Keeping Tabs on IBD

PROACTIVE VS. REACTIVE: THERAPEUTIC DRUG MONITORING

Proactive: Su Bin Kim, MD, Maria T. Abreu, MD, AGAF and Reactive: Maisa Abdalla, MD, MPH, Hans Herfarth MD, PhD
Welcome to the October/November issue of AGA Perspectives. AGA published clinical practice guidelines on therapeutic drug monitoring in inflammatory bowel disease (IBD) in the September issue of Gastroenterology. As such, therapeutic drug monitoring has now entered the realm of standard clinical practice for our IBD patients. However, one area of ongoing debate is if monitoring should be done proactively or reactively. In our point-counterpoint in this issue, Drs. Su Bin Kim and Maria T. Abreu argue for a proactive strategy whereas Drs. Maisa Abdalla and Hans Herfarth suggest that reactive drug monitoring is the preferred strategy. Both sides in this debate make compelling points!

Other topics in this issue deal with emerging clinical problems in digestive disease today. There has been considerable publicity about the developing problem of colorectal cancer in younger patients and this topic is addressed by Dr. Uri Ladaubam. Similarly, there is increasing attention to screening for pancreatic cancer in this era of “personalized” medicine and Dr. Michael Goggins provides guidance on how to approach this deadly disease. This is a timely article as November is Pancreatic Cancer Awareness Month.

With the emergence of effective therapy for hepatitis C virus, one unintended consequence is recurrence of hepatitis B virus infection. Useful strategies on how to deal with this clinical scenario are provided by Drs. Jason T. Blackard and Kenneth E. Sherman. The current role of fecal microbiota transplantation, along with future directions, is reviewed by Dr. Colleen Kelly. Finally, we are on the cusp of a new era of treatment for eosinophilic esophagitis with ongoing clinical trials of many exciting new compounds. That being said, this is a chronic fibrosing disease with long-term consequences of inadequate therapy for which practical management points are provided by Dr. Nirmala Gonsalves.

Also in this issue, my colleagues at the University of Pennsylvania Drs. Shaizia Mehmoood Siddique and Shivah Mehta provide their perspective on how GIs can embrace patient advocacy. We also get the personal perspectives of the presidents of our four major GI societies, all of whom are women, in a special Q&A.

I hope you enjoy the practical and provoking information in this issue of AGA Perspectives.

Best,

Gary W. Falk, MD, MS, AGAF
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Keeping Tabs on IBD

THE ART OF INDIVIDUALIZED MEDICINE TO STRIVE FOR BETTER OUTCOMES

I n almost all areas of medicine, we accept a role for therapeutic drug monitoring. Whether we consider digoxin levels or tacrolimus and cyclosporine troughs, the principles remain the same — there is a range wherein the drug is effective and also one in which it is useless. For the purposes of this treatise, we posit that measuring levels of monoclonal antibody-based biologics and thiopurines is beneficial for patient management. At present, we have three classes of antibody-based biologics approved for inflammatory bowel disease (IBD). The one for which we have the most experience is anti-TNF therapy. Recently, we have been gathering data and clinical experience with vedolizumab (anti-integrin therapy) and ustekinumab (anti-IL-12/23 therapy). It is our hope that it will take less time than it has for anti-TNF therapy to develop dose optimization strategies.

Therapeutic drug monitoring for monoclonal antibodies involves measuring both the drug and antibodies against the drug (ADAb). Unfortunately for the field, there is variation in the way the measurements are performed with some away from the drug tolerant, i.e., ADAbs can be detected even with drug around and others not. For all intents and purposes, significant ADAbs will lead to increased drug clearance and are generally associated with very low or undetectable levels of the drug. The big message here is to avoid immunizing your patients to the biologics. Once immunized, patients lose response and are highly likely to lose response to the next anti-TNF. Therapeutic drug monitoring for monoclonal antibodies is one of the most talked about topics in IBD medicine. It is the most debated topic because we do not have a gold standard for measuring ADAbs.

Assuming the thresholds for the therapeutic trough levels of each drug at the different stages of treatment are well-established, like in organ transplantation, knowing the drug level and the status of the ADAbs can potentially have great value in objectively guiding treatment decisions. Unfortunately, while the concept sounds very attractive, the data supporting and guiding its use in patients with IBD are very limited. Nevertheless, despite the limited data, therapeutic drug monitoring continues to be widely utilized in IBD clinical practice and has further evolved into two debatable strategic approaches: “reactive therapeutic drug monitoring" in patients with apparent therapy failure and “proactive therapeutic drug monitoring" in patients with quiescent disease. In the next few paragraphs, we will try to make the case for reactive therapeutic drug monitoring.

To set the stage for discussion, it is always important to remember the overall treatment goal for IBD patients. A combined target of both clinical and endoscopic remission has been recently suggested as the optimal therapy goal for patients with ulcerative colitis and Crohn’s disease.1 Biomarkers, such as C-reactive protein (CRP) and fecal calprotectin, are advocated as adjunct targets. Drug levels have not been explored as targets for treatment, but are generally considered as tools to help in achieving the actual target of clinical and endoscopic remission. In patients with apparent therapy failure, reactive therapeutic drug monitoring can objectively assess the underlying mechanisms of failure and guide the next step in management. Based on therapeutic drug monitoring, drug failure can be classified into:

1) Mechanistic failure, with therapeutic drug level and undetectable ADAbs.
2) Non-immune mediated pharmacokinetic failure, with subtherapeutic drug level and undetectable ADAbs.
3) Immune-mediated pharmacokinetic failure, with subtherapeutic drug level and detectable ADAbs.

A different management strategy is proposed for each case scenario; switching to a drug out of class (different mechanism of action) for patients with mechanistic failure; dose escalation of the same drug for patients with non-immune-mediated pharmacokinetic failure; and finally, for patients with immune-mediated pharmacokinetic failure, an addition of an immunomodulator agent to optimize the index therapy in case of low ADAbs titers or switching to a different drug within the same class are proposed. In the recently published AGA clinical guidelines on this issue, the evidence supporting reactive therapeutic drug monitoring was judged to be very low.2 However, the proposed alternative to the therapeutic drug monitoring-guided approach, empirically escalating the

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In the case of biologic therapies, therapeutic drug monitoring involves measurement of the trough drug levels and anti-drug antibodies (ADAb). Assuming the thresholds for the therapeutic trough levels of each drug at the different stages of treatment are well-established, like in organ transplantation, knowing the drug level and the status of the ADAb can potentially have great value in objectively guiding treatment decisions. Unfortunately, while the concept sounds very attractive, the data supporting and guiding its use in patients with IBD are very limited. Nevertheless, despite the limited data, therapeutic drug monitoring continues to be widely utilized in IBD clinical practice and has further evolved into two debatable strategic approaches: “reactive therapeutic drug monitoring" in patients with apparent therapy failure and “proactive therapeutic drug monitoring" in patients with quiescent disease. In the next few paragraphs, we will try to make the case for reactive therapeutic drug monitoring.

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The main potential downside of the therapeutic drug monitoring-guided approach is the lack of established guidelines for therapeutic trough levels and ADAb concentrations for our currently approved biological therapies in IBD, which means treatment classification and therapy changes in patients who may still benefit from dose escalation. For example, in the randomized controlled trials, several authors et al. therapeutic drug monitoring-guided therapeutic approach was compared to empiric dose escalation in CD patients with secondary failure of response to infliximab. A threshold of 0.55 µg/ml was used to define therapeutic drug levels.4 This low threshold may explain why, in a large proportion of patients (70%) in the therapeutic drug monitoring-guided arm were classified as having a mechanistic failure and were treated by switching to out of class agent as opposed to dose escalation which would be the appropriate action if a higher threshold was utilized. Nevertheless, the risk-benefit profile would still favor the therapeutic drug monitoring-guided approach. In fact, the advantage of the therapeutic drug monitoring-guided approach is to identify the less controversial clinical situations that insurance companies will change their therapy keeping in mind the gap in knowledge and the limitations of the current evidence.7

In patients with apparent therapy failure, reactive therapeutic drug monitoring can objectively assess the underlying mechanism of failure and guide the next step in management.

The study by Papamichail et al. demonstrated that patients whose trough levels of infliximab were kept higher than 5 µg/ml maintained response significantly longer than those with lower levels and were less likely to be hospitalized and require therapy. The study by Vande Casteele et al. is often quoted as an example that proactive therapeutic drug monitoring is useful. In patients randomized to therapeutic drug monitoring-based optimization (levels 3-7µg/ml) versus interventions based on clinical parameters. The devil is in the details, the intervals between doses — after fights with insurance companies! In general, ADAbs appear to be less common a problem with newer monoclonal antibodies, but immunomodulators are still used in manufacturing of cell-derived products.

Another reason it makes sense to check for drug levels and ADAb status is to guide choices in therapy. Lost response to anti-TNF in a patient may be due to the patient creating ADAbs, having low levels of drug or having high levels of drug. Each scenario is handled differently Patients with ADAbs are likely to respond to a change in the anti-TNF but not a change in the therapeutic level of drug, keeping in mind the gap in knowledge and the limitations of the current evidence.
KENTUCKY

GI Motility

The Division of Gastroenterology, Hepatology and Nutrition at the University Of Louisville School Of Medicine is seeking a gastroenterologist with a primary clinical and research interest in GI motility and functional bowel disease to join our current National/Internationally recognized motility program. There is considerable support for clinical and bench research and excellent collaboration with the departments of neuroscience and surgery. The University of Louisville is an equal opportunity affirmative action employer.

Interested candidates are invited to submit their curriculum vitae to Kristine Krueger, MD, Professor and Chief of Academic and Clinical Affairs, Division of Gastroenterology, Hepatology and Nutrition, University of Louisville School of Medicine, Louisville, Kentucky 40292 or gimed@louisville.edu.

Hepatologist

The Division of Gastroenterology, Hepatology and Nutrition at the University Of Louisville School Of Medicine is recruiting a hepatologist to join our expanding liver transplant program. The hepatology section has extensive grant funding to support interested clinicians and scientists as well as clinical transplant hepatologists. The University of Louisville is an equal opportunity affirmative action employer.

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IBD Specialist

The Division of Gastroenterology, Hepatology and Nutrition at the University Of Louisville School Of Medicine is seeking faculty with a career interest in Inflammatory Bowel Disease. There is considerable support for both clinical/bench research and excellent collaboration. The University of Louisville is an equal opportunity affirmative action employer.

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What to Make of Colorectal Cancer in Patients Younger Than Age 50?

In light of these concerning trends, it may be tempting to extend our enthusiasm for screening to younger people. However, the recent U.S. Multi-Society Taskforce on Colorectal Cancer guidelines conclude that population-based screening at younger ages is unlikely to be practical or cost-effective at this time. The increasing incidence of CRC in persons younger than age 50 in the U.S. has made headlines in academic circles and in the popular press. What to make of it?

We must appreciate the trends, but also the absolute rates. Recent annual increases in colon cancer incidence and rectal cancer incidence have been, respectively, 2.4 percent and 3.2 percent in 20-29 year-olds, 1.3 percent and 2.3 percent in 40-49 year-olds.1 In contrast, incidence rates in persons over 50 have decreased by even larger fractions,2 which is attributed at least in part to screening. These population-based screening rates operate on top of very different baseline rates by age, however. The current annual incidence rates per 100,000 persons for colon and rectal cancer, respectively, are approximately one and less than one for 20-29 year-olds, four and three in 30-39 year-olds, and 15 and 10 in 40-49 year-olds.3 For comparison, the respective rates per 100,000 persons in 50-84 year-olds range from approximately 30 to 200, and 20 to 50.4 Thus, the vast majority of CRCs still occur after age 50. However, at the individual level, death from CRC in a young person is particularly devastating.

Why is this happening? Nobody knows. The genetic pool cannot have changed quickly, so we must look at the environment. Obesity or diabetes? There is no firm evidence to confirm this. Anecdotally, many of my young patients with CRC have never been obese. Is it diet, independent of obesity? Increased use of colonoscopy resulting in earlier diagnosis? I don’t think this can explain the trends in adults younger than 40. There may be unique molecular phenotypes in young onset CRC, but this remains to be confirmed, and it is not clear how this may help elucidate etiology.

Persons with CRC at ages younger than 50 tend to be diagnosed at more advanced stages than older patients.

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HCV often inhibits HBV replication in those with dual infections; thus, DAAs that eradicate HCV may inadvertently lead to increased HBV replication.

**Key Takeaways**

- In HCV-infected patients, pre-treatment testing should include HBsAg, anti-HBs and anti-HBc.
- Patients with HBsAg are at risk and should be treated during/after HCV therapy with an HBV suppressive regimen.
- In lower risk patients (prior infection or occult HBV), close monitoring is recommended at intervals of four or more weeks. Some experts would treat occult HBV with aminovirals.
- Thoughtful pre-treatment evaluation and management of HCV coinfections will improve patient safety and yield optimal treatment results.

**REFERENCES**

Much progress has been made since the first studies of pancreatic screening were published almost 20 years ago. We have a better understanding of the risk factors that define high-risk individuals, and we have begun to understand the benefits and risks of pancreatic screening using endoscopic ultrasound (EUS) and other imaging tests. However, we have not generated the necessary evidence to state that pancreatic cancer screening should be offered routinely for high-risk individuals.

The best evidence indicating that pancreatic screening is beneficial for high-risk individuals is from studies that have reported the results of long-term surveillance; these studies find that most pancreatic cancers detected by screening average 44 cancers, an improvement compared to the approximately 80 percent of pancreatic cancers diagnosed outside of screening that present with stage III/IV disease, and also that many of the patients who undergo pancreatic resection for lesions identified by screening have high-grade dysplasia (i.e. as pancreatic intraepithelial neoplasia-3, PanIN-3 and/or intraductal papillary mucinous neoplasia [IPMN]) as their highest-grade lesion, indicating that their screening and surgical resection was probably worthwhile. The major advantage of pancreatic imaging tests over blood tests is that pancreatic imaging can identify precancerous lesions that help define future cancer risk and can provide an opportunity to intervene and resect precursor lesions before they progress to pancreatic cancer, where cure is more elusive. Most of the precancerous lesions identified by pancreatic imaging in high-risk individuals are small, often multiple, pancreatic cysts (small IPMNs) of low malignant potential. Although these pancreatic cysts reflect an increased susceptibility to pancreatic neoplasia, the vast majority of high-risk individuals with these cysts will not develop to invasive pancreatic cancer. The limitation of current pancreatic imaging tests is the inability to detect PanIN. PanIN are the most common precursor lesion to pancreatic cancer, but these lesions usually do not create a discrete lesion visible by pancreatic imaging and so often the earliest lesion detected by imaging is a solid pancreatic cancer mass that emerged from a PanIN not a pancreatic cyst. Approaches to detect evidence of PanIN such as collecting and analyzing pancreatic juice samples for biomarkers, or novel molecular imaging approaches, needs further investigation.

The goal of pancreatic screening is to reduce the mortality and morbidity from pancreatic cancer. This will only be achieved once we have highly accurate screening tests that we can offer to individuals at sufficiently high-risk to warrant screening. Identifying individuals at sufficiently high-risk reduces the likelihood of having false positive results of any subsequent screening tests. The average lifetime risk of developing pancreatic cancer in the general U.S. population is approximately 1.4 percent; this risk is spread out over many decades. Individuals identified as high-risk for developing pancreatic cancer usually have a lifetime risk that is roughly five to 20 times higher than average risk. The risk of pancreatic cancer can be estimated by identifying the number of first-degree relatives who have developed the disease. Pancreatic screening guidelines recommend screening based on family history of individuals who have at least one first-degree and one second-degree relative with pancreatic cancer; if the individual carries a germline mutation in a pancreatic cancer susceptibility gene (in BRCA2, ATM, CDKN2A, PALB2, BRCA1, MLH1, MSH2, STK11), their risk is increased even without a family history of pancreatic cancer, but a detailed family history remains important to estimate their pancreatic cancer risk. The average age of pancreatic cancer at diagnosis for patients with a familial clustering of pancreatic cancer is somewhat younger than it is for those without a family history; for those diagnosed with pancreatic cancer carrying a deleterious germline pancreatic cancer susceptibility gene mutation, the average age is younger still (early 60s). For this reason, we recommend initiating pancreatic screening at age 55 for those who have a family history of pancreatic cancer in multiple close blood relatives and age 50 for most individuals who carry a germline mutation in a pancreatic cancer susceptibility gene, although more evidence is needed to better define risk in these populations. With direct-to-consumer gene tests becoming available, more patients are undergoing gene tests to identify the cause of their susceptibility to pancreatic and other cancer. There is also an emerging debate about the value of offering gene testing to all newly diagnosed individuals with pancreatic cancer because roughly 5 percent of them carry a deleterious germline mutation in a pancreatic cancer susceptibility gene and identification of these mutation carriers may not only inform treatment decisions for their pancreatic cancer, it can provide an opportunity to identify mutation-carrying relatives who might benefit from screening and other cancer prevention strategies. There is also a risk of harm from providing these gene tests so their value needs further study.

A blood test for pancreatic screening has a lot of appeal, but such tests aim to detect pancreatic cancer rather than pancreatic cancer precursors, and in order for it to be effective, such a test has to be able to detect potentially curable (stage I) cancers. Because so few patients (current less than 1 percent of patients) present with stage I disease, biomarker diagnostic accuracy is poorly evaluated in this setting. Instead, circulating biomarkers are generally evaluated in patients with higher tumor burden where they appear to have better diagnostic performance. For now, annual EUS and MRCP/MRCP are the standard tests for pancreatic screening.

Patients enrolled into a pancreatic screening program need regular long-term surveillance. Although most high-risk individuals are willing to undergo this surveillance, there are still many unanswered questions about the benefits and risks of pancreatic screening in high-risk populations. For this reason, these patients should continue to be enrolled in research studies that evaluate the long-term risks and benefits of pancreatic screening.

REFERENCES
QUICK HITS: PATIENT CARE

Associate Professor of Medicine (Gastroenterology 
MD
GONSALVES, 

What is the Optimal Long-Term Management?

EoE — is it histologic remission, endoscopic resolution with a target to achieve stricture diameter of 12mm, they are likely to have dysphagia and therefore treatment has not yet been achieved. The treatment endpoints that I aim for are the following: histologic remission as defined by <15 eosinophils per high-powered field, endoscopic resolution with a target to achieve stricture diameter of >16mm, and improvement of patient’s dysphagia symptoms so that they are eating more naturally without food avoidance or modification. In achieving these targets, we hope to prevent disease complications including stricture formation, food impactions and esophageal perforation.

When discussing therapy with patients, I review the pros and cons of all available medical and dietary therapy approaches. If they choose medical therapy, we discuss the various available swallowed topical corticosteroids, but the decision on which to use tends to be determined in large part by which formulation is covered by the patient’s insurance. If choosing oral viscous budesonide (OVB), I typically start with 1mg swallowed twice daily for at least 8 to 12 weeks prior to endoscopy. If the patient has achieved histologic remission at this point, I will taper dosing down to 1mg OVB at bedtime or 1mg OVB alternating with 0.5mg OVB. I would continue on this regimen for maintenance. Prior studies have shown that dosing below 0.5 mg is not enough to maintain histologic remission. If choosing fluticasone 220mg inhaler, based on the severity of the disease, I would recommend starting with two to four puffs swallowed twice daily. Another option is to swallow the fluticasone diskus powder. This method has been described in small case reports and abstracts. Dosing for this approach is 500-1000mg twice daily. With either fluticasone preparation, I would use the following approach. If patients have a significant history of intolerance to one of the foods (such as milk allergy as a child), this may be a person that would benefit from a single-food elimination diet.

It is important to note that there have been no head-to-head studies comparing dietary elimination with medical therapy so it is difficult to answer the question if either therapy is better. It should therefore be based both on patient preference as well as available local resources. If patients are motivated to try and identify food triggers as a cause for their EoE with a goal of ultimately avoiding the trigger food, then dietary therapy would be a good first choice. However, a patient’s travel and/or work schedule would make it difficult for them to adhere to a strict diet, we would typically table this approach and pursue medical therapy until a more convenient time. Patients who are not interested in ultimate adjustment of their diet would be counseled to embark on medical therapy. No matter which therapy is chosen, clinical care has focused on maintenance therapy given the chronicity of the disease. Periodic surveillance endoscopy may be pursued to assure continued remission and this may become easier for patients in the future with the development of non-invasive assessments of the esophagus. Despite the fact that EoE is a chronic disease, there are well-established and effective treatments which can achieve histologic, endoscopic and symptomatic remission all with the aim of preventing long-term complications of the disease, ultimately improving the quality of life of our patients.

Optimal management of this chronic disease encompasses targeting all treatment endpoints: histologic, endoscopic and symptomatic remission.

NIRMALA GONSALVES, 

 Associate Professor of Medicine (Gastroenterology and Hepatology, Northeastern University and Beth Israel Deaconess Medical Center)
Within the last few years, fecal microbiota transplantation (FMT) has become more widely utilized to treat CDI. FMT is inarguably the most effective treatment available for recurrent CDI with efficacy rates of over 90 percent demonstrated in multiple prospective clinical trials. Various methods have been used to deliver the donor material including nasoenteric tube, enema, lower endoscopy and most recently orally administered capsules; however, endoscopic lower GI routes of delivery appear to be the most effective and permit examination of the colonic mucosa to exclude other processes such as inflammatory bowel disease (IBD) or microscopic colitis. Current treatment guidelines support FMT for patients who have suffered a third recurrence of CDI.\(^1\)

There is hope that FMT will prove useful in other conditions marked by intestinal dysbiosis, such as IBD. Several recent randomized controlled trials looking at FMT for treatment of ulcerative colitis have shown remission rates as high as 32 percent after serial FMT administration. Though these results are exciting, and patients are eager for safer and more “natural” therapies, more data is needed before we can recommend FMT for routine clinical use in IBD. Questions including which disease phenotypes are likely to respond, the optimum composition of donor microbiota, best routes of delivery and dosing schedule will be addressed in future studies. FMT is currently being investigated to treat a number of other conditions, from hepatic encephalopathy to obesity, with a number of ongoing clinical trials.

The U.S. FDA permits physicians to treat patients suffering from CDI with FMT provided there is informed consent, detailing potential risks and stating that the treatment is considered investigational. Stool banks, such as OpenBiome (Somerville, MA) have greatly facilitated the clinical practice of FMT by centralizing the process of donor identification and screening, providing material that can be stored frozen until needed for clinical use. As a physician, I appreciate the safety and efficiency of this process, which entails comprehensive testing of healthy volunteer donors and saves hours of time previously spent identifying and screening a new donor for each patient treated. Though I still offer directed donor FMT, the majority of my patients prefer banked donor stool, rather than asking a friend or family member to go through the time consuming and expensive screening process. Insurance companies do not generally pay for the banked donor stool, which is not an FDA-approved product. My hospital and others, understanding the value of decreased CDI infection and readmission rates, have wisely decided to absorb the cost of the donor material.

Industry is working to develop a form of FMT which can be evaluated through the FDA drug development and approval process, though we are still a few years away from a commercially available “FMT product.” Disappointing results from recent phase 2 clinical trials of several FMT-based therapeutics highlight the difficulties in conducting clinical trials in this population. Nevertheless, a number of companies are forging ahead with phase 3 trials of various forms of FMT. An approved encapsulated product will certainly increase availability; however, I am concerned that the costs of this treatment will become prohibitive for some patients, and hopeful that physicians will be permitted to continue utilizing conventional FMT at their discretion.

FMT appears safe, though reports of infection transmission and complications related to the procedure, such as aspiration pneumonia, are reminders that the procedure is not without risk. Given that alterations in gut bacteria have been associated with a number of conditions — including the metabolic syndrome, autoimmune and neurologic diseases — there is theoretical concern that engraftment of donor microbiota through FMT may affect the recipient’s risk of developing these diseases. The Fecal Microbiota Transplantation National Registry, an NIH-funded study being administered through AGA, is an important step forward in understanding the long-term safety of FMT. This registry, which aims to enroll 4,000 patients from 75 clinical sites who will be followed for up to 10 years post-FMT will assess safety outcomes; a biobank consisting of before and after fecal specimens from FMT recipients as well as their donors will help us better understand the microbial mechanisms of FMT and investigate any safety findings that emerge.\(^2\)

### Do you practice FMT?
If so, we encourage you to participate in the AGA FMT National Registry, which will provide the medical community with important real-life data on the short- and long-term patient outcomes associated with this procedure. Learn more at www.gastro.org/fmtregistry

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### What is FMT?

JOIN THE MOVEMENT

FMT NATIONAL REGISTRY

For more information, visit www.gastro.org/FMRegistry

### REFERENCES


As gastroenterologists, we are understandably concerned with cuts in reimbursement, time pressures on clinic visits and other financial metrics that may set us back. Such issues often guide physicians’ stances on health reform, and it is easy to feel overwhelmed. However, as the health care debate continues, we should also remember that we have a responsibility to serve as advocates for our patients.

When we took the Hippocratic Oath, we made a promise to treat our patients as a whole, and not only their disease: “I will remember that I do not treat a fever chart, a cancerous growth, but a sick human being, whose illness may affect the person’s family and economic stability. My responsibility includes these related problems, if I am to care adequately for the sick.”

We see barriers that our patients face in their care everyday: the young patient with severe inflammatory bowel disease who ends up hospitalized due to a delay in infliximab coverage; the patient with cirrhosis who doesn’t qualify for home health care, but for whom access to virtual visits could be life changing; and the patient with functional bowel disease who bounces from doctor to doctor, undergoing repetitive imaging and procedures who really needs a comprehensive multidisciplinary team to take ownership over his or her care.

And although we may feel undervalued on Capitol Hill, members of Congress often turn to us for our expertise, and we are fortunate to have a respected role in society.

You can probably rattle off even more barriers from your own experiences caring for these patients. While legislators may be well-intentioned, they are far removed from these everyday realities. And although we may feel undervalued on Capitol Hill, members of Congress often turn to us for our expertise, and we are fortunate to have a respected role in society. Our patients, on the other hand, struggle to have a similar voice, particularly in aggregate. So, if we don’t advocate for our patients, who will?

It’s helpful to remember that we are all already patient advocates in our own way. We help patients navigate the health care system, we stay at the office late to follow up on prior authorizations, and we often double-book our patients to ensure they receive a timely follow-up.

On the other hand, legislative advocacy can seem more daunting, and feel like a greater time commitment when our plates are already so full. We’ve often heard colleagues worry about not knowing the details of Congressional bills or all the statistics behind a certain policy proposal. This makes many wary to write a letter or set up a meeting with a legislator. But it’s often the personal stories that are the most powerful and have the most impact. Studies have shown that Congressional members want to hear how policy will impact their constituents on a personal level, and our legislative history teaches us that sharing a powerful narrative can shift policies. Of course, supporting our recommendations with statistics and a few key legislative facts will help: the AGA Political Action Committee provides updated key information on recent legislation to help with your advocacy efforts (www.gastro.org/take-action). Also, keep an eye out for AGA advocacy initiatives that members can work on together across the country — larger-scale visits or mass calls and letters have an even bigger impact.

At this time in our history, when health costs are spiraling and the system is at the edge of rapid reform, it is crucial that we engage as patient advocates. Just like our legislators have a duty to serve their constituents, we have a duty to relay our patients’ stories and advocate for a more effective and equitable health care system.
Q&A with GI Women Society Presidents

Sheila E. Crowe
MD, AGAF
AGA President

Carol A. Burke
MD, FACC
ACG President

Karen L. Woods
MD, FASGE
ASGE President

Anna S. Lok
MD, FAASLD
AASLD President

The four U.S. gastroenterology and hepatology societies have made history this year. For the first time, Society Presidents

Sheila E. Crowe

What motivated you to take on a leadership position?
I enjoyed being involved in the activities of the AGA starting from 1995 when I was appointed to the research committee. I continued to serve as a member and chair to a variety of AGA committees. I was encouraged by Gail Hecht, the second women AGA President who served in 2009-2010, and other friends and colleagues. Given my interests and encouragement of colleagues, I applied to serve as a AGA president and in 2015 I was selected as the AGA vice-president. How do you see the profession evolving?
I believe that there will be changes in health care delivery, a greater focus on value of health care, attempts to reduce health care costs and a greater team focus on research to enhance outcomes in digestive diseases and increased impactful basic discoveries.
What advice do you have for women in the profession considering a leadership position?
You need to have experience working within AGA and a good understanding of the mission and vision of AGA. Be prepared to effect change and support AGA members and AGA office staff. Serve on a committee and ideally as a chair, providing you are an effective leader. Consider your existing positions/roles (day job, family, etc.) before taking on a new role. Note that this advice applies to both genders. Once you decide that you want to apply for an AGA Leadership position, prepare and then go for it.

Carol A. Burke

What motivated you to take on a leadership position?
I began my involvement with the American College of Gastroenterology (ACG) as a trainee member in 1993. My attachment to the life of the College was inspired by many of my mentors including Edgar Achkar, MD, MACG, and William D. Carey, MD, MACG, both past presidents of the society. Through my pathway from secretary, treasurer, vice president, president, president-elect to president, I never turned down an opportunity to serve the College anyway that I could. My motivation and approach to leading the College this year is to gently, if only temporarily, help steward an organization whose mission and vision remain steadfast: to champion the evolving needs of clinicians in the delivery of high-quality, evidence-based, and compassionate health care to gastroenterology patients through excellence, innovation and advocacy in scientific investigation, education, disease prevention and treatment.
How do you see the profession evolving?
The stunning and rapid transformation in medicine is leading to shifts in health care delivery and payment schemas, widespread regulatory and reporting requirements, massive increases in medical knowledge, and declining funding of medical research. Our specialty is evolving to become laser focused on creating opportunities to improve the quality and value of health care we provide to our patients and to support our members in their practice and educational needs.
What advice do you have for women in the profession considering a leadership position?
Follow your passion, and be true to yourself. Leadership is not about a title, rather the ability to influence and inspire those around you. As I have found in my road to ACG president, it is not what the society can do for you, but what you can do for the society.

Karen L. Woods

What motivated you to take on a leadership position?
Working with the American Society for Gastrointestinal Endoscopy (ASGE) over many years has allowed me to do two things that I love — learn and educate. Additionally, the professional connections and friendships I have made over the years have been instrumental in my professional development and rise to leadership. When the opportunity arose for me to serve the society, I was honored to give back to ASGE, initially as a committee member and ultimately as an officer.
How do you see the profession evolving?
The specialty of GI has not been immune to the enormous changes in how and where we practice medicine created by the Affordable Care Act and the Medicare Access and CHIP Reauthorization Act (MACRA). It is becoming more difficult for the solo or small group practice to survive on our typical business model. I see the future of private practice consisting of many virtual groups or mega-groups, and I predict we will continue to see a shift of physicians from private practice to an employed model within hospital systems or large multi-specialty groups. ASGE is positioned to strongly support every practice as it is operating today, but we’re also looking at how things may change for many practitioners in the future.
What advice do you have for women in the profession considering a leadership position?
If you want it, go for it, but realize that you don’t have to have it all at the same time! We are many things: mothers, wives, physicians and leaders. These things are not mutually exclusive, but because of all the roles we play, may not always be done well at the same time. Becoming president of a society requires time and dedication that I did not have, and would not have been able to give when my children were young. Striving to have even a small service role at times when I could not lead was rewarding, and ultimately led me to my current position.

Anna S. Lok

What motivated you to take on a leadership position?
I want to be able to make changes. I also want to show that women and minorities can become leaders. Asians are not considered minorities in the US, but I am a foreign medical graduate who did my training outside the US, so my path is atypical.
How do you see the profession evolving?
The progress and rapid transformation of medicine is leading to shifts in health care delivery and payment schemas, widespread regulatory and reporting requirements, massive increases in medical knowledge, and declining funding of medical research. Our specialty is evolving to become laser focused on creating opportunities to improve the quality and value of health care we provide to our patients and to support our members in their practice and educational needs.
What advice do you have for women in the profession considering a leadership position?
Trust yourself, believe that you can do it. Learn from others before you and also share your experience with others. There is no right way or wrong way when it comes to leadership, as long as you have your heart in the right place, are fair and transparent, and give it your best, you will do well. Listen and be open to input and criticisms. Balance the needs of different constituents and resources, so you can set the right goals and have the right plans to reach those goals. Embrace the help of others — you can’t do everything yourself. This also allows you to give an opportunity to others to lead and to participate.

The GI Society Presidents at the 2017 Women’s Luncheon.
Harvoni is the #1 prescribed treatment for HCV GT 1 patients in the US.a

EPclusa is the first and only pan-genotypic single-tablet regimen for patients with chronic HCV2

• 97% overall cure (SVR12) rate in GT 1 subjects with Harvoni (n=1042/1079; ION-1, -2, -3)1,4-6
• 99% and 95% overall cure rates in GT 2 and GT 3 subjects, respectively, with EPclusa (n=397/411; ASTRAL-2, -3).2

Harvoni is indicated with or without ribavirin for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype (GT) 1, 4, 5, or 6 infection.

EPclusa is indicated for the treatment of adult patients with chronic HCV GT 1, 2, 3, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis and in combination with ribavirin for those with decompensated cirrhosis.

See full study information on following pages.

Cure is sustained virologic response (SVR). SVR12 was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the end of treatment in the Harvoni ION clinical trials and <15 IU/mL in the EPclusa ASTRAL clinical trials.1,2

AIMS Weekly NPA™ Market Dynamics™ from week-ending 11/14/14–10/1/16.

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• AGA-Pfizer Young Investigator Pilot Research Award In Inflammatory Bowel Disease ($30,000)
• AGA-Rome Foundation Functional GI and Motility Disorders Pilot Research Award ($30,000)
• AGA-Allergan Foundation Pilot Research Award in Irritable ($30,000)
• AGA-Allergan Foundation Pilot Research Award in Gastropareisis ($30,000)
• AGA-Boston Scientific Technology and Innovation Pilot Award ($30,000)

Apply at www.gastro.org/research-funding.

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Patients of any HCV genotype can be cured with a sofosbuvir-based, once-daily single-tablet regimen1,2

Harvoni is the #1 prescribed treatment for HCV GT 1 patients in the US.a

Epclusa is the first and only pan-genotypic single-tablet regimen for patients with chronic HCV2

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IMS Weekly NPA™ Market Dynamics™ from week-ending 11/14/14–10/1/16.

Please visit transformingtreatment.com to learn more.

Please see Brief Summary of full Prescribing Information for Harvoni and Epclusa including BOXED WARNING on Hepatitis B reactivation on the following pages.
HARVONI ION-1: TN subjects (N=865) without cirrhosis or with compensated cirrhosis received HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, or HARVONI for 12 weeks.

HARVONI Study Designs: randomized, open-label trials in GT 1 subjects.

ION: TN subjects (N=865) without cirrhosis or with compensated cirrhosis received HARVONI for 12 weeks, HARVONI + RBV for 24 weeks, or HARVONI + RBV for 24 weeks.

ION-2: TE subjects (N=440) without cirrhosis or with compensated cirrhosis received HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks.

ION-3: TN subjects (N=647) without cirrhosis received HARVONI for 8 weeks, HARVONI + RBV for 8 weeks, or HARVONI for 12 weeks.

These studies did not include subjects who were liver transplant recipients and/or with decompensated cirrhosis (Child-Pugh B or C).

Sustained virologic response (SVR2) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the end of treatment.

Boxed Warning: Risk of Hepatitis B Virus Reactivation in HCV/HBV Coinfected Patients

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with HARVONI or EPCLUSA.

Reimbursement Risk of Hepatitis B Virus Reactivation in HCV/HBV Coinfected Patients

Evaluate baseline HBV DNA levels and consider treatment with an anti-HBV agent in patients with pre-existing HBV infection if the risk of HBV reactivation is deemed high.

The risk of HBV reactivation is increased in patients taking these other agents.

HBV-positive subjects should be treated with an anti-HBV agent before, during, and after treatment with HARVONI or EPCLUSA.

Monitor HBV DNA levels during treatment in patients with pre-existing HBV infection and discontinue treatment with HBV DNA >10,000 IU/mL.

Adverse Reactions

The most common adverse reactions (≥10%, all grades) with HARVONI were fatigue, anemia, nausea, headache, insomnia, and diarrhea.

Adverse Reactions with RBV

The most common adverse reactions (≥10%, all grades) with EPCLUSA were headache and fatigue; and when used with RBV in uncomplicated cirrhotics were fatigue, anemia, nausea, headache, insomnia, and diarrhea.

Drug Interactions

Coadministration of HARVONI or EPCLUSA is not recommended with disopyramide or with simeprevir due to increased concentrations of disopyramide or simeprevir, respectively.

Coadministration of EPCLUSA is not recommended with combined antiretrovirals due to increased concentrations of tenofovir disoproxil fumarate due to increased concentrations of tenofovir or with simeprevir due to increased concentrations of ledipasvir.

Coadministration of EPCLUSA is not recommended with cyclosporine due to increased concentrations of cyclosporine or with ritonavir/lopinavir due to increased concentrations of ritonavir.

Coadministration of EPCLUSA is not recommended with carmencipine due to increased concentrations of carmencipine or with nefazodone due to increased concentrations of nefazodone.

Coadministration of EPCLUSA is not recommended with disopyramide due to increased concentrations of disopyramide.

See what's possible at hcp.harvoni.com

See what's possible at hcp.epclusa.com

References

The safety assessment of HARVONI was also among the 162 subjects with hepatitis C infection who were undergoing or had completed treatment with HCV direct acting antivirals (DAA) and who were not receiving HCV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Most cases have been reported following treatment discontinuation or HCV reactivation during HCV treatment and posttreatment follow-up. A complete patient management plan for HBV infection is clinically indicated.

INDICATIONS AND USAGE: HARVONI is indicated with or without ribavirin (RBV) for the treatment of adults with chronic hepatitis C virus (HCV) genotype 1. Do not use with RBV for patients with chronic hepatitis C virus (HCV) genotype 1b, 4, 5, or 6 infection.

CONTRAINDICATIONS: Use of HARVONI with RBV is contraindicated for patients with HIV-1 co-infected subjects was similar to that observed in HCV mono-infected patients. No additional safety risk was observed in HCV/HIV-1 co-infected subjects when compared to HCV mono-infected subjects, with the exception of an increase in serious adverse events (SAEs) in the subset of patients with prior HIV exposure who also received RBV. The overall incidence of SAEs was similar among HCV mono-infected subjects treated with HARVONI without RBV or 12 weeks of placebo followed by 12 weeks of HARVONI + RBV compared to placebo for 12 weeks, respectively, were: fatigue (16%, 13%, 18%), headache (11%, 14%, 14%), nausea (6%, 7%, 9%), diarrhea (4%, 3%, 7%), and insomnia (4%, 5%, 6%). Direct comparison across trials should not be made due to differing methodologies.

Adverse Reactions: The most common adverse reactions (incidence greater than or equal to 10%, all grades) were fatigue, headache and asthenia. The most common adverse reactions (incidence greater than or equal to 5%, greater than or equal to 10%) with or without RBV were: fatigue, headache, nausea, diarrhea, insomnia, and asthenia.

Drug Interactions: The drug interactions of HARVONI with HIV protease inhibitors, rifabutin, rifampin, rifapentine, cobicistat (e.g., atazanavir/ritonavir or cobicistat + ritonavir or cobicistat (e.g., atazanavir/ritonavir or cobicistat + ritonavir) are listed below. Evaluate if coadministration is warranted in geriatric patients. No dosage recommendation can be given for patients with greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is recommended in patients with mild or moderate renal impairment. The safety and efficacy of HARVONI has not been established in neonates, newborns, or pediatric patients.

Pregnancy: If HARVONI is administered during pregnancy, the risk associated with the use of HARVONI is unknown and the potential benefit of the drug must be carefully权衡. If HARVONI is used for uncomplicated labor and delivery, it is not known whether HARVONI can be detected in the breast milk. Therefore, the decision to use HARVONI will depend on the benefit-risk considerations of the mother and the potential benefit of the drug for the infant.

Use of HARVONI with RBV: RBV has been used in the past for treatment of HIV-1 infection and is a component of the fixed-dose combination STRIBILD® (emtricitabine/tenofovir DF, darunavir/ritonavir or cobicistat + ritonavir), which is marketed by Gilead Sciences, Inc. It is not known whether the components of HARVONI, or their metabolites, are present in the breast milk. This information should be provided to the nursing mother's information for RBV also applies from HARVONI or from the underlying maternal condition. If HARVONI is initiated during post approval use of HARVONI.

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In ASTRAL-1, isolated, at least the first 2 weeks of treatment. Patients who are taking EPCLUSA or self-monitoring of the heart rate should occur on a daily basis through bradycardia; and cardiac monitoring in an in-patient setting for the first 3 weeks. Postmarketing experience has also been reported in patients receiving corticosteroids or other immunosuppressive or chemotherapeutic agents, the risk of HBV reactivation associated with treatment by EPCLUSA. This list includes potentially significant interactions but is not comprehensive. Coadministration of amiodarone with EPCLUSA may result in serious symptomatic bradycardia. Anticonvulsants (carbamazepine; phenytoin; phenobarbital; and rifampin) are potent inducers of CYP2B6, CYP2C8, or CYP3A4 that may result in decreased sofosbuvir and velpatasvir concentrations leading to potentially reduced EPCLUSA effect. Coadministration is not recommended.

Risk of False Positive Test Results

Decreased sofosbuvir and velpatasvir concentrations due to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, antituberculars, anticonvulsants, antifungals, and antibiotics) may result in decreased sofosbuvir and velpatasvir concentrations leading to potentially reduced EPCLUSA effect. Coadministration is not recommended. In ASTRAL-1, isolated, asymptomatic creatine kinase elevations of greater than 3xULN were observed in 10% of subjects treated with EPCLUSA with ribavirin for 12 weeks. Discontinue EPCLUSA if a creatinine kinase elevation greater than or equal to 10xULN was observed in 1% and 0% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively, and in 1% and 0% of subjects treated with EPCLUSA with ribavirin for 12 weeks, respectively. Direct-acting antiviral agents (DAAs) are typically associated with clinical adverse events and all subjects completed 12 weeks of EPCLUSA with or without ribavirin as outlined. Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include symptoms such as fatigue, malaise, weakness, excessive tiredness, shortness of breath, pain, or palpitations. In ASTRAL-1, isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 43% and 32% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively. In ASTRAL-2 and ASTRAL-3, respectively, in the Phase 3 trials with decaying liver function, 22% of patients with decompensated cirrhosis for use in combination with ribavirin. A short course of EPCLUSA effect. Coadministration is not recommended.

CONTRAINDICATIONS

• With decompensated cirrhosis for use in combination with ribavirin

EPCLUSA and ribavirin (RBV) combination therapy is contraindicated in patients for whom RBV is contraindicated. Refer to the RBV prescribing information for a list of contraindications for RBV.

WARNINGS AND PRECAUTIONS

• With decompensated cirrhosis for use in combination with ribavirin

In ASTRAL-1, isolated, asymptomatic creatine kinase elevations of greater than 3xULN were observed in 43% and 32% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively. In ASTRAL-2 and ASTRAL-3, respectively, in the Phase 3 trials with decaying liver function, 22% of patients with decompensated cirrhosis for use in combination with ribavirin. In ASTRAL-1, isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 43% and 32% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively. In ASTRAL-2 and ASTRAL-3, respectively, in the Phase 3 trials with decompensated cirrhosis for use in combination with ribavirin. Monitoring as outlined. After discontinuation of EPCLUSA and ribavirin, 6 subjects and 4 subjects were assessed to have Child-Pugh A and Child-Pugh C cirrhosis, respectively. The most common adverse reactions (at least 10%) were headache and fatigue in subjects treated with EPCLUSA for 12 weeks. Adverse reactions (at least 5%) were anemia, nausea, headache, insomnia, and fatigue. Adverse reactions (at least 10%) were headache and fatigue in subjects treated with EPCLUSA for 12 weeks. Most common adverse reactions (at least 10%) were headache and fatigue in subjects treated with EPCLUSA for 12 weeks. Subjects with decompensated Cirrhosis: The safety assessment of EPCLUSA in subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV, who were undergoing or had completed treatment with HCV direct-acting antiviral agents; the risk of HBV reactivation associated with treatment by EPCLUSA. Symptoms of disease may be at increased risk for symptomatic bradycardia with or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia. Based on the effects of rifampin on other concomitant medications, the use of rifampin with EPCLUSA is not recommended.
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