WHICH SIDE ARE YOU ON?

Debating The Use of Imaging Surveillance vs. EUS-FNA for Asymptomatic Pancreatic Cysts

PAGE 4

By James M. Scheiman, MD, AGAF, and Nuzhat A. Ahmad, MD.
**AGA Perspectives**

**Vol. 12, No. 4 | August/September 2016**

**In this issue**

**WHICH SIDE ARE YOU ON?**

Debating the Use of Imaging Surveillance vs. EUS-FNA for Asymptomatic Pancreatic Cysts

**PAGE 4**

**AGA PERSPECTIVES DEPARTMENTS**

Classifieds........................................................................................................... 15

**Advances in HCV Therapy: Beginning of the End?**

Joseph K. Lim, MD, AGAF .................................................. 10

**Exploring the Growing Role of GI in the Management of Obesity**

Christopher T. Thompson, MD, MSc, FACQ, FAGSE ......................... 12

**Will Research Consortium Mean Progress in Eosinophilic GI Disorders?**

Glenn T. Furuta, MD, AGAF, and Marc E. Rotenberg, MD, PhD ............... 14

**Where Does Vedolizumab Fit in IBD Treatment?**

Edward V. Loftus Jr, MD, AGAF ........................................... 16

**How Close Are We? Utilizing Big Data to Improve Clinical Research and Care**

Manish Gala, MD, and Andrew T. Chan, MD, MPH .................................. 18

**A Welcome Note From the New Editors of Gastroenterology**

Douglas A. Corley MD, PhD, MPH, and Richard M. Peek Jr., MD, AGAF ....... 20

**AGA PERSPECTIVES DEPARTMENTS**

Classifieds........................................................................................................... 15

**EDITOR**

Gary W. Falk, MD, MS, AGAF

**AGA Institute Staff**

Emily Poe

**Director of Communications**

Matthew A. Nickols

**Director of Digital Media**

Chris Kacsmarek

**KEYWORD INDEX**

**AGA Perspectives Editor**

Gary W. Falk, MD, MS, AGAF

**Officers of the AGA Institute**

Timothy C. Wang, MD, AGAF (President)

Sheila E. Crowe, MD, AGAF (Immediate Past President)

David A. Labrum, MD, AGAF (President-Elect)

Francis M. Giardiello, MD, AGAF (Vice President)

Richard M. Peek Jr, MD, AGAF (Past President)

**Note From the Editor**

A key goal of AGA Perspectives is to provide our readership with crisp updates delivered by content experts in rapidly evolving areas of gastroenterology and hepatology. Optimal management of asymptomatic pancreatic cystic lesions is one such area of debate. The publication of the AGA guideline on the management of asymptomatic pancreatic cysts last year led to three accompanying commentaries in the April 2015 issue of Gastroenterology. To address this controversy, Drs. Jim Scheiman and Nuhat Ahmad present an engaging point-counterpoint debate focusing on the use of EUS/FNA versus continued imaging surveillance for a patient with an asymptomatic 3 cm pancreatic cystic lesion.

One of the greatest clinical advances in recent years has been the rapid growth of effective treatments for HCV. However is this disease now technically 'solved'? Dr. Joseph Lim provides his perspective on unresolved dilemmas in HCV in this era of rapidly acting, highly effective antiviral therapy.

The role of vedolizumab in the treatment of both ulcerative colitis and Crohn’s disease also continues to evolve. How does this agent best fit into current clinical practice? Expert guidance on the current place of this agent in IBD treatment is provided by the Mayo Clinic’s Dr. Ed Loftus.

We also provide updates in this issue about the impact of the new Consortium of Eosinophilic GI Disorders Research (CEGIR) Group by Drs. Glen Furuta and Marc Rotenberg, who are well-recognized experts in the field and lead this novel effort. Additionally, Dr. Chris Thompson highlights the developing role of the gastroenterologist in the epidemic of obesity, a significant niche of GI clinical practice that will continue to increase in coming years. In the technology sphere, Drs. Manish Gala and Andrew Chan provide their insights into the realm of big data in gastroenterology and medicine in general.

Finally, the new editors of our flagship journal, Gastroenterology, introduce themselves to the readership and inform us of their vision for the publication over the next five years.

I hope you enjoy reading these timely and quick-hitting updates on a wide variety of common, evolving issues facing today’s gastroenterologists and hepatologists.

Best,

Gary W. Falk, MD, MS, AGAF

**EDITOR**

@DrGaryFalk

**Correction:** In the June/July 2016 issue of AGA Perspectives, the article “New Options On The Horizon For HBS-D” by Ron Schey, MD, FACQ, included text from a previous AGA Perspectives article (three paragraphs) that should not have been included. For the updated version of this article, please visit agaperspectives.gastro.org.
Pancreatic cystic lesions are widely identified now because of the increased use and improved resolution of cross-sectional imaging. The majority of these cysts are found in older patients, often when imaging is performed for an unrelated condition such as our patient with a suspected kidney stone. This leads to tremendous anxiety for the patient and provider to characterize the etiology of the cyst, and most importantly, its malignant potential. While there are small numbers of very uncommon cyst types in the pancreas, most cysts are either non-neoplastic or benign without malignant potential, such as pseudocysts, serous cystadenomas, or lesions that are neoplasms with some risk for malignancy. These include mucinous cystic neoplasms (MCN), and intraductal papillary mucinous neoplasms (IPMN). Historical literature has suggested that pseudocysts were the most common cysts, but it is clear now with improved imaging that IPMNs represent the majority of these incidental lesions.

AGA recently published the first evidence-based guidelines to guide clinicians facing this common clinical problem.1 Developed through a multi-stakeholder process utilizing the GRADE method to assess the quality of evidence from a comprehensive technical review,2 it offers guidance on all incidentally found pancreatic cysts, recognizing that invasive testing with endoscopic ultrasound (EUS) is often performed in an attempt to characterize the cyst, often with misclassification and perhaps leading to unnecessary surgery.

The key decision points for a pancreatic cystic lesion are 1) is the cyst neoplastic or not? and 2) if neoplastic, what is the risk of malignancy? In an asymptomatic patient, such as the case presented, we cannot make

Case Example:
A 65-year-old male with back pain undergoes a CT colonography and an incidental 3 cm pancreatic cyst is found in the pancreatic head. There is no mass or ductal dilatation. There is also no history or risk factors for pancreatic disease.

In the absence of robust prospective data, the conversation about pancreatic cysts has mostly been driven by low-quality evidence, expert consensus and opinion. Hence, when debating an issue such as the role of endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) in pancreatic cysts greater than 3 cm, one can, within reason, construct an argument to support either side of the coin. Having said that, our evolving understanding of the biological behavior of pancreatic cysts has enabled us to draw certain rational conclusions, which form the framework for our management plan for the patient.

The key question in pancreatic cyst management, with the assumption that the cyst is mucinous, remains accurate identification of cysts that harbor malignancy at the time of diagnosis or those that have the potential to develop invasive carcinoma in the future. In other words, identifying patients who have cancer now, and those who will develop cancer in the future, is crucial. While currently, there are no reliable criteria to predict the latter, there are factors — specifically size and cyst characteristics — that can help us assess the former and stratify the risk of malignancy.

When considering the role of EUS-FNA in asymptomatic cysts greater than 3 cm in size, the issue needs to be considered in the context of two basic questions: is cyst size by itself a predictor of cancer and does cross-sectional imaging provide adequate information to risk stratify cysts, hence rendering EUS-FNA redundant?

Although the literature is controversial for cyst size as a predictor of cancer, there is evidence that size matters. In a meta-analysis evaluating the risk of malignancy in patients with intraductal papillary mucinous neoplasms (IPMN), cyst size greater than 3 cm was the feature most strongly associated...
them better, we can only alter the natural history of a condition, which can be in a positive or a negative way, because there is harm both with and without further testing in some cases, and the same thing can be said for treatment. Cross-sectional imaging can be diagnostic for the pancreatic cyst type. There are classic morphologic features of microcystic serous cystadenomas, including a central scar with calcification. However not every serous cystadenoma has this appearance, and although they are far more common in women, men can have them as well. Thus, a macrocystic serous cystadenoma can engender diagnostic uncertainty, and in selected circumstances, one could proceed with further invasive testing to attempt to confirm a diagnosis to obviate for surveillance. IPMN in the pancreas is by far the most common lesion and is distinguished from an MCN by ductal communication. As our patient is a man, MCN is quite unlikely, with IPMN vs. a non-neoplastic cyst the primary diagnostic differential. While high-quality magnetic resonance imaging (MRI) with MRCP can often make this distinction, as can EUS in highly skilled hands, the tests are neither 100 percent sensitive, nor specific. Thus, the approach to all cysts must consider these diagnostic and therapeutic uncertainties. The AGA guideline recommends that patients with a pancreatic cyst under 3 cm without a solid component or a dilated duct undergo surveillance. MRI is preferred because of its non-invasive nature and lack of radiation, and, if the cyst is stable after the second imaging test, that it can be followed every two years, for a total of five years. Viewed by some as very controversial recommendations, recall that the vast majority of these cystic lesions are seen in older patients. Thus, the potential of the cyst to cause harm has to be balanced with the patient’s risk of pancreatic resection, both immediate and long-term, as well as the likelihood that the patient’s life expectancy, as well as future quality of life, will be maximized. We performed a systematic review of the prevalence of cysts in the general population and used the National Cancer Institute’s Surveillance, Epidemiology and End Results (SEER) database to estimate mortality from pancreatic adenocarcinoma. The overall prevalence of cysts was 15 percent; the prevalence of cysts greater than 2 cm was just under 1 percent. There was a dramatic increasing prevalence with age, such that 25 percent of patients in the seventh decade of life were found to have a cyst, and the cyst prevalence great than 2 cm approached 2 percent in that patient population. We made estimates of the point prevalence of malignancy using SEER data on cystic adenocarcinomas, as well as pancreatic adenocarcinoma, and both were vanishingly small, all less than 1 percent. In the review, pancreatic cysts larger than 3 cm increased risk nearly three-fold. While this is a significant increase in risk, due to low baseline absolute risk, an asymptomatic cyst without worrisome features has extremely low risk of malignancy — even at 3 cm in size.

EUS cannot be routinely justified for all pancreatic cysts. There is little doubt that EUS is the best test for identifying small masses and associated nodules. But it has real challenges in differentiating a mural nodule from associated masses and is markedly operator dependent (as are all imaging tests). Despite considerable research in the past decades, currently an asymptomatic cyst without worrisome features has extremely low risk of malignancy — even at 3 cm in size.

EUS-FNA - CONTINUED FROM PAGE 5

with malignancy with an OR 62.4 (95 percent CI 30.8-126.3). The AGA technical review describes the prevalent malignancy in cysts greater than 3 cm versus less than 3 cm in size as mildly increased with an OR 2.97/95 percent CI 1.82-4.85). In the 2016 consensus-based Sendai guidelines, cyst size of greater than 3 cm was one of the triggers for recommending a surgical resection.

However, in validation studies, these guidelines were found to be flawed, with patients undergoing unnecessary resections for low-risk cysts greater than 3 cm in size. The subsequent Fukusaka and the evidence-based AGA guidelines have advocated a more conservative approach, with the intention of avoiding unnecessary resections. Nonetheless, even though the import of cyst size has diminished, it has not been relegated to the low-risk category altogether. The Fukusaka guidelines use cyst size of greater than 3 cm as a worrisome feature requiring EUS-FNA for risk stratification, while the AGA guideline includes cyst size greater than 3 cm as one of the features that, along with the presence of other high-risk features, should prompt an EUS-FNA. Thus, the available evidence and expert consensus does suggest that patients with cysts greater than 3 cm in size are at a higher risk, and further stratification with EUS-FNA is a reasonable next step.

The subsequent logical question is whether cross-sectional imaging alone can accurately diagnose and risk-stratify cysts. The evidence suggests that while we have seen significant improvement over the years in the quality of imaging and reporting, particularly with respect to serous cystadenomas and main-duct IPMNs, both multidetector CT (MDCT) and magnetic resonance imaging (MRI) have suboptimal accuracy in determining the correct histologic diagnosis in other cysts. In a study from a large tertiary-care center, both MDCT and MRI had a limited positive predictive value for classification of small pancreatic cysts into aggressive and non-aggressive categories (MDCT PPV of 25 percent and MRI 50 percent). Another study demonstrated an accuracy of only 39 percent for MDCT in predicting malignant potential of pancreatic cystic neoplasms.

Similarly, Visser, et. al, also reported on the relative accuracy of MDCT and MRI in the characterization of pancreatic cysts and found that the reviewer was correct in only 57 percent of cases. Even when evaluating specific high-risk stigmata such as mural nodule or solid component, the performance of cross-sectional imaging has been suboptimal. One can reasonably conclude from this data that in a cyst greater than 3 cm in size without any other risk factors, an EUS-FNA should be recommended to improve stratification. One can reasonably conclude from this data that in a cyst greater than 3 cm in size without any other risk factors, an EUS-FNA should be recommended to improve stratification. One could question whether EUS-FNA offers incremental advantage over cross-sectional imaging alone. While EUS, because of its superior resolution, allows for evaluation of mural nodules and associated masses, and the ability to sample the cyst contents for cytological and fluid analysis, and because of these reasons offers an advantage over cross-sectional imaging. This advantage is borne out by data where EUS with or without FNA was significantly superior to MDCT in accurately classifying a cyst as neoplastic (75 percent vs. 40 percent, p less than 0.0001) and in predicting malignancy (49 percent vs. 11 percent, p less than 0.0001). Similarly, EUS was superior to MRI alone for a correct diagnosis (76 percent vs. 34 percent, p less than 0.0001). Moreover, MRI did not predict malignancy in any patient. In another study of 159 patients with incidental cystic lesions, EUS-FNA had an impact on management in 72 percent of cases: 27.6 percent of patients were discharged who were initially recommended for resection, 20.7 percent received surgery, and 6.9 percent received follow up visits. One can reasonably conclude from this data that in a cyst greater than 3 cm in size without any other risk factors, an EUS-FNA should be recommended to improve stratification.
Pancreatic Cysts Greater Than 3 cm

Imaging Surveillance for Asymptomatic Pancreatic Cysts Greater Than 3 cm

the only clinically useful tumor marker to differentiate a mucinous from a non-mucinous lesion is the cyst fluid carcinoembryonic antigen (CEA). We know that a carcinoembryonic antigen level greater than 192 was first demonstrated to differentiate between a mucinous from a non-mucinous lesion with an AUC of .79. This unfortunately means that as many as one in five patients will be misclassified. A cyst without worrisome features on cross sectional imaging, such as the patient presented today, rarely will have worrisome features on EUS.

The data that we have regarding the outcome of surveillance with imaging evaluated 6,000 patient-years of follow up noted only 42 invasive cancers—a rate of malignancy development of 24.4 percent per year. This is quite analogous to our evolution in the understanding of other pre-cancerous conditions. Barrett’s esophagus is a great example, where we initially thought all dysplasia became cancer, and that the risk of malignancy was extraordinary. We know now that the rate is well less than 1 percent and that very aggressive intervention in that condition, which carries far less morbidity and mortality for surgery than pancreatic surgery, should be balanced with a very low risk.

In summary, the AGA guideline informs clinicians across specialties that invasive cancer in asymptomatic pancreatic cysts is actually quite rare. We have to be aware that we are applying diagnostic tests such as EUS-FNA of limited sensitivity and specificity to our evolution in the understanding of other cancers—a rate of malignancy development of 24.4 percent per year. This is quite analogous to our evolution in the understanding of other pre-cancerous conditions. Barrett’s esophagus is a great example, where we initially thought all dysplasia became cancer, and that the risk of malignancy was extraordinary. We know now that the rate is well less than 1 percent and that very aggressive intervention in that condition, which carries far less morbidity and mortality for surgery than pancreatic surgery, should be balanced with a very low risk.

REFERENCES
7. Ardengh JC, Lopes CV, de Lima-Filho ER, Kemp RD, dos Santos JS. The role of EUS-FNA in categorizing cysts will help us in the era of profiling cysts based on mutational analysis.
12. Ardengh JC, Lopes CV, de Lima-Filho ER, Kemp RD, dos Santos JS. The role of EUS-FNA in categorizing cysts will help us in the era of profiling cysts based on mutational analysis.
13. Ardengh JC, Lopes CV, de Lima-Filho ER, Kemp RD, dos Santos JS. The role of EUS-FNA in categorizing cysts will help us in the era of profiling cysts based on mutational analysis.
Beginning of the End?

In light of these accomplishments, it is easy to understand the sentiment that we’ve solved the hepatitis C puzzle, and that eradication of HCV is near. For baby boomers, the population known to represent over 80 percent of all HCV-infected individuals in the U.S. per NHANES, the memory of the historic eradication of polio in 1979 can declare HCV a rare disease in this country, much less across the globe. The reality is that there remains a striking lack of awareness by the public and health professionals regarding HCV. In addition, there is a lack of support and funding by the U.S. government and global non-governmental organizations, a lack of knowledge by clinicians, underscreening of at-risk populations, poor linkage to care, a shortage of specialists who treat HCV, limited attention to quality of care provided for patients with HCV and treatment is not covered for all patients with HCV who desire treatment, which will require broad advocacy efforts to decrease the cost of HCV treatment and remove barriers to drug access by payors. Thus, we have much work to do before we accomplish with HCV in the U.S. But make no mistake, we have much work to do before we can declare HCV a rare disease in this country.

There are many treatment options available that have been approved, including NS3/4A protease inhibitors, NS5a inhibitors and non-nucleoside NS5B polymerase inhibitors. With the exception of daclatasvir and ombitasvir, all oral regimens do not require a daily injection and cause few adverse effects, have a day for 2 or 3 months, eliminate interferon injections, cause few adverse effects, have a total of 12 oral direct acting antiviral agents (DAAs) have been approved, including the subset of treated patients who continue to fail treatment in primary care: only patients who fail to achieve SVR.

Multiple studies have documented the “waterfall” effect of key deficits along each step of the care cascade for HCV, in which only half of all infected individuals in the U.S. have been diagnosed, and even fewer have been confirmed with HCV viral load and genotype, linked to care, offered, started and completed antiviral therapy, and achieved viral eradication. A sobering study published in the New England Journal of Medicine in 2013 revealed that only an estimated 18 percent of HCV RNA+ individuals had ever received treatment, and only 5 to 6 percent of the infected cohort had achieved SVR.

Urgent action is needed to address key deficits in the care cascade to ensure that our goal of HCV eradication in the U.S. can be achieved. The key rate-limiting step is screening and diagnosis, for which innovative strategies are sorely needed. Recommendations of the CDC and U.S. Prevention Services Task Force to screen baby boomers born between 1945 and 1965 are an important first step, but will be insufficient alone to identify all infected patients, and therefore strategies to screen both baby boomers (e.g. using electronic medical record-based prompts and clinical reminders) and other at-risk individuals (e.g. young injection drug users) require formal examination and validation so we can provide clinicians and health systems evidence-based guidance.

Once patients are diagnosed and confirmed to have HCV, the major treatment options available to them are oral direct acting antiviral agents (DAAs) that are effective against all genotypes. In light of these accomplishments, it is easy to understand the sentiment that we’ve solved the hepatitis C puzzle, and that eradication of HCV is near. For baby boomers, the population known to represent over 80 percent of all HCV-infected individuals in the U.S. per NHANES, the memory of the historic eradication of polio in 1979 can declare HCV a rare disease in this country.
EXPLORING THE GROWING ROLE OF GI IN THE MANAGEMENT OF OBESITY

Obesity is a worsening pandemic that affects more than 35 percent of the U.S. adult population and hundreds of millions of people on a global scale. This dwarfs other common medical conditions, such as colon cancer, esophageal cancer, cirrhosis, HIV and AIDS, and is several fold more prevalent than all of these combined. Obesity is also the root cause of a variety of co-morbid medical conditions, including hypertension, hypercholesterolemia, cardiovascular disease, type 2 diabetes, obstructive sleep apnea and fatty liver disease. As such, the estimated annual medical cost of obesity in the U.S. is over $200 billion dollars.

Until recently, the medical field has focused its attention on the treatment of comorbidities, rather than the underlying disease process. We have developed an impressive continuum of care to address these comorbidities, from physical therapy and medicine (including multiple medical algorithms for the treatment of hypertension and type 2 diabetes), to minimally invasive treatments such as drug-eluting cardiovascular stents and arthroscopy, to major surgical options such as coronary artery bypass grafting and joint replacement surgery. Nevertheless, we have failed to contain the ever-worsening underlying obesity epidemic. In fact, it was not until June 2013 that the American Medical Association formally classified obesity as a disease, and very few medical professionals have had formal training in the care of patients with obesity. Additionally, bias still exists toward patients with obesity, which likely further contributes to health-care disparities in this underserved population.

Prevention and non-invasive therapies, including lifestyle modification and medical therapy, are important to the care of these patients and can yield a 7 to 10 percent reduction in total weight. Unfortunately, sustained weight loss is typically achieved in only 5 percent of obese patients using these modalities alone. Nevertheless these treatments are critical to the durable success of other therapies including surgery, and remain of primary importance. Surgery is thus far the most effective treatment of morbid obesity, type 2 diabetes and other related comorbidities. However, surgery has been insufficient in containing the worsening epidemic. There are roughly 20 million morbidly obese patients in the U.S. that are eligible for traditional surgery, yet there are only an estimated 1,500 bariatric surgeons as of 2006. At the current rate bariatric surgery is performed, assuming roughly 200,000 procedures annually at a cost of $20,000 per procedure, it would take roughly 100 years and cost $400 trillion to treat existing eligible patients. This is an underestimate for several reasons. The cost for many procedures is above $30,000, without considering complications, inflation or other indirect costs. Additionally, the prevalence of obesity continues to increase and there are many more patients who are not eligible for traditional surgery. If the goal is to treat everyone who suffers from obesity, this would bring the current number to approximately 80 million.

A full spectrum of care that draws on the strengths of multiple disciplines is needed to contend with this epidemic.
In order to facilitate progress in this field, we have developed strong relationships with key EGID stakeholders, including the patients themselves, primarily through the support of patient advocacy groups, the National Institutes of Health (NIH), FDA, industry, physicians and investigators.

As a result of these efforts, NIH has helped us to establish the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), which is part of the Rare Diseases Clinical Research Network and supported by the National Center for Advancing Translational Sciences (NCATS). CEGIR is directly funded by NCATS and two other NIH institutes (the National Institute of Allergy and Infectious Diseases and the National Institute of Diabetes and Digestive and Kidney Diseases), and two patient advocacy groups (the American Partnership for Eosinophilic Disorders and the Campaign Urging Research for Eosinophilic Disease).

CEGIR aims to improve the lives of individuals with EGID through innovative research, clinical expertise and education via collaboration between scientists, health-care providers, patients and professional organizations.

However, key to the completion of these studies is recruitment of eligible subjects. Interested colleagues can learn more about present studies and goals at http://www.rarediseasenetwork.org/cms/cegir. We anticipate that the collaborative efforts of CEGIR will provide important advances in the care of patients with EGID.

CEGIR is already making major advances concerning understanding, treating and educating patients and the public about these diseases. The formation of CEGIR is also particularly timely, as the first generation of anti-eosinophil therapy (humanized anti-interleukin 5 monoclonal antibody therapy) has been recently approved by FDA for eosinophilic asthma. CEGIR, due to its national collaborative nature, is poised to apply these and other developing anti-eosinophil therapy advances to treating EGID.

In addition, CEGIR is already making major advances concerning understanding, treating and educating patients about these diseases. The formation of CEGIR is also particularly timely, as the first generation of anti-eosinophil therapy (humanized anti-interleukin 5 monoclonal antibody therapy) has been recently approved by FDA for eosinophilic asthma. CEGIR, due to its national collaborative

In order to facilitate progress in this field, we have developed strong relationships with key EGID stakeholders, including the patients themselves, primarily through the support of patient advocacy groups, the National Institutes of Health (NIH), FDA, industry, physicians and investigators.

As a result of these efforts, NIH has helped us to establish the Consortium of Eosinophilic Gastrointestinal Disease Researchers (CEGIR), which is part of the Rare Diseases Clinical Research Network and supported by the National Center for Advancing Translational Sciences (NCATS). CEGIR is directly funded by NCATS and two other NIH institutes (the National Institute of Allergy and Infectious Diseases and the National Institute of Diabetes and Digestive and Kidney Diseases), and two patient advocacy groups (the American Partnership for Eosinophilic Disorders and the Campaign Urging Research for Eosinophilic Disease).

CEGIR aims to improve the lives of individuals with EGID through innovative research, clinical expertise and education via collaboration between scientists, health-care providers, patients and professional organizations. CEGIR provides a framework for clinicians, researchers, patients, NIH and other stakeholders to partner around EGID and strengthens momentum for better outcomes for EGID in several ways: establishing frequent, structured communication between stakeholders, jumpstarting new research, training physicians in these rare disorders and conducting multicenter clinical trials. CEGIR’s pilot program supports a series of preliminary investigations testing new hypotheses concerning EGID and is a kick starter for promising research. CEGIR’s training program is designed to equip the next generation of physicians with expertise in EGID, educational material and a full description are available through the CEGIR website (https://www.rarediseasenetwork.org/cms/cegir).

CEGIR is now conducting several clinical studies, including an observational study investigating outcome measures for EGID across ages, also known as OMEGA. It is a prospective multicenter study to compare and validate endoscopic, histologic, molecular and patient-reported outcomes in pediatric and adult patients with EGID, eosinophilic gastritis and eosinophilic colitis. The OMEGA study will be
QUICK HITS: RESEARCH/PATIENT CARE

Dr. Loftus has consulted for and has received research support from LOFTUS JR, Division of Gastroenterology and Hepatology, @EdwardLoftus2

Vedolizumab (Entyvio, Takeda Pharmaceuticals America, Deerfield, IL) is a humanized monoclonal antibody to α4β7 integrin, which mediates lymphocyte trafficking to the gut mucosa and in the lamina muscularis. α4β7 integrin is uniquely expressed on lymphocytes and is the ligand to mucosal vascular addressin cell adhesion molecule-1 (MAdCAM-1), preferentially expressed on intestinal dendritic cells in the gut vasculature. Vedolizumab selectively interferes with lymphocyte homing to the gut, thus affording the potential for a generally gut-selective mechanism of action, which could impact not only the efficacy of the drug, but also its safety. Vedolizumab was approved by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of moderate to severe ulcerative colitis and Crohn’s disease in mid-2014. Now is a good time to review the data on its efficacy and safety.

Vedolizumab is a selective gut-directed therapy for ulcerative colitis and Crohn’s disease. It is currently indicated for induction and maintenance therapy in patients with moderate to severe ulcerative colitis and Crohn’s disease. In addition, vedolizumab has been approved for the treatment of ulcerative colitis and Crohn’s disease in certain patient populations in the European Union and Japan.

The GEMINI 1 trials were designed to assess the efficacy and safety of vedolizumab in patients with moderate to severe Crohn’s disease.

The primary induction endpoint, achieved by 100 percent of patients who achieved endoscopic improvement at week 6, was met in all comparisons. The primary maintenance endpoint, achieved by 75 percent of patients who achieved remission at week 6, was also met in all comparisons. The primary response endpoint, achieved by 60 percent of patients who achieved clinical remission at week 6, was also met in all comparisons.

At the end of the year, vedolizumab therapy was associated with higher percentages of patients who achieved clinical remission compared to placebo. The percentage of patients who achieved clinical remission at week 12 was 31 percent in the vedolizumab group, compared to 20 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 52 was 35 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 104 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001).

The GEMINI 2 trials were designed to assess the efficacy and safety of vedolizumab in patients with moderate to severe ulcerative colitis.

The primary induction endpoint, achieved by 100 percent of patients who achieved endoscopic improvement at week 6, was met in all comparisons. The primary maintenance endpoint, achieved by 60 percent of patients who achieved remission at week 6, was also met in all comparisons. The primary response endpoint, achieved by 50 percent of patients who achieved clinical remission at week 6, was also met in all comparisons.

At the end of a year, vedolizumab therapy was associated with higher percentages of patients who achieved clinical remission compared to placebo. The percentage of patients who achieved clinical remission at week 12 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 52 was 35 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 104 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001).

The GEMINI 3 trials were designed to assess the efficacy and safety of vedolizumab in patients with moderate to severe ulcerative colitis and Crohn’s disease.

The primary induction endpoint, achieved by 100 percent of patients who achieved endoscopic improvement at week 6, was met in all comparisons. The primary maintenance endpoint, achieved by 60 percent of patients who achieved remission at week 6, was also met in all comparisons. The primary response endpoint, achieved by 50 percent of patients who achieved clinical remission at week 6, was also met in all comparisons.

At the end of a year, vedolizumab therapy was associated with higher percentages of patients who achieved clinical remission compared to placebo. The percentage of patients who achieved clinical remission at week 12 was 32 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 52 was 35 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 104 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001).

The GEMINI 4 trials were designed to assess the efficacy and safety of vedolizumab in patients with moderate to severe ulcerative colitis and Crohn’s disease.

The primary induction endpoint, achieved by 100 percent of patients who achieved endoscopic improvement at week 6, was met in all comparisons. The primary maintenance endpoint, achieved by 60 percent of patients who achieved remission at week 6, was also met in all comparisons. The primary response endpoint, achieved by 50 percent of patients who achieved clinical remission at week 6, was also met in all comparisons.

At the end of a year, vedolizumab therapy was associated with higher percentages of patients who achieved clinical remission compared to placebo. The percentage of patients who achieved clinical remission at week 12 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 52 was 35 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 104 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001).

The GEMINI 5 trials were designed to assess the efficacy and safety of vedolizumab in patients with moderate to severe ulcerative colitis and Crohn’s disease.

The primary induction endpoint, achieved by 100 percent of patients who achieved endoscopic improvement at week 6, was met in all comparisons. The primary maintenance endpoint, achieved by 60 percent of patients who achieved remission at week 6, was also met in all comparisons. The primary response endpoint, achieved by 50 percent of patients who achieved clinical remission at week 6, was also met in all comparisons.

At the end of a year, vedolizumab therapy was associated with higher percentages of patients who achieved clinical remission compared to placebo. The percentage of patients who achieved clinical remission at week 12 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 52 was 35 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 104 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001).

The GEMINI 6 trials were designed to assess the efficacy and safety of vedolizumab in patients with moderate to severe ulcerative colitis and Crohn’s disease.

The primary induction endpoint, achieved by 100 percent of patients who achieved endoscopic improvement at week 6, was met in all comparisons. The primary maintenance endpoint, achieved by 60 percent of patients who achieved remission at week 6, was also met in all comparisons. The primary response endpoint, achieved by 50 percent of patients who achieved clinical remission at week 6, was also met in all comparisons.

At the end of a year, vedolizumab therapy was associated with higher percentages of patients who achieved clinical remission compared to placebo. The percentage of patients who achieved clinical remission at week 12 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 52 was 35 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 104 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001).

The GEMINI 7 trials were designed to assess the efficacy and safety of vedolizumab in patients with moderate to severe ulcerative colitis and Crohn’s disease.

The primary induction endpoint, achieved by 100 percent of patients who achieved endoscopic improvement at week 6, was met in all comparisons. The primary maintenance endpoint, achieved by 60 percent of patients who achieved remission at week 6, was also met in all comparisons. The primary response endpoint, achieved by 50 percent of patients who achieved clinical remission at week 6, was also met in all comparisons.

At the end of a year, vedolizumab therapy was associated with higher percentages of patients who achieved clinical remission compared to placebo. The percentage of patients who achieved clinical remission at week 12 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 52 was 35 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 104 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001).

The GEMINI 8 trials were designed to assess the efficacy and safety of vedolizumab in patients with moderate to severe ulcerative colitis and Crohn’s disease.

The primary induction endpoint, achieved by 100 percent of patients who achieved endoscopic improvement at week 6, was met in all comparisons. The primary maintenance endpoint, achieved by 60 percent of patients who achieved remission at week 6, was also met in all comparisons. The primary response endpoint, achieved by 50 percent of patients who achieved clinical remission at week 6, was also met in all comparisons.

At the end of a year, vedolizumab therapy was associated with higher percentages of patients who achieved clinical remission compared to placebo. The percentage of patients who achieved clinical remission at week 12 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 52 was 35 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001). The percentage of patients who achieved clinical remission at week 104 was 33 percent in the vedolizumab group, compared to 22 percent in the placebo group (p < 0.001).
Utilizing Big Data to Improve Clinical Research and Care

**MANISH GALA, MD**
Massachusetts General Hospital, Boston, MA
Dr. Gala is the co-founder and has equity in New Amsterdam Genomics, Inc.

**ANDREW T. CHAN, MD, MPH**
Massachusetts General Hospital, Boston, MA
Dr. Chan consults to GlaxoSmithKline, Pﬁzer, and Lilly Pharma. He also advises on the Council on Aggen to Health Protection and the American Association for Cancer Research.

**GALA, MANISH, ANDREW T. MD**

**Quick Hits: Technology**

Utilizing Big Data to Improve Clinical Research and Care

Massachusetts General Hospital, Boston, MA
Dr. Gala is the co-founder and has equity in New Amsterdam Genomics, Inc.

Dr. Gala consults to GlaxoSmithKline, Pﬁzer, and Lilly Pharma. He also advises on the Council on Aggen to Health Protection and the American Association for Cancer Research.

**Chan**

The increased digitization and subsequent dissemination of large volumes of electronic medical records, research and development information, billing data, and biometrics have created unprecedented opportunities to improve outcomes, reduce costs and accelerate innovation in health care. Colloquially referred to as “big data,” these enormous datasets are often both structured and unstructured, and difficult to analyze using conventional analytic techniques. Although agreement on a precise definition of big data is elusive, the general concept of what constitutes big data is fairly consistent among those in the research community focused on analyzing such datasets. In particular, the specific characteristics inherent to big data, known as the five v’s — volume, variety, velocity, variability and veracity — are perhaps the characteristics that best distinguish big data from traditional data. There are already early examples of success in effective analysis of big data. However, there remain significant challenges for the research community that will require forging novel collaborations and deploying additional resources to fully harness the potential of big data into potentially transformative discoveries that will impact clinical care.

Big data approaches have already moved beyond theoretical promise to demonstrate tangible gains in health-care quality. Big data approaches have already moved beyond theoretical promise to demonstrate tangible gains in health-care quality. They are able to project non-adherence with 94 percent accuracy up to one year in advance using 400 data points derived from the patient, physician, disease and medication. Impressively, this accuracy is several-fold higher than traditional approaches that rely on self-reported surveys. Moving forward with this tool, Express Scripts is now able to tailor specific compliance programs to high-risk individuals to reduce waste and improve health-care delivery.

Within gastroenterology, robust efforts are presently underway to leverage big data technologies that have been generated by interoperability among different hospital systems and electronic medical records. This integration has boosted research in pharmaco-surveillance for widely prescribed medications such as proton pump inhibitors. In addition, longitudinal medical records integrated with large datasets offer the potential to advance precision medicine through the development of diagnostics, biomarkers and risk prediction tools derived from these high-dimensional data sets. Finally, patient-centered engagement tools and collaborative learning and artificial intelligence. Since such expertise is often internally unavailable at most major academic medical centers, researchers will increasingly depend on interdisciplinary collaborations with engineers, computer scientists and mathematicians. In addition, these projects may require collaborations beyond traditional academic and non-proﬁt spheres. For example, Google (through its subsidiary Verily Life Sciences) has partnered with Stanford and Duke Universities to initiate the Baseline Study, a longitudinal effort to collect and analyze detailed medical records, whole body MRI images, blood, urine, saliva and tears to develop diagnostics and algorithms to predict and prevent cardiovascular disease and cancer. Similarly, Amgen Genetics and Foundation Medicine have deposited large volumes of their data for public research projects. Given the strong interest and expertise of many information technology ﬁrms in big data, academic-industry partnerships will likely become a critical model for research training and collaboration.

Another barrier to fully realizing the potential of big data within the research community is the lack of adequate resources for such projects. Despite recent high-proﬁle initiatives such as the National Institutes of Health Big Data to Knowledge Program (BD2K), President Obama’s Precision Medicine Initiative and Vice President Biden’s Cancer Moonshot program, governmental funding for interdisciplinary proposals remains at a signiﬁcant disadvantage compared to those that can be traditionally ﬁt into a single area of expertise. Further disadvantaging big data projects are low funding rates. To address these challenges, some subspecialty societies have already taken bold steps to bridge this funding gap. For example, the American Gastroenterological Association has created and endowed the Institute for Precision Cardiovascular Medicine to provide funding to its big data investigators and to serve as an honest broker among academic institutions, industry and the government. In the future, the American Gastroenterological Association, perhaps in partnership with other organizations, may be able to develop a similar vehicle to support big data investigators in digestive disease research.

Finally, irrespective of active participation in big data analytics, all stakeholders in the health-care system will need to be carefully attuned to discoveries made by these technologies. Similar to our experience with perhaps the first wave of big data in the form of genome-wide association studies, observations from future studies leveraging even more complex datasets will require validation, mechanistic studies and perhaps clinical trials before discoveries are fully integrated into clinical care.
A Welcome Note from the New Editors of Gastroenterology

Douglas A. Corley, MD, PhD, MPH
Kaiser Permanente, Northern California and University of California, San Francisco, California

Richard M. Peek Jr., MD, AGAF
Vanderbilt University Medical Center, Nashville, Tennessee

Change. An old adage stipulates it is the one true constant in life, or stated another way, “Change is inevitable except from a vending machine” (Robert Gallagher). On behalf of our new Board of Editors, we are honored, humbled and excited to oversee the next editorship team for Gastroenterology.

The next iteration of Gastroenterology’s Board of Editors embraces change by developing a new editorial structure for the journal that integrates an interjournal collaboration to recognize joint first authorship; increased integration of in vivo and in vitro mechanistic findings that extend into in vivo models with human validation will be highly valued. Clinical research articles with paradigm-shifting potential or those that alter practice parameters predict a successful submission? First and foremost, the Gastroenterology’s educational mission; an interjournal mentoring and education section to further the journal’s educational mission; an interjournal for encapsulating concise advances; a new role for HARVONI and EPCLUSA on the following pages.

NOW APPROVED EPCLUSA is the first and only pan-genotypic single-tablet regimen for patients with chronic HCV:

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

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.

Please see Brief Summary of full Prescribing Information for HARVONI and EPCLUSA on the following pages.
HARVONI DELIVERED HIGH CURE (SVR12) RATES IN A BROAD RANGE OF GT 1 SUBJECTS

97% OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS

=9/1042/1079)

NOW APPROVED

THE FIRST AND ONLY PAN-GENOTYPIC ONCE-DAILY SINGLE-TABLET REGIMEN FOR CHRONIC HCV PATIENTS

WHAT’S POSSIBLE

EPCLEUSA FULFILLS A SIGNIFICANT UNMET NEED FOR GT 2 AND GT 3 PATIENTS, DELIVERING HIGH CURE (SVR12) RATES WITH A RBV-FREE SINGLE-TABLET REGIMEN

99% OF GT 2 SUBJECTS OVERALL ACHIEVED A CURE

=9/113/134; ASTRAL-2)

95% OF GT 3 SUBJECTS OVERALL ACHIEVED A CURE

=9/264/277; ASTRAL-3)

IMPORTANCE SAFETY INFORMATION FOR HARVONI AND EPCLEUSA

CONTRAINDICATIONS

If HARVONI or EPCLEUSA 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 EPCLEUSA 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 EPCLEUSA. P-gp inducers may significantly decrease ledipasvir, sofosbuvir and/or velpatasvir plasma concentrations. Moderate to potent inducers of CYP3A4, CYP2C8, CYP2C9 and CYP3A4 may significantly decrease sofosbuvir and/or velpatasvir plasma concentrations.

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

No hepatic or hematologic monitoring is required when HARVONI is used alone.

No baseline resistance testing is required with HARVONI.

HARVONI is RBV-free, regardless of prior HCV treatment history; the presence of compensated cirrhosis, or GT 1 or ‘b subtype’.

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. These studies included subjects with decompensated cirrhosis. 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. Achieving SVR is considered a virologic cure.

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

ION-1: TN subjects (N=858) 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.

No hepatic or hematologic monitoring is required when EPCLEUSA is used alone.

No baseline resistance testing is required with EPCLEUSA.

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

ION-1: TN subjects (N=1015/1035) were randomized to receive EPCLUSA for 12 weeks or SOF + RBV for 24 weeks. Overall SVR was 99% (n=984/1005).

ION-2: open-label trial in GT 2 subjects (N=266). Subjects were randomized to receive EPCLUSA or SOF + RBV for 12 weeks. SVR12 for EPCLUSA ranged from 89% (TE with cirrhosis) to 98% (TN without cirrhosis).

ION-3: double-blind, placebo-controlled trial in GT 1, 2, 4, 5, or 6 subjects (n=140). GT 1, 2, 4, 5, or 6 subjects were randomized 1:1 to receive EPCLUSA or placebo for 12 weeks; GT 1 subjects received EPCLUSA for 12 weeks. Overall SVR was 99% (n=984/1005).

ION-3: open-label trial in GT 3 subjects (N=552). Subjects were randomized to receive EPCLUSA 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. Achieving SVR is considered a virologic cure.

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

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

=9/1015/1035; ASTRAL-1, -2, -3)

• GT 1-6 patients take 12 weeks of RBV-free EPCLEUSA.

• No baseline resistance testing is required with EPCLEUSA.

• No hepatic or hematologic monitoring is required when EPCLEUSA is used alone.

• Adverse reactions (all grades) reported in ≥5% of subjects receiving 12 weeks of treatment with EPCLEUSA (ASTRAL-1): headache (22%), fatigue (15%), nausea (9%), asthma (5%), and insomnia (5%).

• The adverse reactions observed in subjects treated with EPCLEUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1.

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

• Adverse reactions observed in subjects treated with EPCLEUSA in ASTRAL-3 were consistent with those observed in ASTRAL-1. In ASTRAL-3, irritability was observed in ≥5% of subjects treated with EPCLEUSA.

• Coadministration of HARVONI or EPCLUSA is not recommended with cobicistat/emertricitabine/tenofovir disoproxil fumarate due to increased concentrations of sofosbuvir, ledipasvir and/or velpatasvir.

• Coadministration of HARVONI or EPCLUSA is not recommended with omeprazole or raloxifene due to decreased concentrations of ledipasvir, sofosbuvir and/or velpatasvir.

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

• Coadministration of HARVONI or EPCLUSA is not recommended with cobicistat/emertricitabine/tenofovir disoproxil fumarate due to increased concentrations of sofosbuvir, ledipasvir and/or velpatasvir.

• Coadministration of HARVONI or EPCLUSA is not recommended with omeprazole or raloxifene due to decreased concentrations of ledipasvir, sofosbuvir and/or velpatasvir.

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

• Coadministration of HARVONI or EPCLUSA is not recommended with cobicistat/emertricitabine/tenofovir disoproxil fumarate due to increased concentrations of sofosbuvir, ledipasvir and/or velpatasvir.

• Coadministration of HARVONI or EPCLUSA is not recommended with omeprazole or raloxifene due to decreased concentrations of ledipasvir, sofosbuvir and/or velpatasvir.

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

• Coadministration of HARVONI or EPCLUSA is not recommended with cobicistat/emertricitabine/tenofovir disoproxil fumarate due to increased concentrations of sofosbuvir, ledipasvir and/or velpatasvir.

• Coadministration of HARVONI or EPCLUSA is not recommended with omeprazole or raloxifene due to decreased concentrations of ledipasvir, sofosbuvir and/or velpatasvir.
Among the 162 subjects with bradycardia with coadministration of amiodarone. Bradycardia generally also taking beta blockers, or those with underlying cardiac comorbidities due to amiodarone's long half-life for patients discontinuing amiodarone or end stage renal disease. The safety assessment of HARVONI with or without RBV was based on a randomized double-blind placebo controlled parallel-group trial. Subjects were randomized to receive HARVONI once daily for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively.

Bradycardia generally and/or advanced liver disease may be at increased risk for symptomatic bradycardia has been reported when amiodarone is coadministered with HARVONI. Bradycardia generally was reported after discontinuation of the trial. The mechanism for this effect is unknown. Coadministration of amiodarone with HARVONI is not recommended. Amiodarone will be coadministered with HARVONI in those who have no other alternative, viable treatment options; and decompensated liver disease (pre- or post-transplant) who received RBV, in particular pregnancy avoidance, apply to this combination regimen. If HARVONI is administered with RBV, the lactation information for RBV with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to RBV prescribing information. If HARVONI is coadministered with or without RBV to subjects with compensated end stage renal disease (ESRD) or end stage renal disease. The safety assessment of HARVONI with or without RBV was based on a randomized double-blind placebo controlled parallel-group trial. Subjects were randomized to receive HARVONI once daily for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively.

Foster City, CA. June 2016. Drugs for Treatment. May 2016. Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. May 2016. HMG-CoA Reductase Inhibitors (rosuvastatin): Significant increase in rosuvastatin concentrations and risks of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended. Drug Interactions with RBV: Based on drug interaction studies conducted with HARVONI or its components, the components of HARVONI as individual agents or in combination with RBV have not been observed or expected when used with the following drugs: abacavir, azathioprine, celecoxib, cladirecel, elvitegravir/cobicistat/efavirenz/tipranavir alafenamide, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, ranolazine, raltegravir, rilpivirine, tacrolimus, or verapamil.

Refer to the full prescribing information for RBV for additional information that may be available to establish whether or not HARVONI poses a risk to pregnancy outcomes. ALT/AST elevations were observed in 3%, <1% and 2% of subjects treated with HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI. The development of symptoms consistent with liver disease (e.g., fatigue, nausea, vomiting) in subjects with chronic HCV GT 1 infection with compensated liver disease (pre- or post-transplant) who received RBV, in particular pregnancy avoidance, apply to this combination regimen. If HARVONI is administered with RBV, the lactation information for RBV with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to RBV prescribing information.

In general, no dosage adjustment of HARVONI is warranted 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. No adverse events related to sample collection were 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%).

The safety assessment of HARVONI with or without RBV was based on a randomized double-blind placebo controlled parallel-group trial. Subjects were randomized to receive HARVONI once daily for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively. Subjects were randomized to receive HARVONI once daily for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively.

GT 1 Treatment-Experienced Subjects with Cirrhosis (SIRUS): The safety assessment of HARVONI with or without RBV was based on a randomized double-blind placebo controlled parallel-group trial. Subjects were randomized to receive HARVONI once daily for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively. Subjects were randomized to receive HARVONI once daily for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively.

of this publication, information will not be available to establish whether or not HARVONI poses a risk to pregnancy outcomes. ALT/AST elevations were observed in 3%, <1% and 2% of subjects treated with HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI. The development of symptoms consistent with liver disease (e.g., fatigue, nausea, vomiting) in subjects with chronic HCV GT 1 infection with compensated liver disease (pre- or post-transplant) who received RBV, in particular pregnancy avoidance, apply to this combination regimen. If HARVONI is administered with RBV, the lactation information for RBV with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to RBV prescribing information. If HARVONI is coadministered with or without RBV to subjects with compensated end stage renal disease (ESRD) or end stage renal disease. The safety assessment of HARVONI with or without RBV was based on a randomized double-blind placebo controlled parallel-group trial. Subjects were randomized to receive HARVONI once daily for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively.

Foster City, CA. June 2016. Drugs for Treatment. May 2016. Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. May 2016. HMG-CoA Reductase Inhibitors (rosuvastatin): Significant increase in rosuvastatin concentrations and risks of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended. Drug Interactions with RBV: Based on drug interaction studies conducted with HARVONI or its components, the components of HARVONI as individual agents or in combination with RBV have not been observed or expected when used with the following drugs: abacavir, azathioprine, celecoxib, cladirecel, elvitegravir/cobicistat/efavirenz/tipranavir alafenamide, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, ranolazine, raltegravir, rilpivirine, tacrolimus, or verapamil.

Refer to the full prescribing information for RBV for additional information that may be available to establish whether or not HARVONI poses a risk to pregnancy outcomes. ALT/AST elevations were observed in 3%, <1% and 2% of subjects treated with HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI. The development of symptoms consistent with liver disease (e.g., fatigue, nausea, vomiting) in subjects with chronic HCV GT 1 infection with compensated liver disease (pre- or post-transplant) who received RBV, in particular pregnancy avoidance, apply to this combination regimen. If HARVONI is administered with RBV, the lactation information for RBV with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to RBV prescribing information. If HARVONI is coadministered with or without RBV to subjects with compensated end stage renal disease (ESRD) or end stage renal disease. The safety assessment of HARVONI with or without RBV was based on a randomized double-blind placebo controlled parallel-group trial. Subjects were randomized to receive HARVONI once daily for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively. Subjects were randomized to receive HARVONI once daily for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively.

Foster City, CA. June 2016. Drugs for Treatment. May 2016. Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment. May 2016. HMG-CoA Reductase Inhibitors (rosuvastatin): Significant increase in rosuvastatin concentrations and risks of rosuvastatin associated myopathy, including rhabdomyolysis. Coadministration is not recommended. Drug Interactions with RBV: Based on drug interaction studies conducted with HARVONI or its components, the components of HARVONI as individual agents or in combination with RBV have not been observed or expected when used with the following drugs: abacavir, azathioprine, celecoxib, cladirecel, elvitegravir/cobicistat/efavirenz/tipranavir alafenamide, emtricitabine, lamivudine, methadone, oral contraceptives, pravastatin, ranolazine, raltegravir, rilpivirine, tacrolimus, or verapamil.

Refer to the full prescribing information for RBV for additional information that may be available to establish whether or not HARVONI poses a risk to pregnancy outcomes. ALT/AST elevations were observed in 3%, <1% and 2% of subjects treated with HARVONI, the components of HARVONI as individual agents, or are predicted drug interactions that may occur with HARVONI. The development of symptoms consistent with liver disease (e.g., fatigue, nausea, vomiting) in subjects with chronic HCV GT 1 infection with compensated liver disease (pre- or post-transplant) who received RBV, in particular pregnancy avoidance, apply to this combination regimen. If HARVONI is administered with RBV, the lactation information for RBV with regard to pregnancy testing, contraception, and infertility also applies to this combination regimen. Refer to RBV prescribing information. If HARVONI is coadministered with or without RBV to subjects with compensated end stage renal disease (ESRD) or end stage renal disease. The safety assessment of HARVONI with or without RBV was based on a randomized double-blind placebo controlled parallel-group trial. Subjects were randomized to receive HARVONI once daily for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively. Subjects were randomized to receive HARVONI once daily for 24 weeks or HARVONI + RBV for 12 weeks compared to placebo for 12 weeks, respectively.
Brief Summary of full prescribing information. See full prescribing information before dispensing EPCLUSA. See full prescribing information before dispensing EPCLUSA.

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

• Without cirrhosis or with compensated cirrhosis 

• With decompensated cirrhosis for use in combination with ribavirin

CONTRAINDICATIONS: EPCLUSA and ribavirin combination regimen is contraindicated in patients for whom RBV is contraindicated. Refer to the RBV prescribing information.

WARNINGS AND PRECAUTIONS: Due to amiodarone’s long half-life, patients discontinuing amiodarone who need to start amiodarone therapy due to no other alternative viable medications should be monitored closely for at least the first 2 weeks of treatment. Patients who are taking EPCLUSA with RBV for 12 weeks due to adverse reactions. 

Subjects with Decompensated Cirrhosis: The safety assessment of EPCLUSA in subjects infected with genotype 1, 2, 3, 4, or 6 HCV with compensated cirrhosis treated with EPCLUSA for 12 weeks and in subjects treated with EPCLUSA with RBV for 12 weeks. 

Less Common Adverse Reactions: 

• With decompensated cirrhosis for use in combination with ribavirin

LABORATORY ABNORMALITIES: 

• With or 12 hours apart from EPCLUSA. Use with other proton pump inhibitors has not been studied.

• Tipranavir/ritonavir: Antacids: A total of 4 (5%) subjects permanently discontinued with RBV due to an adverse event; there was no adverse event leading to discontinuation that occurred in more than 1 subject. Treatment with EPCLUSA in ASTRAL-1, depressed mood occurred in 1% of subjects without cirrhosis or with compensated cirrhosis treated with EPCLUSA for 12 weeks; in patients with decompensated cirrhosis treated with EPCLUSA, the adverse reaction of depressed mood occurred and all events were mild or moderate in severity.

• Anticonvulsants (carbamazepine, phenytoin, phenobarbital, oxcarbazepine): Drugs that are inducers of P-gp and/or narrow therapeutic index. Coadministration of drugs with clinically significant interactions with P-gp, BCRP, OATP1B1, OATP1B3, and OATP2B1. Coadministration of EPCLUSA is not recommended. 

• Pregnancy: 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 the use of RBV in pregnancy. 

• Use of EPCLUSA with RBV is not recommended in patients with severe renal impairment or end-stage renal disease (ESRD) requiring hemodialysis. No dosage adjustment of EPCLUSA is warranted in geriatric patients. 

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

• Hematologic: Significant Interactions with EPCLUSA: Based on drug interaction studies conducted with either EPCLUSA, the components of EPCLUSA (sofosbuvir and velpatasvir) as monotherapy or as part of a combination therapy, the following drugs should be administered with caution or be avoided concomitantly with EPCLUSA. This list includes potentially significant interactions but is not all inclusive.

• Antituberculosis drug regimens, as clinically indicated, is recommended 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/1.73 m²) or end-stage renal disease (ESRD) requiring hemodialysis. No dosage adjustment of EPCLUSA is warranted in geriatric patients. 

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

• Hematologic: Significant Interactions with EPCLUSA: Based on drug interaction studies conducted with either EPCLUSA, the components of EPCLUSA (sofosbuvir and velpatasvir) as monotherapy or as part of a combination therapy, the following drugs should be administered with caution or be avoided concomitantly with EPCLUSA. This list includes potentially significant interactions but is not all inclusive.
AGA Drug Development Conference: Clinical Endpoints in Upper GI Disorders

OCT. 27-28, 2016, WASHINGTON, DC

Organized by the AGA Center for Diagnostics and Therapeutics

- Identify promising new medicines and diagnostic tests for upper GI disorders.
- Network and collaborate with your colleagues and other stakeholders in drug development.
- Learn how to define appropriate clinical endpoints and improve clinical trial designs.
- Have your voice heard in an open forum and in Q&A sessions.

Advance GI therapeutics. Register today at ddc.gastro.org.