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Pancreatic cancer incidence rates were found to be increasing at a higher rate in younger women, compared with younger men.

Pancreatic cancer incidence increases among young women in U.S.

BY CAROLYN CRIST
MDedge News

The age-adjusted incidence rate of pancreatic cancer is increasing in young women in the United States, and it doesn't show signs of slowing down, according to a new study published in Gastroenterology (2023 Feb 10. doi: 10.1053/j.gastro.2023.01.022).

Between 2001 and 2018, there was a greater than 200% difference in the incidence trend between men and women for ages 15-34, wrote Yazan Abboud, MD, a postdoctoral research fellow in the pancreaticobiliary department of the Karsh Division of Gastroenterology and Hepatology at Cedars-Sinai Medical Center, Los Angeles, and colleagues.

"The exact cause of the trend among younger women is unclear and may be driven by sex-based

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New influx of Humira biosimilars may not drive immediate change

BY JENNIFER LUBELL
MDedge News

Gastroenterologists in 2023 will have more tools in their arsenal to treat patients with Crohn's disease or ulcerative colitis. As many as 10 adalimumab biosimilars are anticipated to come on the market this year, giving mainstay drug Humira some vigorous competition.

Three scenarios will drive adalimumab biosimilar initiation: insurance preference for the initial treatment of a newly diagnosed condition, a change in a patient's insurance plan, or an insurance-mandated switch, said Edward C. Oldfield IV, MD, assistant professor at Eastern Virginia Medical School's division of gastroenterology in Norfolk.

Even with more drugs to choose from, some gastroenterologists may be hesitant to make a switch. "Outside of these scenarios, I would encourage patients to remain on their current biologic so long as cost and accessibility remain stable," said Dr. Oldfield.

Many factors will contribute to the success of biosimilars. Will

See **Biosimilars** · *page 7*

AGA Clinical Practice Update: Commentary

Guidance for telemedicine

BY CAROLYN CRIST
MDedge News

Although virtual visits have decreased and in-person visits have risen since the initial COVID-19 wave in 2020, telemedicine remains an important option in gastroenterology and requires clear guidance for best practices moving forward, according to a new clinical practice update from the American Gastroenterological Association (Gastroenterology. 2023 Feb 10. doi: 10.1053/j.gastro.2022.12.043).

The postpandemic era

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LETTER FROM THE EDITOR

Implicit bias in medicine and beyond

Recently, I reported to the Washtenaw County Circuit Courthouse in Ann Arbor, Mich., to fulfill my civic responsibility of jury duty. After check-in, a pool of 250 potential jurors were shown a video about implicit bias and shuttled off to different courtrooms for the jury selection process (voir dire, or "to speak the truth" in French).

While not personally called up to the juror box on this day, I did have the opportunity to observe the attorneys and judge as they questioned potential jurors to uncover any indication that they might not be fair or impartial in judging the facts of this criminal case. After over 3 hours of questioning and several peremptory challenges, a jury was empaneled, and the rest of us were dismissed for the day.

As I left the courthouse, I could not help but reflect on the parallels between the legal and health care systems in terms of the negative impacts of unconscious or implicit bias. In the legal system, implicit bias can adversely affect legal outcomes by impacting the beliefs and attitudes of multiple stakeholders, including attorneys and judges, litigants, witnesses, and of course jurors, threatening one of our society's most fundamental principles of equal justice under the law. In the health care arena, implicit bias has been shown to impact patient-clinician communication and contribute to racial and ethnic disparities in patient outcomes.

Dr. Adams

Join me in reflecting on whether and how unconscious attitudes or stereotypes may unintentionally color the way in which you interact with patients.

As a medical community, acknowledging and accepting the existence of implicit bias, its manifestations, and its impact is a critical first step to ensuring that every patient that walks into our exam rooms receives equitable care, and we can begin to move the needle in addressing persistent health disparities in patients with gastrointestinal diseases and beyond. While this is regrettably a politically charged topic in our current environment, I urge you to join me in reflecting on whether and how unconscious attitudes or stereotypes may unintentionally color the way in which you interact with patients in the clinic and serve to create or perpetuate inequities in treatment.

Turning to our April issue, we highlight two recent studies from AGA's flagship journals, one showing an unexpected rise in pancreatic cancer incidence among women under the age of 55, and another evaluating survival outcomes by fibrosis stage in biopsy-proven nonalcoholic fatty liver disease.

In this month's Member Spotlight column, we introduce you to gastroenterologist Daniel Leffler, MD, who shares his experiences transitioning from a traditional academic career to a job in industry to further scientific advancements in celiac disease treatment.

We hope you enjoy these articles and all the content included in our April issue! ■

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

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‘Monumental’ findings cited

Cancer *from page 1*

disproportional exposure or response to known or yet-to-be-explored risk factors,” they wrote. “Future efforts should aim to elucidate the causes of such a trend with the goal to formulate possible preventive measures.”

Although previous studies have found increasing pancreatic cancer incidence rates, especially in younger women, the data haven’t been externally validated outside of the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) data, they wrote. In addition, there are limited data about the contributing factors, such as race, histopathological subtype, tumor location, and stage at diagnosis.

Using SEER-excluded data from the Centers for Disease Control and Prevention’s National Program of Cancer Registries (NPCR), Dr. Abboud and colleagues conducted a population-based time-trend analysis of pancreatic cancer incidence rates from 2001 to 2018 in adults younger than age 55, including the role of demographics and tumor characteristics. They analyzed age-adjusted incidence rates (aIR), mortality rates, annual percentage change (APC), and average annual percentage change (AAPC) for ages 55 and older and ages 55 and younger. In addition, the research team evaluated the impact of incidence trends on sex-specific mortality trends in younger adults using the CDC’s National Center of Health Statistics database.

Between 2001 and 2018, 748,132 patients were diagnosed with pancreatic cancer. After excluding SEER data, 454,611 patients met the inclusion criteria. About 48.9% were women.

The overall aIR of pancreatic cancer during that time was 12.18 per 100,000 people. Women had a significantly lower aIR, at 10.69 per 100,000, compared with men at 13.95 per 100,000.

In general, pancreatic cancer aIR significantly increased during that time (AAPC = 1.17%). Sex-specific trends increased among both women (AAPC = 1.27%) and men (AAPC = 1.14%), though they showed no significant difference and were parallel.

In ages 55 and older, 401,419 patients (49.7% women) were diagnosed with pancreatic cancer. The aIR significantly increased during the study period (AAPC = 1.11%), with sex-specific aIR increasing in both women (AAPC = 1.11%) and men (AAPC = 1.17%), without a significant difference.

Dr. Abboud

However, a difference appeared in the 53,051 patients (42.9% women) who were ages 55 and younger. The aIR relatively increased (AAPC = 1.29%), with faster jumps in women (AAPC = 2.36%), compared with men (AAPC = .62%). There was an absolute significant difference of 1.74%.

The trends continued in breakdowns by age. For 50,599 patients (42.2% women) between ages 35 and 54, the aIR relatively increased (AAPC = 1.10%). Sex-specific aIR increased among women (AAPC = 2.09%) but remained stable among men (AAPC = 0.54%), with an absolute significant difference of 1.55%.

In the youngest cohort of 2,452 patients (57.3% women) between ages 15 and 34, aIR relatively increased (AAPC = 4.93). Sex-specific aIR also increased in both women (AAPC = 6.45%) and men (AAPC = 2.97%), with an absolute significant difference of 3.48%.

By race, although White women under age 55 experienced increasing aIR at a greater rate than men (AAPC difference = 1.59%), an even more dramatic increase was seen in Black women, as compared to counterpart men (AAPC difference = 2.23%). Sex-specific trends in people of other races were parallel.

Based on tumor characteristics in ages 55 and younger, the pancreatic ductal adenocarcinoma histopathological subtype had an AAPC difference of 0.89%, and a tumor location in the head of pancreas had an AAPC difference of 1.64%.

For tumors evaluated based on stage at diagnosis, the AAPC difference was nonsignificant in all subgroups. However, sex-specific trends differed in tumors diagnosed at localized stages, suggesting that aIR in women may be increasing at a greater rate than in men (AAPC difference = 1.64%).

Among 64,239 patients (39.3% women) who died from pancreatic cancer under age 55, the mortality rates were unchanged in women (AAPC = –0.09%) but declined in men (AAPC = –0.64%), with an absolute significant AAPC difference of 0.54%.

Dr. Issa

“Pancreatic cancer has a very poor overall survival, accounting for 7% of cancer-related deaths. The incidence of cancers, in general, is expected to rise as life expectancy increases in the United States,” said Danny Issa, MD, a gastroenterologist at the University of California, Los Angeles, who wasn’t involved with this study.

“Recently, noncomparative studies showed a possible increase in the incidence of pancreatic cancer in younger White women and in older White men and women. These reports had limitations,” he said. “The findings of this study are monumental as they confirmed that age-adjusted incidence rates have been increasing at a higher rate in younger women compared to younger men.”

In addition, Dr. Issa said, the significant increases among Black women for adenocarcinoma and for cancers located in the head of the pancreas are notable and should be studied further.

“Over the past few decades, research studies have helped improve cancer treatment by uncovering risk factors and identifying the most affected (or protected) population,” he said. “Therefore, epidemiologic studies are crucial, especially for hard-to-treat cancers such as pancreatic cancer.”

The study was supported in part by a philanthropic grant from the Widjaja Family Fund for Pancreatic Cancer Research. The authors disclosed no conflicts of interest. Dr. Issa reported no relevant disclosures. ■

Potential impact: ‘Wait and see’

Biosimilars *from page 1*

physicians be prescribing them? How are biosimilars placed on formularies and will they be given preferred status? How will manufacturers price their biosimilars? “We have to wait and see to get the answers to these questions,” said Steven Newmark, JD, MPA, chief legal officer and director of policy, Global Healthy Living Foundation/CreakyJoints, a nonprofit advocacy organization based in New York.

Prescribing biosimilars is no different than prescribing originator biologics, so providers should know how to use them, said Mr. Newmark. “Most important will be the availability of patient-friendly resources that providers can share with their patients to provide education about and confidence in using biosimilars,” he added.

Overall, biosimilars are a good thing, said Dr. Oldfield. “In the long run they should bring down costs and increase access to medications for our patients.”

Others are skeptical that the adalimumab biosimilars will save patients much money.

Biosimilar laws were created to lower costs. However, if a patient with insurance pays only $5 a month out of pocket for Humira – a drug that normally costs $7,000 without coverage – it’s unlikely they would want to switch unless there’s comparable savings from the biosimilar, said Stephen B. Hanauer, MD, medical director of the Digestive Health Center and professor of medicine at Northwestern Medicine, Northwestern University, Evanston, Ill.

Like generics, Humira biosimilars may face some initial backlash, said Dr. Hanauer.

2023 broadens scope of adalimumab treatments

The American Gastroenterological Association describes a biosimilar as something that’s “highly similar to, but not an exact copy of, a biologic reference product already approved” by the Food and Drug Administration. Congress under the 2010 Affordable Care Act created a special, abbreviated pathway to approval for biosimilars.

Dr. Oldfield

AbbVie’s Humira, the global revenue for which exceeded $20 billion in 2021, has long dominated the U.S. market on injectable treatments for autoimmune diseases. The popular drug faces some competition in 2023, however, following a series of legal settlements that allowed AbbVie competitors to release their own adalimumab biosimilars.

“So far, we haven’t seen biosimilars live up to their potential in the U.S.

Continued on following page

Continued from previous page

in the inflammatory space," said Mr. Newmark. This may change, however. Previously, biosimilars have required infusion, which demanded more time, commitment, and travel from patients. "The new set of forthcoming Humira biosimilars are injectables, an administration method preferred by patients," he said.


Mr. Newmark

The FDA will approve a biosimilar if it determines that the biological product is highly similar to the reference product, and that there are no clinically meaningful differences between the biological and reference product in terms of the safety, purity, and potency of the product.

The agency to date has approved eight adalimumab biosimilars. These include: Idacio (adalimumab-aacf, Fresenius Kabi); Amjevita (adalimumab-atto, Amgen); Hadlima (adalimumab-bwwd, Organon); Cyltezo (adalimumab-adbm, Boehringer Ingelheim); Yusimry (adalimumab-aqvh from Coherus BioSciences); Hulio (adalimumab-fkjp; Mylan/Fujifilm Kyowa Kirin Biologics); Hyrimoz (adalimumab-adaz, Sandoz); and Abrilada (adalimumab-afzb, Pfizer).

"While FDA doesn't formally track when products come to market, we know based on published reports that application holders for many of the currently FDA-approved biosimilars plan to market this year, starting with Amjevita being the first adalimumab biosimilar launched" in January, said Sarah Yim, MD, director of the Office of Therapeutic Biologics and Biosimilars at the agency.

At press time, two other companies (Celltrion and Alvotech/Teva) were awaiting FDA approval for their adalimumab biosimilar drugs.

Among the eight approved drugs, Cyltezo is the only one that has a designation for interchangeability with Humira.

An interchangeable biosimilar may be substituted at the pharmacy without the intervention of the prescriber – much like generics are substituted, depending on state laws, said Dr. Yim. "However, in terms of safety and effectiveness, FDA's standards for approval mean that biosimilar or interchangeable biosimilar products can be used in place of the reference product they were compared to."

FDA-approved biosimilars undergo a rigorous evaluation for safety, effectiveness, and quality for their approved conditions of use, she continued. "Therefore, patients and health care providers can rely on a biosimilar to be as safe and effective for its approved uses as the original biological product."

Remicade as a yardstick

Gastroenterologists dealt with this situation once before, when Remicade (infliximab) biosimilars came on the market in 2016, noted Miguel Regueiro, MD, AGAF, chair of the Digestive Disease and Surgery Institute at the Cleveland Clinic.


Dr. Regueiro

Remicade and Humira are both tumor necrosis factor inhibitors with the same mechanism of action and many of the same indications. "We already had that experience with Remicade and biosimilar switch 2 or 3 years ago. Now we're talking about Humira," said Dr. Regueiro.

Most GI doctors have prescribed one of the more common infliximab biosimilars (Inflectra or Renflexis), noted Dr. Oldfield. Cardinal Health, which recently surveyed 300 gastroenterologists, rheumatologists, and dermatologists about adalimumab biosimilars, found that gastroenterologists had the highest comfort level in prescribing them. Their top concern, however, was changing a patient from adalimumab to an adalimumab biosimilar.

For most patients, Dr. Oldfield sees the Humira reference biologic and biosimilar as equivalent.

However, he said he would change a patient's drug only if there were a good reason or if his hand was forced by insurance. He would not make the change for a patient who recently began induction with the reference biologic or a patient with highly active clinical disease.

"While there is limited data to support this, I would also have some qualms about changing a patient from reference biologic to a biosimilar if they previously had immune-mediated pharmacokinetic failure due to antibody development with a biologic and were currently doing well on their new biologic," he said.

Those with a new ulcerative colitis or Crohn's diagnosis who are initiating a biologic for the first time might consider a biosimilar. If a patient is transitioning from a reference biologic to a biosimilar, "I would want to make that change during a time of stable remission and with the recognition that the switch is not a temporary switch, but a long-term switch," he continued.

A paper (Biodrugs. 2022 Jul 26. doi: 10.1007/s40259-022-00546-6) that reviewed 23 observational studies of adalimumab and other biosimilars found that switching biosimilars was safe and effective. But if possible, patients should minimize the number of switches until more robust long-term data are available, added Dr. Oldfield.

If a patient is apprehensive about switching to a new therapy, "one may need to be cognizant of the 'nocebo' effect in which there is an unexplained or unfavorable therapeutic effect after switching," he said.

Other gastroenterologists voiced similar reservations about switching. "I won't use an adalimumab biosimilar unless the patient requests it, the insurance requires it, or there is a cost advantage for the patient such that they prefer it," said Doug Wolf, MD, an Atlanta gastroenterologist.

"There is no medical treatment advantage to a biosimilar, especially if switching from Humira," added Dr. Wolf.

Insurance will guide treatment

Once a drug is approved for use by the FDA, that drug will be available in all 50 states. "Different private insurance formularies, as well as state Medicaid formularies, might affect the actual ability of patients to receive such drugs," said Mr. Newmark.

Patients should consult with their providers and insurance companies to see what therapies are available, he advised.

Dr. Hanauer anticipates some headaches arising for patients and doctors alike when negotiating for a specific drug.

Cyltezo may be the only biosimilar interchangeable with Humira, but the third-party pharmacy benefit manager (PBM) could negotiate for one of the noninterchangeable ones. "On a yearly basis they could switch their preference," said Dr. Hanauer.

In the Cardinal Health survey, more than 60% of respondents said they would feel comfortable prescribing an adalimumab biosimilar only with an interchangeability designation.

A PBM may offer a patient Cyltezo if it's cheaper than Humira. If the patient insists on staying on Humira, then they'll have to pay more for that drug on their payer's formulary, said Dr. Hanauer. In a worst-case scenario, a physician may have to appeal on a patient's behalf to get Humira if the insurer offers only the biosimilar.

Taking that step to appeal is a major hassle for the physician, and leads to extra backdoor costs as well, said Dr. Hanauer.

Humira manufacturer AbbVie, in turn, may offer discounts and rebates to the PBMs to put Humira on their formulary. "That's the AbbVie negotiating power. It's not that the cost is going to be that much different. It's going to be that there are rebates and discounts that are going to make the cost different," he added.

As a community physician, Dr. Oldfield has specific concerns about accessibility.

The ever-increasing burden of insurance documentation and prior authorization means it can take weeks or months to get these medications approved. "The addition of new biosimilars is a welcome entrance if it can get patients the medications they need when they need it," he said.

When it comes to prescribing biologics, many physicians rely on ancillary staff for assistance. It's a team effort to sift through all the paperwork, observed Dr. Oldfield.

"While many community GI practices have specialized staff to deal with prior authorizations, they are still a far cry from the IBD [inflammatory bowel disease] academic centers where there are often pharmacists, nursing specialists, and home-monitoring programs to check in on patients," he explained.

Landscape on cost is uncertain

At present, little is known about the cost of the biosimilars and impact on future drug pricing, said Dr. Oldfield.

Humira biosimilars will be considered Medicare Part D drugs if used for a medically accepted indication, said a spokesperson for the Centers for Medicare and Medicaid Services. Part D sponsors (pharmacy and therapeutic committees) "will make the determination as to whether Amjevita and other products will be added to their formularies," said the spokesperson.

Patients never saw a significant cost savings with Remicade biosimilars. "I imagine the same would be true with biosimilars for Humira," said Dr. Regueiro. Patients may see greater access to these drugs, however, because the insurance plan or the pharmacy plan will make them more readily available, he added.

The hope is that, as biosimilars are introduced, the price of the originator biologic will go down, said Mr. Newmark. "Therefore, we can expect Humira to be offered at a lower price as it faces competition. Where it will sit in comparison

Continued on following page

Decisions in GI remain nuanced

Telemedicine *from page 1*

must balance patient and provider preferences, medical needs, quality of care, regulatory requirements, and reimbursement, Ziad Gellad, MD, AGAF, associate professor of medicine in the gastroenterology division at Duke University, Durham, N.C., and colleagues wrote. "Spurred by the COVID-19 pandemic, telehealth, and specifically telemedicine, has become an integral part of outpatient gastrointestinal care in the United States."

Dr. Gellad and colleagues wrote a clinical practice update based on recent studies and the experiences of the authors, who are active gastroenterologists and hepatologists with extensive experience using telemedicine in clinical practice. First, the group addressed patient preferences for telemedicine in gastroenterology based on emerging data. During the past 2 years, studies in both the United States and Australia found that most patients voiced ongoing interest and willingness to use video visits, as well as satisfaction with their medical concerns being addressed via telemedicine. They also reported significantly decreased absenteeism, as compared with face-to-face visits.

Patient preferences may vary based on age, race, and other factors. Younger adults, those with higher incomes, and Hispanic and Latino patients appear more likely to prefer video visits than older adults, those with lower incomes, and White or Black patients. In gastroenterology telemedicine studies, especially among patients with inflammatory bowel disease (IBD) or chronic liver disease, older patients, Black patients, and those with Medicaid or Medicare insurance were more likely to complete a phone-based visit rather than video.

Barriers exist for some patients, which should be recognized, the authors wrote. Studies have found racial and socioeconomic disparities in accessing telemedicine, including video visits. When possible, ambulatory practices, institutions, and health systems should provide technical solutions and individual support to help patients overcome these barriers.

So far, telemedicine appears to be better suited for stable chronic conditions rather than acute illnesses, which are more likely to require a follow-up in-person visit or ED care. At the gastrointestinal level, patients being evaluated for liver transplantation via telemedicine had a reduced time from referral to evaluation by a hepatologist and to transplant listing, and liver transplant recipients had lower readmission rates, improved physical function, and better general health. Among IBD patients, telemedicine led to similar quality of care metrics and higher IBD-specific quality of life.


Dr. Gellad

Decisions about using telemedicine for patients with digestive diseases remain nuanced, the authors wrote. In general, those with stable conditions, such as gastroesophageal reflux, irritable bowel syndrome, IBD, chronic constipation, chronic liver disease, and chronic pancreatitis, appear to be good candidates for telemedicine. Patients who are considering a change in therapy and wish to schedule a visit for additional information may also use telemedicine.

Those living in remote areas could be candidates for telemedicine as long as they have access, particularly for video visits. Among these patients, studies have shown that telemedicine can be appropriate for patients with IBD and the transition of care from pediatric to adult gastroenterologists. The decision depends on several factors, including the practice setting and complexity of care.

Many times, the main barrier to virtual care is the regulatory requirement to be licensed in the state where the patient lives. Although these requirements were eased during the COVID-19 pandemic, many restrictions have now returned in most states. Some practices may now support their clinicians in obtaining licenses for surrounding states, but ultimately, some regulatory compromise will be needed to continue multistate telemedicine without additional licensure, the authors wrote.

Reimbursement rules have also remained a barrier. Despite some changes during the pandemic, reimbursement will likely shift in the future, and additional documentation requirements are suggested. For instance, it's important to document patient consent to telemedicine, the method of telemedicine (whether a secure two-way interactive video or phone call), patient location, provider location, a listing of all clinical participants' roles and actions, and other individuals (such as trainees) present at the visit.

Office staff should connect with patients before the visit to address any technical issues and ensure a proper connection, set up any assistive services such as an interpreter, complete previsit questionnaires via secure messaging, and conduct standard practices such as medication review. Postvisit instructions should be sent through a secure portal or mail.

Additional studies are needed to verify long-term outcomes associated with telemedicine, as well as the optimal ratio of in-person versus telemedicine visits for various disease states.

"Telemedicine is accepted by both patients and providers, and is associated with certain key advantages, including reducing patient travel time and cost and work absenteeism," they wrote. However, "gastroenterology providers need to be cognizant of certain patient and illness barriers to telemedicine and adhere to best practices to ensure high-quality gastrointestinal virtual care."

The update received no funding support.

Dr. Gellad disclosed financial relationships with Higgs Boson; Merck; and Novo Nordisk. A coauthor consults for IngenioRx and has research funding from Freenome, Guardant, and Exact Sciences. Another coauthor disclosed financial relationships with AbbvVie, BMS, Fzata, Janssen, Magellan Health, Pfizer, and Takeda and support from the Crohn's and Colitis Foundation, IBD Education Group, and CorEvitas.

Continued from previous page

to the forthcoming biosimilars will depend on how much biosimilar companies drop their price and how much pressure will be on PBMs and insurers to cover the lowest list price drug," he said.

Ideally, insurers will offer designated biosimilars at a reduced or even no out-of-pocket expense on their formularies. This should lead to a decreased administrative burden for approval with streamlined (or even removal) of prior authorizations for certain medications, said Dr. Oldfield.

Without insurance or medication assistance programs, the cost of biosimilars is prohibitively expensive, he added. "Biosimilars have higher research, development, and manufacturing costs than what people conventionally think of [for] a generic medication.

Educating, advising patients

Dr. Oldfield advised that gastroenterologists refer to biologics by the generic name rather than branded name when initiating therapy unless there is a very specific reason not to. "This approach should make the process more streamlined and less subjected to quick denials for brand-only requests as biosimilars start to assume a larger market share," he said.

Uptake of the Humira biosimilars also will depend on proper education of physicians and patients and their comfort level with the biosimilars, said Dr. Regueiro. Cleveland Clinic uses a team approach to educate on this topic, relying on pharmacists, clinicians, and nurses to explain that there's no real difference between the reference drug and its biosimilars, based on efficacy and safety data.

Physicians can also direct patients to patient-friendly resources, said Mr. Newmark. "By starting the conversation early, it ensures that when/if the time comes that your patient is switched to or chooses a biosimilar they will feel more confident because they have the knowledge to make decisions about their care."

The Global Healthy Living Foundation's podcast, Breaking Down Biosimilars (https://ghlf.org/breaking-down-biosimilars/), is a free resource for patients, he added.

It's important that doctors also understand these products so they can explain to their patients what to expect, said the FDA's Dr. Yim. The FDA provides educational materials (www.fda.gov/drugs/biosimilars/curriculum-materials-health-care-degree-programs-biosimilars) on its website, including a comprehensive curriculum toolkit.

Dr. Hanauer has served as a consultant for AbbVie, Amgen, American College of Gastroenterology, GlaxoSmithKline, American Gastroenterological Association, Pfizer, and a host of other companies. Dr. Regueiro has served on advisory boards and as a consultant for Abbvie, Janssen, UCB, Takeda, Pfizer, BMS, Organon, Amgen, Genentech, Gilead, Salix, Prometheus, Lilly, Celgene, TARGET Pharma Solutions Trellis, and Boehringer Ingelheim Pharmaceuticals.

Dr. Wolf, Dr. Yim, Dr. Oldfield, and Mr. Newmark have no financial conflicts of interest.

Help your patients understand biologics and biosimilars by using AGA resources for providers and patients available at gastro.org/biosimilars.

Mortality increases substantially with fibrosis stage in NAFLD

BY CAROLYN CRIST
MDedge News

The risks of all-cause and liver-related mortality increase substantially based on fibrosis stage in biopsy-confirmed nonalcoholic fatty liver disease (NAFLD), according to a study published in Clinical Gastroenterology and Hepatology (2022 May 2. doi: 10.1016/j.cgh.2022.04.014).

In particular, patients with NAFLD and advanced fibrosis have a 3-fold higher risk of all-cause mortality and 10-fold higher risk of liver-related mortality, as compared with patients with NAFLD but not advanced fibrosis, Cheng Han Ng, with the National University of Singapore, and colleagues wrote.

"These data provide high-level evidence that provides prognostication for each stage of fibrosis to inform care providers and patients," they wrote. "In addition, these findings have important implications for clinical trial design and highlight the importance of developing therapeutics."

Although previous studies have found higher risks of all-cause and liver-related mortality in patients with NAFLD with increasing fibrosis stages, they examined the risk of mortality in reference to stage 0 fibrosis and didn't include comparisons across different stages of fibrosis. In addition, the studies typically used pooled risk ratios, didn't account for time-to-event analysis, or incorporate the most recent data.

The study investigators conducted an updated time-to-event meta-analysis to understand the impact of fibrosis stage on all-cause and liver-related mortality in biopsy-confirmed NAFLD. In addition, they pooled the survival estimates of individual fibrosis stages based on reconstructed individual patient data and compared mortality between fibrosis stages.

In 14 included studies, 17,301 patients had biopsy-proven NAFLD, including 6,069 assessed for overall mortality and 3,421 for liver-related mortality. The studies were conducted in the United States, Canada, Sweden, Israel, Japan, and Hong Kong, with four multicenter studies across multiple regions. The median follow-up duration was 7.7 years, and the average age of patients was 50.5.

For nonadvanced fibrosis (F0-F2), the 1-, 3-, 5-, 8-, and 10-year all-cause mortality were 0.1%, 1.9%, 3.3%, 6%, and 7.7%, respectively. For clinically significant fibrosis (F2-F4), the rates were 0.3%, 8.4%, 14%, 23.7%, and 29.3%, respectively. For advanced fibrosis (F3-F4), the rates were 0.3%, 8.8%, 14.9%, 25.5%, and 32.2%, respectively. For cirrhosis (F4), the rates were 0.3%, 13%, 20.6%, 33.3%, and 41.5%, respectively.

Compared with F0 as a reference, there were no statistically significant differences in all-cause mortality for F1. However, the risk significantly increased for F2 (hazard ratio, 1.46; 95% confidence interval, 1.08-1.98; P = .01), F3 (HR, 1.96; 95% CI, 1.41-2.72; $P < .01$), and F4 (HR, 3.66; 95% CI, 2.65-5.05; $P < .01$). In addition, early fibrosis (F1-F2) resulted in a statistically significant increase in all-cause mortality, as did the presence of clinically significant fibrosis or advanced fibrosis.

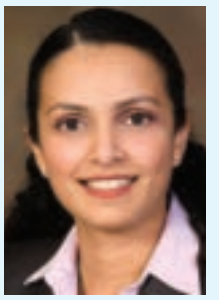
Compared with non–clinically significant fibrosis (F0-F1), clinically significant fibrosis (F2-F4) resulted in a statistically significant increase in mortality (HR, 2.06; 95% CI, 1.52-2.81; $P < .01$).

Compared with nonadvanced fibrosis (F0-F2), advanced fibrosis (F3-F4) resulted in a significantly increased risk of mortality (HR, 3.32; 95% CI, 2.38-4.65; $P < .01$).

In a comparison between F3 and

Continued on following page

Nonalcoholic fatty liver disease is one of the most common liver diseases globally. This meta-analysis shows that all-cause mortality and liver-related mortality increase significantly and exponentially from fibrosis stage F2 onward. The findings have important implications for patients, care providers, health policy, and the NAFLD research agenda.


Dr. Desai

As gastroenterologists and hepatologists, we see individuals at varying stages of NAFLD. While treatment for all stages of NAFLD remains focused on weight loss, this goal can be achieved by interventions of varying cost and intensity, ranging from lifestyle modifications to medication-assisted weight loss to bariatric surgery. Furthermore, ongoing clinical trials are another treatment option. Guided by prognosis provided by this meta-analysis using an internationally representative cohort, patients and providers can participate in more accurate shared decision-making as they consider their weight-loss and treatment options.

At the policy level, the significant increase in all-cause mortality even at early stages of NAFLD also highlights gaps in the need for coverage of well-established weight-loss treatments. While provisions of the Affordable Care Act have tried to reduce health disparities and improve access to weight-loss treatment, many health plans continue to limit or deny coverage for medications and bariatric surgery. Finally, the study emphasizes the urgency of conducting more research to establish successful treatments for individuals with advanced fibrosis, specifically those with cirrhosis.

Overall, the study provides valuable insights into mortality risks associated with different stages of fibrosis in NAFLD for all stakeholders in the NAFLD community.

Achita P. Desai, MD, is an National Institutes of Health–funded clinician scientist, transplant hepatologist, and assistant professor in the division of gastroenterology and hepatology at Indiana University, Indianapolis. She reported no conflicts of interest.

Patient-based mouse MVID model hints at mechanism

BY JIM KLING
MDedge News

Researchers have identified a novel mutation in a patient with microvillus inclusion disease (MVID) and rapidly developed a specific mouse model to find insights into the disease process.

MVID is characterized by severe diarrhea, generally beginning within a few hours of birth. The condition is caused by inactivating mutations in the gene myosin VB (MYO5B). Affected individuals usually require lifetime use of total parenteral nutrition or small-bowel transplantation.

More than 100 MYO5B mutations have been identified in MVID patients, most of whom inherit two unique mutant alleles. This can lead to variability in phenotypes, which single-mutation animal models have been unable to mimic. Generally, patients have atrophy of microvilli on enterocytes as well as inclusion bodies within enterocytes that contain microvilli.

In the study, published in Cellular and Molecular Gastroenterology and Hepatology (2022 Dec 30. doi: 10.1016/j.jcmgh.2022.12.015), researchers describe genetic sequencing of MYO5B mutations in a patient and both parents. One mutation is predicted to lead to protein truncation (c.1821delG), and the other (c.1555G>A) appeared to be inherited from the patient's mother. The patient suffered from severe diarrhea after birth and was intermittently feeding intolerant.

The researchers conducted a range of diagnostic tests and biopsies. One particularly interesting finding was expression of the A-kinase anchoring protein 350 in the vicinity of the inclusion, wrote Andreanna Burman and her coauthors at Vanderbilt University, Nashville, Tenn. This protein takes part in a protein-mediating scaffolding pathway, suggesting that it could play a role in the development of the inclusions.

The researchers used multiplexed immunofluorescence (MxIF) staining of a biopsy of the duodenum to look for expression of a range of proteins. They found a striking decrease in enterocytes that express glucose transporter 2, implying that malabsorption might be due at least in part to enterocytes that fail to mature.

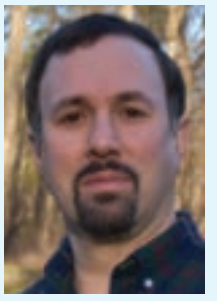
The patient also had internalization of apical nutrient transporters, which has been reported in other MVID patients. The researchers also developed a mouse model that incorporated the patient's novel compound heterozygous genotype, which they cross-bred to produce a tamoxifen-inducible mouse model.

After the tamoxifen injection, the patient-mimicking animals exhibited a severe watery diarrhea, losing 19% of their body weight by day 4. The animals' intestines showed a similar phenotype to that of the patient.

The apical sodium transporters sodium-glucose cotransporter 1 (SGLT1), apical sodium-dependent bile transporter, and NHE3 were internalized away from the apical membrane of the enterocytes in the patient-mimicking model animals. This structural difference may explain the limited absorption of sodium and water and the resultant watery diarrhea. The researchers also noted disruption of the actinin-4+ terminal web structure, as well as increased SGLT1 localization with lysosome-associated membrane protein 1+ lysosomes within the mouse model enterocytes. This association may indicate degradation of mislocalized proteins, the authors noted, which has also been seen in expanded

Continued on page 18

Genetically engineered mouse models have offered tremendous insight into the genetics, biology, and pathobiology of the gastrointestinal tract. Yet, in the past, the time necessary to generate these GEMMs has presented challenges for modeling human diseases. With the ongoing identification of disease-associated polymorphisms or mutations, including through approaches like genome-wide association studies (GWAS), defining the function of these specific genetic alterations in disease pathogenesis is of great importance.


Dr. Katz

This study by Burman et al. demonstrates not only the remarkable speed with which GEMMs can now be generated (using the CRISPR-Cas9 genome editing system) but also the ability to bypass the embryonic lethality associated with certain heritable mutations. Here, the authors identified two different variants in myosin VB (MYO5B), one likely a de novo mutation and one maternally inherited, in a patient with microvillus inclusion disease (MVID), a rare congenital disorder that presents with severe secretory diarrhea typically within hours or days after birth. Using a technique called multiplexed immunofluorescence staining (MxIF), the authors simultaneously examined 15 proteins on a single duodenal biopsy slide and identified changes associated with defective enterocyte maturation. The authors then generated a GEMM to mimic the variants in the MYO5B gene found in this patient. Interestingly, mice with a genotype similar to that of the MVID patient developed severe watery diarrhea and intestinal histology similar to that of the patient, while those with the maternal genotype appeared normal.

Overall, this study demonstrates the value of both patient-mimicking mouse models and multiplexed staining to define the molecular mechanisms of congenital diseases in vivo.

Jonathan P. Katz, MD, is associate professor of medicine, department of medicine, gastroenterology division, University of Pennsylvania Perelman School of Medicine, Philadelphia. He has no relevant conflicts of interest.

Continued from previous page

F4, F4 resulted in a statistically significant increase in mortality (HR, 2.67; 95% CI, 1.47-4.83; $P < .01$), according to the authors.

In a sensitivity analysis with three studies including nonalcoholic steatohepatitis, patients with NASH had a significantly increased risk of mortality in F4 (HR, 5.08; 95% CI, 2.70-9.55; $P < .01$).

For liver-related mortality, F1 didn't result in a statistically significant increase, as compared with F0. However, increased risks were found for F2 (HR, 4.07; 95% CI, 1.44-11.5; $P < .01$), F3 (HR, 7.59; 95% CI, 2.80-20.5; $P < .01$), and F4 (HR, 15.1; 95% CI, 5.27-43.4; $P < .01$). In addition, any fibrosis (F1-F4) resulted in an increased risk of mortality, early fibrosis resulted in a borderline nonsignificant increase, and clinically significant or advanced fibrosis led to an increased risk.

Compared with non–clinically significant fibrosis (F0-F1), clinically significant fibrosis (F2-F4) resulted in an increase in liver-related mortality (HR, 6.49; 95% CI, 3.30-12.8; $P < .01$).

Compared with nonadvanced fibrosis (F0-F2), advanced fibrosis (F3-F4) resulted in a statistically significant increase in liver-related mortality (HR, 10.4; 95% CI, 6.18-17.5; $P < .01$).

In a comparison between F3 and F4, F4 resulted in a significant increase in liver-related mortality (HR, 2.57; 95% CI, 1.22-5.42; $P < .01$).

Although the presence of F4 leads to the greatest risk of mortality, selection criteria in NASH clinical trials have predominately targeted patients with F0-F3, the authors wrote.

"NASH is currently the fastest growing cause for liver transplant and [transplant] remains the only known curative treatment for cirrhosis," they wrote.

"However, with the global shortage of suitable grafts for transplant and lack of viable treatment, our results highlight that there is an urgent need for an efficacious treatment for patients with NASH and F4," they added.

The researchers outlined several limitations of their study. The development of hepatocellular carcinoma and its effects on survival were outside the scope of the study, they wrote.

Analysis of liver-related mortality by proportion was not conducted because of insufficient studies. Data were insufficient to perform subgroup analyses by gender, age, study design, medication use, and diagnostic modality for fibrosis stage.

The authors reported funding support from several national U.S. grants and disclosed consultant and advisory rules for numerous pharmaceutical companies. ■

An earlier hep B biomarker for clinical outcomes?

BY JIM KLING
MDedge News

Low serum levels of the hepatitis B core-related antigen could be an early biomarker of a functional cure of a hepatitis B infection, according to new findings from a retrospective study.

A drop in HBcrAg predicted the seroclearance of hepatitis B surface antigen, the widely accepted measure of optimal liver-related outcomes in patient care and clinical trials, long before HBsAg levels actually fell.

"In a large retrospective cohort study of chronic hepatitis B patients, we found lower levels of HBcrAg were associated with higher probability of clearing HBsAg," wrote Tai-Chung Tseng and coauthors at National Taiwan University Hospital in Taipei. "Reduction of HBcrAg developed 10 years before decline of HBsAg in patients with high HBsAg levels at baseline."

Nearly 300 million people worldwide are estimated to be positive for the HBsAg antigen, a marker of active hepatitis B virus infection. Chronic HBV puts individuals at greater risk of cirrhosis, hepatocellular carcinoma (HCC), and other liver complications.

Seroclearance of HBsAg is generally regarded as signaling a functional cure, because it is associated with low viral activity and good clinical outcomes. Patients with low HBsAg levels may transition to complete clearance, while those with levels of 1,000 IU/mL or higher rarely achieve clearance either spontaneously or through treatment.

As with HBsAg, higher serum levels of HBcrAg have been linked to a raised risk of adverse events, including increased viral activity and heightened risk of developing hepatitis B e antigen-negative hepatitis, cirrhosis, and HCC. Lower HBcrAg levels are associated with a greater likelihood of HBsAg seroclearance in chronic hepatitis B patients who discontinued antiviral therapy.

In a study published in Gastroenterology (2023 Jan 13. doi: 10.1053/j.gastro.2023.01.005), researchers conducted a retrospective Taiwanese cohort study of 2,614 untreated patients with hepatitis B who underwent long-term follow-up at National Taiwan University Hospital. The median age was 38.2 years, and 60.6% were men. At baseline, 14.8% had HBsAg levels of less than 100 IU/mL, and 47.7% had HBcrAg levels less than 10,000 IU/mL. Most (77.5%) were infected with HBV genotype B. From stored serum samples, the researchers quantified levels of HBV DNA, HBsAg, and HBcrAg and evaluated the relationships with spontaneous HBsAg seroclearance.

Over an average follow-up of about 12 years, 465 patients cleared HBsAg, an incidence of 1.43% per year. Researchers stratified patients by levels of viral markers. Compared with those with the highest HBcrAg levels (> 100,000 IU/mL), lower levels of HBcrAg were associated with greater likelihood of HBsAg clearance.

Specifically, intermediate levels (10,000-99,999 IU/mL) were associated with nearly double the chance of HBsAg clearance (hazard ratio, 1.95; 95% confidence interval, 1.44-2.65), and the lowest levels (< 10,000 IU/mL) were associated with just over triple the chance of clearance (HR, 3.15; 95% CI, 2.45-4.05). These associations held up with multivariable analyses, and HBV DNA levels were not significantly associated with HBsAg clearance.

"Not surprisingly, HBsAg levels still serve as a better predictor than the other two biomarkers," the authors wrote. "Notably, the HBsAg levels are more like a short-term predictor" (within 5 years).

For patients with higher HBsAg levels (> 1,000 IU/mL), it took a median of 16 years to achieve HBsAg clearance. A subanalysis of the 1,539 patients with HbsAg levels > 1,000 IU/mL found that only HBcrAg levels below 10,000 IU/mL predicted HBsAg seroclearance versus 100,000 U/mL or higher (adjusted HR, 1.95; 95% CI, 1.16-3.27).

HBsAg levels began to decline later, often between 5 and 9 years before HBsAg seroclearance occurs. However, HBcrAg levels became undetectable 10-14 years before HBsAg seroclearance. Among patients achieving undetectable levels of HBcrAg, the annual HBsAg seroclearance rate was higher in the second decade of follow-up than in the first decade (3.75% versus 0.97%).

HBcrAg levels reflect the transcriptional activity of covalently closed circular DNA, the authors noted, while HBsAg can come from cccDNA and HBV-DNA integrated into the host genome. Several novel hepatitis B therapies in development target cccDNA transcription, but it isn't known if the strategy will result in HBsAg clearance.

In the discussion section, the authors speculated about the possible pathology and treatment implications for several chronic hepatitis B scenarios. For example, the finding

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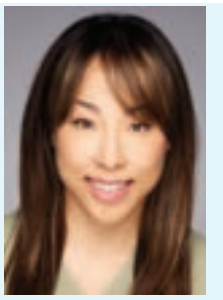
Current hepatitis B virus therapies do not eliminate the covalently closed circular DNA, and a single cccDNA can cause an infection. Hepatitis B core-related antigen has shown positive correlation with serum and hepatic HBV-DNA levels and cccDNA even in patients receiving antivirals for HBV. This is demonstrated by Tseng et al., where undetectable levels of HBcrAg predicted seroclearance of hepatitis B surface antigen by 10-14 years. This and past studies have shown HBcrAg to be a good predictor for cccDNA transcriptional activity, allowing health care providers to predict functional loss of hepatitis B surface antigen, flare-ups, treatment response, and treatment end.

Clinically, HBcrAg could be monitored in chronic HBV infection while patients are receiving treatment. A rise in HBcrAg has the ability to predict HBV flares, while a decrease in HBcrAg can forecast seroclearance of HBsAg. If there is undetectable level of HBsAg with detectable HBcrAg, it can mean the relapse of HBsAg+, and oral treatment could be continued. HBsAg and HBcrAg also can be used to determine when to stop treatment, especially with nucleos(t)ide analogs. The Mayo Clinic laboratories recently opened HBcrAg testing for patients with chronic HBV.

With emerging medications, HBV cure may be possible with multiple therapies. Hepatic cccDNA turnover may be halted by inhibiting capsid assembly and secretion, relaxed-circular DNA nuclear delivery or conversion to cccDNA, and formation of viral RNAs. Since HBcrAg is a good indicator of cccDNA transcriptional activity, it should be used to determine the effectiveness of these new therapies in clinical trials.


Dr. Roma


Dr. Gish

Katerina Roma, DO, is with the department of internal medicine, Kirk Kerkorian School of Medicine at the University of Nevada, Las Vegas. Robert Gish, MD, AGAF, is medical director of the Hepatitis B Foundation in Doylestown, Pa. They have no financial conflicts.

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RAB7+ vesicles within MVID patient tissues.

Other signs pointed to the expansion of immature cells in the upper crypt and lower villus, as well as faster shedding of enterocytes in the villus than in control animals. Scanning electron microscope images also showed immature and disorganized microvilli in the enterocytes of the patient-mimicking mice.

Taken together, "these findings are consistent with a deficit in enterocyte maturation in Myo5b(G519R) mice and in the patient with the MYO5B(G519R) mutation," according to the authors.

The authors suggest that their approach could be used more generally to quickly create mouse models of patient-specific monogenic congenital disorders.

The research was funded by the National Foundation of Science, National Institutes of Health, Vanderbilt Digestive Diseases Research Center Pilot and Feasibility grant, American Physiological Society John F. Perkins, Jr. Research Career Enhancement Award, and a gift from the Christine Volpe Fund.

The authors disclosed that they had no conflicts of interest. ■

Review explores the boundaries of endoscopic resection for esophageal adenocarcinoma

BY WILL PASS
MDedge News

A growing body of evidence shows that deeper and larger tumors can be safely removed with endoscopy instead of surgery when individual patient risk is taken into account, according to a review by Eva P.D. Verheij, a doctoral candidate at Amsterdam University Medical Center, and colleagues.


Ms. Verheij

"Management of patients with superficial esophageal adenocarcinoma (EAC) is becoming less invasive and more patient-tailored," the researchers wrote in Techniques and Innovations in Gastrointestinal Endoscopy (2023 Jan 15. doi: 10.1016/j.tige.2023.01.001). "In the future, watchful waiting may be a valid alternative to surgery in selected cases."

The investigators examined new advances that have been made in the management of superficial esophageal adenocarcinomas by endoscopy, and they address how

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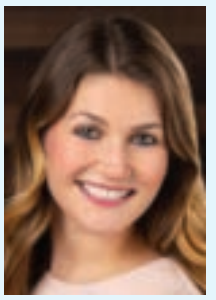
Barrett's esophagus is the only known precursor lesion to esophageal adenocarcinoma, a cancer with rising incidence and stage-dependent survival. Early detection of BE-related neoplasia provides the opportunity to intervene through endoscopic eradication therapy and avoid the morbidity associated with esophagectomy. Verheij and colleagues, a group from a robust BE expert center in the Netherlands, provide a comprehensive and detailed overview of the role of endoscopic therapy for superficial esophageal adenocarcinoma (EAC), which is gaining popularity. In this review, they nicely highlight the benefits of this approach as a minimally invasive, organ-preserving, safe, and effective treatment option.


Dr. Kolb

The importance of appropriate patient selection for endoscopic therapy can't be overstated. After initial staging endoscopic mucosal resection, EACs should be characterized as low risk versus high risk (tumor invasion into the submucosa, poor differentiation, presence of lymphovascular invasion, or tumor-positive deep resection margin). This distinction is critical since these histologic features are currently the best-known predictors of the risk of lymph node metastases and therefore guide therapy to endoscopy versus surgery. Low-risk superficial cancers have very low rates of lymph node metastases and therefore are best managed with endoscopic therapy. The most common technique is multiband mucosectomy, where flat, superficial cancers (Paris type 0-IIa) are removed piecemeal through a repeated sequence of band and snare cautery with high rates of success, rare risk of perforation or bleeding, and reasonably low (< 10%) rates of stricture. Endoscopic submucosal dissection can be considered for larger or bulkier lesions with suspected submucosal invasion where en bloc resection is optimal. At present, high-risk superficial EAC should still be referred to surgery. Some patients may not be candidates for esophagectomy or may be unwilling to undergo a large, morbid operation, however. The authors are involved in the prospective PREFER trial evaluating a protocol of strict endoscopic follow-up (endoscopy with endoscopic ultrasound every 3 months for 2 years, followed by every 6 months in years 3-4, then annually) after endoscopic resection of high-risk superficial EAC in patients without baseline metastases as an alternative to surgery. Whether or not this strategy of watchful waiting may be a reasonable alternative will likely take a few more years to answer. Nonetheless, we have already seen a dramatic shift toward endoscopic therapy for superficial EAC that has been fueled by innovation, new technologies, and improved techniques.

Jennifer M. Kolb, MD, MS, is assistant professor of medicine, Vatche and Tamar Manoukian Division of Digestive Diseases University of California, Los Angeles. She also is affiliated with VA Greater Los Angeles Health Care System. She has no relevant conflicts of interest.

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that HBcrAg clearance usually precedes HBsAg clearance suggests that reduction of cccDNA transcription is a requirement for curing hepatitis B, the authors speculate, but it also suggests that add-on treatment may need to target HBsAg transcribed from the integrated viral genome for a functional cure.

The researchers noted several study limitations, including that the cohort included only Asians largely with HBV genotypes B or C and that "further validation from Caucasian patients infected with genotypes types A or D is mandatory."

Prof. Tseng disclosed financial conflicts with Fujirebio, Bristol-Myers Squibb, and Gilead Sciences. The remaining authors had no conflicts of interest.

The study received grant support from several institutions, including National Taiwan University Hospital.

Member SPOTLIGHT

GI lends itself to multiple career paths, says Boston physician

BY JENNIFER LUBELL
MDedge News

Daniel Leffler, MD, MS, AGAF, has some advice for young physicians starting out in their careers: Don't be afraid of change.

"Just because you're a doctor doesn't mean you have to spend the rest of your career doing patient care. We don't teach that in medical school as well as we should," said Dr. Leffler. "If you're interested in a skill set and move in a different direction, that's totally okay. Many people have major career shifts, whether it's early, mid-, or late career."

Daniel Leffler, MD, MS, AGAF, medical director, Takeda Pharmaceuticals, Boston

Dr. Leffler followed his own advice in 2016 when he left his longtime job as an associate professor at Harvard Medical School and accepted a position with Takeda Pharmaceuticals. As its medical director, he had a specific goal: to find more therapeutic options for patients with celiac disease.

"Gastroenterology is a fantastic field of medicine, and it somehow continues to get more and more exciting," said Dr. Leffler, who continues to see patients at Beth Israel Deaconess Medical Center in Boston. "There are just so many careers you can have within gastroenterology, whether you are a full-time endoscopist, in a teaching career, or doing lab work."

He discussed the events that led to this career change in an interview with GI & Hepatology News.

Q: Why did you choose GI?
Dr. Leffler: I think for a lot of people GI is just an incredibly diverse field where you can see all types of patients and you have an unusually wide armamentarium of diagnostic and therapeutic options. Our ability to see inside in the GI tract relatively easily and obtain tissue and do functional studies is unique. It makes it a very dynamic field.

Q: What gives you the most joy in your day-to-day practice?
Dr. Leffler: I think it's taking a fresh look at somebody whose symptoms have been incorrectly diagnosed or diagnosed preliminarily as one thing and opening different options and working with the patient to hopefully find a more targeted therapy based on a more definitive diagnosis.

Q: Describe your biggest practice-related challenge and what you are doing to address it.
Dr. Leffler: There are two challenges.

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guidelines may be falling short in light of newly published evidence.

Surgery is usually the first choice for the management of advanced esophageal adenocarcinoma. "Endoscopic treatment has become the cornerstone for early cancer confined to the mucosa," the authors wrote.

"For low-risk submucosal EAC, which only invades the superficial submucosa (sm1, i.e. less than 500 mcm) without any other risk factors, endoscopic treatment as an alternative to surgery is gaining acceptance because multiple studies have demonstrated a very low risk of lymph node metastases (less than 2% for these lesions)," the investigators wrote. Although surgical resection with lymphadenectomy is currently the recommended treatment for cases with deep submucosal invasion, poor differentiation, or lymphovascular invasion, the investigators suggested that even these tumors may be within an endoscopist's reach.

While the rate of lymph node metastasis for such patients has been reported to be as high as 46%, more recent endoscopic studies show a metastasis rate range of up to 20% after 23-63 months of follow-up.

"One possible explanation for the discrepancy in lymph node metastases rates between surgical and endoscopic studies could be the different preparation of slides for histopathological assessment," the investigators wrote.

"In general, the cuts in surgical specimen are made with wider intervals (±5 mm) than the cuts in endoscopic resection specimens (2-3 mm), with additional cuts in case of submucosal invasion. The hypothesis is that this wider interval may result in missing the area with the deepest tumor infiltration. This could result in an underdiagnosis of the actual invasion depth, and therefore an overestimation of the associated lymph node metastases risk."

A study published August 2022 in Gastrointestinal Endoscopy (doi: 10.1016/j.gie.2022.03.005) found an annual metastases risk of 6.9% in patients with high-risk T1a EAC.

"Given its invasiveness and associated morbidity and mortality, esophagectomy may be overtreatment in those patients who will not develop lymph node metastases," the investigators wrote. "Given the technical advances in endoscopy that enable us to radically remove large EACs, and to perform more meticulous follow-up, it might be time to swing the pendulum and only send those patients for surgery who have an indisputable indication for surgery, instead of performing esophagectomy as a prophylactic treatment."

To truly find the limits of endoscopic resection for EAC, however, more research is needed.

"Ongoing studies are necessary to evaluate the lymph node metastases risk on an individual basis, using presence of histological risk factors.

"By predicting the risk of lymph node metastases, and considering patients' wishes and condition, one might decide to perform esophagectomy or watchful waiting with strict endoscopic follow-up. In high-risk cases, we may use sentinel node navigated surgery in the future as an extra safety check before deciding on optimal management," the authors wrote.

The investigators disclosed relationships Medtronic, C2 Therapeutics/Pentax Medical, MicroTech, and Aqua Medical. ■

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For celiac disease, all I have is a gluten-free diet. It would be nice to have other options, the same way we do with almost every other GI disease, whether it's acid-related disorders or chronic constipation or inflammatory bowel disease. We have a range of therapies we can pick and choose from, tailoring those to the individual. We are not there yet, unfortunately, in celiac disease, so that's a huge challenge.

Another challenge is awareness of celiac disease. It's not what it should be. We see a lot of patients who either were misdiagnosed or went many years without getting a proper diagnosis or got diagnosed and did not have proper education or follow-up.

"I think for a lot of people GI is just an incredibly diverse field where you can see all types of patients and you have an unusually wide armamentarium of diagnostic and therapeutic options."

Q: How has your job changed since you first began your career? Perhaps we could discuss your switch from Harvard/Beth Israel Deaconess to Takeda Pharmaceuticals.
Dr. Leffler: I became convinced some years ago that the next big thing for celiac disease was an effective therapy beyond the gluten-free diet. Takeda had acquired rights to two of the therapies that I was most interested in, even though they were very early. There was a new glutenase, TAK-062, and a new immune-tolerizing molecule that became TAK-101. Takeda had moved its research center to Boston, and they were looking for someone to work on their celiac program. Moving from an academic position, which I loved, was a really difficult decision.

I didn't leave without a conversation with the division chief at the time, Tom Lamont, MD. I basically said, "If this doesn't work out, will you take me back?" I wasn't sure how much I'd like working in industry. The other thing, on both sides, was that I was allowed to keep a clinic. I still see patients on Fridays and really, to me, I have the best of both worlds.

Q: What teacher or mentor had the greatest impact on you?
Dr. Leffler: I really think of Ciaran Kelly, MD, at Beth Israel Deaconess, Detlef Schuppan, MD, who also was at Beth Israel Deaconess, but is now at the University of Mainz in Germany. And Peter Green, MD, at Columbia University. These three are the physicians I've interacted with the most and learned the most from.

Q: What habits have you established that have benefited your career most?
Dr. Leffler: I do try to focus on being a good collaborator. Playing that long game of working for the good of the project and not necessarily what is next for you, has served me very well over the years. ■

Dr. Leffler is on LinkedIn.

Lightning round

Superpower?
Optimism

Favorite movie to quote?
The Big Lebowski

Favorite form of exercise?
Elliptical

One thing on your bucket list?
Ethiopia travel

Number of cups of coffee you drink per day?
Two-ish

New coding policies to prevent surprise billing for CRC screening

BY AGA GOVERNMENT AFFAIRS COMMITTEE COVERAGE AND REIMBURSEMENT SUBCOMMITTEE

New policies are making colorectal cancer (CRC) screenings free to more people and eliminating surprise bills, but only if doctors and facilities submit the correct codes and modifiers.

The Departments of Labor, Health & Human Services, and the Treasury issued guidance in 2022 that plans and insurers "must cover and may not impose cost sharing with respect to a colonoscopy conducted after a positive non-invasive stool-based screening test" for plan or policy years[1] beginning on or after May 31, 2022, and, further, "may not impose cost-sharing with respect to a polyp removal during a colonoscopy performed as a screening procedure."[2] So why are so many patients still being charged fees for these screening services? In many cases, the answer comes down to missing code modifiers.

Commercial insurers want you to use modifier 33

AGA spoke to Elevance (formerly Anthem), Cigna, Aetna, and Blue Cross Blue Shield Association about how physicians should report colorectal cancer screening procedures and tests. They said using the 33 modifier (preventive service) is essential for their systems to trigger the screening benefits for beneficiaries. Without the 33 modifier, the claim will be processed as a diagnostic service, and coinsurance may apply.

According to the CPT manual, modifier 33 should be used "when the primary purpose of the service is the delivery of an evidence-based service in accordance with a U.S. Preventive Services Task Force A or B rating in effect and other preventive services identified in preventive mandates (legislative or regulatory) ..." Use modifier 33 with colonoscopies that start out as screening procedures and with colonoscopies following a positive non-invasive stool-based test, like fecal immunochemical test (FIT) or Cologuard™ multi-target stool DNA test.

It is important to note that modifier 33 won't ensure all screening colonoscopy claims are paid, because not all commercial plans are required to cover 100 percent of the costs of CRC screening tests and procedures. For example, employer-sponsored insurance plans and legacy plans can choose not to adopt the expanded CRC benefits. Patients who are covered under these plans may not be aware that their CRC test or procedure will not be fully covered. These patients may still receive a "surprise" bill if their screening colonoscopy requires removal of polyps or if they have a colonoscopy following a positive non-invasive CRC test.

Medicare wants you to use modifiers PT and KX, but not together

CMS uses Healthcare Common Procedural Coding System (HCPCS) codes to differentiate between screening and diagnostic colonoscopies to apply screening benefits. For Medicare beneficiaries who choose colonoscopy as their CRC screening, use HCPCS code G0105 (Colorectal cancer screening; colonoscopy on individual at high risk) or G0121 (Colorectal cancer screening; colonoscopy on individual not meeting the criteria for high risk) for screening colonoscopies as appropriate. No modifier is necessary with G0105 or G0121.

Effective for claims with dates of service on or after 1/1/2023, use the appropriate HCPCS codes G0105 or G0121 with the KX modifier for colonoscopy following a positive result for any of the following non-invasive stool-based CRC screening tests:

- Screening guaiac-based fecal occult blood test (gFOBT) (CPT 82270)
- Screening immunoassay-based fecal occult blood test (iFOBT) (HCPCS G0328)
- Cologuard™ – multi-target stool DNA (sDNA) test (CPT 81528)

According to the guidance in the CMS Manual System, if modifier KX is not added to G0105 or G0121 for colonoscopy following a positive non-invasive stool-based test, Medicare will return the screening colonoscopy claim as "unprocessable."[3] If this happens, add modifier KX and resubmit the claim.

If polyps are removed during a screening colonoscopy, use the appropriate CPT code (45380, 45384, 45385, 45388) and add modifier PT (colorectal cancer screening test; converted to diagnostic test or other procedure) to each CPT code for Medicare. However, it is important to note that if a polyp is removed during a screening colonoscopy, the Medicare beneficiary is responsible for 15% of the cost from 2023 to 2026. This falls to 10% of the cost from 2027 to 2029, and by 2030 it will be covered 100% by Medicare. Some Medicare beneficiaries are not aware that Medicare has not fully eliminated the coinsurance responsibility yet.

When to use each modifier

Modifier 33 for Commercial/ Medicaid	Modifier PT for Medicare	Modifier KX for Medicare
Screening colonoscopy, including following a positive non-invasive stool-based test. Use with 45378. Screening colonoscopy with polypectomy. Use with 45380, 45384, 45385, 45388.	Screening colonoscopy with polypectomy. Use with 45380, 45384, 45385 and/or 45388.	Screening colonoscopy following a non-invasive stool-based test. Use with G0105 or G0121.

What to do if your patient gets an unexpected bill

If your patient gets an unexpected bill and you coded the procedure correctly with the correct modifier, direct them to the AGA GI Patient Care Center's "Colorectal cancer screening: what to expect when paying" resource for help with next steps.[4]

The authors have no conflicts to declare.

References

1. U.S. Department of Labor (2022, Jan. 10) FAQs About 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.

2. Centers for Medicare and Medicaid Services (n.d.) Affordable Care Act Implementation FAQs - Set 12. https://www.cms.gov/CCIIO/Resources/Fact-Sheets-and-FAQs/aca_implementation_faqs12.

3. Centers for Medicare and Medicaid Services (2023, Jan. 27) CMS Manual System Pub 100-03 Medicare National Coverage Determinations Transmittal 11824. https://www.cms.gov/files/document/r11824ncd.pdf.

4. American Gastroenterological Association (2023, Feb. 21) AGA GI Patient Center Colorectal Cancer Screening: What to expect when paying. https://patient.gastro.org/paying-for-your-colonoscopy/.

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New AGA guideline recommends blood and stool tests for monitoring ulcerative colitis

In new evidence-based guidelines, the American Gastroenterological Association recommends noninvasive biomarkers as a first-line strategy for monitoring many patients with ulcerative colitis (UC). These guidelines were published in Gastroenterology (2023 March. doi: 10.1053/j.gastro.2022.12.007.

The AGA guidelines outline use cases for three biomarkers that provide accurate insights into UC disease activity: serum C-reactive protein (CRP) (blood), fecal calprotectin (stool), and fecal lactoferrin (stool). AGA recommends a monitoring strategy that integrates noninvasive biomarkers for patients with UC in remission (no current symptoms) as well as those with current symptoms.

Patients with UC in symptomatic remission

- Perform interval biomarker monitoring every 6-12 months.
- AGA recommends stool-based biomarkers over blood testing.
- If biomarkers are normal, AGA suggests continuing biomarker monitoring and avoiding routine endoscopic assessment.
- If biomarkers are elevated, AGA suggests endoscopic assessment by a gastroenterologist.
- Listen to your body! Talk to your doctor about any new symptoms.

Patients with symptomatically active UC

- Biomarker testing should be the first step to determine the need for endoscopic assessment.
- For patients with mild symptoms who have normal or elevated biomarkers, AGA suggests endoscopic assessment by a gastroenterologist.
- For patients with moderate to severe symptoms who have normal biomarkers, AGA suggests endoscopic assessment by a gastroenterologist.
- For patients with moderate to severe symptoms and elevated biomarkers, AGA suggests treatment adjustment and avoiding endoscopic assessment.

With AGA guidelines guiding the use of noninvasive biomarkers, physicians can confidently offer a more convenient and closer monitoring option for their patients.

AGA will advocate for all insurers to cover the cost of biomarker testing in UC. ■

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