SLAMDUNK DECISION?

Reviewing Endoscopic Eradication Therapy for Confirmed Low-Grade Dysplasia

By Stuart Spechler, MD, and Prasad Iyer, MD
In this issue

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The management of patients with Barrett’s esophagus and low-grade dysplasia remains a controversial area in GI and reminds me of the old debates of surgery versus continued surveillance for high-grade dysplasia. To provide some clarity for clinicians, AGA has recently published a clinical practice update dedicated to this subject. In this issue of AGA Perspectives, the topic of the management of low-grade dysplasia takes center stage and is debated by two distinguished authorities in the field, Dr. Stuart Spechler and Dr. Prasad Iyer. I think you will find the discussion by both to be enlightening and the points they make highlight the conundrum of low-grade dysplasia.

Pouchitis was an entity that did not exist when I was in GI fellowship training many years ago. The pathobiology of pouchitis and underlying management is addressed by another internationally recognized expert, Dr. Bo Shen of the Cleveland Clinic.

This issue of our magazine also tackles two common clinical problems today: the diagnosis of chronic pancreatitis and the management of refractory Helicobacter pylori \( (H. pylori) \) infection. Drs. Ahmad Anaizi and Darwin Conwell provide their approach to the diagnosis of chronic pancreatitis while Dr. Nimish Vakil offers practical and important insights into how to approach treatment of \( H. pylori \) infection, again emphasizing that old fashioned “triple therapy” is now of historical interest only.

Direct-acting antivirals have revolutionized the care of patients with HCV infection. Unfortunately, the cost of these agents is a barrier to obtaining them. Dr. Vincent Lo Re highlights some of these barriers, as well as strategies to overcome them. This issue is especially topical given the impending discussions around health-care access and financing that will likely emerge from Washington this year with a new Congress and administration.

Lastly, AGA Perspectives would like to introduce the readership to the work of the AGA Diversity Committee and the recent launch of the AGA Community networking forum, which provides an easily accessible, online communications platform for all AGA members to ask questions and contribute ideas.

I would like to wish each of you a happy and healthy 2017, and hope you enjoy this issue of our publication.

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SLAM DUNK DECISION?

Reviewing Endoscopic Eradication Therapy for Confirmed Low-Grade Dysplasia
For patients found to have low-grade dysplasia (LGD) in Barrett’s esophagus, two recent studies suggest that the decision between treating with radiofrequency ablation (RFA) or simply continuing endoscopic surveillance is a slam dunk for RFA. In a European, randomized trial of surveillance versus radio frequency ablation (SURF) for 136 patients who had LGD confirmed by expert pathologists, progression to high-grade dysplasia (HGD) or cancer was

**NOT A SLAM-DUNK DECISION**

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The primary goal of ablation in Barrett’s esophagus is to reduce progression to high-grade dysplasia (HGD) and esophageal adenocarcinoma (EAC). The decision to perform endoscopic therapy (with the goal to eliminate intestinal metaplasia), is based on the principles of: 1. documenting an elevated risk of progression, 2. demonstrating reduction in risk of progression using robust clinical studies, and 3. proving the cost effectiveness of this

**A SLAM-DUNK DECISION**

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Dr. Iyer has received research support from Exact Sciences, C2 Therapeutics and Intromedic Inc.
observed at three years in 26.5 percent of the surveillance group, but in only 1.5 percent of the RFA group \((P<0.001)\). These results favoring RFA so impressed the study's data and safety monitoring board that they terminated the trial early. A retrospective study of patients with LGD diagnosed by pathologists at three academic medical centers in the U.S. found progression to HGD or cancer occurred during a median follow-up of approximately 29 months in 36 (28.8 percent) of 125 patients who had endoscopic surveillance alone, but in only 1 (2.2 percent) of 45 patients treated with RFA \((\text{adjusted HR}=0.06; 95\% \text{ CI} \ 0.008-0.48)\). As straightforward as these results seem for RFA, the devil is in the details. One bedeviling detail is the remarkably high rate of neoplastic progression in the surveillance groups of both studies. Patients in the SURF trial's surveillance group developed cancer at a rate some 14-fold higher than that described in other large cohorts of patients with LGD. The reasons underlying the enormous disparities among studies on the natural history of LGD are not entirely clear, but a major factor appears to be differences in how study pathologists diagnose LGD. A number of investigations have documented poor inter-pathologist agreement on that diagnosis, and other studies suggest that “expert” pathologists will usually downgrade a diagnosis of LGD made by community pathologists. Studies of patients chosen by pathologists who eliminate the mild or equivocal cases of LGD likely will be skewed to include only those at the highest risk for neoplastic progression.

Because of the notoriously poor inter-observer agreement in grading dysplasia, all major GI society guidelines recommend that any diagnosis of dysplasia should be confirmed by an expert pathologist. While I have made this recommendation myself, I consider it untenable for several reasons. First, there are no consensus criteria to establish a pathologist as an “expert” in this area. Furthermore, some studies document poor inter-observer agreement in diagnosing LGD even among pathologists deemed experts in Barrett’s esophagus. Since a diagnosis of dysplasia is meant to indicate high cancer risk, the only unequivocal way to establish a pathologist’s expertise in this area is with a study documenting that patients whom that pathologist has diagnosed with dysplasia frequently develop cancer. By that criterion, there are very few “experts” in the world. Finally, even though the pathologists of the SURF trial and the aforementioned American study fulfill that stringent criterion for expertise in diagnosing LGD, approximately 30 percent of patients in the surveillance group of both studies had no dysplasia found on subsequent endoscopies. It is not clear whether that dysplasia truly regressed or simply was missed due to biopsy sampling error. Nevertheless, had those patients been treated with RFA, this finding would have been considered “complete eradication of dysplasia” (CE-D). Thus, spontaneous CE-D
The risk of progression in HGD has been estimated to be high at 7 percent a year (compared to 0.2-0.3 percent a year in those without dysplasia). Endoscopic therapy (combining endoscopic resection and ablation to eradicate intestinal metaplasia) has been shown to be successful in reducing the risk of progression to adenocarcinoma in those with HGD in two multicenter randomized trials with results of endoscopic therapy also being shown to be comparable to esophagectomy.\(^1,2\) Lastly, this approach has been shown to be cost effective when compared to esophagectomy in multiple modeling studies.

Low-grade dysplasia (LGD), on the other hand, has been somewhat of a challenge given limitations in making a robust histopathological diagnosis. Community pathologists may overcall a LGD diagnosis and even academic pathologists have poor inter-observer agreement in making this diagnosis. This has led to varying reports of natural history and estimates of progression, with some studies estimating the risk of progression in LGD to be similar to that of no dysplasia.

However, recent studies have shed more light on this situation. A meta-analysis including 24 studies with 2,694 cases, estimated the annual risk of progression in LGD to EAC to be 0.7 percent, and risk of progression to HGD or EAC to be 1.5 percent.\(^3\) The study also shed some light on the possibility of “non-LGD” cases diluting the risk of progression, by stratifying studies into two categories: those where the diagnosis of LGD was less than 15 percent of all Barrett’s esophagus diagnoses and those where the diagnosis of LGD was more than 15 percent of all Barrett’s diagnoses (indicating the possibility of over-diagnosis). The rate of progression in the former group was higher at 0.7 percent a year compared to 0.32 percent a year in the latter group. Additionally, several recent population-based studies from Europe have demonstrated that those diagnosed with LGD have a substantially higher risk of progression to EAC compared to those with no dysplasia.\(^4,5\)

Indeed, studies have shown that while the vast majority (greater than 70 percent) of those diagnosed with LGD in the community are down-staged to no dysplasia upon review by gastrointestinal pathologists with the risk of progression in those with confirmed LGD being substantially higher than those who are down-staged to no dysplasia.\(^6\) Confirmation of the LGD diagnosis by additional pathologists has also been associated with a higher risk of progression.

Most importantly we now have level one evidence from a multicenter, randomized controlled trial showing substantially reduced risk of progression to HGD or EAC in those with confirmed LGD when randomized to ablation versus endoscopic surveillance. Indeed, radiofrequency ablation (RFA) was
RFA does not eliminate the need for subsequent endoscopic surveillance and does not entirely eliminate the risk of neoplastic progression.

NO DUNK - CONTINUED FROM PAGE 6

occurs frequently, even in LGD diagnosed by expert pathologists.

Another detail calling into question the benefit of RFA for LGD is the lack of a clear demonstration that RFA improves patient outcomes. In the SURF trial, RFA significantly decreased the rate of neoplastic progression.1 However, that neoplastic progression involved submucosal invasion for only one patient in the surveillance group who was treated with esophagectomy and remained tumor-free at follow-up 37 months later. For the other 17 surveillance patients who exhibited neoplastic progression, it was to an intramucosal neoplasm that was both detected by surveillance and amenable to endoscopic treatment. In the retrospective American study, two patients (1.6 percent) in the surveillance group developed submucosal neoplasms, but the report provides no information on their outcomes.2 Furthermore, that study found that RFA was associated with a significant reduction in the neoplastic progression of LGD, but not in progression to adenocarcinoma specifically, and the authors acknowledged that selection bias might have influenced their findings. Thus, neither study has established that RFA is better than endoscopic surveillance (with treatment when neoplastic progression is documented) for preventing incurable cancers for patients with LGD.

Another disturbing detail is that RFA involves considerable expense and inconvenience, and some risk. Patients often require three or more expensive ablation sessions to eradicate their Barrett’s metaplasia. Adverse events caused by RFA were not rare in the SURF trial, in which 12 percent of patients developed esophageal strictures that required dilation.1 Furthermore, since recurrence of metaplasia occurs frequently after RFA, the procedure does not eliminate the need for regular endoscopic surveillance.10

In summary, the large majority of diagnoses of LGD in Barrett’s esophagus are made by community pathologists who often over-read dysplasia and, if the diagnosis is confirmed at all, it is often by a pathologist whose credentials as an expert are unestablished. The efficacy of RFA for preventing neoplastic progression of LGD has been demonstrated in only one randomized trial in which the rate of neoplastic progression in the control group was extraordinarily high, in which surveillance alone detected all progressors at a curable stage, and in which more than one-quarter of patients randomized to surveillance had no dysplasia detected on subsequent endoscopies. No study has established that RFA improves outcomes for patients with LGD, and RFA involves substantial expense, inconvenience and risk. RFA does not eliminate the need for subsequent endoscopic surveillance and does not entirely eliminate the risk of neoplastic progression. Despite all these caveats, I admit that I usually advise RFA for the treatment of LGD but I do not consider it a slam-dunk decision. Increased endoscopic surveillance is a very reasonable alternative.

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Taking into account all the recent evidence, it is not surprising that recent societal guidelines are recommending the consideration of endoscopic therapy in those with confirmed LGD as the preferred approach. Given the variation in the rates of progression, endoscopic surveillance can be offered as an option for those opting against endoscopic therapy. My approach to those presenting with confirmed LGD is to perform a careful endoscopic examination to exclude prevalent HGD or carcinoma and discuss both options (endoscopic therapy versus surveillance) with the patient. This involves explaining the need for multiple treatments, potential adverse effects, possibility of recurrence and need for continuing endoscopic surveillance. Evaluation should also focus on factors predicting a higher risk of progression: longer Barrett’s segments, prevalent LGD, multifocal LGD (LGD present at multiple levels of the Barrett’s segment) and those with nodularity. In those with potential high risk factors and those with a diagnosis of LGD, ablation is certainly a reasonable therapeutic option, given the accumulation of evidence supporting this strategy.

Ablation is certainly a reasonable therapeutic option given the accumulation of evidence supporting this strategy.

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WHAT’S NEW IN POUCHITIS?

Clinicians may have noticed that pouchitis is no longer a simple, antibiotic-responsive disease. Over the years, we have seen a growing number of patients with chronic antibiotic-refractory pouchitis (CARP). While the Asian “carp” fish has invaded our rivers and lakes, the CARP disease has become a threat to the wellness and even survival of the pouch in patients with restorative proctocolectomy.

The last half century has witnessed many advances on both the medical and surgical fronts. Ileal pouch-anal anastomosis (IPAA) has become the treatment of choice for patients with ulcerative colitis (UC) or familial adenomatous polyposis (FAP) who require colectomy. The main advantage of the surgery is that the patient can avoid a permanent ileostomy bag. On the other hand, the procedure is associated with various mechanical, inflammatory and functional complications, ranging from pouchitis to irritable pouch syndrome. While the majority of mechanical complications, such as stricture and anastomotic leaks, can be avoided in experienced hands, inflammatory complications, such as pouchitis, cuffitis and Crohn’s disease of the pouch, do not appear to be preventable.

UC can be cured, if the diseased large bowel is removed surgically (total proctocolectomy) and a permanent ileostomy is created. The “destructive” surgical procedure, similar to appendectomy, cholecystectomy and partial gastrectomy, alters the anatomy of the gut far less than IPAA, which is a “reconstructive” procedure. Reconstructive surgeries, from cosmetic facial procedures to weight reduction surgeries and now IPAA, significantly change the natural anatomy of a patient. After artificially or surgically changing human anatomy, we should be prepared for potential unwanted consequences. For example, de novo Crohn’s disease can occur in approximately 7 percent of patients who undergo a total proctocolectomy and IPAA for a well-defined preoperative diagnosis of UC. IPAA surgery may create a Crohn’s disease-friendly environment with altered bowel anatomy, surgical anastomosis and fecal stasis in genetically susceptible individuals. Could pouchitis also result from the change in anatomy and the subsequent alteration of bowel function?

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Dr. Shen has no conflicts to disclose.
No doubt, microbiota play an important role in the pathogenesis of pouchitis among published studies, in specific culprit microbiota or bacterial profiles, which are responsive for the initiation and progression of pouch inflammation. Dysbiosis as the initial triggering factors for pouchitis has been challenged as well.

The “Inside Out” vs. the “Outside In” Theories

No doubt, microbiota play an important role in the pathogenesis of pouchitis as well as IBD. The current theory holds that the alteration in the quantity or quality in gut microbiota leads to aberrant innate and adaptive immune responses in genetically susceptible individuals, causing mucosal or intramural inflammation in pouchitis and IBD (the “Inside Out” theory). This theory may not explain the distribution pattern of segmental disease in patients with Crohn’s disease or the sharp demarcation between the inflamed and non-inflamed parts of bowel in those with left-sided UC or UC proctitis. This theory could not explain why some patients with CARP responded to surgical revision or redo of the pouch; or why Clostridium difficile pouchitis and CARP are predominantly seen in male patients. It is possible that microbiota play a key role in the initial acute episode of pouchitis, and that the change in microbe in the development and evolution of chronic pouchitis may be secondary to local and systemic factors. IPAA surgery is technically demanding. Over the years, I have noticed that the frequency of pouchitis is far less in patients who received surgery from experienced colorectal surgeons. CARP is more commonly seen in male patients with significant weight gain since the surgery and visceral obesity. It appears that adipose tissue in the mesentery, along with its proinflammatory components of immune system. The breach of the human body between microbiota; between microbiota and host factors such as adipose tissue, mesenteric vasculature, play a key role in the pathogenesis of pouchitis, especially CARP. Under this circumstance, the alteration in microbiota or the microbiome in the pouch is a secondary event, the “outside in” theory. That may explain why patients CARP have no response to antibiotic therapy.

The “inside out” and “outside in” theories are not mutually exclusive in the pathogenesis of pouchitis or IBD and one theory may play a more dominant role in certain phenotypes of pouchitis over the other. Between microbiota and host factors appear to be bidirectional.

Pouchitis: A Spectrum of Diseases

Pouchitis is not a single disease entity and it represents a disease spectrum, with various etiology factors, pathogenetic pathways, disease phenotypes and disease courses. The interplay between genetic factors, fecal stasis, underlying immune-mediated disease process, and surgical alteration in the bowel anatomy with sutures and anastomosis contributes to the various forms of clinical phenotypes. Clinically, pouchitis has been classified into acute versus chronic pouchitis, based on the duration of symptoms; antibiotic-response versus antibiotic-dependent versus. Anti-bacterial-refractory based on the response to antibiotic therapy; acute versus relapsing versus. persistent, based on the pattern of disease activity; and idiopathic vs. secondary, based on the etiology. According to the current understanding of pathogenesis, pouchitis can be classified into three main categories: microbiota-associated pouchitis, immune-mediated pouchitis (primary sclerosing cholangitis-associated pouchitis and IgG4-associated pouchitis) and ischemia-associated pouchitis. There is a great overlap in the etiology and pathogenesis of different phenotypes of pouchitis, presumably representing “overlap syndrome of the pouch.” In addition, the etiological and pathogenetic factors may play different roles at different stages of pouchitis in a given patient.

The “Immune Thermostat” and Its Dialers

There is a definite ying-yang balance of the human body between microbiota; between microbiota and immune system; and between components of immune system. The breach of these delicate balances can result in various forms of disease conditions. Therefore, the human body has an immune thermostat that adjusts in response to extrinsic and intrinsic factors. The aberrant setting of immune thermostat can lead to disease. For the development of new disease or flare ups of underlying disease, the dialers for the change in the immune thermostat could be infection (e.g. post-infectious irritable bowel syndrome), bowel-altering surgery (e.g. post-colectomy enteritis syndrome), solid organ transplantation (e.g. post-liver transplant de novo IBD), stem cell transplantation (e.g. cord colitis syndrome) or medications (e.g. mycophenolate-associated IBD-like colitis and anti-tumor necrosis factors). On the other hand, these bowel surgeries, stem cell transplantations and biological agents have been successfully used to treat chronic inflammatory conditions of the gut, including Crohn’s disease and UC, by turning the immune thermostat in the right direction, at the right time. Therefore, those “dialers” are double-edged swords. While IPAA surgery may cause de novo Crohn’s disease, the procedure may also cure the patients with a preoperative diagnosis of Crohn’s disease-colectitis.

Could pouchitis also result from a aberrantly set “immune thermostat”? It is possible. The dialers of the thermostat to disease-oriented direction could be dysbiosis, pathogenic microbiota, fecal stasis, surgery-associated ischemia, mesenteric tension, visceral obesity, a foreign body (such as mesh used in the repair of incisional hernia), non-steroidal anti-inflammatory drugs or combination a few of these things. Then the strategy for the management of pouchitis should be designed beyond antibiotic therapy. Pouchitis, especially CARP, has recently been treated in non-traditional approaches, such as hyperbaric oxygen, anti-integrin, weight reduction and surgical pouch revision. Evidence still continues to emerge.

The heterogeneity of clinical presentations and underlying etiopathogenetic pathways prompt an individualized approach to the patients. A combined assessment of symptomology, distribution of endoscopic and histologic inflammation, laboratory tests and comorbid conditions, can usually point out the disease category the patient has: microbiota-associated pouchitis, immune-mediated pouchitis or IBD-like colitis and anti-tumor necrosis factor-associate psoriasis. On the other hand, these bowel surgeries, stem cell transplantations and biological agents have been successfully used to treat chronic inflammatory conditions of the gut, including Crohn’s disease and UC, by turning the immune thermostat in the right direction, at the right time. Therefore, those “dialers” are double-edged swords. While IPAA surgery may cause de novo Crohn’s disease, the procedure may also cure the patients with a preoperative diagnosis of Crohn’s disease-colectitis.

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HOW CAN WE BE SURE OF THE DIAGNOSIS OF CHRONIC PANCREATITIS?

Chronic pancreatitis has a wide spectrum of symptoms and severity, making it difficult to diagnose. While the advent of numerous radiographic, endoscopic and functional testing has certainly advanced our ability to reliably diagnose chronic pancreatitis, it can, at times, complicate diagnosis in an age of unclear interpretation of results. Given that this condition is not curable and treatment modalities are aimed at delaying progression and controlling symptoms, providers must be certain prior to diagnosing (“labeling”) patients with chronic pancreatitis. Diagnosis should follow a progressively invasive approach in a patient with a suspicious clinical presentation and risk factors that raise his or her pre-test probability of disease. Currently, the most widely used risk factor classification system is the Toxic Idiopathic Genetic Autoimmune Recurrent Obstructive system or TIGAR-O, and one approach for diagnosis follows the STEP-wise (survey tomography endoscopy pancreas function) algorithm.

Initial evaluation of a patient presenting with recurrent pancreatitis and abdominal pain should be a thorough office evaluation during which providers screen for weight loss, diabetes, jaundice and anorexia followed by laboratory testing of amylase, lipase, metabolic panel, fecal elastase-1, or serum trypsin and review of any previous imaging.
When the diagnosis remains unclear, pancreatic-function tests can be helpful to rule out chronic pancreatitis.

Once this is complete, imaging is appropriate starting with an abdominal contrast-enhanced computerized tomography (CT). This technique relies on changes to pancreatic parenchyma that are consistently seen in more advanced cases and may be absent in early chronic pancreatitis. Changes classically seen with CT include pancreatic calcifications, parenchymal atrophy or fibrosis, and dilation of the main pancreatic duct.2 In addition to visualizing these changes, CT is also helpful in detecting complications of chronic pancreatitis such as pseudo cysts, venous thrombosis and pancreatico-pleural fistulas. Finally, a CT should be performed in all patients to rule out a mass or malignancy.

In patients with equivocal CT scans, magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP) and secretin enhanced MRCP (sMRCP) should be obtained in cases where a high clinical suspicion for chronic pancreatitis remains. The advantage of an MRI is the increased sensitivity to pancreatic ductal abnormalities, as these changes typically precede glandular atrophy and are not typically seen using CT. In addition, these modalities evaluate for depressed signal intensities within the gland indicative of parenchymal atrophy, and when sMRCP is utilized, the evaluation of pancreatic duct compliance can be assessed. Definitive diagnosis of chronic pancreatitis can be made with MRI/MRCP when ductal irregularities are observed in both the main pancreatic duct as well as side branches. Cambridge-type grading criteria have yet to be established for MRCP but are generally used.

Endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography (ERCP) are more invasive measures that are at times used to assist in the diagnosis of chronic pancreatitis. The advantage of EUS is the superb parenchymal and ductal visualization of the pancreas. EUS criteria (standard or Rosemont) have been established for chronic pancreatitis. These include both parenchymal features (hyperechoic foci and strands, lobular contour, cysts) as well as ductal features (main duct dilation, irregularity, hyperechoic margins, visible side branches and stones). At least five of these standard EUS criteria need to be met prior to definitively diagnosing chronic pancreatitis (grade 3 recommendation). Fewer than five criteria can be seen in normal, asymptomatic patients and carry unclear significance. These cases should be correlated with imaging, pertinent risk factors as well as the patient’s clinical presentation.

ERCP has historically been used as a last line diagnostic tool in the work up of chronic pancreatitis once other modalities have been exhausted. It has been replaced by MRI imaging. Its diagnostic utility lies in defining the main pancreatic duct as well as its side branches. These changes are graded based on the Cambridge classification system. Two major limitations for use of ERCP in diagnosing chronic pancreatitis include procedural complications (such as acute pancreatitis) as well its inability to visualize the pancreatic parenchyma.

Pancreatic-function tests (PFTs) are defined as either direct or indirect. Indirect pancreatic function tests (serum trypsinogen, fecal elastase, fecal fat measurements) are often obtained at the start of the work up of chronic pancreatitis and are more likely to detect advanced cases of chronic pancreatitis. Direct pancreatic function tests which utilize secretin or cholecystokinin (CCK) stimulation, can help detect cases of chronic pancreatitis prior to development of exocrine gland dysfunction or clarify subtle radiographic abnormalities. Its greatest use is as an adjunct diagnostic tool when the diagnosis is not definitive with CT or MRI. It is best at ruling out chronic pancreatitis in patients with chronic abdominal pain.

In summary, the diagnosis of chronic pancreatitis can be elusive in early disease. The evaluation should follow a combined approach from a noninvasive to a more invasive diagnostic algorithm (STEP-wise). Radiologic testing should be obtained to assess definitive changes consistent with chronic pancreatitis as well as ruling out a mass. In equivocal cases, one should progress to endoscopic approaches (such as EUS) to evaluate for moderate to significant changes. When the diagnosis remains unclear, pancreatic function tests can be helpful to rule out chronic pancreatitis. Further studies of biomarkers (cytokines, mRNA and proteins) are needed to diagnose early chronic pancreatitis before definitive changes develop.

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The availability of highly efficacious and tolerable all-oral direct-acting antiviral (DAA) regimens for the treatment of chronic hepatitis C virus (HCV) infection in 2014 was met with a mix of joy and relief among both HCV providers and chronically infected patients. Finally we could do away with the low cure rates and toxicities associated with interferon-based therapy. The clinical benefits and cost-effectiveness of achieving a cure for chronic HCV with these agents provided a strong rationale for treating all chronically infected patients with DAA therapy. Consequently, the American Association for the Study of Liver Diseases and Infectious Diseases Society of America jointly developed national HCV treatment guidelines that recommended DAA treatment for all chronic HCV-infected patients. The ability to cure chronic HCV in nearly all infected people made the prospect of eliminating HCV in the US possible.

However the high costs of DAAs led public and private insurers to restrict access to these medications. Soon after their release, DAAs were classified as “specialty” drugs and placed on the highest cost-sharing tier. Insurers established criteria for prescription approval, such as evidence of advanced liver fibrosis and consultation with a specialist. Many insurers required a specified period of abstinence from use of alcohol and illicit drugs, and some requested drug screening to confirm sobriety. State Medicaid programs were especially aggressive at rationing DAA therapies. Two reports in 2015 highlighted the restrictions on reimbursement of DAAs across these programs. One of these reviews found that 74 percent of Medicaid programs require evidence of advanced hepatic fibrosis or cirrhosis, 69 percent requested prescription by or consultation with a specialist and 50 percent required a period of abstinence from drugs and alcohol. No reviews have reported restrictions to DAA therapies among U.S. Medicare and commercial insurance beneficiaries.
As a result of the varying restrictions imposed by insurers, obtaining approval for DAA prescriptions became labor-intensive. Insurers required that DAA prescriptions undergo prior authorization, a pre-approval process to determine if the patient meets insurer-specific criteria for HCV treatment. Providers now spend considerable time and effort to complete these prior authorization requests and face the possibility of insurer denials and the need for subsequent appeals. This onerous process has dissuaded many health-care providers from trying to obtain DAA treatment for chronic HCV-infected patients.6

Two recent studies have highlighted the current limitations in access to DAA therapy. One prospective cohort study determined the incidence of absolute denial of DAA prescription (defined as lack of approval of prescription fill by the insurer) by type of insurance (Medicaid, Medicare, commercial insurance) among chronic HCV-infected patients who had a DAA prescription submitted to a specialty pharmacy covering Delaware, Maryland, New Jersey and Pennsylvania between November 1, 2014 and April 30, 2015.7 Among 2,321 patients prescribed a DAA regimen, 16.2 percent were absolutely denied. The most common reasons for absolute denial were insufficient information to assess medical need (35.5 percent) and lack of medical necessity (35.0 percent). Notably, absolute denial was significantly more common among patients covered by Medicaid (46.3 percent) than by Medicare (5.0 percent) or commercial insurance (10.2 percent).

A separate cohort study evaluated the incidence and reasons for not starting Sofosbuvir-based treatment among chronic HCV-infected patients prescribed these regimens between December 2013 and September 2014 within Trio Health.8 Among 3,841 patients, 8 percent did not start the prescribed Sofosbuvir-containing regimen. Insurance-related processes and financial reasons accounted for 81 percent of the non-starts. Consistent with the prior report, the incidence of non-start was higher among Medicaid beneficiaries (35 percent) compared to patients covered with Medicare (2 percent) or commercial insurance (6 percent).

Although denials of DAA treatment hit Medicaid beneficiaries particularly hard, restrictions in access to these regimens also affected patients covered by Medicare and commercial health insurance. Through the first three quarters of 2015, 25 percent of Medicare beneficiaries and 39 percent of patients with commercial insurance sought DAA treatment access assistance through the Patient Advocate Foundation’s Hepatitis C CareLine.6 Further, after approval of the prescription, the copay may be too high to permit proceeding with treatment.9 Thus access to DAA treatment has also been challenging for patients covered by Medicare and commercial health insurance.

These limitations in access to DAA therapy have been frustrating for HCV providers. Patients denied access to new DAA therapies can have continued progression of hepatic fibrosis and remain at risk for the development of cirrhosis, end-stage liver disease and hepatocellular carcinoma. Denial of DAA treatment allows ongoing HCV-associated inflammation, which might increase the risk of extra-hepatic complications. Further, failure to treat and cure chronic HCV can lead to continued risk of HCV transmission. Finally, denial of DAA therapy can promote anxiety and stress about HCV disease progression and may provoke distrust among patients of the healthcare system and their HCV providers.

Thus the groundswell against the restrictions in DAA reimbursement and the lack of access to HCV treatment has been growing, and stakeholders have used the above evidence to galvanize support for increasing access to these regimens. Given the disparity in access to DAA therapies among Medicaid beneficiaries, the Centers for Medicare and Medicaid Services notified state Medicaid directors on November 5, 2015, that restricting access to DAs based on cost containment violates federal law. This notification prompted class action lawsuits and threats of legal action against some state Medicaid programs. In February 2016, chronic HCV-infected patients in the state of Washington initiated a class-action lawsuit against the state’s Medicaid agency to expand access to DAA therapies after the agency rationed these therapies to only those with advanced hepatic fibrosis or cirrhosis. On May 27, 2016, the federal district court ordered that access to DAA treatment be provided without regard to the extent of liver fibrosis. In addition, in March 2016, attorneys notified Delaware Division of Medicaid and Medical Assistance officials that unless it immediately agreed to remove existing restrictions to DAA therapies from its Medicaid policy, Delaware would face a federal class action lawsuit. On June 3, 2016, Delaware Medicaid issued a formal policy change stating that as of January 2018, DAs will be approved for all chronic HCV-infected patients regardless of fibrosis stage. On September 19, 2016, the American Civil Liberties Union initiated a class-action lawsuit against Colorado’s Medicaid program, seeking a permanent injunction barring the state from denying access to DAs.

Recently voluntary improvements in access to DAA therapy have occurred within a variety of settings. This February, the Department of Veterans Affairs, the nation’s largest integrated health-care system, agreed to cover DAA treatment without restrictions. In April New York State Drug Utilization Review Board voted to allow Medicaid recipients in fee-for-service plans to receive coverage for all DAs regardless of hepatic fibrosis stage, and a few other states have followed suit.

Thus over the past several months, progress has been made in improving access to DAA therapies for chronic HCV. However major restrictions in access to these agents remain in place within many public and private health plans across the U.S. Researchers must provide additional data on the limitations in access to DAAs, confirm the cost effectiveness of HCV treatment for all patients and evaluate the outcomes of rationing policies on patient outcomes. Additionally, stakeholders must use this evidence to advocate for improved access to DAAs and solutions need to continue to be negotiated between insurers and pharmaceutical companies. These actions are necessary to achieve the goal of elimination of chronic HCV.

References


HOW TO APPROACH REFRACTORY H. PYLORI
Standard triple therapy is becoming obsolete as clarithromycin resistance rates rise.

R efractory is a term used to describe something that is difficult to treat or cure. *H. pylori* infection can be refractory to treatment for a number of reasons. The refractoriness may not be real. Successfully cured patients are sometimes referred to specialists because of positive serology tests. A stool antigen test or a breath test rapidly resolves this issue. The patient may not adhere to the treatment regimen. In some randomized controlled trials, 30 percent of failures were attributed to poor adherence with the regimen. I spend time describing the anticipated side-effects: diarrhea with amoxicillin and altered taste with clarithromycin to avoid premature discontinuation of the treatment regimen, which can lead to treatment failure and emergence of resistance. When adherence drops below 80 percent, treatment failure is likely and patients who are not adherent with one treatment regimen are often not adherent with subsequent ones. Misguided attempts to reduce the duration of treatment, reduce side effects by decreasing anti-microbial doses are physician-driven causes of apparent refractoriness.

Anti-microbial resistant strains of *H. pylori* are increasing in prevalence in the U.S. In a small recent study of US Veterans, only half of the *Helicobacter pylori* strains tested were susceptible to commonly used antibiotics and approximately one in three were resistant to at least one antibiotic. Half of the 65 strains studied were susceptible to all five antibiotics tested, 31 percent were resistant to levofloxacin, 20 percent were resistant to metronidazole 16 percent were resistant to clarithromycin, 0.8 percent were resistant to tetracycline, and none were resistant to amoxicillin. European studies have shown that levofloxacin resistance rises rapidly when it becomes widely used in the community and this is why I don’t use this regimen much although some guidelines recommend it as a second line treatment. In vitro testing for anti-microbial sensitivity is not widely available in the U.S. PCR based methods are promising but well-validated assays are still not widely available in the U.S.

Standard triple therapy is becoming obsolete as clarithromycin resistance rates rise. I no longer recommend this regimen as a first-line treatment. I think that every doctor who treats *H. pylori* (particularly those who still use triple therapy) should have some measure of the outcome of treatment in their population. Testing patients for cure a month or more after treatment ends using a urea breath test or a stool antigen test is an easy way of determining whether your first line treatment still works. I like bismuth based quadruple therapy for 14 days as a primary regimen. It’s quite inexpensive if the drugs are purchased separately. A single capsule preparation is also available, combining all three anti-microbials but the cost is higher and insurance coverage varies. In patients who cannot or will not take bismuth, I use non-bismuth quadruple therapy for 14 days. Extending the duration of treatment to 14 days improves eradication rates but I fully expect that some patients will not make it beyond 10 days and I like the additional buffer. If I prescribe treatment for 10 days and the patient takes it for seven days, I know results will be unacceptable. A single open-label US trial reported an 89 percent eradication rate with the LOAD therapy (levofloxacin, omeprazole, nitazoxanide, and doxycycline) but I think it needs additional validation before I can recommend or use it.

Patients sent to me when triple and quadruple therapy fail, are a challenge. These patients often have multi-drug resistant strains. An exception is amoxicillin because resistance to this organism is so rare. In these patients I think the option of high dose PPI with amoxicillin is a good one (rabeprazole 20 mg or esomeprazole 20 mg and amoxicillin 750 mg, four times a day for 14 days). It has been studied in Asia with excellent results in patients failing traditional treatment regimens (90–95 percent). Esomeprazole and Rabeprazole have better results in high dose dual therapy and therefore I choose one of them. If I lived in Asia, I would choose vonoprazan in acid inhibitors have shown an improvement in eradication rates in Japan with traditional anti-microbials and may be the next development in eradication for the rest of the world. We await a drug designed specifically for *H. pylori* eradication and tailored for conditions in the stomach where it needs to work. In conclusion, if triple and quadruple therapy fail, I turn to treatment with high dose proton pump inhibitor and amoxicillin and if that fails, rifabutin triple therapy.
Diversity is who we are. From our DNA to our interaction with the world around us, it’s through diversity that we can interpret our individuality and gauge our inclusivity. Diversity transcends race, ethnicity and gender, to which it is most commonly associated, and is the very fabric of our nation and planet.

As a member of AGA I am proud of our diversity and with every Digestive Disease Week® (DDW) conference I attend, I am reminded of it. It is the pulse of our organization. Throughout the history of AGA, this pulse has strengthened and our leadership is devoted to making it stronger by cultivating diversity of thought and people.

This commitment spawned the genesis of the Diversity Committee (formerly known as the
we can strengthen our efforts towards increasing diversity in academic advancement, retention and leadership succession within the field of GI and throughout our GI societies. The AGA Diversity Committee is one thread within this intricate fabric. It is only through the united front of all AGA members and members of the other GI societies that we can continue to move beyond settling for the cliché of diversity and instead progress purposefully towards improving the landscape of our workforce and reconciling the disparities in GI health in our communities.

This year, the Diversity Committee devised AGA's first policy on diversity:

AGA is committed to diversity, which is an inclusive concept that encompasses race, ethnicity, national origin, religion, gender, age, sexual orientation and disability. We strive to cultivate diversity within the organization at all levels, including governance, committee structure, staffing, and program and policy development. We are committed to the following goals intended to reflect the interests of the diverse patient population we serve:

1. Promotion of diversity within the practice of gastroenterology and in the individual care of patients of all backgrounds.
2. Recruitment and retention of GI providers and researchers from diverse backgrounds and the support of the advancement of their careers.
3. Elimination of disparities in GI diseases through community engagement, research and advocacy.

It is through this commitment that we will improve the digestive health of our communities and cultivate a GI workforce that more accurately reflects the demographics of our diverse patient populations. As of August 2016, fewer than 6 percent of AGA members self-identified as African American, American Indian/Alaskan Native, Hispanic or multi-racial. Only 22 percent were female. This is comparable to the demographic distribution of gastroenterologists across the U.S. as determined by the American Medical Association.

The Diversity Committee leads AGA's involvement or is an active participant in several key initiatives aimed at addressing these gaps. One initiative is the Investing in the Future (IITF) Program that started in 2011 as a collaboration between AGA and the American Society for Gastrointestinal Endoscopy, with funding from the National Institutes of Health (Grant# R25DK096968). IITF is aimed at increasing the representation of minorities in GI through the engagement of medical students and residents from underrepresented groups. This includes formal presentations and a hands-on endoscopy simulation facilitated by gastroenterologists. The IITF has held 27 such presentations involving over 2,200 students, seven institutions, and 19 national or regional conferences.

A separate offering, the IITF Student Research Program, supports undergraduate and medical students for an eight-to-10-week research project with an AGA member. AGA has supported 10 students annually. Additionally, AGA has supported the participation of underrepresented minority investigators in the biennial AGA-AASLD Academic Skills Workshop.

There is ample opportunity for improvement, however. Certainly, we can begin by ensuring that we understand the needs of all of our membership, including our LGBTQIA (lesbian, gay, bisexual, transsexual, queer, intersex, asexual) and disabled members for whom we currently have no data reference. Additionally, we can strengthen our efforts towards increasing diversity in academic advancement, retention and leadership succession within the field of GI and throughout our GI societies. The AGA Diversity Committee is one thread within this intricate fabric. It is only through the united front of all AGA members and members of the other GI societies that we can continue to move beyond settling for the cliché of diversity and instead progress purposefully towards improving the landscape of our workforce and reconciling the disparities in GI health in our communities.

**Figure 1. Distribution of gastroenterologists in the U.S. by race/ethnicity.**

![Figure 1](image)

**REFERENCES**

GET TO KNOW AGA COMMUNITY

AGA Community is an online forum, library and directory that launched in April 2016, providing a secure, AGA member-only network to connect colleagues based on their professional interests. The social platform creates a progressive year-round forum for collaboration with peers outside of the conference, lab, classroom or clinic.

It has naturally evolved into a sounding board for physicians and researchers alike, with case-based questions and journal-club type inquiries fluctuating throughout posts.

You’ve probably seen the de-identified patient cases in the forum — clinicians bring forward their questions regarding specific and often unusual cases. With the vast breadth and depth of experience among AGA members, physicians get a varied and valuable second opinion for these cases and other questions that may come up in their day-to-day.

The AGA Community has also uncovered controversial and original topics by working hand-in-hand with AGA Perspectives, spurring a healthy dialogue with the potential to augment the future of the GI field. For example, Paul Moayyedi, MB, CHB, PhD, MPH, AGAF, authored a piece for the August/September 2016 issue of AGA Perspectives on the adverse effects of proton pump inhibitors (PPIs), comparing some recent studies with the rise of reality television.

The article sparked a discussion among members in the AGA Community and raised additional questions for clinicians to consider: “On the other hand, don’t you feel that PPIs are being grossly overprescribed?” “How about good old H2 blockers?” “What is the place for H2 antagonist in stopping PPIs or as primary treatment for non-erosive reflux symptoms?”

This natural connection between AGA Perspectives and AGA Community creates a platform for the voices of opposition, innovators, pioneers and leaders alike. The give and take has proven that you don’t have to agree with what’s being shared, and that voicing your thoughts and opinions strengthens the forum’s ability to move the field forward. As Cellular and Molecular Gastroenterology and Hepatology (CMGH) Associate Editor Jim Goldenring, MD, PhD, AGAF, mentioned in a recent CMGH column, healthy scientific discourse and an exchange of ideas ultimately can enrich the GI field.

An example of this is a conversation about injuries to the endoscopist. Posted anonymously in the beginning of May, the post notes that 89 percent of gastroenterologists obtain musculoskeletal injuries and brings up a concern for the careers of endoscopists everywhere. The member asks “Besides ergonomics, is it worth looking at preventative measures that endoscopists can take to minimize and prevent injuries?”

The resounding response to this discussion, which is one of the top five discussions in the forum to date, was that GIs aren’t taught about the biomechanics of repetitive movement injuries and that this subject needs to be studied in more detail. This helped AGA leadership recognize the importance of this issue and led them to create a working group to support the cause.

Recent conversations have exposed honest sentiments on maintenance of certification (MOC) and the future of the board exam. With the American Board of Internal Medicine’s ongoing announcements to change MOC, both AGA members stepped up to the mic to address next steps, concerns and objectives to keep clinicians informed. Don’t forget: When you share your thoughts in the forum, you’re speaking directly to decision makers on issues that impact your day-to-day, whether it’s a large issue such as MOC or something on a smaller scale, like local-level payor issue or your opposing view on the latest AGA Perspectives counterpoint article.

Hopefully by this point you’ve visited community.gastro.org, but if you’re still unsure or perhaps questioning what you can add to the discussion forum, you’re not alone. Staff and leaders have received helpful feedback from members — specifically early career GIs — who question what they can add to a discussion when an expert in the field has already chimed in. To include early career GIs and create a safe space to ask questions, we’re creating a separate group for fellows, trainees and GIs who are within 7 years out of their fellowship program.

The Early Career Group — scheduled to launch this Spring — will host a calendar of relevant deadlines and conferences, regular Ask-Me-Anything sessions with subject-matter experts, and a library of webinars, articles and tip sheets. The forum will feature virtual events to discuss patient cases and high-impact research, and a career corner will consolidate resources that outline what to expect during the job search, tips and supplementary résumé tools.

We hope to see your questions and opinions in the AGA Community forum in 2017. You can start with your thoughts on endoscopic eradication therapy for confirmed low-grade dysplasia. Which side are you on?

REFERENCES
Research Funding Opportunity

The AGA Research Foundation will award over $2 million in research funding to support researchers in gastroenterology and hepatology.

**JAN. 6, 2017**
- AGA-Elsevier Pilot Research Award ($25,000)
- AGA-Elsevier Gut Microbiome Pilot Research Award ($25,000)
- AGA-Medtronic Research and Development Award in Technology ($31,000)

**JAN. 13, 2017**
- AGA Microbiome Junior Investigator Award ($60,000)
- AGA-Pfizer Pilot Research Award in Inflammatory Bowel Disease ($30,000)
- AGA-Rome Foundation Functional Gastroenterology and Motility Pilot Research Award ($50,000)

**JAN. 20, 2017**
- AGA-Caroline Craig Augustyn and Damian Augustyn Award in Digestive Cancer ($40,000)
- AGA-June and Donald O. Castell, MD, Esophageal Clinical Research Award ($25,000)

**FEB. 3, 2017**
- AGA Investing in the Future Student Research Fellowship ($5,000)

Learn more and register for free at [www.gastro.org/research-funding](http://www.gastro.org/research-funding).

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AGA Regional Practice Skills Workshops

Trainees and early-career GIs — get insight from GI leaders on navigating the various practice options and developing an action plan to achieve your career goals. You’ll also be able to explore topics rarely discussed during fellowship.

- Health-Care Reform/MACRA
- Financial Management
- Contract Negotiations
- Employment Models

Learn more and register for free at [www.gastro.org/psw](http://www.gastro.org/psw).
Fostering Innovation and Technology in Digestive and Metabolic Diseases: A Conference for Inventors, Investigators, and Investors

Explore critical elements impacting how GI technology evolves from concept to reality, including what it takes to obtain adoption, coverage and reimbursement in today’s health-care environment.

REGISTER AT techsummit.gastro.org

April 13 & 14
Boston Intercon, Boston, MA

Developed in collaboration with SAGES.

Engage your patients in their health care

Improve your patient care with AGA’s new patient education materials. They are free to members, easy to access and easy to understand.

For more information, visit patientinfo.gastro.org.
A CURE FOR EVERY TYPE

Patients of any HCV genotype can now be cured with a sofosbuvir-based, once-daily single-tablet regimen\(^1,2\)

**HARVONI** is the #1 prescribed treatment for HCV GT 1 patients in the US\(^3,4,5\).

**NOW APPROVED EPCLUSA** is the first and only pan-genotypic single-tablet regimen for patients with chronic HCV\(^2\)

- 94%-99% overall cure (SVR12) rates in GT 1 subjects with HARVONI (ION-1, -2, -3)\(^1\)
- 99% and 95% overall cure rates in GT 2 and GT 3 subjects, respectively, with EPCLUSA (ASTRAL-2, -3)\(^2\)

**INDICATIONS**

**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.

**Study Designs\(^1,2\)**
The HARVONI clinical trial program evaluated the efficacy and safety of 8 or 12 weeks of HARVONI \pm \text{RBV} in HCV GT 1 TN subjects without cirrhosis (ION-3; N=647) and 12 or 24 weeks of HARVONI \pm \text{RBV} in GT 1 TN (ION-1; N=865) and GT 1 TE (ION-2; N=440) subjects with or without cirrhosis.

The EPCLUSA clinical trial program (ASTRAL-1, -2, -3; N=1558) evaluated the efficacy and safety of 12 weeks of EPCLUSA in TN and TE HCV GT 1-6 subjects with or without cirrhosis.

See full study information on following pages.

Cure = 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\(^1,2\).

Cirrhosis = compensated cirrhosis (Child-Pugh A). RBV = ribavirin, TE = treatment-experienced (patients who have failed a peginterferon alfa + RBV-based regimen \pm \text{an HCV protease inhibitor}), TN = treatment-naïve

\(^a\)IMS Weekly NPA\(^\text{TM}\) Market Dynamics\(^\text{TM}\) from week-ending 11/14/14–4/1/16.

Please see Brief Summary of full Prescribing Information for HARVONI and EPCLUSA on the following pages.
Achieving SVR is considered a virologic cure. 5

CONTRAINDICATIONS

Virologic response (SVR12) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment. 1

HARVONI for 12 weeks.

TN subjects (N=647) without cirrhosis were randomized to receive HARVONI for 8 weeks, HARVONI + RBV for 8 weeks, or

TE subjects (N=440) with or without cirrhosis were randomized to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks,

ION-1: TN subjects (N=865) with or without cirrhosis were randomized to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks,

HARVONI DELIVERED HIGH CURE (SVR12) RATES IN A BROAD RANGE OF GT 1 SUBJECTS1

97% OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS1

(n=1042/1079)

HARVONI IS THE ONLY HCV TREATMENT THAT OFFERS AN 8-WEEK COURSE OF THERAPY1

• The recommended treatment duration for HARVONI is 12 weeks for TN GT 1 patients with or without cirrhosis. Eight weeks can be considered for TN GT 1 patients without cirrhosis who have pre-treatment HCV RNA <6 million IU/mL1

• HARVONI is RBV-free, regardless of prior HCV treatment history, the presence of compensated cirrhosis, or GT 1a or 1b subtype1

• No baseline resistance testing is required with HARVONI1

• No hepatic or hematologic monitoring is required when HARVONI is used alone1

• Adverse reactions (all grades) reported in ≥5% of GT 1 subjects receiving 8, 12, or 24 weeks of treatment with HARVONI (in ION-3, ION-1, and ION-2): fatigue (13%-18%), headache (11%-17%), nausea (6%-9%), diarrhea (3%-7%), and insomnia (3%-6%)1

HARVONI Study Designs: randomized, open-label trials in GT 1 subjects1

ION-1: TN subjects (N=865) with or without cirrhosis were randomized to receive HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks.

ION-2: TE subjects (N=440) with or without cirrhosis were randomized to receive 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 were randomized to receive 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 (SVR12) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the cessation of treatment.1 Achieving SVR is considered a virologic cure.1

Cirrhosis = compensated cirrhosis (Child-Pugh A), RBV = ribavirin, SOF = sofosbuvir, TE = treatment-experienced (patients who have failed a peginterferon alfa + RBV–based regimen with or without an HCV protease inhibitor), TN = treatment-naive

IMPORTANT SAFETY INFORMATION FOR HARVONI AND EPCLUSA

CONTRAINDICATIONS

• If HARVONI or 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

• Risk of Serious Symptomatic Bradycardia When Sofosbuvir Is Coadministered with Amiodarone and Another HCV Direct Acting Antiviral: Amiodarone is not recommended for use with HARVONI or 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. 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 Use with P-gp Inducers and/or Moderate to Potent Inducers of CYP: Rifampin, St. John’s wort and carbamazepine are not recommended for use with HARVONI or with EPCLUSA, P-gp inducers may significantly decrease ledipasvir, sofosbuvir and/or velpatasvir plasma concentrations. Moderate to potent inducers of CYP2B6, CYP2C8 or CYP3A4 may significantly decrease sofosbuvir and/or velpatasvir plasma concentrations. See what’s possible at hcp.harvoni.com
Achieving SVR is considered a virologic cure.

- Risk of Serious Symptomatic Bradycardia When Sofosbuvir Is Coadministered with Amiodarone and Another HCV

WARNINGS AND PRECAUTIONS

IMPORTANT SAFETY INFORMATION FOR HARVONI AND EPCLUSA

peginterferon alfa + RBV–based regimen with or without an HCV protease inhibitor), TN = treatment-naïve

Cirrhosis = compensated cirrhosis (Child-Pugh A), RBV = ribavirin, SOF = sofosbuvir, TE = treatment-experienced (patients who have failed a

HARVONI for 12 weeks.

ION-3:

HARVONI for 24 weeks, or HARVONI + RBV for 24 weeks.

ION-2:

ION-1:

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

1

- The adverse reactions observed in subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. In ASTRAL-3, irritability was observed in ≥5% of subjects treated with EPCLUSA.

98% OF GT 1-6 SUBJECTS OVERALL ACHIEVED A CURE ACROSS THREE PHASE 3 TRIALS

n=1015/1035; ASTRAL-1, -2, -3)

- GT 1-6 patients take 12 weeks of RBV-free EPCLUSA

- No baseline resistance testing is required with EPCLUSA

- No hepatic or hematologic monitoring is required when EPCLUSA is used alone

- Adverse reactions (all grades) reported in ≥5% of subjects receiving 12 weeks of treatment with EPCLUSA

ASTRAL-1): headache (22%), fatigue (15%), nausea (9%), asthenia (5%), and insomnia (5%)²

- The adverse reactions observed in subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. In ASTRAL-3, irritability was observed in ≥5% of subjects treated with EPCLUSA²

EPCLUSA Study Designs: randomized trials in TN and TE subjects without cirrhosis or with compensated cirrhosis

ASTRAL-1: double-blind, placebo-controlled trial in GT 1, 2, 4, 5, or 6 subjects (N=740). GT 1, 2, 4, or 6 subjects were randomized 5:1 to receive EPCLUSA or placebo for 12 weeks; GT 5 subjects received EPCLUSA for 12 weeks. Overall SVR was 99% (n=618/624).

ASTRAL-2: open-label trial in GT 2 subjects (N=266). Subjects were randomized to receive EPCLUSA or SOF + RBV for 12 weeks.

ASTRAL-3: open-label trial in GT 3 subjects (N=552). Subjects were randomized to receive EPCLUSA for 12 weeks or SOF + RBV for 24 weeks. SVR12 for EPCLUSA ranged from 89% (TE with cirrhosis) to 98% (TN without cirrhosis).

These studies did not include subjects with decompensated cirrhosis. Sustained virologic response (SVR12) was the primary endpoint and was defined as HCV RNA <15 IU/mL at 12 weeks after the cessation of treatment.² Achieving SVR is considered a virologic cure.

IMPORTANT SAFETY INFORMATION FOR HARVONI AND EPCLUSA

ADVERSE REACTIONS

- The most common adverse reactions (≥10%, all grades) with HARVONI were fatigue, headache, and asthenia

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

DRUG INTERACTIONS

- Coadministration of HARVONI or EPCLUSA is not recommended with oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifapentine, and tiperanavi/ritonavir due to decreased concentrations of sofosbuvir, ledipasvir and/or velpatasvir.

- Coadministration of EPCLUSA is not recommended with proton-pump inhibitors or efavirenz due to decreased concentrations of velpatasvir; or with topotecan due to increased concentrations of topotecan.

- Coadministration of HARVONI is not recommended with co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of tenofovir; or with simeprevir due to increased concentrations of ledipasvir and simeprevir; or with rosuvastatin due to increased concentrations of rosuvastatin.

Consult the full Prescribing Information for HARVONI or for EPCLUSA for more information on potentially significant drug interactions, including clinical comments.
Among the 162 subjects with genotype (GT) 1, 4, 5, or 6 infection.

WARNINGS AND PRECAUTIONS:
Serious Symptomatic Bradycardia When Coadministered with Amiodarone: Postmarketing cases of symptomatic bradycardia, as well as fatal cardiac arrest and cases requiring pacemaker intervention, have been reported when amiodarone is coadministered with HARVONI. 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 HARVONI is not recommended. For patients taking amiodarone who will be coadministered HARVONI and patients taking HARVONI who need to start amiodarone, who have no other alternative, viable treatment options; and due to amiodarone's long half-life for patients discontinuing amiodarone just prior to starting HARVONI: 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 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 Use With P-gp Inducers: Concomitant use may significantly decrease ledipasvir and sofosbuvir concentrations and may lead to a reduced HARVONI effect. Use of HARVONI with P-gp inducers (e.g., rifampin or St. John's wort) is not recommended.

Risks Associated with RBV Combination Treatment If HARVONI is administered with RBV, the warnings and precautions for RBV, in particular pregnancy avoidance, apply to this combination regimen. Refer to the RBV prescribing information.

Related Products Not Recommended: Use of HARVONI with products containing sofosbuvir is not recommended.

ADVERSE REACTIONS:
Most common adverse reactions (incidence greater than or equal to 10%, all grades) were fatigue, headache and asthenia.

GT 1 Subjects with Compensated Liver Disease (With and Without Cirrhosis): The safety assessment of HARVONI was based on pooled data from three randomized, open-label Phase 3 clinical trials (ION-1, ION-3 and ION-2) in subjects who received HARVONI once for 8, 12 or 24 weeks. Adverse events led to permanent treatment discontinuation in 0.4%, 0.3% and 1% and of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. Adverse Reactions (adverse events assessed as causally related by the investigator; all grades; majority Grade 1) observed in at least 5% of subjects receiving HARVONI for 8, 12 or 24 weeks, respectively, were: fatigue (16%, 13%, 18%), headache (11%, 14%, 17%), nausea (6%, 7%, 9%), diarrhea (4%, 3%, 7%), and insomnia (3%, 5%, 6%). Direct comparison across trials should not be made due to differing trial designs.

GT 4, 5 or 6 Subjects with Compensated Liver Disease (With or Without Cirrhosis): The safety assessment of HARVONI was also based on pooled data from three open-label trials (Study 1119, ION-4 and ELECTRON-2) in 118 subjects who received HARVONI once daily for 12 weeks. The safety profile in this group was similar to that observed in subjects with chronic HCV GT 1 infection with compensated liver disease. The most common adverse reactions occurring in at least 10% of subjects were asthenia (18%), headache (14%) and fatigue (10%).

Liver Transplant Recipients and/or Subjects with Decompensated Cirrhosis: The safety assessment of HARVONI + RBV in liver transplant recipients and/or those who had decompensated liver disease was based on pooled data from two Phase 2 open-label clinical trials including 336 subjects who received HARVONI + RBV for 12 weeks. Subjects with Child-Pugh-Turcotte (CPT) scores greater than 12 were excluded from the trials. The adverse events observed were consistent with the expected clinical sequelae of liver transplantation and/or decompensated liver disease, or the known safety profile of HARVONI and/or RBV. Decreases in hemoglobin to less than 10 g/dL and 8.5 g/dL during treatment were observed in 38% and 13% of subjects treated with HARVONI + RBV for 12 weeks, respectively. RBV was permanently discontinued in 11% of subjects treated with HARVONI + RBV for 12 weeks.

Liver Transplant Recipients with Compensated Liver Disease: Among the 174 liver transplant recipients with compensated liver disease who received HARVONI + RBV for 12 weeks, 2 (1%) subjects permanently discontinued HARVONI due to an adverse event. Subjects with Decompensated Liver Disease: Among the 162 subjects with decompensated liver disease (pre- or post-transplant) who received HARVONI + RBV for 12 weeks, 7 (4%) subjects died, 4 (2%) subjects underwent liver transplantation, and 1 subject (<1%) underwent liver transplantation and died during treatment or within 30 days after discontinuation of treatment. Because these events occurred in patients with advanced liver disease who are at risk of progression of liver disease including liver failure and death, it is not possible to reliably assess the contribution of drug effect to outcomes. A total of 4 (2%) subjects permanently discontinued HARVONI due to an adverse event.

Less Common Adverse Reactions Reported in Clinical Trials (less than 5% of subjects receiving HARVONI in any one trial): These events have been included because of their seriousness or assessment of potential causal relationship. Psychiatric disorders: depression (including in subjects with pre-existing history of psychiatric illness). Depression, particularly in subjects with pre-existing history of psychiatric illness, occurred in subjects receiving sofosbuvir containing regimens. Suicidal ideation and suicide have occurred in less than 1% of subjects treated with sofosbuvir in combination with RBV or pegylated interferon/RBV in other clinical trials.

Laboratory Abnormalities: Bilirubin Elevations: Elevations of greater than 1.5x ULN were observed in 3%, <1% and 2% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively and in the SIRIUS trial, 3%, 11% and 3% of subjects with compensated cirrhosis treated with placebo, HARVONI + RBV for 12 weeks and HARVONI for 24 weeks, respectively. Lipase Elevations: Transient, asymptomatic elevations of greater than 3x ULN were observed in less than 1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively and in the SIRIUS trial, 1%, 3% and 9% of subjects with compensated cirrhosis treated with placebo, HARVONI + RBV for 12 weeks and HARVONI for 24 weeks, respectively. Creatine Kinase: was not assessed in Phase 3 trials ION-1, ION-3 or ION-2 of HARVONI but was assessed in the ION-1 trial. Isolated, asymptomatic creatine kinase elevations of greater than or equal to 10x ULN was observed in 1% of subjects treated with HARVONI for 12 weeks in ION-4 and has also been previously reported in subjects treated with sofosbuvir in combination with RBV or peginterferon/RBV in other clinical trials.
**Brief Marketing Summary (cont.)**

**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 initiate treatment with HARVONI during post approval use of HARVONI. **Skin and Subcutaneous Tissue Disorders:** Skin rashes, sometimes with blisters or angioedema-like swelling.

**DRUG INTERACTIONS:**

Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters. Ledipasvir and sofosbuvir are substrates of P-gp and BCRP while the inactive sofosbuvir metabolite GS-331007 is not. P-gp inducers (e.g., rifampin or St. John’s wort) may decrease ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect; use of HARVONI with P-gp inducers is not recommended.

**Established and Potentially Significant Drug Interactions:** The drug interactions described are based on studies conducted in healthy adults with either HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI. 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 HARVONI:**

**Acid Reducing Agents:** Ledipasvir solubility decreases as pH increases. Drugs that increase gastric pH are expected to decrease ledipasvir concentration. **Antacids:** Separate HARVONI and antacid administration by 4 hours. H₂-receptor antagonists: Doses comparable to famotidine 40 mg twice daily or lower may be administered simultaneously with or 12 hours apart from HARVONI. **Proton-pump inhibitors:** Doses comparable to omeprazole 20 mg or lower can be administered simultaneously with HARVONI under fasted conditions.

**Antiarrhythmics (amiodarone; digoxin):** Amiodarone: Coadministration of amiodarone with HARVONI 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 digoxin concentration. Monitor digoxin therapeutic concentration during coadministration with HARVONI.

**Anticonvulsants (carbamazepine; phenytoin; phenobarbital; oxcarbazepine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

**Antimycobacterials (rifabutin; rifampin; rifapentine):** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

**HIV Antiretrovirals:**

Regimens containing tenofovir disoproxil fumarate (DF) without a HIV protease inhibitor/ritonavir or cobicistat: Due to increased tenofovir concentrations, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.

Regimens containing tenofovir DF and a HIV protease inhibitor/ritonavir or cobicistat (e.g., atazanavir/ritonavir or cobicistat + emtricitabine/tenofovir DF; darunavir/ritonavir or cobicistat + emtricitabine/tenofovir DF, lopinavir/ritonavir + emtricitabine/tenofovir DF): The safety of increased tenofovir concentrations has not been established. Consider alternative HCV or antiretroviral therapy to avoid increases in tenofovir exposures. If coadministration is necessary, monitor for tenofovir-associated adverse reactions. Refer to VIREAD or TRUVADA prescribing information for renal monitoring recommendations.

Elvitegravir/cobicistat/emtricitabine/tenofovir DF: The safety of increased tenofovir concentrations has not been established. Coadministration is not recommended.

**Tipranavir/ritonavir:** Decreased ledipasvir and sofosbuvir concentrations leading to reduced HARVONI effect. Coadministration is not recommended.

**HCV Products (simeprevir):** Increased ledipasvir and simeprevir concentrations. Coadministration is not recommended.

**Herbal Supplements (St. John’s wort):** Decreased ledipasvir and sofosbuvir concentrations. Coadministration is not recommended.

**HMG-CoA Reductase Inhibitors (rosuvastatin):** Significant increase in rosuvastatin concentrations and risk of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended.

**Drugs without Clinically Significant Interactions with HARVONI:**

Based on drug interaction studies conducted with HARVONI or its components, no clinically significant drug interactions have been observed or are expected when used with the following drugs: abacavir, atazanavir/ritonavir, cyclosporine, darunavir/ritonavir, dolutegravir, efavirenz, elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, raltegravir, rifapentine, tacrolimus, or verapamil.

Consult the full Prescribing Information prior to and during treatment with HARVONI for potential drug interactions and use with certain HIV antiretroviral regimens; this list is not all inclusive.

**USE IN SPECIFIC POPULATIONS:**

**Pregnancy:** If HARVONI 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 for more information on use in pregnancy. No adequate human data are available to establish whether or not HARVONI poses a risk to pregnancy outcomes.

**Lactation:** It is not known whether ledipasvir or sofosbuvir, the components of HARVONI, or their metabolites are present in human breast milk, affect human milk production or have effects on the breastfed infant. Studies in rats have demonstrated that ledipasvir and GS-331007 are secreted in milk without clear effect on nursing pups. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for HARVONI and any potential adverse effects on the breastfed infant from HARVONI or from the underlying maternal condition. If HARVONI is administered with RBV, the lactation information for RBV also applies to this combination regimen. Refer to the RBV prescribing information.

**Females and Males of Reproductive Potential:** If HARVONI is administered with RBV, the information for RBV with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to RBV prescribing information.

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

**Geriatric Use:** Clinical trials of HARVONI included 225 subjects aged 65 and over (9% of total number of subjects in the 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 HARVONI is warranted in geriatric patients.

**Renal Impairment:** No dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in patients with severe renal impairment (eGFR <30 mL/min/1.73m²) 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 regarding use in patients with renal impairment.

**Hepatic Impairment:** No dosage adjustment of HARVONI is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B, or C). Clinical and hepatic laboratory monitoring, as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with HARVONI and RBV.

**References:**

EPCLUSA® (sofosbuvir 400 mg and velpatasvir 100 mg) tablets, for oral use

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

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 RBV is contraindicated. Refer to the RBV prescribing information.

WARNINGS AND PRECAUTIONS: Serious Symptomatic Bradycardia When Sofosbuvir is Coadministered with Amiodarone and Another HCV Direct-Acting Antiviral: Postmarketing cases of symptomatic bradycardia and cases requiring pacemaker intervention have been reported when amiodarone is coadministered with sofosbuvir in combination with daclatasvir or simeprevir. A fatal cardiac arrest was reported in a patient taking amiodarone who was coadministered a sofosbuvir-containing regimen (daclatasvir/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, conduction, 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. The use of these agents with EPCLUSA is not recommended.

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.

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 RBV 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 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 RBV for 12 weeks. All 87 subjects had Child-Pugh B cirrhosis at screening. On the first day of treatment with EPCLUSA with RBV, 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 RBV 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 RBV 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% subjects treated with EPCLUSA with RBV for 12 weeks, respectively. RBV was permanently discontinued in 17% of subjects treated with EPCLUSA with RBV 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 RBV for 12 weeks. Creatine Kinase: 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 ASTRAL-4, isolated, asymptomatic creatine kinase elevations greater than or equal to 10xULN were reported in 1% of subjects treated with EPCLUSA with RBV 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 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.
Brief Summary (cont.)

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.

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. H₂-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 EPCLUSA may result in serious symptomatic bradyarrhythmia 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 concentration 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: Expected increase in atorvastatin concentrations and risk of atorvastatin associated 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 ritiravir; Sofosbuvir: ethyl estradiol/norgestimate, methadone, or tacrolimus; Velpatasvir: ethyl estradiol/norgestimate, ketoconazole, or pravastatin.

Consult the full Prescribing Information prior to and during treatment with EPCLUSA for potential drug interactions and use with certain HIV antiretroviral regimens; this list is not all inclusive.

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 for more information on RBV-associated risks of use during pregnancy. 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 infant. When administered to lactating rats, velpatasvir was detected in the milk of lactating rats and in the plasma of nursing pups without effects on the nursing pups. 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 infant from EPCLUSA or from the underlying maternal condition. If EPCLUSA is administered with RBV, the lactation information for RBV also applies to this combination regimen. Refer to the RBV prescribing information.

Females and Males of Reproductive Potential: If EPCLUSA is administered with RBV, the information for RBV with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to 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/1.73m²) 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 regarding use of RBV 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). Clinical and hepatic laboratory monitoring (including direct bilirubin), as clinically indicated, is recommended for patients with decompensated cirrhosis receiving treatment with EPCLUSA and RBV.
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