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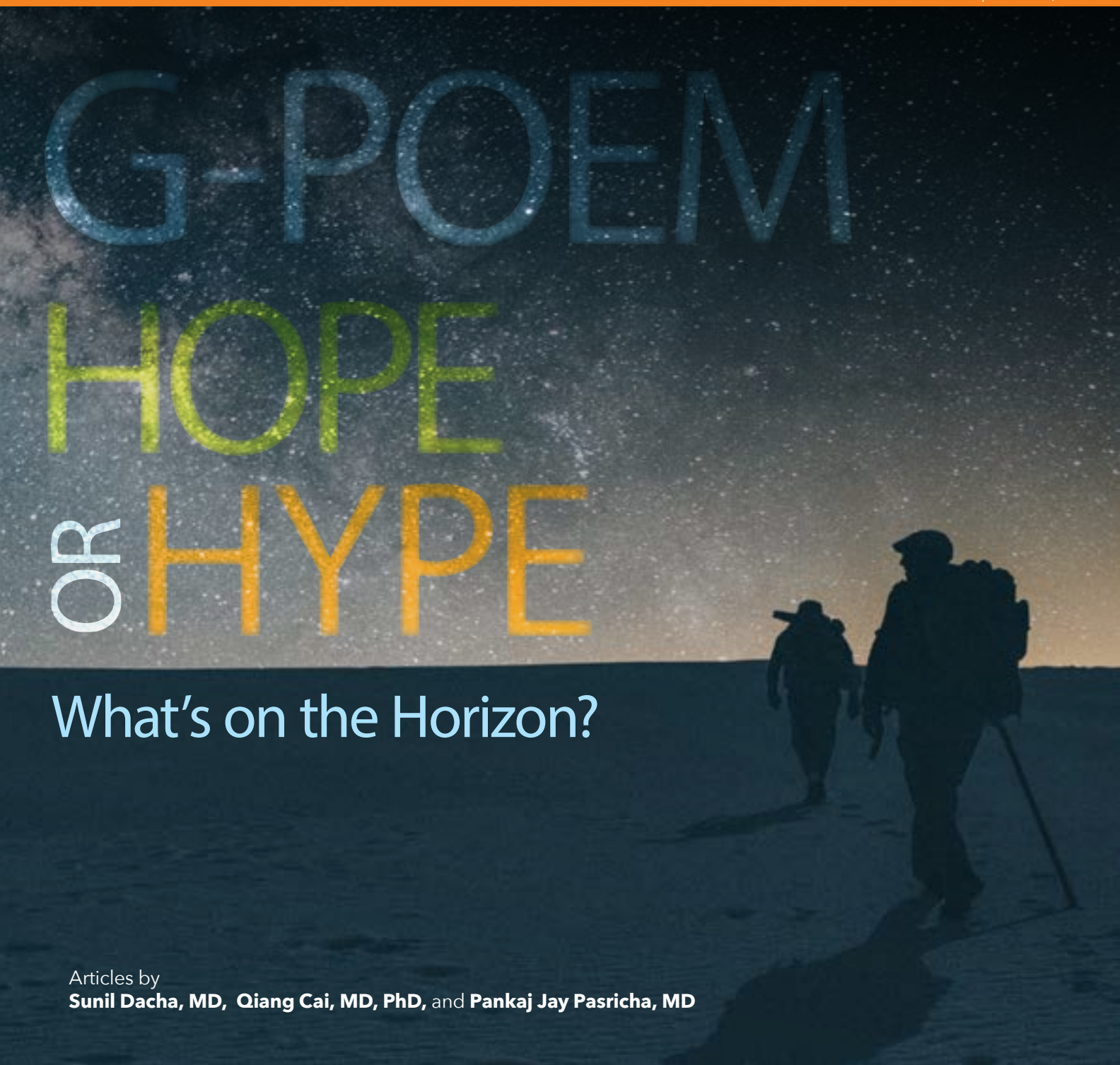

What's on the Horizon?

Articles by
Sunil Dacha, MD, Qiang Cai, MD, PhD, and **Pankaj Jay Pasricha, MD**

AGA Perspectives

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Note From the Editor

The last issue of *AGA Perspectives* highlighted new pharmacologic approaches to gastroparesis. In this issue, our point counterpoint debate focuses on the role of gastric peroral endoscopic myotomy (G-POEM) in our therapeutic toolbox for this disease. Advocating for this approach are Drs. Sunil Dacha and Qiang Cai and arguing for a more cautious approach to this new therapy is Dr. Pankaj Jay Paschricha. Given the challenges posed by this patient group, this debate should help give the reader some perspective on this newly proposed solution.

Our understanding of eosinophilic esophagitis (EoE) continues to accelerate along with extensive efforts in new drug development for a disease with no FDA approved therapies. Proton pump inhibitors (PPIs) are one option for EoE, but considerable confusion remains about PPI–responsive esophageal eosinophilia (PPI-REE). Dr. Stuart Spechler outlines nicely why the term *PPI-REE* should now be discarded and why a PPI trial is no longer needed for a diagnosis of EoE.

Irritable bowel syndrome remains a challenging disorder for the entire GI community. A variety of new drugs have been developed to help our patients and practical guidance for application of these new therapeutic agents is provided by Dr. Lin Chang. Another area of confusion involves the impact of our highly effective, new antiviral agents for hepatitis C on hepatocellular carcinoma. This conundrum is put into perspective nicely by Drs. Amit Singal and Neehar Parikh.

Updates by leading experts are also included in this issue on the topics of nonsteroidal anti-inflammatory drugs (NSAIDs) and their effects on the gut, the emerging role of telemedicine in GI practice, cryotherapy in Barrett's esophagus and the current status of endoscopic bariatric procedures.

As always, the goal of *AGA Perspectives* is to provide quick updates on important clinical issues in gastroenterology and hepatology today. With DDW behind us and the summer underway, I hope you enjoy this issue.

Best,

Gary W. Falk, MD, MS, AGAF
EDITOR
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G-POEM HOPE OR HYPE

What's on the Horizon?

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Gastroparesis is a chronic and debilitating disorder with a complex pathophysiology yet to be fully understood. Unfortunately, the incidence of gastroparesis and the hospital stays associated with it have been increasing in the U.S. during the past decade. Treatment options are limited, and metoclopramide is the only medication approved by the U.S. Food and Drug Administration for this disabling condition. Treatment success rates are disappointing, even in tertiary centers, leading to frequent visits to the emergency department (ED) and hospital stays.[1,2]

Also known as peroral endoscopic pyloromyotomy, gastric peroral endoscopic myotomy (G-POEM) is a novel, minimally

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Despite what the title of this commentary may suggest, I want to state at the onset that I am not a Luddite. I trained in therapeutic endoscopy and have embraced new technology throughout my career. Nothing would please me more than a relatively simple endoscopic solution for a complicated problem such as gastroparesis. So, the question is: Does gastric peroral endoscopic pyloromyotomy (G-POEM) represent that "magic bullet" we've all been waiting for?

Let's begin with the rationale for this procedure. Pyloric dysfunction can certainly be associated with gastroparesis, and it is reasonable to hypothesize that this results in impaired gastric emptying. Advocates of G-POEM have

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invasive, flexible endoscopic procedure that is emerging as a new treatment option for select patients with refractory gastroparesis. Pylorus-directed therapies, such as surgical pyloroplasty and pyloric stenting, in open-label and retrospective reports were shown to improve symptoms of gastroparesis. Thus, G-POEM emerged as an extension to these pyloric-directed therapies.

The procedure has gained popularity due to its exciting potential in a debilitating disease for which available therapeutic options are quite limited. Early experience in the U.S. and Europe showed good clinical response rates. Overall, the clinical response rate, as determined by symptomatic improvement, following G-POEM reached 73 to 86 percent after up to 12 months of follow-up.[1,3-5] The overall complication rate of G-POEM is low, ranging from 0 to 6.7 percent. Available data suggest that it improves symptoms of gastroparesis (measured by an improvement in the Gastroparesis Cardinal Symptom Index [GCSI]), improved quality of life (as measured by an improvement in 36-Item Short Form Health Survey score) and decreased gastric emptying time during short- and mid-term follow-up in as many as 70 percent of patients. Serious adverse events have been rare but have included gastrointestinal bleeding, pyloric ulcer and tension capnoperitoneum.[1,2,5] The long-term effectiveness of G-POEM is still unknown. We suggest the following two selection criteria for G-POEM: an average GCSI score larger than two and gastric retention at four hours of more than 20 percent. As more data become available, it will be important to identify a specific patient population who would benefit most from this novel procedure. The big question would then be: Where do we place G-POEM in the treatment algorithm? Do we consider it only in patients with refractory gastroparesis or in those with early gastroparesis?

The procedure is technically feasible and safe, and, in the hands of an experienced specialist, it has a low risk of complications. However, it is a technically challenging procedure compared with esophageal peroral endoscopic myotomy due to antral contractions, curved submucosal tunnel, extensive vascularity and a very thin duodenal wall, which predisposes patients to a high risk of perforation.

We started performing G-POEM in 2015 and have now established a very successful G-POEM program. As part of a major tertiary center, we have a high referral rate for patients with gastroparesis. We offer G-POEM to patients with refractory gastroparesis whose predominant symptoms are nausea and vomiting. We do not offer G-POEM for patients whose predominant symptoms are abdominal pain and bloating. In our opinion, patients taking long-term narcotic therapy and those with end-organ damage due to long-term diabetes are not ideal candidates for the procedure because they are unlikely to benefit from it.

Compared with surgical pyloroplasty, G-POEM is more appealing to patients because it is a minimally invasive endoscopic procedure — no need exists for an invasive surgical procedure — and it provides shorter lengths of hospital stays and is a less painful procedure.

Gastroparesis is a heterogeneous disorder, and not all patients with gastroparesis will have pyloric dysfunction. Thus, not all patients will benefit from G-POEM. Therefore, we strongly advocate for the use of pyloric diagnostic techniques such as impedance planimetry. Impedance planimetry is a novel tool for assessing pyloric distensibility and compliance, and it could potentially be used to identify a subgroup of patients for whom endoscopic techniques for pyloric-directed therapies could be utilized.

Compared with surgical pyloroplasty, G-POEM is more appealing to patients because it is a minimally invasive endoscopic procedure — no need exists for an invasive surgical procedure — and it provides shorter lengths of hospital stays and is a less painful procedure. In addition, the cost of the procedure will be significantly lower.

As we make steady progress in the field of G-POEM, it is important to acknowledge that these results were derived from small retrospective studies. Although large, prospective, randomized trials are needed, several limitations exist because a gold standard does not exist to which the effectiveness of G-POEM can be compared. Gastric-emptying scintigraphy is the only objective testing with

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taken this argument to its logical conclusion: Decreasing pyloric resistance should improve gastric emptying and, hence, clinical benefit. Setting aside the fact that a delay in gastric emptying does not necessarily correlate with symptom severity, let us examine the clinical experience with therapies based on pyloric intervention, beginning with botulinum toxin. Initial reports generated much enthusiasm, with success rates as high as 90 percent — reminiscent of the current buzz about G-POEM — but two randomized trials failed to show any improvement in symptoms in the active treatment group.[1,2] It has been argued that this was due to the small numbers of patients, lack of selectivity or technical factors related to the injection itself. What is not widely recognized is that gastric emptying did improve after botulinum toxin injection in at least one of these controlled studies, indicating that the treatment was effective in producing the desired physiologic outcome without a change in symptoms.

Advocates of G-POEM propose, with some merit, that a much greater reduction of pyloric resistance is needed to affect clinical outcomes. Let us therefore examine the historic experience with patients undergoing truncal vagotomy for peptic ulcer disease for whom the procedure was combined with surgical pyloroplasty to prevent symptoms from the expected delay in gastric emptying. In many ways, this is an ideal "experiment" to analyze — loss of vagal function to the stomach is expected to produce similar pathophysiologic changes as in other forms of gastroparesis (indeed, vagal neuropathy is considered to be a possible etiologic factor in these conditions). So, does pyloroplasty actually ameliorate symptoms of gastroparesis in patients undergoing truncal vagotomy? One prospective trial randomized nearly 250 patients to truncal vagotomy and pyloroplasty, selective vagotomy with pyloroplasty and parietal cell vagotomy alone, and the researchers followed them for more than 10 years.[3] Between 50 and 70 percent of patients with pyloroplasty developed dyspeptic symptoms (pain, heartburn, nausea and vomiting). In these patients, dumping (about 30 to 40 percent) and diarrhea (about 35 to 50 percent) were common, although it was usually described as mild or intermittent. One could therefore conclude that rendering the pylorus wide open does not ameliorate symptoms in a "surgical model" of gastroparesis and may have adverse events.

Which brings us to G-POEM — to date, nearly half a dozen studies have been undertaken, with all of them being open-label, having small numbers of heterogeneous patients, varying metrics and no long-term follow-up periods. Nevertheless, at least two of these studies are reasonably comparable but with results that are somewhat incongruous. In a study of 16 patients, Dacha et al showed dramatic improvements in overall Gastroparesis Cardinal Symptom Index (GCSI; measured on a scale of zero to five) score, which decreased from 3.4 to 1.5.[4] However, a much larger study (47 patients) from the Cleveland Clinic showed a much less robust improvement: the change in GCSI only went from 4.6 to 3.3.[5] Hopefully, a truer picture will emerge if and when controlled studies are performed. But, at least one question to ask is: If G-POEM is simply pyloroplasty by a different route, then why should the results be different than open pyloroplasty performed by experienced surgeons?

With only 100 or so cases described in the medical literature and no consensus on outcomes, G-POEM is unarguably an experimental procedure with the potential to permanently alter gastric anatomy with unknown consequences.

This is a good segue to the final and more philosophical part of this commentary. First, I want to commend endoscopists and surgeons for wading into this area — we need all the help we can get! However, some rules must be followed. Importantly, let us all acknowledge that G-POEM as a procedure is not standardized, no training requirement or credentialing is in place regarding how to perform it, and we have no data on long-term outcomes. With only 100 or so cases described in the medical literature and no consensus on outcomes, G-POEM is unarguably an experimental procedure with the potential to permanently alter gastric anatomy with unknown consequences. This should be made explicitly clear to the patient, of course, but it also means that G-POEM should be performed only after approvals have been received from an institutional review board and an

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symptoms for all patients with gastroparesis. Logistically, a sham-controlled trial would not be possible to perform. The procedure will become widely acceptable if results from earlier studies are reproducible and the procedure shows long-term effectiveness in maintaining symptomatic improvement. Thus, more robust data are needed on its long-term outcomes and safety, refining the procedural technique and demonstrating benefit from an economic perspective.

We strongly believe that G-POEM is a viable treatment option for a subset of patients with gastroparesis refractory to medical therapy. Ideally, it should be performed by an experienced endoscopist in a research setting. The procedure should be performed under an approved protocol only. Currently, the ideal patient population and long-term outcomes are unclear, thus should not be performed in the clinical setting yet. It should be offered to patients with nausea and vomiting as the predominant symptoms.

Concomitant gastric electrical stimulation can be performed in select patients with nausea-predominant diabetic gastroparesis. Pyloric diagnostic techniques such as impedance planimetry or a wireless capsule motility should be performed when available to determine the appropriate candidates for G-POEM. Our goal is to provide symptomatic relief for this group of patients with limited treatment options, and, in turn, decrease their need for supplemental nutrition, medications, ED visits and hospital stays.

Key takeaways

- G-POEM is a safe and effective treatment for select patients with refractory gastroparesis.
- G-POEM should be offered to patients in the research setting who present with nausea and vomiting as their predominant symptoms. It does not benefit patients with abdominal pain or bloating.
- Clinical outcomes of G-POEM in short- and mid-term studies are promising and consistent in all of the reported retrospective studies.
- No parameters currently identify target patients for G-POEM, and no factors reliably predict a patient's clinical response to G-POEM.

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independent safety board has been established to monitor safety and outcomes.

Beware of tempting but possibly false analogies: Just because achalasia responds to a sphincteric intervention does not mean that gastroparesis will, too. However, if you are convinced about the merits of this approach based on your understanding of the disease process, then show your commitment to the patient by continuing to take care of him or her if the procedure fails (the old adage of "if you break it, you own it").

Respect the power of controlled trials. I have already discussed botulinum toxin injections into the pylorus and how this continues to be practiced despite scientific evidence to the contrary. Another similar example is illustrated by the practice of endoscopic sphincterotomy for the so-called syndrome of sphincter of Oddi dysfunction. For decades, patients with unexplained pain were having their biliary (and often pancreatic) sphincters excised by experts claiming response rates of 60 to 80 percent. Thousands of patients underwent this procedure, many of whom developed acute pancreatitis. It took the landmark EPISOD trial to show that sphincterotomy not only had no benefit in these patients but that it actually led to worse outcomes.[6] Yet the practice continues in many parts of the country, and patients are still being told that this is a viable and beneficial approach to their pain.

I have no doubt that motility specialists and their interventional colleagues are highly motivated to help patients with a disorder for which current treatment options are very limited. However, we must resist the temptation — no matter how well intentioned — to do the wrong thing for the right reason. Let us not jump on the same bus that has taken us down dead-end streets before (sphincterotomy for sphincter of Oddi dysfunction, pancreatectomy for minimal-change pancreatitis and botulinum toxin for gastroparesis) with patients paying the costs for us clinicians to "learn." G-POEM is a promising procedure, but it must be rigorously tested in randomized controlled trials before we can offer it to patients outside of a research setting. Until then, here's to hoping!

Key takeaways

- G-POEM is a new way to perform pyloromyotomy in patients with gastroparesis with the rationale that functional pyloric obstruction is the root cause of the pathophysiology and symptoms.
- As with most open label interventions in motility disorders, short-term results in very small numbers of patients are generally promising.
- Much more needs to be learned about the efficacy and safety of the procedure particularly beyond a few months as well as who the appropriate candidate is.
- Until then, G-POEM should be considered experimental and done under a research protocol.

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Proton pump inhibitor – responsive esophageal eosinophilia

What is the relevance in 2018?

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A meaningful discussion on the relevance of proton pump inhibitor–responsive esophageal eosinophilia (PPI-REE) in 2018 should first consider this question: How did we ever end up with this cumbersome term? Well, it arose as an artifact of early confusion regarding the need to distinguish eosinophilic esophagitis (EoE) from gastroesophageal reflux disease (GERD). This confusion led to adoption of an early, unrealistic EoE definition that excluded patients whose condition responded to proton pump inhibitors (PPIs). The term *PPI-REE* has persisted because physicians have been slow to abandon the traditional, erroneous notion that only an acid peptic disease like GERD responds to PPIs.

EoE is a relatively new disease, first described in 1993, and it has many features that resemble GERD. Consequently, the onus on early investigators of EoE was to prove that they indeed were studying a new disease, not just an unusual manifestation of GERD. Those investigators knew that PPIs were a highly effective treatment for GERD, presumably because they induced profound gastric acid suppression. Indeed, responsiveness to PPIs has been widely regarded as *de facto* evidence of acid peptic disease in any upper gastrointestinal organ. Because GERD is the only acid peptic disease of the esophagus, response to PPIs seemed like a reliable way to establish a diagnosis of GERD for patients with esophageal symptoms and eosinophilia.

Accordingly, AGA Institute guidelines published in 2007 excluded a diagnosis of EoE for such patients whose disease was responsive to PPIs. Physician recognition of EoE was not yet widespread in 2007, and the AGA guidelines were born of necessity to exclude GERD and convince skeptics of the very existence of the new disease. Nevertheless, the guidelines were unrealistic in implying that GERD and EoE were mutually exclusive disorders. This idea would make sense only if one disorder protected against the other — and that is clearly not the case.

In addition, in 2007, Dr. Bob Genta, Dr. Rhonda Souza and I published a report contending that the interaction between GERD and EoE might be complex, and that the concept of establishing a clear distinction between the two via a PPI trial was far too simplistic. During this same time, investigators began to see patients who had symptoms and findings on endoscopy and esophageal histology typical of EoE but not of GERD and whose disease responded to PPIs nevertheless. What could we call this condition? It didn't seem to be GERD, even though it responded to PPIs, but it was not EoE because our definition excluded patients responsive to PPIs. So, for lack of a better term, we called the condition PPI-REE.

In 2011, I was a member of a working group that proposed a new, conceptual definition for EoE as an immune-/antigen-mediated esophageal disease characterized clinically by symptoms of esophageal dysfunction and histologically by eosinophil-predominant inflammation. Unlike the 2007 definition, which established primarily what EoE *was not* (i.e., it was not GERD), I was pleased that this new definition established what EoE *was* (i.e., immune-/antigen-mediated esophageal disease). However, I was disappointed when the working group still insisted that responsiveness to PPIs excluded a diagnosis of EoE.

By 2011, enough data had accumulated to suggest that PPIs might have important anti-inflammatory effects entirely independent of their effects on gastric acid secretion, and that those anti-inflammatory effects might enable PPIs to heal inflammatory disorders beyond acid peptic diseases. A report published by my group in 2012 showed that PPIs blocked the secretion of an eosinophil chemoattractant (eotaxin-3) by esophageal epithelial cells that were stimulated with allergic (Th2) cytokines, and we suggested that this anti-inflammatory mechanism might underlie PPI-REE. We also suggested that some patients with PPI-REE might have subclinical GERD exacerbating antigen-mediated EoE, perhaps through GERD-induced increases in esophageal permeability that enable food antigens to penetrate the epithelium. Thus, antigen-driven EoE might benefit from both the anti-inflammatory and antisecretory effects of PPIs.

In 2018, the traditional notion that PPIs can only benefit patients with acid peptic disease and not an antigen-driven disease (e.g., EoE) is simply untenable. Irrespective of the mechanism, the evidence is overwhelming that many patients with the antigen-mediated, clinicopathologic syndrome we recognize as EoE also have disease that responds to PPIs. The clinical, endoscopic, histologic and gene-expression features of EoE and PPI-REE are nearly identical, and multivariate analyses have not identified any feature that distinguishes them. Studies have documented that some patients with EoE whose disease initially responds to elimination diets also responds to PPIs when those diets are stopped. Conversely, some patients with PPI-REE on unrestricted diets have disease that responds to elimination diets (with food triggers identified) when PPIs are stopped. A growing — but not yet universal — consensus is that PPI-REE *is* EoE in many, if not most, cases.

The term *PPI-REE* has persisted because physicians have been slow to abandon the traditional, erroneous notion that only an acid peptic disease like GERD responds to PPIs.

The term *PPI-REE* was proposed with all the good intentions, and confusion about PPI-REE has had consequences, specifically regarding how clinicians manage the use of PPIs during diagnostic endoscopy. For patients with symptoms of GERD whose disease incompletely responds to PPIs, it is not common clinical practice to stop PPIs before diagnostic endoscopy, even when endoscopy is specifically performed to look for alternative diagnoses such as EoE. Clinicians might be aware of the condition called PPI-REE, but they have been told that, by definition, it is *not* EoE. If you accept the dictum that responsiveness to PPIs excludes EoE, then why would you stop PPIs that have helped, but not eliminated, your patient's symptoms? How could PPIs obscure a diagnosis that they already have excluded?

My group has just published a report in *Gastroenterology* describing patients in whom the diagnosis of EoE was considerably delayed because diagnostic endoscopies were performed while the patients were on PPI therapy and yet had eliminated all endoscopic and histologic evidence of EoE. I think it is time we started thinking of PPIs as a treatment for EoE, not as a means to exclude the diagnosis. PPI-REE is a description, not a disease.

How do I integrate new IBS therapies into clinical practice?

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Irritable bowel syndrome (IBS) is a complex, multifactorial disorder characterized by chronic or recurrent abdominal pain associated with altered bowel habits. My general approach is to identify the predominant or most bothersome symptoms and the most likely pathophysiologic mechanisms underlying these symptoms. Then I target treatment toward these predominant symptoms and mechanisms. Validating symptoms, building trust, developing a therapeutic alliance and establishing continuity of care are the cornerstones of treating IBS.

Patients often require medications to help treat their symptoms associated with IBS. Factors I consider when choosing a therapy include the patient's response to previous treatments, including their effectiveness and associated side effects, the severity of symptoms, drug cost, the patient's motivation and preference for certain types of treatment, comorbid conditions, and potential adverse events of the treatment. These factors, as well as the available scientific evidence, and my clinical experience help guide my choice of therapies.

One of the newer therapies approved by the U.S. Food and Drug Administration (FDA) for IBS with constipation (IBS-C) is plecanatide, which is a guanylate cyclase-C agonist in the same class of agents as linaclotide. Plecanatide is available as a once-daily 3-mg oral tablet. Compared with placebo, plecanatide significantly improves abdominal pain, increases the number of complete spontaneous bowel movements, and improves stool consistency. Alternatively, linaclotide is a once-daily gel capsule available in 72-, 145- and 290-µg doses. Similar to plecanatide, linaclotide, at a daily dose of 290-µg, also significantly relieves abdominal pain and symptoms related to IBS-C when compared with placebo.

Improvement in bowel habits with these medications typically occurs within the first week of treatment, but the maximal effect in abdominal pain and bloating relief may take up to 12 weeks. Thus, if pain is a predominant symptom, then these medications should be continued for two to three months to assess their maximal effect. If the patient's stool frequency is more than three times per week, I may start linaclotide at 145 µg daily and see how they respond. Although this is the FDA-approved dose for chronic idiopathic constipation, if I have any concern about diarrhea — the main adverse event of linaclotide — I will try this dose first. If patients do not have significant relief of constipation within one to two weeks, then I increase the dose to 290 µg daily, which is the FDA-approved dose for IBS-C. If I have difficulty finding an optimal dose to treat symptoms, then I advise the patient to dissolve the gel capsule contents of linaclotide in a small amount of water. I ask the patient to use this liquid form and take a portion of the dose. In this regard, I like the flexibility of the linaclotide dosing.

Factors I consider when choosing a therapy include the patient's response to previous treatments, including their effectiveness and associated side effects, the severity of symptoms, drug cost, the patient's motivation and preference for certain types of treatment, comorbid conditions, and potential adverse events of the treatment.

Because plecanatide was only recently approved by the FDA for IBS-C, some insurance companies may not yet approve the use of plecanatide without the patient first trying lubiprostone, a chloride channel 2 activator, or linaclotide. Because no head-to-head comparisons of linaclotide and plecanatide currently exist, I cannot accurately compare their efficacy. However, my impression in the limited number of patients in whom I have used plecanatide is that the 3-mg dose of plecanatide is comparable to the 145-µg dose of linaclotide. Although plecanatide showed a relatively lower incidence of diarrhea than linaclotide, this adverse event can still occur. Some of my patients prefer the effect of plecanatide on their IBS-C symptoms over linaclotide. They report that their stool is more formed, which is associated with improved sensation of evacuation.

If a patient with IBS-C has mild to moderate symptoms that are unresponsive to fiber supplementation and over-the-counter laxatives, then I will prescribe lubiprostone or plecanatide. In some of my elderly patients, I prefer to use a medication with little risk of diarrhea, because these patients have more difficulty reaching the bathroom in time and they tend to prefer medications that have been on the market for a longer period of time. For moderate to severe symptoms, I prescribe plecanatide or linaclotide. For more severe symptoms related to IBS-C, especially in patients with decreased stool frequency and increased abdominal pain and bloating, I initially prescribe linaclotide once-daily 290 µg.

Approved for the treatment of IBS with diarrhea (IBS-D), eluxadoline is a first-in-class, mixed µ- and κ-opioid receptor agonist and δ-opioid receptor antagonist that is minimally absorbed. When compared to placebo, both doses of twice-daily eluxadoline (75 and 100 mg) improved abdominal pain and stool consistency in patients with IBS-D, including those whose condition did not respond to loperamide. However, a significant effect on lowering abdominal pain alone was not observed (i.e., 30 percent reduction in pain rating). Due to its increased risk of pancreatitis and sphincter of Oddi dysfunction, eluxadoline is contraindicated in patients without a gallbladder and in those with a history significant for alcohol abuse.

Based on my experience with eluxadoline, I prefer to use the lower, twice-daily dose of 75 mg in patients whose moderate symptoms occur two to three days per week. Eluxadoline can be associated with constipation and, if this occurs, patients taking it can feel more uncomfortable than when they were experiencing diarrhea. If patients have moderate to severe symptoms most days of the week, then I usually prescribe twice-daily eluxadoline 100 mg. If they have predominant abdominal pain with diarrhea, then eluxadoline can be tried; however, a low-dose tricyclic agent should be considered first due to the visceral analgesic and anticholinergic effects of this drug class.

Although the focus of this article is on the newer pharmacologic treatments for IBS, it is important to consider that patients can also significantly benefit from nondietary and nonpharmacologic therapies (e.g., behavioral therapy) as well as other pharmacotherapy. In summary, the choice of a pharmacologic agent depends on multiple factors, including scientific evidence, and patient- and clinician-related factors. Typically, I discuss the various therapeutic options with a patient and we make a decision together — a process called shared decision-making. I feel that this approach gives patients a greater sense of control and empowerment. It also supports the concept that treating IBS is based on a partnership between the patient and the health care professional. ▯

What is the impact of HCV therapy on HCC development?

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Chronic hepatitis C is the most common cause of hepatocellular carcinoma (HCC) in the United States and Europe. Antiviral therapy against hepatitis C virus (HCV) has long been regarded as one of the most effective chemopreventive strategies for HCC. Sustained viral response (SVR) in patients without cirrhosis can halt disease progression, thereby decreasing the risk of HCC to near zero. In patients with cirrhosis, interferon (IFN)-based SVR was associated with an 81 percent reduction in the incidence of HCC and related mortality.[1] Similarly, SVR was associated with a 67 percent reduction in HCC recurrence after complete response in the IFN era.[2] However, whether a reduction in HCC risk was related to clearance of HCV or a direct IFN-mediated antitumor effect remains unclear. This debate over the impact of antiviral therapy for HCV infection on hepatocarcinogenesis became particularly relevant after the introduction of IFN-free direct-acting antiviral (DAA) regimens, which have replaced IFN-based therapy.

The results of early studies reported a higher-than-expected HCC incidence and recurrence after DAA therapy, raising concern that DAA therapies may not decrease a person's risk of HCC. Conti *et al* and Cardoso *et al* reported incident HCC in 3.2 percent of patients within six months and 7.4 percent within 12 months of DAA therapy, respectively.[3,4] Similarly, Reig *et al* reported that, of 58 patients with complete response to HCC-directed therapy, HCC recurred in 16 (27.6 percent) patients after a median follow-up period of 5.7 months.[5] It is unlikely the DAAs have a direct oncogenic effect, so this association is hypothesized to be related to decreased immunosurveillance of microscopic HCC tumor clones in the setting of a rapid decrease in HCV viral load and related hepatic inflammation.

Recently, the results from several large studies with longer follow-up times demonstrated significant reductions in HCC incidence after DAA therapy. A study that enrolled 62,354 patients from the U.S. Veterans Affairs Health Care System who initiated antiviral therapy found that SVR was associated with significantly decreased HCC risk in multivariable models, irrespective as to whether the antiviral treatment was IFN-based (hazard ratio [HR] 0.32; 95 percent confidence interval [CI], 0.28 to 0.37) or IFN-free (HR 0.29; 95 percent CI, 0.23 to 0.37).[6] Being treated with IFN-free therapy was not associated with an increased HCC risk when compared with receiving an IFN-containing regimen (HR 0.97; 95 percent CI, 0.77 to 1.22) after adjusting for baseline differences in patient characteristics. Similarly, a study from Scotland comparing patients who achieved SVR after IFN-based and IFN-free therapies found that the increased HCC risk observed with IFN-free therapy disappeared after adjusting for baseline differences in patient characteristics, such as patient age, Child-Pugh class and degree of portal hypertension (HR 1.15; 95 percent CI, 0.49 to 2.71).[7] In light of these recent data, we recommend treatment for patients with HCV infection without the need to alter HCC surveillance frequency during therapy. Patients with cirrhosis should undergo surveillance ultrasonography and alpha-fetoprotein testing every six months, including before initiating DAA therapy, to exclude the presence of HCC.[8,9]

Although these data have alleviated concerns about increased incident HCC risk, debate continues about the impact of DAA therapy on risk of HCC recurrence in patients with a complete response to HCC-directed therapy. Whereas some studies have shown high recurrence rates, such as Conti *et al* (28.8 percent recurrence after a median follow-up period of 5.5 months), others have found substantially lower recurrence rates, such as Ogawa *et al* (17.5 percent during a 17-month follow-up period) and Cabibbo *et al* (20.3 percent during an 8.7-month follow-up period).[3,10,11] In comparison, historic, actuarial HCC recurrence rates after curative treatments in patients naïve to HCV therapy were 7.4 percent at six months and 47.0 percent at two years.[12] We recently completed a systematic review and found a pooled estimate of 24.4 percent for HCC recurrence after DAA therapy, although significant clinical heterogeneity was present within and between studies, including tumor burden, HCC treatments leading to complete response, and follow-up periods.[13] Further, we noted most studies had significant methodologic limitations, including high potential for misclassification and ascertainment biases, potentially leading to overestimates and underestimates of HCC recurrence, respectively. The few existing comparative studies between patients treated with DAA and IFN or those naïve to treatment suggest that those receiving DAA therapy have similar, if not lower, recurrence rates than their counterparts; however, these studies were limited by potential selection bias and residual confounding. Finally, all studies have reported intermediate outcomes, such as early recurrence, but no studies have sufficient follow-up to examine longer-term outcomes such as overall survival. Ongoing prospective studies have addressed several of these limitations and should provide higher quality data in the near future.

Given the known benefits of HCV therapy, such as improvement in liver dysfunction and quality of life, current data are not sufficiently strong to withhold DAA therapy from patients with a history of HCC. However, delaying DAA therapy has been associated with a lower risk of recurrence in several studies.[5,13] This may allow for a longer duration of immunosurveillance for microscopic tumor clones as well as to verify HCC complete response, thereby minimizing the likelihood of misclassification bias. Given the unclear benefit of HCV treatment in patients with active HCC and lack of urgency for HCV therapy, we recommend confirming durable complete response of HCC by multiphase computed tomography (CT) or magnetic resonance imaging (MRI) for four to six months prior to initiating DAA therapy. We often perform more intensive surveillance monitoring for patients with recurrent HCC using multiphase CT or MRI every three months while the patient is on DAA therapy and during the subsequent six-month period. If patients remain recurrence free at that time, they can then return to multiphase CT or MRI every six months. However, this institutional practice is based primarily on theoretical concerns, with limited high-quality data to inform optimal surveillance algorithms in these patients.

In summary, recent data have demonstrated that IFN-free DAA therapy significantly decreases the risk of incident HCC, highlighting the safety of treating patients with HCV infection and no prior history of HCC. However, uncertainty still exists about the risk of HCC recurrence following DAA therapy, with large variations in reported HCC recurrence rates between studies and notable methodological limitations that make the studies difficult to interpret. Ongoing prospective studies should provide higher-quality data in the near future to better address the optimal timing and potential impact of HCV therapy on HCC recurrence risk. While awaiting those data, DAA therapy does not need to be withheld from patients with a history of HCC, but it can be delayed four to six months to ensure complete response and mitigate any potential risk of HCC recurrence.

Given the known benefits of HCV therapy, such as improvement in liver dysfunction and quality of life, current data are not sufficiently strong to withhold DAA therapy from patients with a history of HCC.

Key takeaways

- IFN-free DAA therapy for chronic HCV infection significantly decreases the risk of incident HCC in HCV-infected patients with or without cirrhosis, highlighting the benefit of treating these patients.
- There are conflicting data, with methodological limitations, about a potential increased risk of HCC recurrence after DAA therapy. Ongoing prospective studies should provide higher quality data to address this issue in the near future.
- While awaiting these data, we recommend confirming durable HCC complete response for four to six months by multi-phase CT or MRI scans before initiating DAA therapy.

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AND THE GUT

What do I need to know now?

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Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce pain and inflammation. Damage to the upper gastrointestinal (GI) tract remains the most common serious adverse event (AE) related to NSAID use; however, small bowel and colonic injury also have clinical consequences. Cardiovascular (CV)-related AEs of these drugs have further complicated an approach to optimize clinical outcomes. Clinicians must estimate individual risk for GI- and CV-related AEs, and then consider the impact of various risk modifiers — individual drug(s) and dose(s) — to estimate the overall risk to a patient when prescribing NSAIDs.

NSAID-induced upper GI injury develops due to a relative deficiency of mucosal prostaglandins that weakens the epithelial barrier, allowing acid-related ulceration. Mucosal repair is also prostaglandin dependent. Although the majority of prostaglandins are derived from cyclo-oxygenase (COX) 1, both COX-1 and COX-2 must be inhibited for ulceration to occur. Serious GI AEs of NSAID use include symptomatic gastric and duodenal ulcers; their complications — perforation and hemorrhage — may occur with acute or long-term therapy. In general, drugs with more prolonged and complete COX-1 inhibition will produce more ulcers and, due to their antiplatelet action, promote bleeding. The annual incidence of NSAID-related clinical upper GI events (complicated and symptomatic ulcers) is estimated to be between 2.5 and 4.5 percent, and the annual incidence rate of serious NSAID-related complications (perforation, hemorrhage, and obstruction) is approximately 1.0 to 1.5 percent.

Risk factors for NSAID-related AEs include the amount used, the type, dose, duration of use, and concomitant drug prescriptions such as antiplatelets (e.g., aspirin), anticoagulants, corticosteroids, or selective serotonin reuptake inhibitors. Non–drug-related risk factors include patient age, prior history of peptic ulcer, dyspepsia — particularly if it persists on antisecretory therapy — *Helicobacter pylori* infection status, and comorbidities.

The upper GI AEs of NSAIDs can be reduced in several ways — most effectively by discontinuing the drug, by selecting a less-toxic NSAID, or by adding a second drug. Introducing COX-2–selective NSAIDs revolutionized NSAID therapy by providing patients with effective control of inflammation accompanied by fewer ulcers and complication events. Adjunctive therapeutic options include H2-receptor antagonists (H2RAs), proton pump inhibitors (PPIs) and prostaglandin analogs — each of which possess varying effectiveness as protective agents; some cause additional challenges due to their own specific AEs. A recent *Cochrane* review concluded that standard doses of H2RAs should not be used for prophylaxis against NSAID-related toxicity. Double doses of H2RAs and standard doses of PPIs are effective at preventing duodenal and gastric ulcers (although PPIs are superior), thereby reducing NSAID-related dyspepsia; they are also better tolerated than misoprostol. In patients at high risk for GI events, a COX-2 inhibitor alone or a traditional NSAID in combination with a PPI offer similar but potentially insufficient protection from recurrent bleeding, and use of a COX-2 in combination with a PPI was recommended.

Use of NSAIDs can induce small intestinal and colonic injury with a wide spectrum of manifestations, from clinically silent mucosal injury and anemia to significant ulceration with overt bleeding, intestinal obstruction or perforation. Discontinuation of NSAIDs is the most effective management option. When choosing selective or nonselective NSAID formulations for the patient who requires anti-inflammatory therapy, a key practical consideration is whether NSAID-associated small intestinal injury is clinically relevant. CONDOR, a large, randomized trial, evaluated sustained-release diclofenac in combination with omeprazole (to reduce gastric and duodenal ulcers) compared with celecoxib. The results confirmed a low rate of symptomatic and complicated ulcers in both study groups; however, the presumed, small rate of intestinal blood loss was significantly less with study participants receiving the COX-2 inhibitor. Adjunctive misoprostol has also been shown to reduce damage in short-term studies in both the NSAID and aspirin settings.

A personalized approach to NSAID therapy is driven by assessment of an individual's risk of CV and GI diseases.

Both nonselective and COX-2–selective NSAIDs have been associated with an increased incidence of serious CV events, including myocardial infarction and death. Although theoretical reasons exist as to why COX-2 selective agents may be prothrombotic, the mechanisms remain incompletely understood. A recent meta-analysis has confirmed that CV risk is not unique to celecoxib, but comparable risks were also noted with diclofenac and possibly high-dose ibuprofen. Naproxen was not associated with increased CV adverse outcomes but had similar GI effects as other nonselective NSAIDs. Recently, the results of PRECISION, a trial of 24,081 patients randomly assigned celecoxib, naproxen or ibuprofen, were reported. During the trial, 68.8 percent of participants stopped taking the study drug, and 27.4 percent of them withdrew from the trial. The study authors concluded that no difference could be observed in the CV hazard ratio from the three NSAIDs; no evidence suggested that naproxen was safer than the other two drugs; and fewer serious GI events and renal-related AEs were observed in the participants assigned to celecoxib treatment. Many issues preclude these results in significantly altering our current understanding of the risk of NSAID use. The study population did not consist of individuals with a particularly high CV risk, and PPIs were given to everyone — but, similar to aspirin use, this therapy was not monitored. Pharmacologically equivalent doses of the NSAID were likely not used, biasing the results toward the safety outcomes observed in the celecoxib group.

A personalized approach to NSAID therapy is driven by the assessment of an individual's CV and GI risk. CV risk can be calculated by methods such as the Framingham score. Patients at high risk of CV events are those with established CV disease or, in those without established CV disease, an estimated 10-year CV risk of greater than 20 percent. For each patient, clinicians should consider the GI risk associated with treatment as well as the CV risk of the individual. The choice between GI sparing and increased CV risk must be considered, because it will influence the type of therapy, dose and duration of treatment. If small bowel blood loss is an additional consideration, then celecoxib, in the absence of aspirin use, may offer a specific treatment advantage. One size cannot fit all, and balancing the competing risk remains essential and challenging! ▯

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Telemedicine and the future

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As medical students, if we were lucky and trained in the right era, we were taught how to interact with patients in the clinic in a compassionate and professional manner so that patients would trust that we care about them and understand how to keep them well. As technology and reimbursement strategies evolved, barriers to this goal emerged, including lurking in the electronic medical record and the increasing pressure for shorter clinic visits. For patients, their clinic visit with us may have been the most important task they did that week, month or year. They may have taken a day off from work and lost wages, driven many miles, spent money on childcare, and worried about what they might hear, only to be shuffled in and out of the visit. I often worry that patients don't feel that they've gotten what they deserve from the commitment they made to come to the office. When I first learned about telemedicine, my initial reaction was that it would make all of this worse. But I've since discovered that this is wrong.

The term *telemedicine* is actually quite broad, because it is an umbrella term that includes telemonitoring, tele-education, teleconsulting and telecare. Telemonitoring refers to the monitoring of patients through mobile apps, phone calls or other reporting systems to "track" your patient. Tele-education includes webinars and otherr forms of online teaching. Teleconsultation refers to programs such as remote intensive care units and emergency departments (EDs) or real-time neurology consultation. Telecare is the patient–doctor interaction via video conferencing — and I am the most intrigued by this! Based primarily on watching *The Jetsons* (Warner Bros., Burbank, CA) as a kid, I was sure that health care could be successfully delivered remotely. Once technology caught up to us, an entire new way of being a doctor has emerged.

The Institute of Medicine's Triple Aim framework includes providing cost-effective care across a population and coupling that with an excellent patient experience. The newer Quadruple Aim framework adds to this by improving the clinician experience. These aims are difficult in day-to-day practice, but telemedicine can help. At Dartmouth-Hitchcock Medical Center in Lebanon, NH, we run a regular telemedicine clinic for patients with inflammatory bowel disease (IBD).[1] One-half of our patient population drives between two and four hours round trip for an office visit. It is probably difficult for most of you to think of the last time you drove this distance for a 20- to 30-minute conversation. Although it is easier for patients, telecare is at real risk of tainting the quality of care delivered. So, we studied this and asked patients. These patients consistently felt that they had enough time with their health care professional and that his or her physician understood their current disease state, and most preferred to continue with telecare visits rather than coming to the office. Quality metrics such as ED visits, hospital stays and steroid and narcotic use were no different than the metrics we gathered prior to instituting the tele-IBD clinic. This was all while saving costs, improving the patient experience and spreading our reach of care for our northern New England patient population. If we add in a satisfying and relatively low-burden (and fun) experience for the health care professional, then we also showed that the Quadruple Aim framework can be achieved with telemedicine.

Telemedicine still has a long way to go. I went through a tedious process of obtaining state licenses in Maine and Vermont (in addition to my regular license in New Hampshire); however, the laws are changing. I am not receiving relative value units (RVUs) or reimbursement for these visits, but keeping patients who live a long distance as part of our IBD Center brings far more downstream revenue that is lost from giving away the relatively nominal telemedicine charges. This, too, will change, and I suspect that, in the near future, telemedicine visits will be covered just like any office visit and generate RVUs.

The Jetsons first aired in 1962 and depicted a utopian society set in 2062, where people lived in houses in the sky, had talking dogs and drove flying saucers. Their far-out imagination is fun to consider, but their prediction of doctors taking care of patients using telemedicine came true nearly 50 years earlier than expected. There is no question that telemedicine will be part of our future. It is just a matter of learning how to use it properly and letting the regulatory and reimbursement aspects catch up to the technology. We must also respect the fact that technology is not perfect. *The Jetsons* also predicted video-assisted endoscopy with a device called the "peekaboo prober." It misdiagnosed George, who was told he was dying. It turned out the device was wrong: he lives on eternally.

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A cool alternative?

Cryotherapy

for Barrett's esophagus

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Endoscopic eradication therapies for Barrett's esophagus (BE) have evolved and improved in the last 20 years. We excise nodular disease using endoscopic mucosal resection (EMR) and treat flat BE with radiofrequency ablation (RFA) based on accumulated, abundant and high-quality scientific evidence that shows pooled RFA eradication rates of 91 and 78 percent for dysplasia and BE, respectively.[1] Why should we even think about cryotherapy in this era of RFA success?

How does cryotherapy work? The effects of cryotherapy begin with rapid intracellular and extracellular freezing, resulting in cell necrosis. Freezing causes cell membrane interruption, protein denaturation and changes in vascular flow, leading to the cessation of blood flow. Delayed effects of freezing include self-induced apoptosis. Unlike burning heat, the tissue injury continues over several days.

Up until 20 years ago, we used devices for the endoscopic delivery of compressed carbon dioxide gas (Polar Wand, GI Supply, Camp Hill, PA; Figure 1) or liquid nitrogen (the Cryospray system, truFreeze, CSA Medical, Lexington, MA; Figure 2) developed to treat BE and mucosal bleeding. In 2011, we became interested in a new form of cryoablation involving a disposable compliant balloon containing cryogen and nitrous oxide that would freeze mucosa on contact. It was called the cryoballoon focal ablation system (CbFAS; CryoBalloon Ablation System, C2 Therapeutics, Redwood City, CA; Figure 3). After years of repeated freeze–thaw cycles and tank changing with cryotherapy via carbon dioxide, we were ready for something different.

Why might we consider cryotherapy if we already use RFA, argon plasma coagulation, or both methods in our endoscopy units? Cryotherapy can be part of a multimodality approach when standard "burning" treatments have failed.[2,3] The pooled success rate for eliminating dysplasia after unsuccessful RFA in a recent meta-analysis involving nearly 3,800 patients treated with liquid nitrogen Cryospray was approximately 76 percent (95 percent confidence interval, 57 to 88).[4] Using CbFAS, our early experience also suggested a high success rate for dysplasia eradication (95 percent) in patients previously ablated.[3]

What about first-line treatment for neoplastic BE? In several retrospective and some prospective, nonrandomized studies using liquid nitrogen Cryospray, the success rate for eliminating high-grade dysplasia (HGD) in the setting of BE is between 81 and 94 percent, with a five-year durability rate of 93 percent.[5,6] Recently, we reported the results of the Coldplay 2 trial,[3] a prospective clinical study in which we used multifocal CbFAS in 41 patients with intramucosal cancer, HGD and low-grade dysplasia (LGD). We demonstrated complete eradication of dysplasia and intestinal metaplasia in 95 and 88 percent of study patients after one year and following an average of two procedures (for a BE length of at least 8 cm). Its safety profile appears to compare favorably with RFA. The stricture rate (9.7 percent) in the Coldplay 2 trial was comparable with that reported in other RFA trials with similar high rates of EMR (9 percent in the U.K. RFA registry[7] and 11.8 percent in the SURF trial[8]). Moreover, BE within pre-existing strictures following EMR/RFA may also be successfully treated without causing wall disruption or worsening of the stenosis.[3] This early experience with CbFAS is encouraging, but more research is needed. Large, multicenter trials are ongoing.

We could consider cryotherapy for other reasons. It seems to be a "gentler," less-painful ablative therapy than RFA. A small number (1.5 to 3.0 percent) of patients with RFA are hospitalized for severe pain. Pain is more common with RFA than cryotherapy.[9] Similarly, in the cryoballoon ablation trial, pain was mild following the procedure and was generally absent the following postoperative day.[3] Results from a Dutch study demonstrated that severe pain occurred in 46 percent of patients undergoing RFA after 48 hours compared with 18 percent of patients following cryoballoon ablation; the results also demonstrated significantly lower pain scores and the need for pain management (narcotic analgesics) for two weeks following cryotherapy.[8] We have used carbon dioxide cryotherapy for many years at our hospital, but we shifted to CbFAS because of the research, as well as for its several user-friendly features: no need for tank changing or tube decompression, short procedure times (no more than 30 minutes), no need for freeze–thaw cycling, and the lightweight, portable, lower-cost, handheld controller and disposable balloons that occupy a small storage space.

> Cryotherapy can be part of a multimodality approach when standard "burning" treatments have failed.

We might also consider cryotherapy for esophageal cancer. Cryotherapy injury can be applied to deeper levels by increasing the cryogen dose. This cannot be achieved by RFA, which superficially coagulates. Complete eradication of intramucosal adenocarcinoma in BE has been well described. Although endoscopic resection is still preferred for staging purposes and for the removal of nodules and known intramucosal adenocarcinoma, certain patients have recurrent disease, nonlifting lesions, positive deep margins from incomplete resections or disease that is unresponsive to standard therapies. Such patients may be likely to achieve cure without the need for esophagectomy.

Is cryotherapy a cool alternative to RFA? Stay tuned.... ▯

FIGURE 1.

During carbon dioxide cryotherapy, a polyethylene catheter releases compressed carbon dioxide gas and ice forms via the Joules-Thompson principle (expansion of gas leading to freezing temperature).

FIGURE 2.

Liquid nitrogen spray cryotherapy. The image shows a cap-fitted endoscope and ice forming from sprayed liquid nitrogen. Image courtesy of Arvind Trindade.

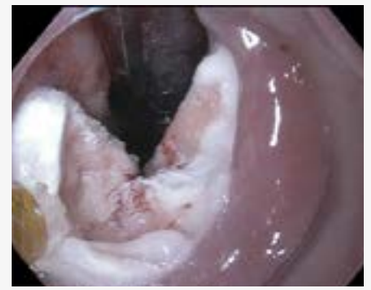
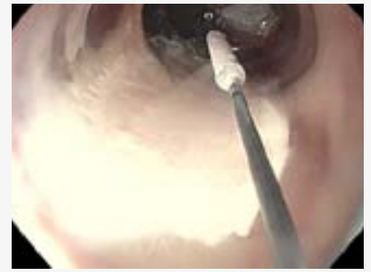


FIGURE 3.

Nitrous oxide cryotherapy (cryoballoon ablation) combined with the next-generation system. With the endoscope tip abutting the proximal balloon, the clinician can look through the endoscope.



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Where are we now?

Endoscopic bariatric therapies

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The obesity epidemic is upon us. The most recent data from the Behavioral Risk Factors Surveillance System on self-reported rates of obesity show that, even in the "fittest" states in the country, obesity is reported in one in five individuals.[1] The obesity epidemic has overwhelmed our practices, bariatric surgeons and health care systems. The direct and indirect costs of obesity and the metabolic complications of type 2 diabetes mellitus and nonalcoholic fatty liver disease continue to grow. The less-visible costs of the epidemic that include cardiovascular disease and the increased incidence of cancers, joint disease and other comorbidities also continue to grow. Despite this, payors are largely unwilling to provide uniform coverage of obesity care. Many patients find that their insurance will not cover lifestyle modification therapy, dietary visits related to obesity, medications for obesity, endoscopic bariatric therapy (EBT) or bariatric surgery. These factors in turn cause us as clinicians to miss opportunities to intervene before the complications of obesity are prominent, harmful and expensive to treat.

It has been two years since the U.S. Food and Drug Administration (FDA) approved modern EBT. Currently available EBT has been recently reviewed.[2] Its impact on the obesity epidemic has been, quite frankly, minimal. Patients wishing to undergo endoscopic therapy often pay out of pocket for the procedure, and, if complications arise, they also assume all the risk (and cost). Although centers across the U.S. have begun programs that incorporate EBT, the number of patients evaluated and treated remains small and likely will not significantly change until payors recognize EBT as a viable option for these patients.

Current offerings for patients interested in EBT include fluid- and gas-filled intragastric balloons, aspiration therapy and gastric restriction with approved tissue apposition devices — mainly endoscopic sleeve gastroplasty with an endoscopic suturing system. Many centers offering these techniques have incorporated them into a multidisciplinary approach to allow patients the ability to explore all options, from lifestyle modification therapy to bariatric surgery. EBT is the most effective when it is incorporated into a multidisciplinary approach that offers patients lifestyle modification therapy, which can include dietary counseling, supportive services from a navigator/life coach, physician follow-up and psychology resources. In addition to being trained in the procedural aspects of EBT, physicians using EBT to treat obesity and its related comorbidities must be well educated and trained in all aspects of obesity management. This can be accomplished through participation in either the AGA POWER[3] program or in the pursuit of formal certification in obesity medicine by participating in continuing medical education and passing a board certification examination.

Several types of EBT are approved for use in the U.S. The FDA has approved gas- and saline-filled intragastric balloons for implantation for a period of six months. Weight loss can persist after balloon removal. Additional studies are ongoing to demonstrate the amount of weight loss we can expect to see in clinical use. Gas-filled balloons continue to be better tolerated than those filled with saline, and additional efficacy data for gas-filled balloons is forthcoming. Reports of significant adverse events (AEs) due to saline-filled balloons have been reported to the FDA's Manufacturer and User Facility Device Experience database, although these numbers are small. These reports are not filtered, and, in some cases, the AEs may be difficult to attribute to EBT. Additional updates are anticipated from the FDA regarding the incidence of these AEs by the end of 2018.

Aspiration therapy continues to be offered at select centers, and additional longer-term data are now becoming available. These data suggest that the long-term use of this device by patients who adhere to treatment will result in significant weight loss and continued maintenance of that loss within two to four years.

Endoscopic sleeve gastroplasty has become more widely available both in the U.S. and abroad. A three-center study followed patients for more than 18 months and has demonstrated some durability of the weight loss seen with this technique as well. The results of other trials have demonstrated rates of efficacy and safety similar to these observed with the laparoscopic gastric band. A randomized trial comparing endoscopic with laparoscopic sleeve gastrectomy is currently underway. More single- and multi-center series with safety and efficacy data are expected to be released soon.

Several new devices and approaches are also moving through or toward FDA pivotal trial status. I hope that in my next article I will be able to highlight improved insurance coverage for obesity management, including EBT, as well as an expanded armamentarium of FDA-approved devices that we can use to help treat our patients.

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FOR TREATING CHRONIC HCV **EXPAND WHAT'S POSSIBLE**

INDICATION

EPCLUSA (sofosbuvir 400 mg/velpatasvir 100 mg tablets) is indicated for the treatment of adults with chronic hepatitis C virus (HCV) **genotype (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.

IMPORTANT SAFETY INFORMATION

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 EPCLUSA. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals (DAAs) and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are HBsAg positive, in patients with serologic evidence of resolved HBV, and also in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV DAAs may be increased in patients taking these other agents. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

Contraindications

- If EPCLUSA is used in combination with ribavirin (RBV), all contraindications, warnings and precautions, in particular pregnancy avoidance, and adverse reactions to RBV also apply. Refer to RBV prescribing information.

Warnings and Precautions

- **Serious Symptomatic Bradycardia When Coadministered with Amiodarone:** Amiodarone is not recommended for use with EPCLUSA due to the risk of symptomatic bradycardia, particularly in patients also taking beta blockers or with underlying cardiac comorbidities and/or with advanced liver disease. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir containing regimen. In patients without alternative, viable treatment options, cardiac monitoring is recommended. Patients should seek immediate medical evaluation if they develop signs or symptoms of bradycardia.
- **Risk of Reduced Therapeutic Effect Due to Concomitant Use of EPCLUSA with P-gp Inducers and/or Moderate to Potent Inducers of CYP2B6, CYP2C8 or CYP3A4:** Rifampin, St. John's wort, and carbamazepine are not recommended for use with EPCLUSA as they may significantly decrease sofosbuvir and/or velpatasvir plasma concentrations.

WHAT DOES SIMPLE DOSING LOOK LIKE?

1 TABLET ONCE A DAY

TAKEN WITH OR WITHOUT FOOD

The dosing information above does not include patients with decompensated cirrhosis (Child-Pugh B or C).

EPCLUSA HAS THE SAME 12-WEEK DOSING REGIMEN FOR MOST HCV PATIENTS REGARDLESS OF TREATMENT HISTORY, GENOTYPE (1-6), OR THE PRESENCE OF COMPENSATED CIRRHOSIS[1]

- Test all patients for evidence of current or prior HBV infection by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) before initiating HCV treatment with EPCLUSA[1]

IMPORTANT SAFETY INFORMATION

Adverse Reactions

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

Drug Interactions

- Coadministration of EPCLUSA is not recommended with topotecan due to increased concentrations of topotecan.
- Coadministration of EPCLUSA is not recommended with proton-pump inhibitors, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, efavirenz, and tipranavir/ritonavir due to decreased concentrations of sofosbuvir and/or velpatasvir.

Consult the full Prescribing Information for EPCLUSA for more information on potentially significant drug interactions, including clinical comments.

Please see Brief Summary of full Prescribing Information for EPCLUSA, including **BOXED WARNING**, on the following pages.

Compensated cirrhosis = Child-Pugh A, RBV = ribavirin, TE = treatment-experienced (subjects who have failed a peginterferon alfa + RBV–based regimen with or without an HCV protease inhibitor [boceprevir, simeprevir, or telaprevir]), TN = treatment-naïve

An increasing number of insurance plans cover EPCLUSA for GT 1 patients[2]

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sofosbuvir/velpatasvir
400 mg/100 mg tablets

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Brief Summary of full Prescribing Information. See full Prescribing Information. Rx Only.

BOXED WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS COINFECTED WITH HCV AND HBV

Test all patients for evidence of current or prior hepatitis B virus (HBV) infection before initiating treatment with EPCLUSA. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Monitor HCV/HBV coinfected patients for hepatitis flare or HBV reactivation during HCV treatment and post treatment follow up. Initiate appropriate patient management for HBV infection as clinically indicated.

INDICATIONS AND USAGE

EPCLUSA is indicated for the treatment of adult patients with chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection:

- Without cirrhosis or with compensated cirrhosis
- With decompensated cirrhosis for use in combination with ribavirin

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Risk of HBV Reactivation in Patients Coinfected with HCV and HBV: HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HCV direct acting antivirals and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients with serologic evidence of resolved HBV infection (HBsAg negative and hepatitis B core antibody (anti-HBc) positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct-acting antivirals may be increased in these patients. HBV reactivation is characterized as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection, reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increase in aminotransferase levels; and, in severe cases, increases in bilirubin levels, liver failure, and death can occur. Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment with EPCLUSA. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with EPCLUSA and during posttreatment follow up. Initiate appropriate patient management for HBV infection as clinically indicated.

Serious Symptomatic Bradycardia When Coadministered with Amiodarone: Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with a sofosbuvir-containing regimen. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir-containing regimen (HARVONI [ledipasvir/sofosbuvir]). Bradycardia has generally occurred within hours to days, but cases have been observed up to 2 weeks after initiating HCV treatment. Patients also taking beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease may be at increased risk for symptomatic bradycardia with coadministration of amiodarone. Bradycardia generally resolved after discontinuation of HCV treatment. The mechanism for this effect is unknown. Coadministration of amiodarone with EPCLUSA is not recommended. For patients taking amiodarone who have no other alternative viable treatment options and who will be coadministered EPCLUSA: Counsel patients about the risk of serious symptomatic bradycardia; and cardiac monitoring in an in-patient setting for the first 48 hours of coadministration is recommended, after which outpatient or self-monitoring of the heart rate should occur on a daily basis through at least the first 2 weeks of treatment. Patients who are taking EPCLUSA who need to start amiodarone therapy due to no other alternative viable treatment options should undergo similar cardiac monitoring as outlined. Due to amiodarone's long half-life, patients discontinuing amiodarone just prior to starting EPCLUSA should also undergo similar cardiac monitoring as outlined. Patients who develop signs or symptoms of bradycardia should seek medical evaluation immediately. Symptoms may include near-fainting or fainting, dizziness or lightheadedness, malaise, weakness, excessive tiredness, shortness of breath, chest pains, confusion, or memory problems.

Risk of Reduced Therapeutic Effect Due to Concomitant Use of EPCLUSA With Inducers of P-gp and/or Moderate to Potent Inducers of CYP: Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may significantly decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to potentially reduced therapeutic effect of EPCLUSA.

Risks Associated with RBV and EPCLUSA Combination Treatment: If EPCLUSA is administered with RBV, the warnings and precautions for RBV apply to this combination regimen. Refer to the RBV prescribing information for a full list of the warnings and precautions for RBV.

ADVERSE REACTIONS

Most common adverse reactions (greater than or equal to 10%, all grades) with EPCLUSA for 12 weeks were headache and fatigue; EPCLUSA and ribavirin for 12 weeks in patients with decompensated cirrhosis were fatigue, anemia, nausea, headache, insomnia, and diarrhea.

Subjects without Cirrhosis or with Compensated Cirrhosis: The adverse reactions data for EPCLUSA in patients without cirrhosis or with compensated cirrhosis were derived from three Phase 3 clinical trials (ASTRAL-1, ASTRAL-2, and ASTRAL-3) which evaluated a total of 1035 subjects infected with genotype 1, 2, 3, 4, 5, or 6 HCV, who received EPCLUSA for 12 weeks. The proportion of subjects who permanently discontinued treatment due to adverse events was 0.2% for subjects who received EPCLUSA for 12 weeks. The most common adverse reactions (at least 10%) were headache and fatigue in subjects treated with EPCLUSA for 12 weeks. Adverse reactions (all grades) reported in ≥5% of subjects receiving 12 weeks of treatment with EPCLUSA in ASTRAL-1 were: headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%). Of subjects receiving EPCLUSA who experienced these adverse reactions, 79% had an adverse reaction of mild severity (Grade 1). The adverse reactions observed in subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. Irritability was also observed in greater than or equal to 5% of subjects treated with EPCLUSA in ASTRAL-3.

Subjects Coinfected with HCV and HIV-1: The safety assessment of EPCLUSA in subjects with HCV/HIV-1 coinfection was based on an open-label trial (ASTRAL-5) in 106 subjects who were on stable antiretroviral therapy. The safety profile in HCV/HIV-1 coinfected subjects was similar to HCV mono-infected subjects. The most common adverse reactions (at least 10%) were fatigue (22%) and headache (10%).

Subjects with Decompensated Cirrhosis: The safety assessment of EPCLUSA in subjects infected with genotype 1, 2, 3, 4, or 6 HCV with decompensated cirrhosis was based on one Phase 3 trial (ASTRAL-4) including 87 subjects who received EPCLUSA with ribavirin for 12 weeks. On the first day of treatment with EPCLUSA with ribavirin, 6 subjects and 4 subjects were assessed to have Child-Pugh A and Child-Pugh C cirrhosis, respectively. The most common adverse reactions (all grades with frequency of 10% or greater) in the 87 subjects who received EPCLUSA with ribavirin for 12 weeks were fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%). Of subjects who experienced these adverse reactions, 98% had adverse reactions of mild to moderate severity. A total of 4 (5%) subjects permanently discontinued EPCLUSA with ribavirin due to an adverse event; there was no adverse event leading to discontinuation that occurred in more than 1 subject. Decreases in hemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were observed in 23% and 7% of subjects treated with EPCLUSA with ribavirin for 12 weeks, respectively. Ribavirin was permanently discontinued in 17% of subjects treated with EPCLUSA with ribavirin for 12 weeks due to adverse reactions.

Less Common Adverse Reactions Reported in Clinical Trials: *Rash*: In ASTRAL-1, rash occurred in 2% of subjects without cirrhosis or with compensated cirrhosis treated with EPCLUSA for 12 weeks and in 1% of subjects treated with placebo. In ASTRAL-4, rash occurred in 5% of subjects with decompensated cirrhosis treated with EPCLUSA with RBV for 12 weeks. No serious adverse reactions of rash occurred in either studies and all rashes were mild or moderate in severity. *Depression*: In ASTRAL-1, depressed mood occurred in 1% of subjects without cirrhosis or with compensated cirrhosis treated with EPCLUSA for 12 weeks and was not reported by any subject taking placebo. No serious adverse reactions of depressed mood occurred and all events were mild or moderate in severity.

Laboratory Abnormalities: *Lipase Elevations:* In ASTRAL-1, isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 3% and 1% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively and in 6% and 3% of subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3, respectively. In the Phase 3 trial of subjects with decompensated cirrhosis (ASTRAL-4), lipase was assessed when amylase values were ≥1.5xULN. Isolated, asymptomatic lipase elevations of greater than 3xULN were observed in 2% of subjects treated with EPCLUSA with ribavirin for 12 weeks. *Creatine Kinase:*

Brief Summary (cont.)

In ASTRAL-1, isolated, asymptomatic creatine kinase elevations of 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 2% and 1% of subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3, respectively. In the Phase 3 trial with decompensated cirrhosis (ASTRAL-4), isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1% of subjects treated with EPCLUSA with ribavirin for 12 weeks. *Indirect Bilirubin:* Increases in indirect bilirubin up to 3 mg/dL above baseline were noted among HIV-1/HCV coinfected subjects treated with EPCLUSA and an atazanavir/ritonavir-based antiretroviral regimen. The elevated indirect bilirubin values were not associated with clinical adverse events and all subjects completed 12 weeks of EPCLUSA without dose adjustment or treatment interruption of either EPCLUSA or HIV antiretroviral agents.

Postmarketing Experience: Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. *Cardiac Disorders:* Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiated treatment with sofosbuvir in combination with another HCV direct-acting antiviral. *Skin and Subcutaneous Tissue Disorders:* Skin rashes, sometimes with blisters or angioedema-like swelling; angioedema.

DRUG INTERACTIONS

Sofosbuvir and velpatasvir are substrates of P-gp and breast cancer resistance protein (BCRP) while GS-331007 (the predominant circulating metabolite of sofosbuvir) is not. Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP2B6, CYP2C8, or CYP3A4 (e.g., rifampin, St. John's wort, carbamazepine) may decrease plasma concentrations of sofosbuvir and/or velpatasvir, leading to reduced therapeutic effect of EPCLUSA. The use of these agents with EPCLUSA is not recommended. EPCLUSA may be coadministered with P-gp, BCRP, and CYP inhibitors. Velpatasvir is an inhibitor of drug transporters P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1. Coadministration of EPCLUSA with drugs that are substrates of these transporters may increase the exposure of such drugs. Fluctuations in international normalized ratio (INR) may occur in patients on concomitant warfarin; frequent monitoring of INR is recommended during EPCLUSA treatment and post-treatment follow-up.

Established and Potentially Significant Drug Interactions: The drug interactions are based on studies conducted with either EPCLUSA, the components of EPCLUSA (sofosbuvir and velpatasvir) as individual agents, or are predicted drug interactions that may occur with EPCLUSA. This list includes potentially significant interactions but is not all inclusive.

Alteration in Dose or Regimen May Be Recommended For The Following Drugs When Coadministered With EPCLUSA:

- **Acid Reducing Agents:** Velpatasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease concentration of velpatasvir. *Antacids:* Separate antacid and EPCLUSA administration by 4 hours. *H_2-receptor antagonists:* Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from EPCLUSA. *Proton-pump inhibitors:* Coadministration of omeprazole or other proton pump inhibitors is not recommended. If considered medically necessary to coadminister, EPCLUSA should be administered with food and taken 4 hours before omeprazole 20 mg. Use with other proton pump inhibitors has not been studied.
- **Antiarrhythmics (amiodarone; digoxin):** *Amiodarone*: Coadministration of amiodarone with a sofosbuvir-containing regimen may result in serious symptomatic bradycardia and is not recommended. Mechanism of effect is unknown. If coadministration is required, cardiac monitoring is recommended. *Digoxin*: Increased concentration of digoxin. Monitor digoxin therapeutic concentration during coadministration with EPCLUSA. Refer to digoxin prescribing information for monitoring and dose modification recommendations for concentrations increases of less than 50%.
- **Anticancers (topotecan):** Increased concentration of topotecan. Coadministration is not recommended
- **Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine):** Decreased sofosbuvir and velpatasvir concentrations leading to reduced EPCLUSA effect. Coadministration is not recommended.
- **Antimycobacterials (rifabutin; rifampin; rifapentine):** Decreased sofosbuvir and velpatasvir concentrations leading to reduced EPCLUSA effect. Coadministration is not recommended.
- **HIV Antiretrovirals (efavirenz; regimens containing tenofovir DF; tipranavir/ritonavir):**
  - *Efavirenz*: Decreased concentration of velpatasvir. Coadministration of EPCLUSA with efavirenz-containing regimens is not recommended.
  - *Regimens containing tenofovir disoproxil fumarate (DF)*: Due to increased tenofovir concentrations, monitor for tenofovir-associated adverse reactions. Refer to the prescribing information of the tenofovir DF-containing product for renal monitoring recommendations.
  - *Tipranavir/ritonavir*: Decreased sofosbuvir and velpatasvir concentrations leading to reduced EPCLUSA effect. Coadministration is not recommended.
- **Herbal Supplements (St. John's wort):** Decreased sofosbuvir and velpatasvir concentrations. Coadministration is not recommended.
- **HMG-CoA Reductase Inhibitors (rosuvastatin; atorvastatin):** *Rosuvastatin:* Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Rosuvastatin may be administered with EPCLUSA at a dose that does not exceed 10 mg. *Atorvastatin*: May be associated with increased risk of myopathy, including rhabdomyolysis. Monitor closely for HMG-CoA reductase inhibitor-associated adverse reactions, such as myopathy and rhabdomyolysis.

Drugs without Clinically Significant Interactions with EPCLUSA: Based on drug interaction studies conducted with the components of EPCLUSA (sofosbuvir or velpatasvir) or EPCLUSA, no clinically significant drug interactions have been observed with the following drugs. *EPCLUSA*: atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, raltegravir, or rilpivirine; *Sofosbuvir*: ethinyl estradiol/norgestimate, methadone, or tacrolimus; *Velpatasvir*: ethinyl estradiol/norgestimate, ketoconazole, or pravastatin.

USE IN SPECIFIC POPULATIONS

Pregnancy: If EPCLUSA is administered with RBV, the combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the RBV prescribing information. No adequate human data are available to establish whether or not EPCLUSA poses a risk to pregnancy outcomes.

Lactation: It is not known whether the components of EPCLUSA and its metabolites are present in human breast milk, affect human milk production, or have effects on the breastfed child. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for EPCLUSA and any potential adverse effects on the breastfed child from EPCLUSA or from the underlying maternal condition. If EPCLUSA is administered with RBV, the nursing mother's information for RBV also applies to this combination regimen. Refer to the RBV prescribing information.

Pediatric Use: Safety and effectiveness of EPCLUSA have not been established in pediatric patients.

Geriatric Use: Clinical trials of EPCLUSA included 156 subjects aged 65 and over (12% of total number of subjects in the Phase 3 clinical studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment of EPCLUSA is warranted in geriatric patients.

Renal Impairment: No dosage adjustment of EPCLUSA is required for patients with mild or moderate renal impairment. The safety and efficacy of EPCLUSA have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2) or end stage renal disease (ESRD) requiring hemodialysis. No dosage recommendation can be given for patients with severe renal impairment or ESRD. Refer to RBV prescribing information use of ribavirin in patients with renal impairment.

Hepatic Impairment: No dosage adjustment of EPCLUSA is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C).

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