THE RIGHT FIT

Is FIT testing the best tool for general colon cancer screening?

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THE RIGHT FIT

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Note From the Editor

March is Colorectal Cancer Awareness Month, and this issue of AGA Perspectives starts off with an insightful point-counterpoint debate of the merits of FIT testing versus colonoscopy for colon cancer prevention. Compelling arguments for both sides of this debate are presented by Drs. Douglas Rex and Douglas Robertson. This debate is especially topical given the ongoing drama in Washington, DC regarding the Affordable Care Act and the implications for further dramatic health-care reform. Speaking of the evolving future of health care, who better to address this than former AGA President John Allen who provides his unique perspective on the future of GI care as we move forward in these uncertain times. Dr. Allen has made numerous contributions to the AGA membership to help us navigate the challenges in the coming years.

Have all the problems of HCV therapy been solved with the recent dramatic advances in antiviral therapy? To provide a glimpse into what lies ahead in 2017, Dr. Anna Lok provides her insights into evolving areas of HCV treatment that we may expect to see this year. Also in hepatology, my colleagues Drs. Therese Bitterman and David Goldberg provide the readership with unique perspectives on organ allocation for end-stage liver disease, which could lead to a paradigm shift in our thinking on this topic.

Just like in HCV, there has been an exciting proliferation of pharmacologic agents to treat IBD. This newfound abundance of choices presents a whole new set of problems, including how to sequence these drugs and what to do when treatment fails. The latter point is addressed in a thoughtful commentary by Dr. Jean-Paul Achkar.

Finally, Dr. Kara Gross Margolis, one of the participants in last year’s AGA Future Leaders Program, provides us with the unique perspective of a pediatric gastroenterologist on the potential childhood roots of diseases encountered by adult gastroenterologists.

As DDW approaches, these contributions provide a glimpse into the future of digestive diseases in these exciting times. If we cross paths at the meeting, please introduce yourself. I welcome all feedback from our AGA Perspective readers.

Gary W. Falk, MD, MS, AGAF
Editor
@GFAgapers

We welcome member feedback on all of the perspectives presented in this issue. Send your letters and comments to communications@gastro.org and include “AGA Perspectives” in the subject line.

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Is FIT testing the best tool for general colon cancer screening?

Colonoscopy Is a Better Choice Than FIT for Opportunistic CRC Screening

Douglas K. Rex, MD, AGAF

In Australia and some European countries, colorectal cancer (CRC) screening occurs in an organized or programmatic setting, usually funded by the national government. Organized screening commonly relies on fecal occult blood testing (FOBT) as the primary means of screening, and usually the fecal immunochemical test (FIT). FIT is a good option for these programs as it is inexpensive, outperforms the guaiac-based tests and has high specificity. These countries with organized screening programs often have limited resources for primary colonoscopy screening. FIT screening focuses colonoscopy resources on a high-prevalence population that benefits most from the therapeutic potential of colonoscopy. Several randomized trials comparing FIT to colonoscopy for endpoints of CRC incidence and mortality reduction are in progress.

In the U.S., there is some organized screening — particularly in large health plans like Kaiser — but most screening originates in the opportunistic setting. Opportunistic colonoscopy is a better choice than FIT for CRC screening. Perhaps the easiest defense for those of us who are enthusiastic about stool-based screening is the quality of evidence supporting it. There are at least three high-quality, large-scale randomized controlled trials that unequivocally demonstrate the effectiveness of programmatic fecal occult blood testing (FOBT) in reducing death from CRC. Moreover, those results were obtained with conventional guaiac FOBT that relies on indirect evidence for blood in the stool. A major advantage of FIT relative to such testing is that it directly assesses the presence of human hemoglobin in stool. That mechanistic difference translates into a host of benefits that result in FIT being a better test than conventional FOBT (table). It recently led an effort by the U.S. Multi-Society Task Force (USMSTF) on Colorectal Cancer.
Colonoscopy Is a Better Choice Than FIT for Opportunistic CRC Screening

The high utilization of colonoscopy in population surveys suggests that this “colonoscopy first, fecal test second” approach has been the predominant approach to screening in the U.S. for some time.

Options are presented to patients along with the strengths and weaknesses of each test. Colonoscopy and FIT should likely both be discussed in this approach, and increasing the number of options discussed beyond two has little value. The other approach is the risk-stratified approach, in which colonoscopy is offered to patients who are estimated (based on modeling) to have a high prevalence of advanced neoplasia, while FIT is offered to patients estimated to have a low prevalence. Again, systems to measure and ensure these levels of adherence are not currently in place in the opportunistic-screening setting in the U.S.

The most important issue for the primary-care physician relying on colonoscopy for screening quality measurements. For example, the U.S. Multi-Society Task Force on Colorectal Cancer has recently recommended that at least 60 percent of patients offered FIT should complete the test, that the rate of returned FIT tests that cannot be processed for any reason should be less than 5 percent, and that at least 80 percent of patients with positive FITs should undergo colonoscopy. Again, systems to measure and ensure these levels of adherence are not currently in place in the opportunistic-screening setting in the U.S.

Advantages of FIT relative to conventional guaiac FOBT

<table>
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<th>Biologic Advantage</th>
<th>Clinical Improvement</th>
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<tr>
<td>Directly measures human hemoglobin</td>
<td>High sensitivity for cancer even with single sample testing with some devices (improved compliance)</td>
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<tr>
<td>No need to adjust diet (improved compliance)</td>
<td>Maintains specificity even at high levels of sensitivity (fewer false positives thereby requiring fewer repeat tests)</td>
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<tr>
<td>Hemoglobin released from upper GI tract</td>
<td>No need to adjust drug intake like NSAIDs or anticoagulants (improved compliance)</td>
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<tr>
<td>Hemoglobin measurement can be quantified</td>
<td>Fewer false positives from the upper GI tract (i.e., improved specificity)</td>
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<td>Hemoglobin measurement can be automated</td>
<td>Definition of a positive test can be matched to colorectal cancer risk</td>
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<tr>
<td>Reduces the likelihood thatchema results are impacted by quality control issues</td>
<td>Opportunity to use quantitative value to stratify risk</td>
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| Maintains specificity even at high levels of sensitivity (fewer false positives thereby requiring fewer repeat tests) | Reduces risk of repeat FOBT falls off dramatically in the average-risk screening setting in the U.S.

Colonoscopy and FIT should be the key elements of perhaps all screening programs. The most relevant question is not whether one or the other is the best or only way to screen for CRC, but rather how the two tests will be presented to patients who are screening candidates. For approximately two decades in the U.S., most physicians have utilized the sequential approach to making the screening offer, in which colonoscopy is offered first and FIT (or perhaps another test) is offered to those who decline colonoscopy. The sequential method of offering screening has the advantage of both maximizing overall adherence as well as adherence to the most effective test (colonoscopy). The sequential approach has been advocated by the American College of Gastroenterology. The high utilization of colonoscopy in population surveys suggests that this “colonoscopy first, fecal test second” approach has been the predominant approach to screening in the U.S. for some time. Although screening in the opportunistic setting is often considered inferior to organized screening by experts, the U.S. has utilized this format – and usually by sequential testing based on colonoscopy first – to reach the world’s highest participation rates in screening and the world’s largest declines in colorectal cancer incidence and mortality (3 to 4 percent per year since 2000).

There are at least two other legitimate approaches to screening in the opportunistic setting. One is the multiple options approach, in which two or more colonoscopies and FIT should likely both be discussed in this approach, and increasing the number of options discussed beyond two has little value. The other approach is the risk-stratified approach, in which colonoscopy is offered to patients who are estimated (based on modeling) to have a high prevalence of advanced neoplasia, while FIT is offered to patients estimated to have a low prevalence. Again, systems to measure and ensure these levels of adherence are not currently in place in the opportunistic-screening setting in the U.S.

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A major disadvantage of both the multiple options and the risk-stratified approach is the greater need for primary-care physicians to develop and adhere to FIT screening options are presented to patients along with the strengths and weaknesses of each test. Colonoscopy and FIT should likely both be discussed in this approach, and increasing the number of options discussed beyond two has little value. The other approach is the risk-stratified approach, in which colonoscopy is offered to patients who are estimated (based on modeling) to have a high prevalence of advanced neoplasia, while FIT is offered to patients estimated to have a low prevalence. Again, systems to measure and ensure these levels of adherence are not currently in place in the opportunistic-screening setting in the U.S.

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In summary, sustained adherence to annual FIT is poor outside the organized-screening setting. Although the long-term relative benefits and harms of colonoscopy and FIT are still unknown and under study, offering colonoscopy first — followed by FIT or another test to those who decline colonoscopy — has been enormously successful in the U.S. The opportunistic-screening setting widely in place in the U.S. is ideally suited to colonoscopy screening.

REFERENCES
1. Hewitson, P., Glasziou, P., Irwig, L., Towler, M., Bell, R., & Irwig, J. (2016). Adherence to competing strategies for colorectal cancer screening (NCT01239082), which aims to enroll 50,000 average-risk veterans to either initial-trial (NCT01239082), which aims to enroll for the U.S.-based effort called the CONFIRM trial. Colorectal cancer screening: a head-to-head study like CONFIRM may one day determine the best test for screening. In the interim, providers should have no hesitation recommending FIT to their patients as a primary screening test for CRC. The test is “simple and safe and RCT-level evidence” supports its use. Given what we know, those advising patients about screening should follow the guidance of the USPSTF, offer options and solutions.

In the U.S., colorectal cancer is the third most common cancer diagnosed among men and women and the second leading cause of death from cancer. Colorectal cancer largely can be prevented through routine screening.

To help your patients, AGA provides credible, accessible education information on the following colorectal cancer topics in English and Spanish.

- What is Colorectal Cancer?
- Symptoms
- Risk Factors
- Getting Tested
- Prevention

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Medical treatment options for patients with inflammatory bowel diseases (IBD) — Crohn’s disease and ulcerative colitis (UC) — have rapidly expanded with several different classes of medications now available. Traditionally, conventional therapy has consisted of mesalazine, steroids, and immunomodulators, but in the era of biologic therapy, new options are available. However, variability remains in approaches to optimizing treatment in patients who don’t respond to initial conventional therapies. The purpose of this review is to give a perspective on how to best approach such situations.

First, prior to making changes in medical therapy in patients who appear not to be responding to conventional treatment, it is important to assess for nonadherence with therapy and to consider possible superimposed etiologies that can mimic symptoms of IBD. The prevalence of nonadherence to medical treatment options for patients with inflammatory bowel diseases (IBD) — Crohn’s disease and ulcerative colitis (UC) — has rapidly expanded with several different classes of medications now available. Traditionally, conventional therapy has consisted of mesalazine, steroids, and immunomodulators, but in the era of biologic therapy, new options are available. However, variability remains in approaches to optimizing treatment in patients who don’t respond to initial conventional therapies. The purpose of this review is to give a perspective on how to best approach such situations.

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The Dilemma of Organ Allocation for Liver Transplantation

The supply of deceased-donor organs in the U.S. is dwarfed by the demand for lifesaving transplants. Thus, transplant physicians are charged with the responsibility of efficiently allocating these scarce resources. However, when a deceased donor becomes available, not all organs are allocated in the same manner. The Lung Allocation Score prioritizes waitlisted candidates according to the survival benefit of receiving lung transplantation, while organ quality is matched to estimated post-transplant survival for those awaiting kidney transplantation (with the top 20 percent of kidneys being allocated first to patients with 20 percent highest predicted post-transplant survival). Both of these systems ensure efficient organ utilization by considering expected post-transplant outcomes. Conversely, the allocation process for liver transplantation operates according to the principle of the ‘sickiest first,’ where the likelihood of receiving a liver is determined by the risk of waitlist mortality and estimated by the Model for End-Stage Liver Disease (MELD) score. Without considering post-transplant outcomes, this process is unable to maximize potential life-years gained, and the end result is an inefficient utilization of one of the scarcest resources in medicine.

In the last decade, efforts have been made to improve the efficiency and equity of the allocation system beyond conventional MELD-based prioritization. Organ-sharing policies, such as Share 35, mandate that organs be allocated outside of their procurement areas available loco-regional therapies, the potential for complete eradication of early HCCs is high, such that the survival benefit of liver transplantation in 80 percent of these patients is negligible at best.7 The policy changes over the last decade have taught us that the dilemma of organ allocation for liver transplantation has yet to be solved.

Though it was initially intended to provide prompt transplantation and avoid the risk of waitlist dropout due to metastatic disease, this policy has led to significant disparity between HCC and non-HCC candidates. And this policy has led to significant disparity between HCC and non-HCC candidates. And despite numerous revisions (the latest of which occurred less than a year ago) the allocation process for HCC candidates remains imperfect. Not only are non-HCC candidates likely to be wait-listed overall, but they must also develop far greater severity of illness to reach the same MELD score as HCC candidates. Moreover, with current advanced diagnostic techniques and readily available loco-regional therapies, the potential for complete eradication of early HCCs is high, such that the survival benefit of liver transplantation is often described as a zero-sum game, where the allocation of an organ to one candidate inherently denies it to another. Therefore, how to most effectively and equitably allocate this scarce resource remains a source of contentious debate: Are the MELD ≥35 patients too sick while those with HCC not sick enough? Perhaps the primary issue at hand is in fact the measure by which candidates are prioritized. Incorporating expected post-transplant outcomes into the equation has the potential to level the playing field and maximize the utility of the organ-allocation system. It may come as no surprise that most treatment decision-making in medicine is influenced by an assessment of anticipated benefit. For example, a cardiothoracic surgeon would never recommend complex bypass surgery to a patient with advanced coronary disease unless clear improvements in health and functional status were expected. The risk-benefit determination with respect to liver transplantation should be no different.

Thus, as the liver-transplantation community looks toward the future state of organ allocation, there must be universal acceptance that our prior policy modifications have been insufficient. We must not only learn from our colleagues in other transplant subspecialties, but also think outside the box. A challenging first step is to clearly define what constitutes an acceptable post-transplant outcome for our liver-transplant recipients.
A s the underlying pathologies of common GI diseases are elucidated, it has become increasingly clear that many prevalent GI conditions first diagnosed in adult practice find their roots during development — from the prenatal period through childhood. Genetic variants or the presence of stressors during these key developmental stages play important roles in negative GI-health outcomes.

Irritable bowel syndrome (IBS) is a prime example of a common developmental GI condition in adults. IBS affects approximately 11 percent of the general population. Despite the fact that IBS is one of the most common problems treated by adult gastroenterologists, data supports the notion that IBS is the product of interactions that occur long before adulthood, with their foundation rooted in genetic variants or negative childhood exposures.

Although the precise genic causes of IBS remain elusive, there is considerable evidence supporting their contribution to both IBS predisposition and pathogenesis. Clustering of IBS in families supports a heritable component as do twin studies that demonstrate a higher concordance among monozygotic compared to dizygotic twins. Twin studies have also revealed that differences can exist between IBS-discordant twins in utero; low birth weight has been associated with the development of IBS, as well as anxiety and depression. These studies support the idea that hypothalamic–pituitary–adrenal axis dysfunction, which is hypothesized to be integral to IBS pathophysiology, may be the connection between impaired fetal development, IBS risk and the association of IBS with anxiety and depression. Studies examining genetic abnormalities have focused primarily on single nucleotide polymorphisms on genes affecting neuronal function, the intestinal barrier and the serotonergic system and immunity.

Genetics, however, are usually not the sole determinant of chronic GI diseases, including IBS. Once considered innocent bystanders, environmental stressors that occur during fetal and child growth have also been found to profoundly influence intestinal development and adult GI function. Early adverse life events (EALs) encompass environmental stressors that occur during childhood, such as abuse and maternal neglect. Multiple studies have confirmed the strong association between the prevalence of EALs, IBS diagnoses and IBS symptom severity.

Although it is not known precisely how EALs are related to the eventual onset of IBS, there is data to suggest that the intestinal microbiota plays a role. The intestinal microbiota modulates both central and enteric nervous system (CNS and ENS, respectively) development, and EALs impact intestinal microbiota composition. Because the CNS and ENS are most vulnerable to influences such as the GI microbiome during early life, it is likely that deviations from an optimal intestinal-microbial community during this stage may disrupt normal ENS and CNS development, with the CNS potentially dysregulation of the hypothalamic–pituitary–adrenal axis, which is of potential significance to the pathophysiology of IBS. The concepts discussed here are not limited to IBS. They also apply to other complex, multifactorial diseases managed by gastroenterologists that have underpinnings rooted in development, including obesity, food allergy and IBD. A further understanding of which specific gene variants and/or developmental external factors contribute to long-term GI development and dysfunction will affect how gastroenterologists diagnose these diseases and, more importantly, when and how these conditions should be treated.

In most conditions, current therapy is overwhelmingly geared toward symptom reversal rather than prevention. In IBS, however, the increased plasticity of the CNS and ENS in development, with the CNS potentially influenced through the third decade of life, suggests that these may be opportune times for prevention of GI disease rather than reversal. As such, the next surge of IBS research may reveal preventative therapies, such as GI microbial manipulation, or aggressive psychotherapy as novel early prevention strategies for those at high risk for IBS, including individuals who experience high degrees of EALs or even primary presentations of anxiety or depression that are heavily associated with eventual IBS onset.

The implications of developmental intervention may expand way beyond the GI field. Studies over the past decade have shown direct correlations between the numbers of EALs and the prevalence of heart disease, diabetes, asthma and mental illness. Further, early-onset dysbiosis has also been associated with the onset of metabolic, psychiatric and immune disorders. Earlier intervention by microbial modulation and/or aggressive treatment of EALs with psychotherapy may thus provide a more holistic approach to overall disease prevention.
Since the approval of the first direct-acting antivirals (DAAs) — telaprevir and boceprevir — for hepatitis C (HCV) in 2011, HCV treatment has continued to evolve at lightning speed. There has never been any area in medicine in which progress has been made at such a rapid pace and a cure so consistently achieved with a short course of well-tolerated therapy that is orally administered and in many instances as simple as one pill a day. At the time of writing, three protease inhibitors (telaprevir, boceprevir, and ritonavir-boosted atazanavir) and three polymerase inhibitors (sofosbuvir, in combination with ribavirin, and telaprevir) have been approved for all genotypes. Three additional DAA combination therapies were shown to have pan-genotypic activity in phase 2/3 trials, and will likely be approved in 2017 or shortly thereafter. They include: (a) sofosbuvir + velpatasvir + voxilaprevir (protease inhibitors); (b) MK-3682 (nucleotide polymerase inhibitor) + grazoprevir + ruxazvir (second-generation NS5A inhibitor); and (c) glecaprevir (second-generation protease inhibitor) + pibrentasvir (second-generation NS5A inhibitor).

The major advantage of combination therapies with pan-genotypic activity is simplicity in selecting an appropriate treatment for the individual patient. This is particularly important in countries where HCV genotyping is not widely available.

During the era of interferon-based therapies, genotypes 2 and 3 were considered to be easy to treat compared to genotype 1. However, genotype 3 has proven to be difficult to treat in the DAA era, and until recently SVR rates for genotype 3 cirrhosis, even with 24 weeks of sofosbuvir + ribavirin or 12 weeks of sofosbuvir + daclatasvir were approximately 65 percent. In addition to sofosbuvir + velpatasvir approved in June 2016, the three new combinations described above can achieve SVR rates greater than 90 percent in this difficult-to-treat group.

A 12-week course of DAAs suffices for the majority of patients with HCV and for treatment-naïve patients with genotype 1, no cirrhosis and low viral load, an eight-week course of sofosbuvir + ledipasvir has similar efficacy to a twelve-12-week course of the same drugs both in clinical trials and in clinical practice. Attempts to shorten the duration of treatment to four or six weeks have generally resulted in lower SVR rates, but eight weeks of treatment with sofosbuvir + velpatasvir or grazoprevir + pibrentasvir may suffice for selected groups of patients. An alternative is to combine DAAs with mir-122, which has been shown to be effective in blocking HCV replication when used as monotherapy.

DAA treatment is highly effective, but a minority of patients have failed to achieve SVR. Treatment failure is more common in patients with Child C cirrhosis who are most in need of a cure. Three new combination therapies: sofosbuvir + velpatasvir + voxilaprevir; glecaprevir + pibrentasvir; and MK-3682 + grazoprevir + ruxazvir have been shown to achieve SVR rates greater than 95 percent in patients who had been previously treated with regimens that contained sofosbuvir +/- NS5A inhibitor.

While quantum jumps are not expected in 2017, new DAA combinations that will simplify HCV treatment, improve SVR rates for genotype 3 cirrhosis and other rescue for DAA failures will come on the scene. Many have wondered when primary-care physicians will start treating HCV.

Besides the high cost and the need to navigate insurance barriers, other new wrinkles will dampen their enthusiasm.
The Red Queen in Lewis Carroll’s “Alice in Wonderland” told Alice, “Now here, you see, it takes all the running you can do to keep in the same place. If you want to get somewhere else, you must run at least twice as fast.” Welcome to our world. I first used this allegory in my presidential address at Digestive Disease Week© 2015 and it remains relevant today. There are some harsh realities of U.S. health care that will affect the GI field in the next decade. Currently, the U.S. spends $3 trillion ($9,534/per person) on health-related costs, representing 17 percent of the gross domestic product (GDP). This will rise to $5 trillion (21 percent of GDP) by 2025. Concomitantly, first-dollar payments have shifted more to individuals through copays and high deductibles. No longer will insurance payments shield people from the high cost of health care. Price sensitivity and a demand for higher value will spur development of lower-cost services, telehealth and other technologies that will disrupt current care processes.

The single greatest challenge we will face in GI will be the shift in reimbursement from fee for service — favoring our high-margin endoscopic procedures — to payments for coordination of care, where efficient resource use is paramount. While painful, we can absorb a 10 percent reduction in payments per procedure. It is more difficult to absorb a 10 to 20 percent reduction in patient or procedure numbers as primary-care managers eliminate low-value referrals. Elimination of unnecessary procedures will occur rapidly as we move to value-based payments and block reimbursement for defined populations.

In response to regulation, economic challenges and mandated electronic medical-record use, GI practices have been consolidating or migrating to large Clinically Integrated Networks (CINs). CINs typically include a hospital network, an employed primary-care base, affiliated or owned specialists, ancillary facilities, and a payer/insurance partner. We are beginning to see multistate CINs and regional health-system oligopolies. Successful CINs will focus on maximizing individual patients’ experiences, efficiently managing high-cost episodes of care and coordinating care of patients with complex multiorgan diseases — remember 5 percent of patients account for 50 percent of all health-care spending. Academic centers can lead this innovation if they understand how to use big data to identify at-risk patients, develop data-driven clinical-care algorithms, achieve patient-focused, easy-access multispecialty care coordination. Innovations in this area likely will come as much from the technological world as the medical world.

Gastroenterologists will survive by providing high-quality consultative and procedural care. Specialists who thrive will provide low-cost, clinically effective options for people and populations that currently suffer from disorganized care that varies in quality and outcomes. Three focus areas in GI include CRC prevention and management of IBD, and cirrhotic patients.

CRC management will move from disparate efforts focused on enhancing screening and increasing adenoma-detection rates to an organized health-system goal of cancer prevention© with emphasis on cost reduction. Care of an IBD patient population will rest on a foundation of guideline-driven medical care, but expand to a multidisciplinary model that integrates psychosocial care, remote monitoring, machine learning, and a financial risk-bearing specialty medical home. Similarly, cirrhotic patients cared for within a large CIN will be identified by administrative data and segregated into different populations — compensated versus uncompensated for example — with different resources proactively deployed according to their medical and social needs.

Gastroenterology has enjoyed financial halcyon days based on high-margin, low-risk, procedural reimbursement. Can our specialty adapt and financially thrive in a period of reduced per-click care and an increasing emphasis on management of complex patients, where we must demonstrate population-level health value? I believe so. Henry Ford said, “There are no small problems, just a lot of little problems.” Begin to enhance care in discreet and modern “health-care quality” movement. Toward the end of his life, he — although a data-driven scientist — reflected on what remains truly important. He said, “Health care is a sacred mission — a moral enterprise and a scientific enterprise but not fundamentally a commercial one. Doctors and nurses are stewards of something precious. Ultimately, the secret of quality is love. You have to love your patient, you have to love your profession, you have to love your God. If you have love, you can then work backwards to monitor and improve the system.”

If we are to keep medicine balanced among science, compassion and efficiency and reign joy in our profession, we will need new leaders who understand both direct-patient care and health-system concerns. It is time to teach medicine in between lessons about large-poly resection or ablation of Barrett’s dysplasia.

Can our specialty adapt and financially thrive in a period of reduced per click care and an increasing emphasis on management of complex patients?

5. Ali, K. Stewards of something precious. Ultimately, the secret of quality is love. You have to love your patient, you have to love your profession, you have to love your God. If you have love, you can then work backwards to monitor and improve the system.”
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Please see Brief Summary of full Prescribing Information for HARVONI and EPCLUSA including BOXED WARNING on Hepatitis B reactivation, on the following pages.
OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS1,4-6

ION-1: GT 1 subjects (N=1042/1079; ION-1, -2, -3)
ION-2: GT 1 subjects (N=4410) without cirrhosis or with compensated cirrhosis received HARVONI for 12 weeks, HARVONI + RBV for 12 weeks, for 24 weeks, or HARVONI + RBV for 24 weeks.
ION-3: GT 1 subjects (N=647) without cirrhosis received HARVONI for 8 weeks, HARVONI + RBV for 8 weeks, or HARVONI for 12 weeks.

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

OVERALL CURE RATE IN GT 2 SUBJECTS

ASTRAL-1: GT 2 subject (N=1333/1370; ASTRAL-1) received EPCLUSA for 12 weeks or SOF + RBV for 24 weeks. Sustained viral response (SVR12) for EPCLUSA ranged from 89% (TE with compensated cirrhosis) to 98% (TN without cirrhosis).

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

ASTRAL-3: open-label trial in GT 2 subjects (N=52). Subjects received EPCLUSA for 12 weeks or SOF + RBV for 12 weeks for 24 weeks. SVR12 for EPCLUSA ranged from 89% (TE with compensated cirrhosis) to 98% (TN without cirrhosis).

These studies did not include subjects with decompensated cirrhosis. Sustained virologic response (SVR24) was the primary endpoint and was defined as HCV RNA <10 IU/mL at 24 weeks after the end of treatment. Achieving SVR is considered a virologic cure.

OVERALL CURE RATE IN GT 3 SUBJECTS

ASTRAL-1: GT 3 subject (N=740). GT 3 subjects were randomized 5:1 to receive EPCLUSA or SOF + RBV for 24 weeks. Sustained viral response (SVR12) for EPCLUSA ranged from 89% (TE with compensated cirrhosis) to 98% (TN without cirrhosis).

ASTRAL-2: GT 3 subject (N=552). Subjects received EPCLUSA for 12 weeks or SOF + RBV for 24 weeks. SVR12 for EPCLUSA ranged from 89% (TE with compensated cirrhosis) to 98% (TN without cirrhosis).

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

DRUG INTERACTIONS

Coadministration of HARVONI or EPCLUSA is not recommended with omeprazole, nefazodone, ritonavir, ritonavir/lamivudine, or other drugs that induce CYP3A4. Coadministration of EPCLUSA is not recommended with proton-pump inhibitors or allopurinol due to increased concentrations of tenofovir; or with simeprevir due to increased concentrations of sofosbuvir and adverse effects; or with other drugs that are substrates of CYP3A4.

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

References:

See what’s possible at hcp.harvoni.com

See what’s possible at hcp.epclusa.info

Please see Brief Summary of full Prescribing Information for HARVONI and EPCLUSA, including BOXED WARNING, on the following pages.
The safety assessment of HARVONI was also acting antivirals and were not receiving HBV antiviral therapy. Some reactivation has been reported in HCV/HBV coinfected patients. Information. Rx Only.

If HARVONI is administered with RBV, the combination regimen

Risks Associated with RBV Combination Treatment

Serious Symptomatic Bradycardia When Coadministered with RBV

Bradycardia has generally occurred within hours to days, but cases have been reported in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients with serologic evidence of resolved HBV infection (anti-HBc positive) and hepatitis B core antibody (anti-HBc) positive. HBV reactivation has also been reported in patients receiving certain immunosuppressant or immunomodulatory agents; the risk of reactivating associated with treatment with RBV for direct-acting antivirals may be increased in these patients. HBV reactivation has been characterized as an abrupt increase in HBV replication manifesting as a rapid increase in HBV DNA levels. In patients with reactivated HBV infection, which can be associated with hepatitis or fulminant hepatitis, the presence of serologic evidence of resolved HBV infection (HBsAg negative and hepatitis B core antibody [anti-HBc] positive). HBV reactivation has also been reported in patients with serologic evidence of resolved HBV infection (HBsAg negative and anti-HBc positive) and hepatitis B core antibody (anti-HBc) positive. HBV reactivation has also been reported in patients receiving certain immunosuppressant or immunomodulatory agents; the risk of reactivating may be increased in these patients. HBV reactivation is unknown. Coadministration of amiodarone with HARVONI is not recommended. Bradycardia has generally occurred within hours to days, but cases have been reported in fulminant hepatitis, hepatic failure, and death. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients with serologic evidence of resolved HBV infection (anti-HBc positive) and hepatitis B core antibody (anti-HBc) positive. HBV reactivation has also been reported in patients receiving certain immunosuppressant or immunomodulatory agents; the risk of reactivating may be increased in these patients. HBV reactivation is unknown. Coadministration of amiodarone with HARVONI is not recommended. 

Postmarketing Experience:

Serious symptomatic bradycardia has been reported in patients taking amiodarone who initiate treatment with HARVONI during post approval use of HARVONI. Some patients, typically with biotransitions of the liver, have been included because of their seriousness or assessment of liver failure and death. It is not possible to reliably assess the contribution of HARVONI to this risk, but serious symptomatic bradycardia is considered a clinically important adverse reaction. In the ION-4 trial. Isolated, asymptomatic creatine kinase elevations of more than 3x the upper limit of normal (ULN) were observed in less than 1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. Adverse Reactions (adverse events) occurring in at least 1% of subjects:

Laboratory Abnormalities:

Elevations of greater than 5x the upper limit of normal (ULN) were observed in less than 1%, 2% and 3% of subjects treated with HARVONI for 8, 12, and 24 weeks, respectively and in the SIRIUS trial, 3%, 2% and 3% of subjects treated with HARVONI for 12 weeks. Increases in alanine aminotransferase (ALT) of greater than 10x the ULN were observed in less than 1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively. Total bilirubin levels of greater than 3x the ULN were observed in less than 1%, 2% and 3% of subjects treated with HARVONI for 8, 12 and 24 weeks, respectively.

Related Products Not Recommended

HIV/HBV/HCV coinfection, treatment with antiviral regimens; this list is not all inclusive.

Geriatric Use:

Based on drug interaction studies conducted with HARVONI or its components, no dosage adjustment of HARVONI is required for patients with mild or moderate renal impairment. The safety and efficacy of HARVONI have not been established in pediatric patients. No overall differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is recommended.

Pediatric Use: Safety and effectiveness of HARVONI have not been established in children.

Geriatric Use: Clinical trials of HARVONI included 225 subjects ages 65 and older, of whom 42 were 75 and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is recommended.

Renal Impairment: No dosage adjustment of HARVONI is required for patients with renal impairment. HARVONI has not been established in patients with severe renal impairment (GFR <30 mL/min/1.73 m²); data are available in patients with moderate renal impairment (GFR 30-59 mL/min/1.73 m²) or end-stage renal disease (ESRD) requiring hemodialysis. No dosage adjustment can be given for patients with severe renal impairment or ESRD.

Hepatitis C Virus: No dosage adjustment of HARVONI is required for patients with HIV infection and hepatitis C or D virus. HARVONI has not been established in patients with severe or moderate hepatic impairment (Child-Pugh Class C, B or A).
48 hours of coadministration is recommended, after which outpatient bradycardia; and cardiac monitoring in an in-patient setting for the first EPCLUSA: Counsel patients about the risk of serious symptomatic recommended. For patients taking amiodarone who have no other unknown. Coadministration of amiodarone with EPCLUSA is not discontinuation of HCV treatment. The mechanism for this effect is generally resolved after coadministration of amiodarone. Bradycardia generally resolved after EPCLUSA with ribavirin due to adverse events (2.0% for subjects who received EPCLUSA for 12 weeks. The most common adverse reactions (at least 10%) were headache and fatigue in subjects treated with EPCLUSA for 12 weeks. Adverse reactions (all grades) reported in ≥10% of subjects treated with EPCLUSA in ASTRAL-1 were headaches (52%), diarrhea (15%), fatigue (15%), nausea (12%), vomiting (10%), and diarrhea (9%). Common adverse reactions (at least 5%) observed in subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were constipation (23%), nausea (21%), and diarrhea (18%) was also observed in greater than or equal to 5% of subjects treated with EPCLUSA who experienced these adverse reactions, 79% had an adverse event reaction that was considered treatment related in ASTRAL-1. Clinical symptoms and laboratory abnormalities associated with clinical adverse events and all subjects completed 12 weeks of EPCLUSA therapy. The patients were advised to avoid adjustment or treatment interruption of either EPCLUSA or HIV antiretroviral agents. Postmarketing Experience: Because postmarketing reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Nucleoside analogs, severe symptomatic bradycardia has been reported in patients undergoing amiodarone who initiated treatment with subcutaneous in combination with another HCV direct-acting antiviral.

Drug Interactions:

Soluble and velpatavir are substrates of P-gp and breast cancer resistance protein (BCRP) while GS-310177 (this predominant circulating metabolite of solfosubvir) is not. Drugs that are inducers of P-gp and/or moderate to potent inducers of CYP3A, CYP2C9, or CYP3A4 (e.g., rifampin, St. John’s wort, carbamazepine) may decrease plasma concentrations of EPCLUSA and velpatavir thereby leading to reduced therapeutic effect of EPCLUSA. The use of these agents with EPCLUSA is not recommended. EPCLUSA is a strong inhibitor of CYP3A and CYP2C9 and inhibitors may increase the exposure of such drugs. The drug interactions are based on studies conducted with either EPCLUSA or PEG-IFN and velpatavir; the drug interactions between EPCLUSA with drugs that are substrates of these transporters may increase the exposure of such drugs.

Ezetimibe: Ezetimibe therapy can result in increased serum concentrations of EPCLUSA and velpatavir due to an increased exposure of EPCLUSA. Ezetimibe therapy can result in increased serum concentrations of EPCLUSA and velpatavir due to an increased exposure of EPCLUSA. Ezetimibe therapy can result in increased serum concentrations of EPCLUSA and velpatavir due to an increased exposure of EPCLUSA. Ezetimibe therapy can result in increased serum concentrations of EPCLUSA and velpatavir due to an increased exposure of EPCLUSA.
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