Which path to take?

Debating whether or not to start anti-TNF therapy immediately after surgery for Crohn’s disease patients.

ARTICLES BY
Miguel D. Regueiro, MD, and Brian Bressler, MD, MS, FRCPC.

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Dr. Bryan Bressler makes the case for selective use of anti-TNF therapy postoperatively, while Dr. Miguel Regueiro argues for a more aggressive approach to such therapy. At the end of the day, both authors provide practical guidance to inform your decision making in these patients.

Direct acting antiviral therapy for HCV has been another area of rapid advance in clinical care that has revolutionized the treatment of patients with hepatitis C. However, recent concerns have emerged on the safety of these agents. One of the leaders in the field of HCV therapy, my own colleague Dr. Raj Reddy, provides a concise summary on these safety concerns. Also in the area of liver disease, Dr. Mack Mitchell provides an update on where we stand on modern therapy of alcoholic hepatitis.

Colon cancer screening remains a key focus of the GI community. While colonoscopy dominates our approach, we need to stay up to date on other potentially disruptive technologies for screening. Stool-based DNA testing has been available for a number of years now, but its niche remains to be determined. An update on the current status of this modality is given by Dr. Thomas Imperiale.

Guideline development and dissemination remains a key focus of AGA and changes are coming in regards to the speed in which guidelines are developed, as detailed by Drs. Brian Hanson and Shahnaz Sultan. This change will benefit all members of AGA as well as our patients.

Lastly, this issue of AGA Perspectives provides an update on the microbiome of AGA members as well as a history of the AGA-Funderburg Award in Gastric Cancer Research. This award has provided critical funding for a who’s who of investigators who have made seminal contributions to the field.

I would like to wish all of our AGA Perspectives readers a good summer and happy reading!

Best,
Which path to take?

Debating whether or not to start anti-TNF therapy immediately after surgery for Crohn’s disease patients.
A surgical resection for a patient with Crohn’s disease is a major milestone in the natural history of their condition. It is without a doubt that patients who require surgery will make avoiding further surgery a priority and accordingly many patients will consider any possible preventive measure. I explain to patients that surgery is usually required for one of two reasons. The first is that our best attempts to control the immune dysfunction of Crohn’s disease have not been effective enough to deal with the persistent damage to their bowel, making surgery a necessity. The second possibility is that there has been such an excessive amount of damage to the bowel over time that the involved segment must be removed as medical therapy cannot reverse that damage. We have traditionally put patients into a high or low recurrence risk category in part based on trying to understand whether their requirement for surgery was reason one or two. Patients with ongoing immune dysfunction would be at a high risk of recurrence, whereas those with no ongoing immune dysfunction would be at low risk. AGA has recently presented reasonable patient characteristics that appropriately select a patient who is at high risk of recurrence: young (less than 30 years old), smoker and two or more prior surgeries for penetrating disease, irrespective of perianal disease. Such high-risk patients likely have ongoing immune dysfunction, which will quickly cause further damage to their bowel, leading to symptom recurrence and ultimately another resection if this process is not effectively interrupted. Therefore, these patients require the most effective form of therapy we can offer. Anti-TNF therapy has been our gold standard to date when effective control of Crohn’s disease is needed. As a result, in high-risk patients who have so much to
In [certain] patients, starting an anti-TNF agent postoperatively would not provide a benefit that would outweigh the risk and cost of this treatment.

and keep their risk of both symptomatic and surgical recurrence at the same rate, as if they were started on their medication immediately after their surgery? These questions have not yet been addressed; however, two studies give me confidence that this ‘wait-and-see’ approach is appropriate for most patients, most of the time. The Postoperative Crohn’s Endoscopic Recurrence (POCER) study did specifically evaluate the strategy of initiating postoperative therapy based on early endoscopy evidence of recurrence compared to empiric treatment which included in high-risk patients azathioprine or adalimumab (if intolerant to adalimumab) to standard of care monitoring. At 18 months, those patients who had a washout early to surgery recurrence were less likely to have endoscopic recurrence compared to those who were offered treatment based on their risk factors but did not have early endoscopic assessment. This study also provided valuable insight into the role of fecal calprotectin monitoring postoperative anti-TNF therapy and likelihood of significant endoscopic recurrence if the fecal calprotectin was <100 μg/g was low. Therefore, in my patients who I particularly recurrent disease recurrence, I consider measuring fecal calprotectin early (three months postoperative), and every three months thereafter (until colorectal cancer screening age) which I perform six-to-nine months after resection. The second study compared early azathioprine initiation to a ‘wait-and-see’ approach. In this study, the initiation of azathioprine only when severe endoscopic recurrence was found. This was a small study (63 patients total), but the rates of both clinical and endoscopic recurrence two years after surgery did not differ and approximately 50 percent of patients in the endoscopic assessment group were able to avoid treatment. However, due to the small sample size, the limited power of this study does not make it possible to be certain that there is no meaningful difference between the two groups. Even though the endoscopy evidence (POCER trial), which treated all high-risk patients with infliximab immediately after their resection, did not reach its primary endpoint (clinical recurrence), but did demonstrate prevention of endoscopic recurrence.

The obvious piece of the puzzle we are missing is a randomized trial in high-risk postoperative Crohn’s disease patients comparing anti-TNF therapy immediately after surgery to initiation of postoperative anti-TNF therapy. The difference in efficacy and safety would be key endpoints to assess. My suspicion is that this trial is not likely to happen anytime soon, so our decisions will remain somewhat uncertain. However, I do feel confident that early endoscopic assessment followed by frequent fecal calprotectin in postoperative Crohn’s disease patients is the optimal way to decide who requires postoperative anti-TNF therapy and who does not require treatment.

postoperative Crohn’s disease prevention? The available data suggest that probiotics, corticosteroids and 5-aminosalicylates are of limited benefit in preventing post- operative recurrence. Antibiotics, specifically metronidazole and oral vancomycin, have been shown to be of some benefit in preventing postoperative recurrence, but most cannot tolerate these long-term. The benefit is lost when these medications are discontinued. Azathioprine and 6-Mercaptopurine are efficacious in maintaining remission in patients with moderate-to-severe Crohn’s disease. However, when used in the postoperative setting, approximately one-half of patients have remission and many patients are intolerant. Anti-TNFs have the best efficacy in preventing postoperative recurrence of Crohn’s disease with several studies and meta-analyses favoring this approach.

The recent AGA technical review and guidelines also support the use of anti-TNFs postoperatively, but the benefit must be weighed against risk and the patient’s personal preferences must be taken into account.1,3

I suggest the decision on treatment be based on the patient’s risk for postoperative recurrence. Those at low-risk for recurrence (such as those who have long-standing Crohn’s disease [more than 10 years], and who have no indication for surgery [a score of less than 10 (10 cm) fiberoptic stenotic). Given the slow progression of disease in a limited segment of bowel, these patients are less likely to have aggressive postoperative recurrence. I do not routinely place these patients on postoperative medications. I perform an ileoscopiosis six months postoperative. If there is no recurrence, and, if there is no endoscopic recurrence (i.e. i0 or i1), I do not start medication and, if there is no evidence of endoscopic recurrence was found. This was a small study of 63 patients total, and approximately 50 percent of patients in the endoscopic assessment group were able to avoid treatment. However, due to the small sample size, the limited power of this study does not make it possible to be certain that there is no meaningful difference between the two groups. Even though the endoscopy evidence (POCER trial), which treated all high-risk patients with infliximab immediately after their resection, did not reach its primary endpoint (clinical recurrence), but did demonstrate prevention of endoscopic recurrence.

I consider patients at low-risk for recurrence as those who have long-standing Crohn’s disease (more than 10 years), and who have no indication for surgery (a score of less than 10 (10 cm) fiberoptic stenotic). Given the slow progression of disease in a limited segment of bowel, these patients are less likely to have aggressive postoperative recurrence. I do not routinely place these patients on postoperative medications. I perform an ileoscopiosis six months postoperative. If there is no recurrence, and, if there is no endoscopic recurrence (i.e. i0 or i1), I do not start medication and, if there is no evidence of endoscopic recurrence (Rutgeerts’ score ≥2), I start an anti-TNF agent. A fecal calprotectin > 100 mg/ml at three months after surgery may be a reasonable method in which to assess for early postoperative recurrence. At present, this is not routinely part of my practice.

I consider patients at moderate risk for postoperative recurrence as those naïve to immunomodulators or biologics, with a relatively short duration of disease (less than 10 years) prior to surgery, who undergo resection for a long segment (greater than 10 cm) of small bowel inflammation. I perform an ileoscopiosis six months postoperatively, and, if there is evidence of endoscopic recurrence (Rutgeerts’ score ≥2), I start an anti-TNF agent. A fecal calprotectin > 100 mg/ml at three months after surgery may be a reasonable method in which to assess for early postoperative recurrence. At present, this is not routinely part of my practice.

I consider patients at high-risk for postoperative recurrence as those naïve to immunomodulators or biologics, with a relatively short duration of disease (less than 10 years) prior to surgery, who undergo resection for a long segment (greater than 10 cm) of small bowel inflammation. I perform an ileoscopiosis six months postoperatively, and, if there is evidence of endoscopic recurrence (Rutgeerts’ score ≥2), I start an anti-TNF agent. A fecal calprotectin > 100 mg/ml at three months after surgery may be a reasonable method in which to assess for early postoperative recurrence. At present, this is not routinely part of my practice.

For patients at high risk for recurrence, I initiate an anti-TNF agent within two-to-four weeks of surgery and, if 0 or 11 recurrence, I will continue. If there is endoscopic recurrence (≥2) at six months, I check anti-TNF levels and optimize accordingly.

In sum, most of my patients who undergo an intestinal resection for Crohn’s disease are at high risk for recurrence and will receive an anti-TNF within four weeks of surgery. I still think that postoperative anti-TNFs are the most effective strategy for prevention of Crohn’s disease. Whether other biologic classes have the same efficacy remains to be seen.
STOOL DNA TESTING

Is there a Future?

This commentary describes the current status of the multi-target stool DNA test (mt-sDNA) (Cologuard®, Exact Sciences, Madison, WI) and of stool-based markers for GI diseases. Approved by both the U.S. Food and Drug Administration and the Center for Medicare and Medicaid Services in August 2014, the mt-sDNA test is a non-invasive screening test for colorectal cancer (CRC) for persons whose preference is to avoid screening colonoscopy. Since approval, clinical use of mt-sDNA has had a steady trajectory among both patients and providers (Figures 1 and 2). Relevant to the “80 percent by 2018” goal of CRC screening, 42 percent of providers (Figure 1) and 96 percent for FIT.1 The potential of non-invasive testing for CRC is great.

The potential of non-invasive testing for CRC is great. While the results may alleviate concerns about missed cancers, more data are needed; these studies are ongoing.

- Mt-sDNA was included into HEDIS measures by the National Committee for Quality Assurance, ensuring that primary care providers receive “credit” for using mt-sDNA for CRC screening.
- Residual clinical concerns with mt-sDNA include its specificity relative to FIT, cost and cost-effectiveness. While mt-sDNA’s specificity in the pivotal study was 86.6 percent (versus 94.9 percent for FIT), the study population was skewed toward older persons within the screening age range. Older age is associated with higher prevalence of background methylation of DNA, one reason for false positivity. In persons younger than 65 years who had non-advanced neoplasia and “clean” colon, respective sensitivities were 91.5 and 94.0 percent. Last, the 5 percent false-positive rate forFIT, when considered programmatically over a three-year interval, may be comparable to that of mt-sDNA every three years. These data should assuage concerns about mt-sDNA’s “low” specificity, particularly in younger persons within the screening age range.
- While mt-sDNA every three years is cost-effective when compared to no screening, it is dominated (i.e., more costly, less effective) by colonoscopy every 10 years and annual FIT when adherence is perfect.2 In the real world, however, adherence for any CRC screening test is usually far less than perfect. For mt-sDNA to be comparable and cost-effective to FIT requires substantially higher participation rates to those of FIT in organized programs and in the opportunistic screening that characterizes most of the U.S. The accompanying navigation system for mt-sDNA has resulted in an adherence rate of 67 percent—twice the rate of adherence to three rounds of FIT3—and in a population with a high proportion of persons resistant to screening. However, it should be noted that there is no comparison of programmatic FIT and mt-sDNA for clinically important outcomes of CRC incidence or mortality.

Beyond CRC screening, stool DNA markers may be useful for surveillance of dysplasia in inflammatory bowel disease. A subgroup of mt-sDNA markers and a panel of methylated markers have demonstrated sensitivity for CRC plus high-grade dysplasia of 92 to 100 percent at specificity of 89 to 94 percent.4 These preliminary findings require clinical validation, with particular attention to specificity and the meaning and management of the scenario in which the stool test is positive, but biopsy for (high-grade) dysplasia are negative. And beyond the colon, there is ongoing investigation of a stool DNA-based test function as a cancer screening test for the GI tract, although this particular indication is nascent and very preliminary.

Identification of discriminating markers in stool (as well as blood) is an active area of research that includes a myriad of “discovery” phase studies of both individual and panels of markers. Nearly all are case-control studies that compare one or markers in a case group with CRC with a CRC-free control group, and may or may not include a group with advanced or non-advanced adenomas. This discovery phase has been driven by technological advances including the digital melt curve method, digital PCR, quantitative real-time target and signal amplification (QuRTS), and beaming, amplification, and magnetism (BEAMing), all of which have improved the detection threshold in stool from 1 percent of mutated copies of DNA to less than 0.1 percent.

Based on the stagnant 65 percent adherence rate for CRC screening in the U.S., there is room for mt-sDNA as well as FIT and other accurate, non-invasive tests to improve adherence. The potential of non-invasive testing for CRC is great, with opportunity to identify biomarkers that are discriminating for CRC and advanced, precancerous polyps as well as for other prevalent gastrointestinal cancers. But much time, effort and cost will be required for meticulous marker selection and careful prospective validation of candidate markers in the target population for which the test is intended.

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The Gastroenterologist’s Microbiome Revisited: Beyond Bacteria in the Guts of AGA Members

EMBRIETE R. HYDE, PhD
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Dr. Knight has no conflicts to disclose.

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The American Gut Project® is the country’s largest open source crowdfunded citizen science project in existence today. As of early 2017, the project has raised over $7 million and processed over 14,000 samples from over 10,000 individuals (and counting). Over the last two years, the American Gut Project has partnered with AGA and its Center for Gut Microbiome Research and Education on the Microbiome Active Learning Sessions at Digestive Disease Week®. In 2016, we performed 16S ribosomal RNA (rRNA) sequencing on stool samples collected from 54 AGA members, and learned that the gut bacteria of gastroenterologists are not particularly different from those of the average American Gut Project participant.2,3 The 16S rRNA gene is a ribosomal gene thought to exist in all bacteria and archaea. Many microbiome studies today target the V4 region of the 16S rRNA gene, as the primers that amplify this portion are least susceptible to bias and able to yield the greatest amount of information taxonomically from most sample types. The 16S method is also cost-effective since hundreds of samples can be sequenced at once. Most American Gut samples have been processed in this way, as the low cost makes personal microbiome sequencing attainable for many.

A limitation of 16S rRNA marker gene analysis is that it surveys only a small portion of each genome. In contrast, the shotgun metagenomics approach sequences all DNA present, yielding information about the entire genomes of all organisms in the sample, including the non-bacterial members of the microbiome such as viruses and fungi. Because most regions of the genome have higher variability than rRNA genes, shotgun data can also give greater resolution and distinguish between closely related organisms. With sufficient sequencing depth, shotgun data can also yield direct information about the presence and abundance of particular functional gene pathways, or be assembled into draft genomes, yielding insights into the physiological capabilities of abundant organisms in the community. Due to the depth of sequencing required for shotgun analysis, it is most useful when more than 16S rRNA sequencing; however, the Knight lab has been working on protocols to lower the cost of shotgun metagenomics sequencing and analysis. In 2017, the samples submitted by 53 AGA members were analyzed by both 16S and shotgun sequencing methods. Ten of these members were returning participants who also submitted a sample in 2016.

As in 2016, we found that the 2017 cohort of AGA member participants were scattered across the greater American Gut Project “map” (Figure 1). 16S rRNA sequencing showed that the major phyla present in AGA member samples were Bacteroidetes and Firmicutes. Interestingly, three AGA participants had notable abundances (near 50 percent to over 78 percent) of Proteobacteria; in comparison, the average shotgun data showed the Proteobacteria observed across all American Gut Project population is less than 1 percent. A number of diseases, including IBD, have been associated with an increase in the relative abundance of Firmicutes and a corresponding lower abundance of Bacteroidetes (and corresponding lower abundance of Firmicutes) overall in the shotgun metagenomics cohort. Additionally, while most of the taxa detected were bacteria, there were also archaea, fungi (eukaryotes) and viruses detected (Figure 2). A total of five archaea genera, one parasitic (eukaryotic) genus, seven fungal (eukaryotic) genera and 25 viral genera were detected. In most cases, non-bacterial taxa were at low abundance, or not detected; in only six of the 53 individuals, non-bacterial taxa were detected at a relative abundance of 0.5 percent or more. These included the archaea Methanobrevibacter, Methanospirillum, Methanosarcinales and Methanobrevibacter, the eukaryotic taxa Candida, and the viral (phage) genera Nonovirus and Pseudomonas_phage_04 and Pseudomonas_phage_PA11.3,4 Finally, assessing the top 20 pathways present across the dataset, we see a stable pattern in which most pathways are at similar relative abundances in all samples. However, in the samples in which Proteobacteria were present at relative abundances of over 70 percent, three pathways are noticeably higher: chorismate biosynthesis from 3-dehydroquinate, chorismate biosynthesis I and peptidoglycan biosynthesis III (Figure 3). The potential significance of the increased abundance of these three pathways is unclear, highlighting a new frontier of research as whole genome sequencing approaches become more common.

This year’s AGA participant report includes much more information than what is discussed here, including a case study of deep shotgun metagenomic sequencing performed on longitudinal stool samples collected from a single patient with IBD over three years. It is important to note that we now have the technology to understand what microbota are in the gut, we do not yet have enough evidence to explain why they are there and how they impact health and disease. There is much more to learn about the relationship between humans and their resident microbiota. Thank you to the gastroenterologists who participated in the 2017 sequencing activity, and we look forward to seeing all of you at the next Microbiome Active Learning Session.5

REFERENCES
SAFETY CONCERNS OF NEW ANTIVIRALS FOR HCV

K. RAJENDER REDDY, MD
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Medical Director of Liver Transplantation, Hospital of the University of Pennsylvania

The advent of direct acting antivirals (DAAs) in HCV has allowed large groups of patients to begin
therapy that offers significant virologic and clinical benefits.1 However, the use of DAAs is not
without challenges. DAAs are highly effective for HCV, but complications can arise with all
antiviral regimens. The advent of DAAs has led to a growing number of cases of hepatitis C
reactivation following the use of DAAs. This may occur with or without the use of ribavirin.

Ribavirin use may be necessary to control symptoms of disease progression, and is also
helpful when treating patients with HCC. This is a rare event, and its frequency and significance
are still under investigation. The use of DAAs should be considered in patients with isolated
antibody positivity for hepatitis B virus (HBV), and in those with prior HCC.2, 4

Recent studies have suggested that the incidence of HCC in patients treated with DAAs is
increased. This may be due to the higher viral load and increased risk of disease progression
in patients with advanced liver disease.3, 4

This is an important consideration for clinicians, as the treatment of HCC is often complex and
requires a multidisciplinary approach. This includes the use of anti-viral therapy, surgical
intervention, and liver transplantation. The use of DAAs in patients with HCC is generally
not recommended, as the risk of HCC recurrence is increased with the use of DAAs.5

However, recent studies have suggested that DAAs may be effective in treating patients with
advanced liver disease and HCC.6 This is an important consideration for clinicians, as the
treatment of HCC is often complex and requires a multidisciplinary approach. This includes
the use of anti-viral therapy, surgical intervention, and liver transplantation. The use of
DAAs in patients with HCC is generally not recommended, as the risk of HCC recurrence is
increased with the use of DAAs.5

While the data is robust for sustained virologic response (SVR) following interferon-based therapy, it has not been well studied for patients with HCC. More recent data suggests that DAAs may be effective in treating patients with HCC, and that the use of DAAs in patients with HCC is generally not recommended, as the risk of HCC recurrence is increased with the use of DAAs.5

References
1.  Dyson J.K., Hutchinson J., Harrison L. et al, “FibroScan has significant limitations in the context of DAAs are of HBV reactivation following interferon-based therapy has demonstrated a decrease in the risk of HCC. It would seem logical to expect similar benefits in patients treated with DAAs. However, alarming reports have emerged indicating that the risk of HCC may not be decreased after achieving SVR with DAAs and, in fact, the risk might be increased. Loss of immune “control” after successful HCV eradication has been implicated as a potential pathogenic mechanism. A recurrence of aggressive HCC after successful treatment of the tumor has also been suggested, while undergoing HCV therapy.” Lastly, a lower rate of SVR in those treated with DAAs in the background of HCC has also been observed.

Most data, however, comes from retrospective studies that lack a well matched comparator cohort. Limited prospective studies suggest that the risk of HCC is lower in patients with successfully treated HCV with DAAs. More prospective data is needed to settle the issue of the rate of de novo HCC, the rate of SVR in those with HCC, the course of newly developed HCC, and of recurrent and well treated HCC.

While the data is robust for sustained virologic response with DAAs along with few adverse events, there is still a need to study the safety and efficacy in special populations — including pregnant women and children. We have come a long way since the days of interferon and ribavirin. There remain challenges with the current DAAs. A knowledge of drug-drug interactions is essential to potentially mitigate any adverse events.

Historical data in patients who achieved sustained virologic response (SVR) following interferon-based therapy has demonstrated a decrease in the risk of HCC.

Although not approved in the US, is associated with abnormalities in hepatic biochemical tests and histopathology has been noted to have subtle and clinically insignificant abnormalities in hepatic biochemical tests.

Following the approval of several regimens, there have been post marketing reports of adverse events related to DAAs. Cardiac events following sofosbuvir-based therapy have been observed and included heart failure, bradycardia, pacemaker intervention and fatal cardiac arrest.7 This has happened in some patients within 24 hours of the first dose of therapy while others have developed these adverse events later on. Amiodarone and sofosbuvir have interactions, and thus, I caution that amiodarone not to be used while sofosbuvir therapy is being pursued. Another limitation of sofosbuvir is that it is contraindicated in patients with eGFR of less than 30 mL. Protease inhibitors as a class are contraindicated in patients with decompensated liver disease.

Following the use of the three drug regimen of paritaprevir boosted by ritonavir, ombitasvir, and dasabuvir, a total of 26 cases worldwide were reported where there was further hepatic decompensation leading to liver failure. Hepatic decompensation and lactic acidosis have been reported following the use of DAAs in those with advanced liver disease.8, 9

Recent contentious issues that have evolved in the context of DAAs are of HBV reactivation following interferon-based therapy. The rate of HBV reactivation is lower with DAAs, and it is generally well tolerated. It is a photosensitiser and may lead to adverse skin reactions, but these rarely lead to withdrawal from therapy. As a sulfoximine, sofosbuvir is photosensitive and active, and thus the cause for photosensitivity reactions. Additionally, elevated bilirubin levels, often of the unconjugated type, may be seen as a consequence of this drug since it is an inhibitor of bilirubin transporters. Asunaprevir, an effective drug in combination with DAAs, but it has its unique adverse events, and is a known teratogen. There are a few unique adverse events related to certain drugs such as simeprevir, a protease inhibitor. While it is generally well tolerated, it is a photosensitiser and may lead to adverse skin reactions, but these rarely lead to withdrawal from therapy. As a sulfoximine, simeprevir is photosensitive and active, and thus the cause for photosensitivity reactions. Additionally, elevated bilirubin levels, often of the unconjugated type, may be seen as a consequence of this drug since it is an inhibitor of bilirubin transporters. Asunaprevir, although not approved in the US, is associated with abnormalities in hepatic biochemical tests and histopathology has been noted to have subtle and clinically insignificant abnormalities in hepatic biochemical tests.

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Rapid reviews are highly variable with respect to terminology (often going by many names including rapid response, evidence advisory, hotline response, evidence summaries or evidence inventories), as well as with respect to methodology. While no two rapid reviews are alike, all may take certain methodological “shortcuts” to reduce the development time. True rapid reviews are akin to traditional systematic reviews with only minor differences in methodology; they are amenable to a shorter timeline because they ask a more targeted question with a reduced scope or are limited to specific outcomes. The timeline for development is often the critical factor that determines the methodological approach. For example, some “rapid reviews” are merely automated/algorithmic lists of titles of relevant references (completed in five minutes) while others are typically completed over eight months and are more consistent with traditional systematic reviews.4,5

Transparency has always been a hallmark of a high-quality systematic review. With no universal guiding methodological principles for rapid reviews, transparency of reporting is even more important when conducting a rapid review.6 When formulating rapid reviews and rapid guidelines, it is imperative to carefully describe the scope and methods of the review so the end-user is informed about any potential limitations. Rapid reviews should be commissioned. AGA’s upcoming guideline pilot the use of “rapid reviews” has been limited to specific outcomes. The timeline for development of an AGA systematic review is 12 months, but the timeline for this rapid review will be three to six months. On average the typical timeline for the development of an AGA systematic review is 12 months, but the timeline for this rapid review will be three to six months. Methodological approaches that the technical review panel will use include limiting the number and scope of questions to be answered. Additionally, the technical review panel will search for and use existing high-quality systematic reviews, include only English language articles, and not include review of grey literature, e.g. conference proceedings and technical reports. An initial title and abstract review followed by a full-text review will be performed by one reviewer and then only excluded titles/abstracts will be reviewed by a second author.7 The end-users of rapid reviews report that one of the most important factors, other than methodology and transparency, in considering the use of rapid reviews is that the review is from a reliable source.8 In a briskly and ever-changing medical field, AGA, a trusted leader in guideline development, is an ideal organization to lead the charge toward high-quality, rapid guideline development.

REFERENCES

INTRODUCING THE RAPID REVIEW
How AGA is Working to Get Trustworthy Clinical Guidelines to Practitioners in Less Time

E aster” is the new normative way of living and the demand for instant results affects every aspect of our lives. We want instant access to movies that can be streamed from our devices. We want our shopping purchases to be shipped to our door on the same day. We want the most reliable and accurate evidence to inform our clinical decisions — and we want it fast. “Rapid reviews” were borne out a desire to meet end-user needs in a rapidly changing health care environment.

Currently, AGA develops and publishes four or more clinical guidelines per year. These guidelines typically take around 12 months to conduct a systematic search and develop a guideline draft of the technical review. In order to get AGA’s trustworthy, evidence-based clinical guidelines into the hands of practitioners in less time, a new project to pilot the use of “rapid reviews” has been commissioned. AGA’s upcoming guideline on the management of opioid-induced constipation (OIC) will be the first to utilize the rapid review approach.

What is a rapid review?

Simply stated, a rapid review is a systematic review completed more quickly than a standard systematic review.4 A traditional systematic review uses a predefined, systematic and transparent approach to identify, select, appraise and summarize primary studies addressing a focused clinical question using methods to reduce the likelihood of bias. Rapid reviews or guidelines are developed on a shorter timeline and use “methods to accelerate or streamline traditional systematic review processes” to meet the needs and timelines of the end-users.4,5

While rapid reviews are conceptually quite simple, in reality, they are an ill-defined entity. The AGA Clinical Guidelines App is a product of the AGA Institute.
Reflecting on 25 Years of Groundbreaking Gastric Cancer Research

AGA-R. Robert and Sally D. Funderburg Research Award in Gastric Cancer Recipients

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<td>2001</td>
<td>Debra G. Silberg, MD, PhD</td>
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<tr>
<td>2002</td>
<td>Steven F. Moss, MD, AGAF</td>
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<tr>
<td>2003</td>
<td>Lopa Mishra, MD</td>
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<tr>
<td>2004</td>
<td>James R. Goldenring, MD, PhD, AGAF</td>
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<thead>
<tr>
<th>Year</th>
<th>AGA–Funderburg Recipient</th>
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<tbody>
<tr>
<td>2005</td>
<td>Jean-Marie Houghton, MD, PhD</td>
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<tr>
<td>2006</td>
<td>Steven H. Itzkowitz, MD, AGAF</td>
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<tr>
<td>2007</td>
<td>Xiaolu Yang, PhD</td>
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<tr>
<td>2008</td>
<td>Sheila E. Cove, MD, AGAF</td>
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<tr>
<td>2009</td>
<td>Mary Bronner, MD</td>
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<tr>
<td>2010</td>
<td>Jason C. Mills, MD, PhD, AGAF</td>
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<tr>
<td>2011</td>
<td>Andrea Todisco, MD, AGAF</td>
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<tr>
<td>2012</td>
<td>Adam J. Bass, MD</td>
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<tr>
<td>2013</td>
<td>Yana Zavros, PhD</td>
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<tr>
<td>2014</td>
<td>Manuel R. Amieva, MD, PhD</td>
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<tr>
<td>2015</td>
<td>Linda C. Samuelsion, PhD</td>
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<tr>
<td>2016</td>
<td>Richard J. DiPaolo, PhD</td>
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<tr>
<td>2017</td>
<td>Zhibin Chen, MD, PhD</td>
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The Funderburg award played a crucial role in my career,” stated Dr. Jim Goldenring, 2004 Funderburg recipient and professor and vice chairman of surgery and professor of cell and developmental biology at Vanderbilt. “While we had been working for some time on the etiology of precancerous metaplasia in the stomach, we had been unable to obtain funding for the work from NIH on five separate attempts, largely due to a lack of enthusiasm or interest in research on gastric cancer, which is relatively rare in the U.S. compared with the rest of the world. I was frankly ready to terminate our work on gastric cancer when I received the Funderburg award. The Funderburg award allowed me to perform our first studies of gene expression profiling of microdissected metaplastic lineages in mice. These studies and those that followed have led to the validation of a rather unexpected hypothesis that metaplasias evolve from mature chief cells through transdifferentiation. This work has now received funding from both the NIH and the VA. None of this would have been possible without the Funderburg award, and I dare say that the others winners of this award would have similar stories.”

Continuous funding from the Funderburg family through the AGA Research Foundation has provided the opportunity for gastric cancer research discoveries that otherwise would not have been funded. Dr. Jason Mills, associate professor at Washington University at St. Louis, 2010 Funderburg recipient states, “The field is greatly indebted to the Funderburg family. Gastric cancer, by most metrics, is the least funded cancer relative to the burden it costs society, which makes it tough to stay focused on stomach and to attract bright young scientist into the field.”

Cellular and Molecular Gastroenterology and Hepatology is pleased to honor the 25th anniversary of the AGA–R. Robert and Sally Funderburg Research Award in Gastric Cancer with a compendium of reviews and commentaries written by recipients of this award.

Visit www.cmghjournal.org to see this special article collection.

AGA is currently accepting applications for the 2018 Funderburg award. Learn more at www.gastro.org/research-funding.
Research Funding Opportunity

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

<table>
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<tr>
<th>OPPORTUNITY</th>
<th>AMOUNT</th>
<th>DEADLINE</th>
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<tbody>
<tr>
<td>AGA-R. Robert and Sally Funderburg Research Award in Gastric Cancer</td>
<td>$100,000</td>
<td>Aug. 4, 2017</td>
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<tr>
<td>AGA Research Scholar Award</td>
<td>$270,000</td>
<td>Sept. 8, 2017</td>
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<tr>
<td>AGA-Takeda Pharmaceuticals Research Scholar Award in Inflammatory Bowel Disease</td>
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<tr>
<td>AGA-Rady Children’s Institute for Genomic Medicine Research Scholar Award in Pediatric Genomics</td>
<td>$270,000</td>
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HARVONI is the #1 prescribed treatment for HCV GT 1 patients in the US.

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

- 97% overall cure (SVR12) rate in GT 1 subjects with HARVONI (n=1042/1079; ION-1, -2, -3).
- 99% and 95% overall cure rates in GT 2 and GT 3 subjects, respectively, with EPCLUSA (n=297/411; ASTRAL-2, -3).

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.

Please visit transformingtreatment.com to learn more.

Please see Brief Summary of full Prescribing Information for HARVONI and EPCLUSA including BOXED WARNING on Hepatitis B reactivation, on the following pages.
ECLIPSA FULLS FILDS A SIGNIFICANT UNMET NEED FOR GT 2 AND GT 3 PATIENTS

OVERALL CURE RATE IN GT 2 SUBJECTS
(n=153/154; ASTRAL-2)
OVERALL CURE RATE IN GT 3 SUBJECTS
(n=264/277; ASTRAL-3)

99% of GT 1-6 SUBJECTS OVERALL ACHIEVED A CURE ACROSS THREE PHASE 3 TRIALS

HARVONI HAS TRANSFORMED TREATMENT IN A BROAD RANGE OF GT 1 SUBJECTS1

97%

OVERALL CURE RATE ACROSS THREE HARVONI PHASE 3 TRIALS1-4
(n=1042/1079; ION-1, -2, -3)

OVERALL CURE RATE IN GT 2 SUBJECTS

99%

OVERALL CURE RATE IN GT 3 SUBJECTS

95%

WHAT'S POSSIBLE

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

(n=1019/1033; ASTRAL-1, -2, -3)3

• ECLIPSA offers a once-daily, single-tablet regimen without IFN or RBV, regardless of prior HCV treatment experience or the presence of compensated cirrhosis2

• Adverse reactions (all grades) reported in >3% of subjects receiving 12 weeks of treatment with ECLIPSA (ASTRAL-1): headache (24%), nausea (21%), insomnia (19%), back pain (14%), diarrhea (12%), fatigue (11%), and anemia (9%).

• Adverse reactions leading to discontinuation of ECLIPSA were reported in >1% of subjects: headache (2%), nausea (2%), and diarrhea (1%).

HARVONI was the only HCV treatment with an established 8-week course of therapy to achieve 91% cure across GT 1 patients within 12 weeks of treatment7,8,9.

BOXED WARNING

RISK OF DECOMPENSATION IN DECOMPENSATED CIRRHOSIS

The risk of decompensation and serious adverse reactions in decompensated cirrhosis (Child-Pugh B or C) was higher for patients treated with HARVONI compared with placebo. Patients with decompensated cirrhosis had significantly increased risk of decompensation compared with compensated cirrhosis.

The most common adverse reactions in decompensated cirrhosis were fatigue, headache, and anemia.

IMPORRTANT SAFETY INFORMATION FOR HARVONI AND ECLIPSA

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 ECLIPSA. HBV reactivation has been reported in HCV/HBV coinfected patients who were undergoing or had completed treatment with HARVONI or ECLIPSA. 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 <6 million IU/mL at 12 weeks after the end of treatment. Achieving SVR is considered a virologic cure.

IMPORTANT SAFETY INFORMATION FOR HARVONI AND ECLIPSA

DRUG INTERACTIONS

Co-administration of HARVONI or ECLIPSA is not recommended with ocrelizumab, phenobarbital, phenytoin, rifabutin, rifampin, and tipranavir/ritonavir due to increased concentrations of sofosbuvir, ledipasvir and/or velpatasvir.

Co-administration of ECLIPSA is not recommended with proton-pump inhibitors or alvarenol due to decreased concentrations of velpatasvir; or with topotecan due to increased concentrations of topotecan.

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

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

REFERENCES

BOXED WARNING: RISK OF HEPATITIS B VIRUS REACTIVATION IN PATIENTS INFECTED WITH HBV AND HIV

Risk of HBV Reactivation in Patients Coinfected with HCV and HBV: Risk of HBV reactivation during HCV treatment with HARVONI: In patients with chronic hepatitis B virus (HBV) infection before initiating treatment with HARVONI. HBV reactivation has been reported in patients who were undergoing or had completed treatment with HCV direct-acting antivirals. Patients with chronic hepatitis B who have undergone or completed HCV direct-acting antiviral therapy should receive HBV prophylaxis for at least 6 months following HCV treatment. For patients with chronic hepatitis B who have undergone or completed HCV treatment and who are hepatitis B surface antigen (HBsAg) positive or have serum hepatitis B e antigen (HBeAg) and HBV DNA detectable, treatment with HARVONI is recommended. Because postmarketing reactions are clinically indicated.

The safety assessment of HARVONI was also based on pooled data from three open-label Phase 3 clinical trials (ION-3, ION-2, ION-1) conducted in a total of 304 subjects who received HARVONI alone or in combination with ribavirin. These events were reported with an incidence of less than 5% of subjects receiving HARVONI in any one trial)

ADVERSE REACTIONS:

Most common adverse reactions (incidence greater than or equal to 10%, all grades) in GT 1 subjects with cirrhosis:

- Headache (28%)
- Fatigue (18%)
- Sleep disturbance (17%)
- Insomnia (13%)

Less Common Adverse Reactions Reported in Clinical Trials

- Nausea (6%, 7%, 9%)
- Diarrhea (4%, 3%, 7%)
- Insomnia (6%, 8%, 10%)
- Asthenia (4%, 5%, 7%)
- Pyrexia (1%, 2%, 3%)

Related Hepatic Adverse Reactions with Use of HARVONI with products containing sobralfir is not recommended.

Increased transaminase levels (defined as aminotransferase levels greater than or equal to 10xULN was observed in 1% of subjects treated with HARVONI in any one trial)

Risk of HBV Reactivation in Patients Coinfected with HCV and HBV:

Risk of reduced therapeutic effect due to use with P-gp inhibitors: Risks Associated with RBV Combination Treatment

For RBV, in particular pregnancy avoidance, apply to this combination regimen. Refer to the RBV prescribing information.

Regimens containing tenofovir DF and a HIV protease inhibitor/ ritonavir or co-formulated (e.g., atazanavir/ritonavir or co-formulated with cobicistat/efavirenz) or with P-gp inhibitors: HTV PRODUCTS

HIV Products (single-patient): Increased sobralfir and tenofovir concentrations. Coactivation is not recommended.

HIV-1 co-infected subjects was similar to that observed in HCV mono-
disease who received HARVONI + RBV for 12 weeks, 2 (1%) subjects died, 4 (2%) subjects
underwent liver transplantation, and 1 subject (<1%) underwent liver
transplantation, and 1 subject (<1%) underwent liver
disease. The most common adverse reactions occurring in at least 10% of subjects receiving HARVONI

Exposure to increases in plasma concentrations of the following drugs when coadministered with HARVONI:

Creatine Kinase:

Risks Associated with RBV Combination Treatment

Based on drug interaction studies conducted with HARVONI or its
related products not recommended.

Related Hepatic Adverse Reactions with Use of HARVONI with products containing sobralfir is not recommended.

A Challenging Area of HBV treatment is the management of patients who have been coinfected with both HBV and HCV. These patients may have been infected with HBV before or after the diagnosis of HCV infection. In such cases, it is important to consider the potential for HBV reactivation during HCV treatment. A review of the literature and clinical experience suggests that HBV reactivation can occur with varying degrees of severity, ranging from asymptomatic increases in HBV DNA levels to symptomatic hepatitis flares or acute liver failure.

The risk of HBV reactivation appears to be highest in patients with chronic HBV infection who have undergone or completed treatment with HCV direct-acting antivirals (DAAs). Therefore, it is important to consider prophylactic measures for patients who have undergone or completed treatment with HCV DAAs and who are infected with both HBV and HCV. Prophylactic measures may include the use of HBV antiviral therapy during HCV treatment or the use of HBV vaccines for patients who have not been vaccinated against HBV.

Serious Symptomatic Bradycardia When Coadministered with P-gp inhibitors: Increased in patients with pre-existing history of psychiatric illness). Depression, anxiety, agitation, confusion, or memory problems.

Based on data from clinical trials, including ELECTRON-1, ELECTRON-2, and ELECTRON-3, the adverse events leading to reduced HARVONI effect are consistent with the adverse events observed in the trials. The adverse events observed were consistent with the adverse events observed in the trials.

For RBV, in particular pregnancy avoidance, apply to this combination regimen. Refer to the RBV prescribing information.

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Exposure to increases in plasma concentrations of the following drugs when coadministered with HARVONI:

Creatine Kinase:
Brief Summary (cont.)

As assessed when amylase values were ≤1.5×ULN. Isolated, asymptomatic, transient elevations in amylase and lipase has been observed in patients treated with EPCLUSA with ribavirin for 12 weeks. Creatinine kinase (CK) elevations greater than or equal to 15×ULN was observed in 1% of subjects treated with EPCLUSA and placebo for 12 weeks, respectively, and in 2% of subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3, respectively. In the Phase 3 trial with decompensated cirrhosis treated with EPCLUSA, a fatal cardiac arrest was reported in a patient who experienced these adverse reactions, 79% had an adverse reaction of grade 3 or 4, and 14% had an adverse reaction of grade 5. The safety and efficacy of EPCLUSA were consigned in these studies. Bradycardia was also observed in greater than or equal to 5% of subjects treated with EPCLUSA and 5% of subjects receiving ribavirin alone.

Subjects with Decompensated Cirrhosis: The safety assessment of EPCLUSA in subjects infected with genotype 1, 2, 3, 4, or 6 HCV, who were decompensated cirrhosis treated with 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 headache (52%), fatigue (15%), nausea (11%), and anemia (9%). Adverse reactions (all grades) reported in ≥10% of subjects treated with EPCLUSA in ASTRAL-2 and ASTRAL-3 were consistent with those observed in ASTRAL-1. Bradley (0.5×ULN). Significant increase in rosuvastatin concentrations and rhabdomyolysis. Monitor closely for HBV reactivation in patients for whom ribavirin is contraindicated. Refer to the RBV prescribing information for a full list of the warnings and precautions for RBV.

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

USE IN SPECIFIC POPULATIONS:

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

Geriatric Use: Clinical trials of EPCLUSA included 156 subjects aged 65 and over (12% of total number of subjects in the Phase 3 clinical trials). No overall differences in safety or effectiveness were observed between EPCLUSA in elderly patients and younger patients with renal impairment. The safety and efficacy of EPCLUSA was evaluated in geriatric patients. No dosage adjustment of EPCLUSA is required for geriatric patients.

Renal Impairment: No dosage adjustment of EPCLUSA is required for patients with mild or moderate renal impairment. Dosage adjustment of EPCLUSA for patients with severe renal impairment is not recommended. Refer to the RBV prescribing information for dose modification recommendations in patients with severe renal impairment or ESRF.

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

Breastfeeding: EPCLUSA is excreted in human milk. The potential for adverse reactions in nursing infants when EPCLUSA is administered to a nursing mother is unknown. Refer to the RBV prescribing information for information use of ribavirin in patients with renal impairment.
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