SURVEILLANCE OF GASTRIC INTESTINAL METAPLASIA

by Ernst J. Kuipers, MD, PhD, AGAF, and M. Brian Fennerty, MD, AGAF
In this issue

Proper Preparation Strategies for Patients On Chronic Anticoagulation Undergoing Endoscopy
John R. Saltzman, MD, AGAF ................................................................. 10

Ready Or Not, Here They Are: Anti-TNF Biosimilars for IBD
Mark T. Ostemen, MD, ............................................................. 12

Medical Management of Severe Alcoholic Hepatitis
Mack Mitchell, MD ............................................................. 16

Duration of HCV Therapy: How Short Can Therapy Be and Who Would Qualify?
Benjamin Emmanuel, MPH, Eleanor M. Wilson, MD, and Shyam Kottilil, MD, PhD ................................................................. 18

Surviving the Daily Email Onslaught
Brijen J. Shah, MD ................................................................. 20

The Current State of Professional Burnout in Gastroenterology
Arthur J. DeCross, MD, AGAF ................................................................. 22

AGA PERSPECTIVES DEPARTMENTS
Classifieds ................................................................. 8

DEBATING
SURVEILLANCE
OF GASTRIC INTESTINAL METAPLASIA
by Ernst J. Kuipers, MD, PhD, AGAF, and M. Brian Fennerty, MD, AGAF
SEE PAGE 4

AGA Perspectives
Vol. 13 No. 4 / August/September 2017

Proper Preparation Strategies for Patients On Chronic Anticoagulation Undergoing Endoscopy

John R. Saltzman, MD, AGAF

Ready Or Not, Here They Are: Anti-TNF Biosimilars for IBD

Mark T. Ostemen, MD, AGAF

Medical Management of Severe Alcoholic Hepatitis

Mack Mitchell, MD

Duration of HCV Therapy: How Short Can Therapy Be and Who Would Qualify?

Benjamin Emmanuel, MPH, Eleanor M. Wilson, MD, and Shyam Kottilil, MD, PhD

Surviving the Daily Email Onslaught

Brijen J. Shah, MD

The Current State of Professional Burnout in Gastroenterology

Arthur J. DeCross, MD, AGAF

AGA PERSPECTIVES DEPARTMENTS

Classifieds

Proper Preparation Strategies for Patients Undergoing Endoscopy

John R. Saltzman, MD, AGAF

This issue of AGA Perspectives is also filled with quick updates on a variety of common clinical issues of importance in every day practice. Dr. John Saltzman provides a succinct update on management strategies for patients undergoing endoscopy in the setting of antiplatelet and anticoagulation therapy. Biosimilars are on their way into clinical practice and Dr. Mark Ostemen provides his perspective on the everyday issues that will come with the arrival of these compounds. In the area of liver disease, colleagues from the University of Maryland examine the topic of shorter duration therapy of HCV and Dr. Mack Mitchell provides an update on where we stand on modern therapy of alcoholic hepatitis.

Finally, this issue addresses two very important topics to gastroenterologists of all ages and in all practice settings. How do you deal with the tidal wave of emails you receive every day and how can you avoid drowning in the deluge? Dr. Brijen Shah provides timely and practical answers to this question. Another “hot topic” in gastroenterology is physician burnout. Dr. Arthur DeCross provides a thought provoking overview of this disturbing problem, which has implications for all of us.

As the summer ends and we head into the fall, I hope you enjoy this issue of AGA Perspectives.

Best,

AGA Perspectives
Vol. 13 No. 4 / August/September 2017

Proper Preparation Strategies for Patients On Chronic Anticoagulation Undergoing Endoscopy

John R. Saltzman, MD, AGAF

Ready Or Not, Here They Are: Anti-TNF Biosimilars for IBD

Mark T. Ostemen, MD, AGAF

Medical Management of Severe Alcoholic Hepatitis

Mack Mitchell, MD

Duration of HCV Therapy: How Short Can Therapy Be and Who Would Qualify?

Benjamin Emmanuel, MPH, Eleanor M. Wilson, MD, and Shyam Kottilil, MD, PhD

Surviving the Daily Email Onslaught

Brijen J. Shah, MD

The Current State of Professional Burnout in Gastroenterology

Arthur J. DeCross, MD, AGAF

AGA PERSPECTIVES DEPARTMENTS

Classifieds

Proper Preparation Strategies for Patients Undergoing Endoscopy

John R. Saltzman, MD, AGAF

This issue of AGA Perspectives is also filled with quick updates on a variety of common clinical issues of importance in every day practice. Dr. John Saltzman provides a succinct update on management strategies for patients undergoing endoscopy in the setting of antiplatelet and anticoagulation therapy. Biosimilars are on their way into clinical practice and Dr. Mark Ostemen provides his perspective on the everyday issues that will come with the arrival of these compounds. In the area of liver disease, colleagues from the University of Maryland examine the topic of shorter duration therapy of HCV and Dr. Mack Mitchell provides an update on where we stand on modern therapy of alcoholic hepatitis.

Finally, this issue addresses two very important topics to gastroenterologists of all ages and in all practice settings. How do you deal with the tidal wave of emails you receive every day and how can you avoid drowning in the deluge? Dr. Brijen Shah provides timely and practical answers to this question. Another “hot topic” in gastroenterology is physician burnout. Dr. Arthur DeCross provides a thought provoking overview of this disturbing problem, which has implications for all of us.

As the summer ends and we head into the fall, I hope you enjoy this issue of AGA Perspectives.

Best,
SURVEILLANCE OF GASTRIC INTESTINAL METAPLASIA

As physicians, we have grown accustomed to the concept of screening for and surveillance of those found to have premalignant conditions with the expectation that by doing so we can prevent cancer and do little if any harm. In reality this concept has rarely been demonstrated to be true and indeed we often do great harm. Examples of this fallacy include the widespread use of prostate-specific antigen (PSA) to screen for prostate cancer (resulting in us resecting many “harmless cancers” while leaving men impotent), mammography starting at age 40 to screen for breast cancer (finding harmless cervical intraepithelial neoplasia lesions resulting in disfiguring surgeries), and in our own field of gastroenterology in screening patients with chronic gastroesophageal reflux disease (GERD) and finding short segment non-dysplastic Barrett’s esophagus (BE) and enrolling those patients in an endoscopic surveillance program (leading to expensive endoscopies, cancer phobia and no evidence...)

ALWAYS - CONTINUED ON PAGE 6

NEVER - CONTINUED ON PAGE 7

SURVEILLANCE SHOULD BE DONE CONSISTENTLY

ERNST J. KUIPERS, MD, PHD, AGAF

Department of Gastroenterology & Hepatology, Erasmus MC University Medical Center, Rotterdam, The Netherlands

Dr. Kuipers has no conflicts to disclose.

International School of Medicine, Indianapolis

M. BRIAN FENNERTY, MD, AGAF

Indiana University School of Medicine, Indianapolis

Dr. Fennerty has no conflicts to disclose.
gastric cancer was common, relatively easy to visualize by fluoroscopy and endoscopy, and we had no invasive screening tools. Studies in the 1960s and 1970s already showed that atrophic gastritis and intestinal metaplasia were precursors to gastric adenocarcinoma, with progression to cancer annually occurring in an average one in 200 patients with more advanced atrophy and metaplasia. Recently, very large population studies confirmed the association between atrophy, metaplasia, and cancer.1 The risk for cancer parallels the severity and extent of intestinal metaplasia, with the highest risk in individuals with marked intestinal metaplasia affecting both antrum and corpus. In later years, the interest shifted towards other gastrointestinal malignancies, in particular esophageal and colorectal adenocarcinoma. In Western countries, there were good reasons for this shift. The incidence of gastric cancer declined while the incidence of esophageal and colorectal adenocarcinoma markedly rose. Similar to premalignant gastric lesions, the incidence of esophageal adenocarcinoma in patients with Barrett’s esophagus was initially reported to be approximately one in 200 patients per year. Later population studies consistently reported incidences around one in 800 patients per year. Studies have shown that these risks differ depending on the characteristics of the population. In the Netherlands, the incidence of esophageal adenocarcinoma occurs only rarely in patients with short segment and non-dysplastic Barrett segment. The second is a male with a 3 cm non-dysplastic Barrett’s segment. Barrett segments are reported to be more marked higher in patients with dysplastic Barrett’s mucosa. Guidelines therefore strictly stratify patients according to these characteristics, but nevertheless recommend surveillance for patients with dysplastic Barrett’s mucosa.

The story for colorectal cancer is similar. The prevalence of adenomatous and serrated polyps and the resulting incidence of colorectal cancer are much higher than for esophageal and gastric lesions. However, colorectal cancer can be removed. This significantly reduces the risk for colorectal cancer. A large U.S. study used 33,870 people to study the characteristic of colorectal cancer. The risk of colorectal cancer within 10 years after adequate colonoscopy approximated one in 2,000 subjects per year. These results and those of similar studies strongly support screening colonoscopy and polyp removal.

This explains why we devote so much of our clinical time and our interest at meetings such as the Digestive Disease Week® to esophageal and colorectal neoplasia. We focus on imaging techniques, endoscopic treatment, quality assurance and guideline development, to name a few. We also focus on specific subgroups at risk for certain cancer such as patients with inflammatory bowel disease. However, the inconsistency in our clinical approach to individual patients remains striking. Let us assume that our Monday morning outpatient clinic includes four patients in their fifties. The first is a woman with a 10-year history of atrophic gastritis, now quiescent colitis. The second is a male with a 3 cm non-dysplastic Barrett’s segment. The third is a female in whom we removed two incipient colorectal adenomas at screening colonoscopy. The fourth is an H. pylori-positive man with dyspepsia and normal endoscopy was normal. We will likely follow guidelines and recommend endoscopic surveillance in the first three patients. When each asks about cancer risks, we will reassuringly say that the risk of cancer in the coming years is very small, likely less than one in 500 patients per year, and that they should thus not be worried. We might add that we used high-resolution equipment, we’re trained to detect lesions, spend much effort on quality assurance and follow guidelines. To each patient, we will likely prescribe H. pylori eradication therapy, and remark that the endoscopy showed no macroscopic lesions. However, even though we used the same equipment, we most likely did not use its full potential to scrutinize the gastric mucosa for dysplastic abnormalities, like we did for the esophagus and colon in our other patients. As a consequence, if we took biopsies, they were not targeted but random (just consider the idea of doing the same in the colon...). If these biopsies reveal atrophic gastritis and intestinal metaplasia, we do not risk stratify our patient and do not recommend surveillance even though atrophy and metaplasia appear severe and affect both antrum and corpus. By the time we end our clinic, we will have used our maximal potential in terms of early diagnosis and prevention for three patients, but not for the fourth. This explains why the rate of gastric cancer after a negative gastroscopy remains at a level that we find completely unacceptably for colorectal cancer after colonoscopy. In our defense, we can say that we were never properly trained in endoscopically visualize and map gastric atrophy and metaplasia, that we need more data to risk stratify individual patients and determine optimal surveillance strategies, and that there is a need for further guidelines on diagnosis and management of premalignant gastric lesions.

We can conclude that atrophic gastritis and intestinal metaplasia are precursor lesions to invasive gastric cancer! Atrophy and metaplasia can be visualized with current endoscopy. There are specific strategies that also allows for targeted biopsy sampling. Patients with advanced atrophy and metaplasia according to the above definition have similar cancer risks as others in our practice, and should thus be managed accordingly recommended by some international guidelines.4 Surveillance is recommended at a three-year interval for subjects with marked intestinal metaplasia in both antrum and corpus. Patients with low- and high-grade dysplasia should receive endoscopic follow-up after 1.5 to 6 months, respectively, combined with resection of visible lesions.

The inconsistency in our clinical approach to individual patients remains striking.

The inconsistency in our clinical approach to individual patients remains striking.

NEVER _CONTINUED FROM PAGE 5_

that improves cancer outcomes). So now we as a gastroenterology community are discussing surveillance of a ubiquitous and even lower risk lesion — gastric intestinal metaplasia or GIM — with short segment non-dysplastic BE? Come on, you cannot be serious! Have we learned nothing from the story of the death of the breast cancer? Let's look at the facts. Gastric cancer is not a common cancer in the Western world or the U.S. (1.7 percent of all cancers) and not all gastric cancers proceed through the intestinal metaplasia (IM) pathway. Furthermore, GIM is not the premalignant lesion, dysplasia in a field of GI M is the premalignant lesion. Twenty-five years ago, we demonstrated that in the U.S., approximately 15 percent of Caucasian adults at very low-risk for gastric cancer have GIM, and as many as 50 percent higher but still low-risk men (Blacks, Latinos, Asians) have GIM. This shows that the prevalence of GIM is high out of 250 million adults in the U.S., somewhere around 50 million harbor GIM. Yet there were only 28,000 cases of gastric cancer this year (and again not all linked to the GIM pathway). Assuming 25 percent of these cancers proceed through a GIM pathway, the incidence of cancer in someone

with GIM in the U.S. is approximately 0.00011. Nearly 8,750 people would have to be screened to detect one case of gastric cancer! So, should we survey everyone with GIM? You’re kidding, right?

So, where does the concept that we should be surveying these folks come from? Not from AGSE — their position is to perform “surveillance endoscopy for patients with GIM who are at increased risk for gastric cancer due to ethnic background e.g. (East Asia, Latin America mountainous regions) or family history. Optimal surveillance intervals have not been extensively studied and should be individualized.” What AGSE is really saying is that we should never test for gastric cancer at all. If these above “survey eligible” populations represent only a small percentage of all our patients with GIM, with GIM.1 I believe this to be the cool recommendation: no surveillance.

I would recommend surveillance only in those very few individuals with GIM associated dysplasia, those with GIM and first-degree relatives with gastric cancer, or those first-generation immigrants from a high gastric cancer incident region that has extensive GIM. Optimal surveillance intervals for these few surveillance candidates are unknown, but for now I would recommend at least yearly surveillance in those with dysplasia (after complete resection of their dysplasia) and surveillance of every two to three years in these few other high-risk GIM individuals.

Remember: above all: first, do no harm.

REFERENCES
1. Fennerty, M.B. Management of precancerous conditions and prevention for three patients, but not for the fourth. This explains why the rate of gastric cancer after a negative gastroscopy remains at a level that we find completely unacceptable for colorectal cancer after colonoscopy. In our defense, we can say that we were never properly trained in endoscopically visualize and map gastric atrophy and metaplasia, that we need more data to risk stratify individual patients and determine optimal surveillance strategies, and that there is a need for further guidelines on diagnosis and management of premalignant gastric lesions.

We can conclude that atrophic gastritis and intestinal metaplasia are precursor lesions to invasive gastric cancer! Atrophy and metaplasia can be visualized with current endoscopy. There are specific strategies that also allows for targeted biopsy sampling. Patients with advanced atrophy and metaplasia according to the above definition have similar cancer risks as others in our practice, and should thus be managed accordingly recommended by some international guidelines.4 Surveillance is recommended at a three-year interval for subjects with marked intestinal metaplasia in both antrum and corpus. Patients with low- and high-grade dysplasia should receive endoscopic follow-up after 1.5 to 6 months, respectively, combined with resection of visible lesions.

The inconsistency in our clinical approach to individual patients remains striking.
GEORGIA
Gastroenterologists

A well-established, thriving two-physician gastroenterology practice with two room endoscopy suite in suburban Atlanta is seeking a well-trained, personable gastroenterologist, with ERCP experience. Additionally, EUS experience highly desirable, but not required.

- Competitive compensation and benefits package.
- Partnership in two years, earlier potential for highly-motivated candidate.
- Practice serves an affluent and diverse community in suburban Atlanta.
- Great location for singles and family. Easy access to downtown Atlanta.
- Practice is growing and progressive with wide and strong referral base.
- Weekend call is one in five.

For more information, please contact Leslie Harris, 404-294-8180, ext. 115 or email lharris@gastrospecialists.com.

KENTUCKY
Gastroenterologists

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

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

Hepatologist

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

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

IBD Specialist

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

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

On Chronic Anticoagulation Undergoing Endoscopy

Aspirin and the thienopyridines (P2Y₁₂ inhibitors) are the main anti-platelet agents. In patients on daily aspirin, there is not an increase in bleeding after upper endoscopy or colonoscopy including with biopsy or removal of small polyps. I do not stop aspirin when given for secondary prophylaxis after a prior cardiac or neurological event, as thrombotic risks from stopping include myocardial infarctions, CVA and death. The thienopyridines inhibit the binding of ADP to the P2Y₁₂ receptor and subsequent activation of the glycoprotein IIb/IIIa receptor and are often given along with warfarin for high-risk conditions undergoing high-risk endoscopic procedures, the warfarin should be discontinued before the procedure and bridging should be considered with standard or low-molecular-weight heparin. The DOACs directly inhibit factor Xa (e.g. rivaroxaban, apixaban and edoxaban) or thrombin (e.g. dabigatran). The oral medications quickly result in anticoagulation and also are relatively quickly cleared in patients with normal renal function. These drugs can be held for one day before low-risk endoscopic procedures and for two to three days before high-risk procedures if renal function is normal, but for more prolonged times if renal dysfunction.

In patients with acute GI bleeding on antithrombotic agents, the management depends on the severity of the bleeding and all of the previously discussed factors. Aspirin can be initially withheld, but should be restarted if given for secondary prophylaxis with one day for low-risk bleeding and within three to seven days for high-risk bleeding, such as bleeding requiring endoscopic therapy. Endoscopic bleeding therapy can be effectively performed with INR ≤ 2.5 and reversal, if needed, is best done with prothrombin complex concentrate. For patients bleeding on DOACs, stopping the DOAC is sufficient in most, although there is an available reversal agent for dabigatran (e.g. idarucizumab) and soon there may be other Xa inhibitors reversal agents available.

All endoscopists need to be familiar with management strategies of antithrombotic medications in patients undergoing endoscopic procedures. An understanding of the bleeding risks of the endoscopic procedure, the thrombotic risk of the patient and the antithrombotic agents allows for an individualized and safe antithrombotic medication is withheld.

The patient’s underlying condition determines the thrombotic risk if the antithrombotic medication is withheld.
Biosimilars

Anti-TNF

Here They Are

QUICK HITS: PATIENT CARE

Takeda and UCB. Dr. Osterman has received a research grant from UCB.

MD

OSTERMAN,

MARK T.

 licensed reference product.”1 As biologic drugs terms of quality, safety and efficacy to an already monoclonal antibody “product that is similar in defines a biosimilar monoclonal antibody as a several factors. The World Health Organization of this change, it is important to consider our eyes. To understand the implications bowel disease (IBD) is changing right before therapies for the treatment of inflammatory available anti-tumor necrosis factor (TNF) available anti-TNF monoclonal antibodies as biosimilar biotherapeutic 1.  World Health Organization.

REFERENCES


3. Ben-Horin, S., Yavzori, M., Benhar, I. et al. A meta-analysis of infliximab cross-react with CT-P13 and vice versa, suggesting that these agents have similar immunogenicity and shared immunodominant epitopes. 2. Second, there are some recently published studies, including a meta-analysis of 11 observational studies1 and results from the prospective Italian cohort, PROSIT-BIO,1 documenting excellent real-world efficacy of CT-P13 in both Crohn’s disease and ulcerative colitis. Thus, even without randomized comparative efficacy data, the use of infliximab biosimilar in IBD seems reasonable.

Another important factor is interchangeability. FDA defines interchangeability as substitution “for the reference product by a pharmacist without the intervention of the health care provider who prescribed the reference product.”9 At the present time, anti-TNF biosimilars are not approved for interchangeability as there are no data for this. In contrast, there are some data regarding single transitions from originator to biosimilar. The recently published NOR-SWITCH randomized controlled trial found that switching from reference infliximab to CT-P13 was not inferior to continued treatment with infliximab in a mixed population of patients with autoimmune disease, although among the subgroup of patients with Crohn’s disease the confidence interval approached inferiority for CT-P13.10 Also worth considering is that U.S. Remicade has undergone multiple evolutions over the years and is no longer the same product as initially created, and that European and U.S. Remicade are not exactly the same product since they are manufactured in different facilities; hence, in some ways these products approach being biosimilars of each other. While the idea of a single transition from originator to biosimilar may be potentially reasonable in certain situations, interchangeability among multiple agents is theoretically more difficult to justify for at least two reasons aside from the lack of data: safety surveillance for individual drugs becomes challenging when making multiple switches, especially if relatively close in time; and even if multiple biosimilars are by definition similar to the reference product, it is not unequivocally apparent that they would necessarily also be biosimilars of each other.

Finally, while in some countries biosimilars may offer substantial cost savings and improve access to anti-TNF therapy, pricing in the U.S. may be neither as homogeneous nor straightforward, given the lack of a single-payer system. The relative cost of biosimilars in the U.S. will likely be determined by negotiations between manufacturers and payors regarding entire portfolios of products and potential discounts that can be provided. Nonetheless, having more competition in the anti-TNF space will likely have certain benefits, such as a drive for competitive pricing in the long term as well as the potential for fulfilling particular data gaps not provided by the reference products.

AGA Takes the Lead in Educating GIs about Interchangeable Biosimilars for IBD

AGA believes that gastroenterologists should have access to all treatments that can benefit patient care. Gastroenterologists and patients rely on biologics to manage IBD, including Crohn’s disease and ulcerative colitis. Biosimilar products, which are “highly similar” to the biologic, have begun to be approved by the FDA for indications, such as IBD. AGA works with the FDA, other regulatory agencies and Congress to ensure that the voice of gastroenterology is heard in relation to biosimilars and interchangeable products.

To prepare for the entry of biosimilars to the market, AGA is taking the lead in educating health-care professionals and patients about biosimilars and how they can be used for IBD patient care.

Review our educational offerings and learn more at www.gastro.org/biosimilars.

Even without randomized comparative efficacy data, the use of infliximab biosimilar in IBD seems reasonable.
Engage and network with accomplished faculty to better understand academic processes and develop the skills necessary to succeed in academic medicine.

Apply online at asw.gastro.org.
Application Deadline: Nov. 1, 2017

Meet your educational needs and maintain professional excellence throughout your career with a diverse, engaging learning platform.

Amazing Flexibility
Access all resources with DDSEP® Complete or buy individual DDSEP® components, including ABIM®-styled mock exams.

Comprehensive
Get an in-depth review of the field with current, comprehensive and case-based content, along with more than 800 exam-style questions.

Web and App Based
You decide when and how you learn with DDSEP® — at your computer or on the go with your mobile device.

Order online today. buyddsep8.gastro.org
**QUICK HITS: PATIENT CARE**

**MEDICAL MANAGEMENT OF SEVERE ALCOHOLIC HEPATITIS**

Acute alcoholic hepatitis is a clinical syndrome characterized by sudden onset of jaundice, malaise, anorexia and occasionally abdominal pain associated with fever, tachycardia, leucocytosis and other evidence of an inflammatory response in an individual who has been drinking heavily within the preceding eight weeks. By definition, serum bilirubin is elevated with modest elevation in aminotransferases less than 400 IU/ml. The AST/ALT ratio is usually greater than 1.5. The term alcoholic hepatitis is also applied to histological changes of steatosis, ballooning degeneration of hepatocytes, infiltration with neutrophils that characterize steatohepatitis. Although not required for the diagnosis of acute alcoholic hepatitis or decisions regarding treatment, liver biopsy can be helpful in patients in whom there are other confounding conditions.

Estimating the severity of alcoholic hepatitis in critically ill patients with high bilirubin and prolonged INR’s guides the need for anti-inflammatory treatments in addition to supportive care for these patients. Laboratory parameters provide more accurate assessment of prognosis than any clinical features. Both the Maddrey discriminant function (MDF) (greater than 32) and the Mayo model for end-stage liver disease (MELD) score (greater than 20) define severe alcoholic hepatitis and high mortality within the first 30 days with supportive treatment alone.

Acute alcoholic hepatitis represents decompensation of underlying alcoholic liver disease in patients with recent heavy drinking. Cirrhosis is present at the time of diagnosis in almost 85 percent of patients with severe alcoholic hepatitis. Normal serum creatinine underestimated the degree of renal impairment in these patients, because muscle mass is often low due to underlying sarcopenia. Acute kidney injury develops frequently in those with severe alcoholic hepatitis and is a harbinger of progression to multi-organ failure syndrome. Pneumonia, urinary tract infections, and spontaneous bacterial peritonitis and bacteremia are also common in these patients and may develop in the second or third week. Some experts classify acute alcoholic hepatitis as a form of acute on chronic liver failure.

Other than recent heavy drinking, the events that trigger the decompensation remain a subject of investigation. Abstinence is critical in long-term prognosis for patients with any form of alcoholic liver disease. Unfortunately, no FDA approved medications have been proven safe to use in patients with advanced alcoholic liver disease, so treatment of the underlying alcohol use disorder should be supportive. Cognitive/behavioral approaches are helpful, but typically patients with alcoholic hepatitis are too ill to begin this treatment immediately. We actively encourage abstinence at the time of diagnosis and continue efforts to engage patients in treatment at every follow-up visit.

Enteral nutritional support in the form of a high calorie (30-40 kcal/kg body weight), high protein (1-1.5 g/kg body weight) diet is recommended and safe in patients with alcoholic hepatitis, even when accompanied by hepatic encephalopathy. Parenteral nutrition provided some benefit in improving biochemical parameters in clinical trials, but did not impact short-term mortality. The gut mucosal barrier in animal models of alcoholic liver disease and in patients with alcoholic hepatitis is impaired and likely contributes to infections in these patients. One of the possible benefits of enteral compared to parenteral nutrition is the favorable impact on the gut mucosa. Micronutrients, particularly zinc, may also restore gut mucosal integrity.

Since most patients with alcoholic hepatitis are zinc deficient, we routinely supplement with 220 mg of zinc sulfate daily.

Careful monitoring for infection, including routine blood cultures at the time of presentation is necessary because of the high risk of infection in these patients. Prompt recognition and treatment of infection is necessary, but we do not use prophylactic antibiotic treatment for more than 48 hours pending results of cultures, since broad spectrum antibiotics increase the risk of C difficile and fungal infections. The high risk of acute kidney injury requires careful attention to fluid balance and avoidance of nephrotoxic agents, including contrast dye. Diuretic therapy in the acute stage of alcoholic hepatitis may be associated with volume depletion and decreased renal perfusion that can precipitate acute kidney injury. In the absence of pulmonary vascular congeion, we avoid diuretics for treatment of ascites and edema. We use both albumin infusion and midodrine for any patient who develops acute kidney injury. Norepinephrine infusion may be used in those with severe impairment.

In those patients not enrolled in clinical trials, we begin anti-inflammatory treatment with 32 mg of methylprednisolone daily in those with an MDF greater than 32 or MELD greater than 20. Most studies and meta-analysis suggest a benefit of glucocorticosteroids on survival within the first 30 days, but not beyond this time. However, glucocorticosteroid therapy increases the risk of infection beginning after the second week of treatment in those who are “non-responders” based on Lille score — a medical tool used to determine mortality risk in patients suffering from alcoholic hepatitis and not reacting to steroid therapy. The Lille score should be assessed at day seven to determine whether continued treatment is likely to be beneficial. Combining glucocorticosteroids with intravenous N-acetylcysteine reduced the risk of infection and improved short-term survival in one study. Shorter durations of treatment combined with enteral nutrition may also provide benefits in short-term survival and theoretically avoid the risk of infection seen with longer treatments. The published trials with pentoxifylline have been disappointing so we no longer use this medication in clinical trials which is combined with other drugs.

A new number of treatments are currently under investigation. These include anakinra, an interleukin 1 receptor blocker, granulocyte colony stimulating factor, amoxicillin, rifaximin, obstetric acid, bovine colostrum and an interleukin 2 analogue. Improved understanding of the pathogenesis of alcoholic liver injury combined with improved recognition and prevention of complications such as infection and acute kidney injury that lead to development of multi-organ failure will hopefully improve the outcome of severe acute alcoholic hepatitis.

**REFERENCES**

# Duration of HCV Therapy

## How Short Can Therapy Be and Who Would Qualify?

**Combination direct-acting antiviral (DAA) therapy of eight to 24 weeks for the treatment of chronic hepatitis C is highly effective. Current guidelines do not encourage treatment for less than 12 weeks. However, mounting evidence indicates that many patients can achieve sustained virologic response (SVR) with only eight weeks of treatment. Thus, treatment for shorter durations may be feasible for select groups of patients in the U.S. and globally.**

Recently, we reviewed the rationale and the clinical evidence for using shorter duration therapy for hepatitis C.1 The rationale for shorter duration therapy includes reducing treatment cost and increasing adherence.1 In the U.S., the wholesale acquisition cost of ledipasvir/sofosbuvir is reduced from $94,500 to $63,000 when treatment is reduced from 12 to eight weeks. Shorter duration therapies may also improve treatment adherence, given that some have argued adherence decreases as dosing frequency and duration increase.2

While several regimens have explored shorter duration therapy, no other regimen is approved for shorter than 12 weeks of therapy. Several attempts have been made to reduce treatment duration below eight weeks in clinical trials.3 While SVR after four or six weeks of therapy have not been comparable to those observed in large clinical trials of patients treated with eight or 12 weeks, these clinical trials have identified potential predictors of SVR with shorter duration treatment such as lower baseline hepatitis C virus (HCV) viral load, younger age, HCV genotype 1b and absence of RAVs that confer greater than 20-fold resistance in vitro.4 So having a predictive algorithm that provides an individualized estimate of SVR with a given DAA regimen and duration based on baseline viral load and host characteristics could streamline clinical decision-making in light of ultra-short duration therapy.5

Recently, a response-guided therapy clinical trial performed in China demonstrated HCV genotype 1b patients without cirrhosis who exhibit an ultra-rapid viral response by the second day of therapy, may be effectively treated for just three weeks with a combination of three DAs.6 Baseline HCV viral load was a predictor of ultra-rapid viral response leading to SVR, which emphasizes that baseline HCV viral load needs to be part of the clinical algorithm, to predict which patients may respond favorably to short duration therapy. Further validation of this concept in larger clinical trials of HCV genotype 1b could be important in wider use of short duration studies for countries where HCV genotype 1b predominates (China, Japan, Mongolia and South Korea).

Just as the current treatment guidelines consider patient characteristics in recommendations regarding durations of 12 to 24 weeks, effective use of shorter DAA treatment durations will likely require identifying the appropriate patient population. A simple, cost-effective clinical algorithm to predict which individuals are likely to respond favorably to shorter duration therapy could provide a simpler management strategy to all type of providers and enhance a broad U.S. uptake of DAA therapy. This algorithm could be based on clinical characteristics such as age, sex, baseline HCV viral load levels, fibrosis stage, HCV genotype, absence of RAVs, and in patients without HIV or HBV coinfection. Such a strategy is preferable over a response-guided therapy from an implementation stand point.

Shortening HCV therapy in targeted populations seems possible and should be further explored. Factors that may predict SVR with ultra-short duration combination DAA therapy (younger age, lower HCV viral load, genotype 1b, no RAVs, no cirrhosis, no decompensation, no HIV or HBV coinfection, and maybe females and IL28B CC genotype) need to be validated further in clinical trials. This will allow the creation of a clinical algorithm to predict which individuals are likely to respond favorably to shorter duration therapy and improve the HCV care continuum and reduce public health burden of the disease.

## References

2. Petersen T, Townsend K, Gordon L, et al. Cost-saving of shorter duration therapies. In the U.S., when the duration of treatment with ledipasvir/sofosbuvir is reduced from 12 to eight weeks, there is a notable reduction in wholesale acquisition cost.
4. Cost Saving of Shorter Duration Therapies

## Cost Saving of Shorter Duration Therapies

In the U.S., when the duration of treatment with ledipasvir/sofosbuvir is reduced from 12 to eight weeks, there is a notable reduction in wholesale acquisition cost.

<table>
<thead>
<tr>
<th>Duration</th>
<th>Cost Saving</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks</td>
<td>$94,500</td>
</tr>
<tr>
<td>8 weeks</td>
<td>$63,000</td>
</tr>
</tbody>
</table>

**While many regimens have explored shorter duration therapy, no other regimen is approved for shorter than 12 weeks of therapy. Several attempts have been made to reduce treatment duration below eight weeks in clinical trials.**

While SVR after four or six weeks of therapy have not been comparable to those observed in large clinical trials of patients treated with eight or 12 weeks, these clinical trials have identified potential predictors of SVR with shorter duration treatment such as lower baseline hepatitis C virus (HCV) viral load, younger age, HCV genotype 1b and absence of RAVs that confer greater than 20-fold resistance in vitro. So having a predictive algorithm that provides an individualized estimate of SVR with a given DAA regimen and duration based on baseline viral load and host characteristics could streamline clinical decision-making in light of ultra-short duration therapy.

Recently, a response-guided therapy clinical trial performed in China demonstrated HCV genotype 1b patients without cirrhosis who exhibit an ultra-rapid viral response by the second day of therapy, may be effectively treated for just three weeks with a combination of three DAs. Baseline HCV viral load was a predictor of ultra-rapid viral response leading to SVR, which emphasizes that baseline HCV viral load needs to be part of the clinical algorithm, to predict which patients may respond favorably to short duration therapy. Further validation of this concept in larger clinical trials of HCV genotype 1b could be important in wider use of short duration studies for countries where HCV genotype 1b predominates (China, Japan, Mongolia and South Korea).

Just as the current treatment guidelines consider patient characteristics in recommendations regarding durations of 12 to 24 weeks, effective use of shorter DAA treatment durations will likely require identifying the appropriate patient population. A simple, cost-effective clinical algorithm to predict which individuals are likely to respond favorably to shorter duration therapy could provide a simpler management strategy to all type of providers and enhance a broad U.S. uptake of DAA therapy. This algorithm could be based on clinical characteristics such as age, sex, baseline HCV viral load levels, fibrosis stage, HCV genotype, absence of RAVs, and in patients without HIV or HBV coinfection. Such a strategy is preferable over a response-guided therapy from an implementation stand point.

Shortening HCV therapy in targeted populations seems possible and should be further explored. Factors that may predict SVR with ultra-short duration combination DAA therapy (younger age, lower HCV viral load, genotype 1b, no RAVs, no cirrhosis, no decompensation, no HIV or HBV coinfection, and maybe females and IL28B CC genotype) need to be validated further in clinical trials. This will allow the creation of a clinical algorithm to predict which individuals are likely to respond favorably to shorter duration therapy and improve the HCV care continuum and reduce public health burden of the disease.

## References

2. Petersen T, Townsend K, Gordon L, et al. Cost-saving of shorter duration therapies. In the U.S., when the duration of treatment with ledipasvir/sofosbuvir is reduced from 12 to eight weeks, there is a notable reduction in wholesale acquisition cost.
PROFESSIONAL TIPS

Surviving the Daily Email Onslaught

BRIJEN J. SHAH
Mount Sinai Medical Center

As a disclaimer, I am not an email expert or aficionado. I am someone who constantly battles the daily onslaught of managing three email accounts, which includes my work and professional life. I have learned some tips from trial and error and in talking to others, and I have found that by following these steps, I am able to better work email into my life instead of the other way around. Depending on your email program and work style, try a few out and see if this helps to ease the email pain!

1. Be deliberate when checking email.

I have learned some tips from trial and error by following these steps, I am able to better manage my email instead of the other way around. Depending on your email program and work style, try a few out and see if this helps to ease the email pain!

2. Take action when managing email.

Email programs allow you to customize email and message portals are good for short, quick questions and issues. However, for more complex issues, I recommend having a scheduled time to read and respond to email. I look at email between meetings and patients, schedule time to read and respond to email. I build in 30 minutes during the day and 30 to 45 minutes at the end of the day to focus on the task of reading and responding to email. At other times, I am scanning messages to look for any urgent messages (patient calls, meeting changes, urgent requests from those I report to).

3. Create folders.

Creating folders and subfolders will help you to keep organized. I have folders for each of my major responsibilities and then subfolders within each. For example, I have a folder for third-year medical student teaching and within that, one for the clerkship, one for a course I co-direct and another for the GI elective.

4. Use delayed delivery.

Email programs will allow you to write an email and then specify a future date and time to send the email. This feature is great to use when you know that a reminder is needed to go out for a deadline. Instead of writing this email in a week, write the email today and have the program send it in a week. I have used this feature to send emails to remind colleagues to submit schedule or call requests. You can use this feature to send yourself an email reminder as well for large tasks that require planning. Most calendar programs will have a reminder pop up, however, if you work better through an email reminder, send yourself an email with delayed delivery.

5. Keep recurrent emails for future use.

Email programs will allow you to send your self an email with delayed delivery. Instead of writing this email in a week, write it. You need to build in time to go back and read these that week.

6. Flags.

Email programs allow you to customize a color-coded flag system. The messages can then be sorted by flag color. This tool can help you to mark items you need to handle later. For example, a message may contain a report or article you need more time to read. Create a color category “To read later”, mark the message and then set aside time later to read it. You need to build in time to go back and read these that week.

7. Don’t play email ping pong.

Part of managing email is knowing when not to use email as the way to communicate. Email does not convey tone and lacks the context clues to make meaning of the message. If there is an email exchange that goes on beyond three to four messages, I suggest a brief call to discuss the issues. I also let my patients know that email and message portals are good for short, quick questions and issues. However, for more extended discussion an office discussion or phone call is more effective or appropriate.

8. Don’t be the person who group replies or replies simply to show you are checking your email. Sometimes, it is important to send a quick, short reply to acknowledge a request; however, part of managing your own email is to not be a burden on others. Keep in mind that the receiver of your email may feel obliged to reply back to you or to a group, which can further burden your inbox.

9. Let your recipient know if you expect a response or not, and let that person know if the response should be via email or by other means. Sometimes the best way to manage your own life is to give guidance to those in your life. When sending out an informative email, add a note that says there is no need to reply. If you expect an in-person response at a meeting or via a phone call, let the recipient know that in your email. If you need an email response, provide a timeline for when you hope to hear back from the person. Designing so offers a courteous way to help the other person manage his or her email, while also communicating with you more effectively.

10. Start fresh.

If you have emails that are unread from months or years back, it is unlikely that they have any relevance today or in the future. Mark them as read, but leave them available for future searches. The reduction in the overall number of unread emails can be a huge mental relief, and it can help you to better manage your current emails.

REFERENCES

1. Redbooth. 10 Tips for Managing Email.
2. PC Magazine. How to Manage Email Overload
3. Leadership Thoughts. How to Manage Email Overload.


Order your resources today at www.gastro.org/PGCR

THE FULL SCOPE OF GI ADVANCES

RESOURCES

Experience the Live Course From Home
eSyllabus • USB Online Sessions

The Current State of Professional Burnout in Gastroenterology

Chances are good that either you, or someone you work with, are suffering from some degree of burnout. Chances are even better that you don’t know it. Burnout isn’t the same as stress. It’s not about being tired, and it’s not about being depressed. Burnout is a state of emotional and mental exhaustion in your professional life, manifest by a loss of joy and meaning in your work; a tendency to withdraw and depersonalize patients and colleagues as objects or obstacles, and a lowered sense of personal accomplishment or self-worth.

If burnout were just a result of exceeding a certain threshold of exposure to the accumulated stresses and failures in one’s professional life, then we might expect burnout to increase in prevalence over the course of a career. Medicine is a stressful job. So maybe we physicians should come to expect a certain amount of burnout, which will increase over time as a career hazard, the way we’ve come to recognize the risks of higher rates of divorce, depression and suicide within our profession?

But that’s not what’s going on. Something’s not right out there. Burnout is being reported in excess of 50 percent among physicians — and the rates may be highest in young physicians, with even residents and medical students reporting burnout rates of 30 to 40 percent. The consequences of burnout include increased rates of medical errors, decreased patient satisfaction, decreased physician leadership and innovation, and increased rates in physician suicide, depression and substance abuse, as well as Exodus from the work force.

This has generated tremendous concern over the burnout phenomenon among medical schools, training programs, hospitals and health care systems.

The AGA Institute Education and Training Committee surveyed gastroenterologists to gain an understanding of how burnout was specifically impacting our specialty, with special attention to gender, career stage, contributors to burnout and the consequences of burnout on our lives. Over 600 gastroenterologists answered the survey. The results are profound and deeply troubling. What follows is a mere overview of the results, but I hope it serves to further discussions and awareness around this quiet epidemic.

We found no significant differences in the prevalence of burnout throughout the different career stages. Shockingly, 50 percent of GI fellows reported burnout, which was not statistically different than rates reported by attending physicians at any stage of their career. This is among the more counter-intuitive (and yet consistent) findings in burnout research. We require a greater understanding of why our trainees would report such a high rate of burnout. Do we cast another stone at the tired and overplayed millennial generation explanation? Or is there something more insidious that has changed in the process of medical education? Is it possible that our trainees are now so over-supervised that they have been relieved of taking responsibility for decision making, which includes the positive consequences of building confidence and self-affirmation? Have their work hour limitations created shift workers without ownership of the patient? Have we deflected and deformed patient interactions to a computer documentation work flow? Have we been robbing trainees of burnout.

The Burnout Breakdown

- For 6 percent of total respondents — difficulty or stresses associated with mastering and performing endoscopic procedures is a top driver of burnout.
- For 9 percent of total respondents — medical knowledge component of practice is a top driver of burnout.
- For 42 percent of total respondents — increasing imposition of external regulatory burdens is a top driver of burnout.
- For 50 percent of total respondents — increasing sacrifice of personal time for work-related activities is a top driver of burnout.

The Gender Breakdown

- 51 percent of all males surveyed reported experiencing burnout.
- 62 percent of all females surveyed reported experiencing burnout.
HARVONI is the #1 prescribed treatment for HCV GT 1 patients in the US.a
EPCLUSA is the first and only pan-genotypic single-tablet regimen for patients with chronic HCV 2
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. 1,2,7

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

Please see Brief Summary of full Prescribing Information for HARVONI and EPCLUSA including BOXED WARNING on Hepatitis B reactivation.

Please visit transformingtreatment.com to learn more.

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

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

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

Although a lot has been published on the drivers of burnout, very little information published has been subspecialty specific. Among gastroenterologists, we found the top drivers of burnout to be 1) the increasing sacrifice of personal time for work-related activities (50 percent of respondents), a complaint which I suspect has increased due to electronic medical records, and 2) the increasing imposition of external regulatory burdens (42 percent). These factors least likely to be associated with driving burnout were any sense of difficulty or stress associated with mastering and performing endoscopic procedures (6 percent of respondents), as well as the medical knowledge component of practice (9 percent).

Lastly, we wanted to examine the impact of burnout on our professional and personal lives. We found that burnout had the greatest detrimental impact on our overall quality of life, as well as our likelihood to exercise, pursue personally satisfying hobbies and volunteer activities. Gastroenterologists were most likely to preserve and protect their family relationships in the face of burnout. Two very important observations arise from this — faced with the stresses leading to burnout, 1) we are prone to preserve and value our family relationships, but at the expense of sacrificing activities that also likely protect us to some degree from burnout as well as depression, and 2) any threats or disruptions to the safety lines symbolized by these family bonds (relationship discord, divorce, illness, death) may threaten a more abrupt collapse of those supports that protect us from burnout and depression.

Please visit transformingtreatment.com to learn more.

Research Funding Opportunity

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

SEPT. 8, 2017
• AGA Research Scholar Award ($270,000)
• AGA-Rady Children’s Institute for Genomic Medicine Research Scholar Award in Pediatric Genomics ($270,000)
• AGA-Takeda Pharmaceuticals Research Scholar Award in Inflammatory Bowel Disease ($270,000)

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

A CURE FOR EVERY TYPE™

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

HARVONI is the #1 prescribed treatment for HCV GT 1 patients in the US3,a
EPCLUSA is the first and only pan-genotypic single-tablet regimen for patients with chronic HCV2
• 97% overall cure (SVR12) rate in GT 1 subjects with HARVONI (n=1042/1079; ION-1, -2, -3)4-6
• 99% and 95% overall cure rates in GT 2 and GT 3 subjects, respectively, with EPCLUSA (n=397/411; ASTRAL-2, -3)2

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

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

See full study information on following pages.

Cure = 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

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

• The recommended treatment duration for HARVONI is 12 weeks for adult TN GT 1 patients without cirrhosis or with compensated cirrhosis. Eight weeks can be considered for adult TN GT 1 patients without cirrhosis who have pre-treatment HCV RNA ≤5 million IU/mL.

• HARVONI is RBV-free, regardless of prior HCV treatment history, the presence of compensated cirrhosis, or GT 1 or 2a subtype.

• Adverse reactions (all grades) reported in ≥5% of GT 1 subjects receiving 8, 12, or 24 weeks of treatment with HARVONI (n=1,432): fatigue (15%-18%), headache (11%-17%), nausea (6%-9%), diarrhea (3%-7%), and insomnia (3%-6%).

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

ION-1: TN subjects (N=647) without cirrhosis or with compensated cirrhosis received HARVONI for 8 weeks, HARVONI + RBV for 8 weeks, or HARVONI for 12 weeks. These studies did not include subjects who were liver transplant recipients and/or with decompensated cirrhosis (Child-Pugh B or C). Sustained virologic response (SVR2) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the end of treatment. Achieving SVR is considered a virologic cure.

IMPORTANT SAFETY INFORMATION FOR HARVONI AND EPCLUSA

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

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

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 Antivirus: 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 advanced, treatable clinic 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 Pgp 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 CYP3A, CYP2C8 or CYP3A4 may significantly decrease sofosbuvir and/or velpatasvir plasma concentrations.

References:


89% of GT 1-6 subjects overall achieved a cure across three phase 3 trials (n=1079/1079; ASTRAL-1, -2, -3). EPCLUSA offers a once-daily, single-tablet regimen without IFN or RBV, regardless of prior HCV treatment experience or the presence of compensated cirrhosis.

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

• The adverse reactions observed in subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1, with the exception of headache, which was observed in ≥5% of subjects treated with EPCLUSA.

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, 3, 4, or 6 subjects (N=740). GT 1, 2, 3, 4, or 6 subjects were randomized 1:1 to receive EPCLUSA or placebo for 12 weeks. GT 5, 6 subjects received EPCLUSA for 24 weeks. Overall SVR was 99% (n=740/742).

ASTRAL-2: open-label trial in GT 2 subjects (N=286). Subjects received EPCLUSA or SOF + RBV for 12 weeks.

ASTRAL-3: open-label trial in GT 1 subjects (N=522). Subjects received EPCLUSA for 12 weeks or SOF + RBV for 24 weeks. SVR12 for EPCLUSA ranged from 98% (TE with compensated cirrhosis) to 98% (TN without cirrhosis).

These studies did not include subjects with decompensated cirrhosis. Sustained virologic response (SVR2) was the primary endpoint and was defined as HCV RNA <25 IU/mL at 12 weeks after the end of treatment. 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 anemia.

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

DRUG INTERACTIONS

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

• Coadministration of EPCLUSA is not recommended with proton-pump inhibitors or alfavirin due to decreased concentrations of velpatasvir; or with tiloposide due to increased concentrations of tipranavir.

• Coadministration of HARVONI is not recommended with co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate due to increased concentrations of ditivasvir and/or simeprevir due to increased concentrations of mesorasin and/or tipranavir.

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

See what’s possible at hcp.epclusainfo.com

Please see Brief Summary of full Prescribing Information for HARVONI and EPCLUSA, including BOXED WARNING, on the following page.
The safety assessment of HARVONI was also reviewed. These events have resulted in fulminant hepatitis, hepatic failure, and death. Most common adverse reactions occurring in at least 5% of subjects receiving HARVONI for 12 weeks in GT 1 or 4 Subjects with HCV/HIV-1 Co-infection (ION-4):

- Nausea (5% or 1% vs 0%)
- Anemia (5% or 1% vs 0%)
- Dizziness (5% or 1% vs 0%)

GT 1 Treatment-Related Subjects with Cirrhosis (SIRUS):

The safety assessment of HARVONI with or without ribavirin (RBV) was based on a randomized, double-blind, placebo-controlled trial. Subjects were randomly assigned to receive HARVONI once daily for 24 weeks plus RBV, HARVONI plus RBV for 12 weeks, or RBV alone. Subjects with cirrhosis (Child-Pugh 10-15) were enrolled. The most common adverse reactions occurring in at least 5% greater frequency reported in subjects receiving HARVONI for 24 weeks compared with RBV alone included anemia (15% vs 0%), nausea (9% vs 1%), vomiting (6% vs 1%), and vomiting (6% vs 1%). In the treatment of cirrhotic patients, including those with compensated cirrhosis, the potential for drug interactions associated with the concomitant use of multiple medications, significant renal impairment or ESRD.

If HARVONI is administered with RBV, the combination regimen has not been established. Consider alternative HCV or antiretroviral therapy to reduce the risk of HARVONI exposure to the mother, fetus, or newborn. No adequate human data are available to establish whether or not HARVONI poses a risk to pregnancy outcomes. Refer to the RBV prescribing information. No adequate human data are available to establish whether or not HARVONI poses a risk to pregnancy outcomes. Refer to the RBV prescribing information.

Lactation: It is not known whether the components of HARVONI or RBV are excreted in human milk. Mothers should be advised that breast milk should be considered radio-opaque in the presence of breastfeeding should be considered along with the mother's clinical judgment about the need for breastfeeding. List of Pregnancy Categories: RBV is contraindicated in pregnant women and in men whose female partners are pregnant. The safety of HARVONI in pregnant women has not been established. Consider alternative HCV or antiretroviral therapy to reduce the risk of HARVONI exposure to the mother, fetus, or newborn. No adequate human data are available to establish whether or not HARVONI poses a risk to pregnancy outcomes. Refer to the RBV prescribing information. No adequate human data are available to establish whether or not HARVONI poses a risk to pregnancy outcomes. Refer to the RBV prescribing information.
Due to amiodarone’s long half-life, patients discontinuing amiodarone who need to start amiodarone therapy due to no other alternative viable treatment options and who will be coadministered discontinuation of HCV treatment. The mechanism for this effect is disease may be at increased risk for symptomatic bradycardia with or those with underlying cardiac comorbidities and/or advanced liver occurred within hours to days, but cases have been observed up to 2 weeks following treatment with EPCLUSA and ribavirin (RBV) combination regimen is contraindicated in pregnant women and in men whose female partners are pregnant. Refer to the RBV prescribing information for a full list of the warnings and precautions for RBV. WARNINGs and PRECAUTIONs: of HBV infection before initiating treatment with EPCLUSA. HBV reactivation occurring in patients with a prior history of HBV infection has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with EPCLUSA in these patients is unknown. HBV reactivation is characterized as an abrupt increase in HBV replication and may result in severe hepatitis and/or fulminant hepatic failure. In patients with resolved HBV infection, reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increase in aminotransferase levels; and, in severe cases, increase in bilirubin levels, liver failure, and death. Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating treatment with EPCLUSA. In the presence of evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during or within 12 weeks of discontinuation of antiretroviral regimen. The safety assessment of EPCLUSA in clinical trials 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 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 severe renal impairment. Monitoring for safety and efficacy of EPCLUSA have not been established in patients with end-stage renal disease (ESRD). Refer to RBV prescribing information for the dosing of EPCLUSA in these patients. Hepatic Impairment: No dosage adjustment of EPCLUSA is required for patients with moderate to severe hepatic impairment (Child-Pugh Class B or C, or severe hepatic impairment (Child-Pugh Class C)).
Register for the Inaugural Crohn’s & Colitis Congress™

Expand your knowledge, network with IBD leaders, and get inspired to improve patient care. This new conference is a comprehensive, collaborative meeting that will cross disciplines and appeal to all levels of IBD health-care professionals. Pre-Congress workshops are also available for selection.

SESSIONS WILL COVER:
- Management of complicated IBD
- Defining optimal treatment algorithms
- Clinical and research challenges

Register at crohnscolitiscongress.org. Save up to $175 if you register by Dec. 8. Abstract submissions begin mid-August and end Oct. 31.