti-inflammatory M2 phenotype among monocytes and macrophages. The drug also inhibited the pro-inflammatory M1 phenotype. The researchers observed similar effects in the mouse model of colitis.

The investigators also linked equilibrative nucleoside transporters (ENTs) with uptake of tofacitinib, specifically as a mediating role. These membrane proteins transport nucleosides, nucleobases, and therapeutic analogs like tofacitinib, which mimics the nucleotide adenosine triphosphate (ATP). Targeted inhibitors could potentially influence this process.

At higher concentrations, it had strong effects on innate immune system cells, including monocytes, macrophages, and human intestinal epithelial organoids.

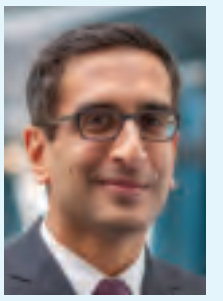
The researchers created three-dimensional, in vitro colonic organoids using intestinal epithelial cells from UC patients and healthy human controls. In this model, tumor necrosis factor–alpha can lead to production of pro-inflammatory cytokines, but tofacitinib blocked this effect. That result suggests that intestinal epithelial cells are a previously unidentified tofacitinib target.

Although a large amount of work has been done on the pharmacokinetics of therapeutic antibodies used to treat IBD, the authors point out that little is known about tofacitinib. In a mouse model, the serum concentration of the drug increased after exposure to dextran sulfate sodium (DSS), which triggers an IBD-like condition, and the spike was higher during more intense inflammation. The finding was surprising, considering that therapeutic antibodies typically get eliminated through feces during inflammation. Mice treated with DSS versus control had similar levels of tofacitinib in both urine and the feces, suggesting that inflammation may somehow inhibit the enzymes that metabolize the drug.

The researchers also noted that uptake of tofacitinib into leukocytes increased following stimulation with lipopolysaccharide. Given its structural similarity to ATP, the researchers propose that tofacitinib may enter the cells through adenosine cell membrane transporters ENT1 and ENT2, and some evidence even suggested that the pathway may be strengthened in activated immune cells.

The study received funding from the Christian Doppler Research Association; the Austrian Federal Ministry of Science, Research, and Economy; and the National Foundation for Research, Technology, and Development. One author is receiving research support from AbbVie and Takeda under the framework of the Christian Doppler Research Society, but the remaining authors have no relevant conflicts of interest.

Growing understanding of underlying immunopathogenic mechanisms of inflammatory bowel diseases (IBD) have led to the development of targeted therapies that have considerably improved patient outcomes. However, insights into their respective effector mechanisms are still scarce.


Dr. Atreya

This translational study by Texler et al. sheds light on the molecular mechanism of action and pharmacokinetic profile of the Janus kinase–inhibitor tofacitinib, which has been approved for the treatment of ulcerative colitis patients. The research group elegantly elucidated that the severity of intestinal inflammation and circulating tofacitinib levels show a strong positive correlation. They identified inflammation induced equilibrative nucleoside transporters as central regulators of cellular tofacitinib uptake. The presented findings are exciting, as there has so far been a glaring lack of studies on the pharmacokinetic properties of tofacitinib in intestinal inflammation. It has already been shown that the degree of intestinal inflammation impacts the pharmacokinetics of available biological therapies (such as anti–tumor necrosis factor antibodies), which not only influences their therapeutic effectiveness but also their required therapeutic dose.

Pharmacokinetics of biological therapies with assessment of serum drug levels have since been an indispensable part of the optimal management of IBD patients. The presented findings on the pharmacokinetics of tofacitinib during inflammation both on a systemic and on a cellular level might have comparable potential therapeutic consequences. Therapeutic modulation of the responsible membrane transport mechanism for the cellular uptake of tofacitinib might lead to enhanced therapeutic efficacy in the future. Further research in humans is needed to confirm the presented findings.

Raja Narayana Atreya, MD is a professor of medicine, Heisenberg Professor of Translational Immunology in IBD and head of the IBD Unit and Clinical Study Centre at the Erlangen University Hospital, Friedrich-Alexander University of Erlangen-Nürnberg, Erlangen, Germany. He has no conflicts.

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Putting a name to a known issue

ARFID *from page 1*

restrictive food intake disorder (ARFID), said Tiffany Taft, PsyD, a research associate professor of medicine (gastroenterology and hepatology), medical social sciences, and psychiatry and behavioral sciences at Northwestern University, Chicago. In a recent study (Clin Gastroenterol Hepatol. 2022 Aug. doi: 10.1016/j.cgh.2021.07.045), she and her colleagues defined ARFID as "failure to meet one's nutritional needs owing to sensory hypersensitivity, lack of interest in eating, or fear of aversive consequences from eating, and is associated with negative medical and psychosocial outcomes."

ARFID "is a hot topic that we really don't understand," she said in an online presentation at the annual Crohn's & Colitis Congress®, a partnership of the Crohn's & Colitis Foundation and the American Gastroenterological Association.

Nutritional deficiencies

Nutritional deficiencies are common among patients with IBD, "and nutritional deficiencies themselves can lead to symptoms or side effects that can cause people to eat less," she said.

"As our vitamin B_{12} goes down, our cognitive functioning starts to decline, and we might not be making clear decisions in how we're deciding what to eat, when to eat, if we should be eating at all – just something to think about in your patients who have nutritional deficiencies," she told the audience.

Other common nutritional deficiencies that can affect eating and food choice among patients with IBD include low folate (B_9) levels associated with sore tongue and weight loss, low iron levels leading to nausea and loss of appetite, and zinc deficiency leading to loss of appetite and alterations in taste and/or smell, she said.

GERENME/THINKSTOCK

Newly recognized in GI

She noted that "ARFID actually originates in the pediatric psychiatric literature, mostly in children with sensory issues [such as] autism spectrum disorder, so this is not a construct that started in digestive disease, but has been adapted and applied to patients with digestive disease, including IBD."

Helen Burton Murray, PhD, director of the gastrointestinal behavioral health program in the Center for Neurointestinal Health at Massachusetts General Hospital, Boston, who is familiar with Dr. Taft's work, said in an interview that inclusion of ARFID in DSM-5 has put a name to a syndrome or symptom cluster that in all likelihood already existed.

However, "the jury is still out about whether, if we do diagnose patients who have digestive diseases with ARFID, that then helps them get to a treatment that improves their relationship with food and improves nutritional issues that may have occurred as a result of a restricted food intake," she said.

"We don't know yet if the diagnosis will actually improve things. In our clinical practice, anecdotally, it has, both for patients with IBDs and for patients with other GI conditions, particularly GI functional motility disorders. We're a little bit more confident about making the diagnosis of ARFID in GI functional motility disorders than we are in IBD of course," she said.

Screening measures

To get a better sense of the prevalence of ARFID, compared with reasonable responses to digestive diseases, Dr. Taft and colleagues conducted their cross-sectional study in 289 adults with achalasia, celiac disease, eosinophilic esophagitis, or IBD.

They found that 51.3% of the total sample met the diagnostic criteria for ARFID based on the Nine-Item ARFID Screen (NIAS) (Am J Gastroenterol. 2018 Oct;113:S247-8), including 75.7% of patients with achalasia. But Dr. Taft cautions: "I can tell you, working with achalasia patients, 75% do not have ARFID." She also noted that the 51.3% of patients with IBD identified by NIAS or the 53% identified by the ARFID+ scale as having ARFID was also highly doubtful.

Dr. Taft and colleagues determined that nearly half of the variance in the NIAS could be accounted for by GI symptoms rather than psychosocial factors, making it less than ideal for use in the clinic or by researchers.

She also noted, however, that she received an email from one of the creators of NIAS, Hana F. Zickgraf, PhD, from the University of South Alabama, Mobile. Dr. Zickgraf agreed that the scale had drawbacks when applied to patients with GI disease, and pointed instead to the Fear of Food Questionnaire, a newly developed 18-item GI disease–specific instrument. Dr. Taft recommended the new questionnaire for research purposes, and expressed hope that a shorter version could

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Species tied to specific symptoms

COVID *from page 1*

COVID, recruited in 2019. The severity of COVID in the enrolled patients was mostly mild to moderate.

At 3 months, 86 of the patients with COVID had post–acute COVID-19 syndrome (PACS) – defined as at least one persistent, otherwise unexplained symptom 4 weeks after clearance of the virus. And 81 patients had PACS at 6 months, most commonly fatigue, poor memory, hair loss, anxiety, and trouble sleeping.

Using stool samples for their analysis, the researchers found that, broadly, the diversity of the types of bacteria, and the abundance of these bacteria, were significantly lower at 6 months for those with PACS, compared with those without PACS and with controls ($P < .05$ and $P < .0001$, respectively). Among those with PACS, 28 bacteria species were diminished and 14 were enriched, both at baseline and follow-up. Those patients who had COVID but not PACS showed just 25 alterations of bacteria species at the time of hospital admission, and they all normalized by 6 months.

Having respiratory symptoms at 6 months was linked with higher levels of opportunistic pathogens such as *Streptococcus anginosus* and *S. vestibularis*. Neuropsychiatric symptoms and fatigue were associated with nosocomial pathogens that are linked to opportunistic infections, such as *Clostridium innocuum* and *Actinomyces naeslundii* ($P < .05$).

"Microbiome modulation is pretty safe, and that's really the next big step that needs to be taken in this."

Bacteria known for producing butyrate, a beneficial fatty acid, were significantly depleted in those patients with hair loss. And certain of these bacteria, including *Bifidobacterium pseudocatenulatum* and *Faecalibacterium prausnitzii*, had the largest inverse correlations with PACS at 6 months ($P < .05$), the researchers found.

"Particular gut microbial profiles may indicate heightened susceptibility," Dr. Ng said.

Although the findings were drawn from patients with earlier strains of the COVID-19 virus, the findings still apply to new variants, including Omicron, since these pose the same problem of persistent disruption of the immune system, Dr. Ng said.

Her group is conducting trials to look at how modulating the microbiome might prevent long COVID and boost antibodies after vaccination in high-risk people, she said.

"Gut microbiota influences the health of the host," Dr. Ng said. "It provides crucial benefits in the form of immune system development, prevention of infections, nutrient acquisition, and brain and nervous system functionality. Considering the millions of people infected during the ongoing pandemic, our findings are a strong impetus for consideration of microbiota modulation to facilitate timely recovery and reduce the burden of post–acute COVID-19 syndrome."

Courtesy Dr. John Haran

Dr. John Haran

John Haran, MD, PhD, associate professor of microbiology and physiological systems and emergency medicine at the University of Massachusetts, Worcester, said the research adds to the evidence base on the gut microbiome's links to COVID, but there was likely be no clinical impact yet. Still, he said the findings linking specific species to specific symptoms was particularly interesting.

"Very early on during hospi-

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be made available for screening patients in clinic.

Dr. Burton Murray said that, while the Fear of Food Questionnaire, perhaps in combination with NIAS, has the potential to be a useful screening tool, cutoffs for it have yet to be established.

"At the end of the day, the diagnosis would be made by a clinician who is able to determine whether the life impairment or if the nutritional impairment or restricted food intake are reasonable in the realm of their digestive disease, or could a treatment for ARFID be warranted to help them to make changes to improve their quality of life and nutrition," she said.

Check biases at the door

Before arriving at a diagnosis of ARFID, clinicians should also consider biases, Dr. Taft said.

"Eating disorders are highly stigmatized and stereotyped diagnoses," more often attributed to young White women than to either men or to people of racial or ethnic minorities, she said.

Cultural background may contribute to food restrictions, and the risk may increase with age, with 68% of patients with later-onset IBD restricting diets to control the disease. It's also possible that beliefs about food and "clean and healthy" eating may influence food and eating choices after a patient receives an IBD diagnosis.

Dr. Taft also pointed out that clinicians and patients may have different ideas about what constitutes significant food avoidance. Clinicians may expect patients with IBD to eat despite feeling nauseated and having abdominal pains or diarrhea; for example, when the same food avoidance might be deemed reasonable in patients with short-term GI infections.

"Severe IBD symptoms are a significant predictor of posttraumatic stress disorder symptoms, and PTSD is hallmarked by avoidance behaviors," she added.

She emphasized the need for clinicians to ask the right questions of patients to get at the roots of their nutritional deficiency or eating behavior, and to refer patients to mental health professionals with expertise in disordered eating or GI psychology.

Dr. Taft and Dr. Burton Murray reported having no conflicts of interest to disclose. ■

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talization, [the researchers] saw these differences and correlated out with people who have longer symptoms, and especially different groups of people that have longer symptoms, too," said Dr. Haran, who has done research on the topic. "It's very different if you have different symptoms; for example, you keep coughing for months versus you have brain fog and fatigue, or other debilitating symptoms."

Dr. Haran noted that the findings didn't identify bacteria types especially linked to COVID, but rather species that have already been found to be associated with a "bad" microbiome. He also pointed out that the patients enrolled in the study were not vaccinated because vaccines weren't available at the time. Still, further study to see whether modulation of gut bacteria can be a therapy seems worthwhile.

"Microbiome modulation is pretty safe, and that's really the next big step that needs to be taken in this," he said.

For now, the findings don't give the clinician much new ammunition for treatment.

"We're not there yet," he added. "It's not as if clinicians are going to tell their COVID patients: 'Go out and buy some kale.' "

Eugene Chang, MD, AGAF, professor of medicine at the University of Chicago, who has studied the gut microbiome and gastrointestinal disease, said it's "too preliminary" to say whether the findings could lead to a clinical impact. The measures used merely identify the microbes present, but not what they are doing.

"These measures are unlikely to perform well enough to be useful for risk assessment or predicting clinical outcomes," he said. "That being said, advances in technology are being made where next generations of metrics could be developed and useful as stratifiers and predictors of risk."

Seeing shifting patterns associated with certain symptoms, he said, is "notable because it suggests that the disturbances of the gut microbiota in PACS are significant."

But he said it's important to know whether these changes are a cause of PACS in some way or just an effect of it.

"If causative or contributory – this has to be proven – then 'microbiota modulation' would make sense and could be a priority for development," he said. "If merely an effect, these metrics and better ones to come could be useful as predictors or measures of the patient's general state of health."

As seen in his group's work and other work, he said, "the gut microbiota is highly sensitive to changes in their ecosystem, which is influenced by the health state of the patient."

Dr. Ng, Dr. Haran, and Dr. Chang reported no relevant disclosures. ■

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