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Transforming the Paradigm of Treatment for Hepatitis C

For more than 25 years, Ira M. Jacobson, MD, Chief of the Division of Gastroenterology and Hepatology at NewYork-Presbyterian/Weill Cornell Medical Center, has been deeply involved in clinical trials for hepatitis B and C therapy, serving as investigator or principal investigator – and even global principal investigator – for many pivotal trials. He has participated firsthand in advancing the field, which has undergone particularly dramatic progress in recent years.

“Particularly in hepatitis C, we are witnessing a fundamental change in the paradigm of treatment, moving from interferon-based therapies to oral therapies with powerful antiviral agents that can be combined to eliminate the virus in most patients,” says Dr. Jacobson. “Some viruses are suppressible, and therefore the diseases they cause are correspondingly controllable, such as HIV or hepatitis B. But hepatitis C is a relative rarity among chronic viral infections, which is

that it’s actually curable. In light of the evidence accumulated over the last few years that once the hepatitis C virus is undetectable in the blood for 12 to 24 weeks after treatment is stopped, it almost never reappears.”

The reason, explains Dr. Jacobson, lies in what is known about the biology of the hepatitis C virus. “Its life cycle and structure suggest that the virus is not capable of hiding out deep inside cells and embedding pieces of itself that can subsequently reactivate the way hepatitis B or HIV can,” says Dr. Jacobson. “For example, the viruses for HIV and hepatitis B can integrate or embed their genetic material into that of human chromosomes, and hepatitis B can actually create a mini-chromosome of its own that can be impervious to antiviral therapies. While we can very successfully suppress active viral replication and the liver inflammation that ensues, long-term therapy or indefinite therapy is needed to keep the hepatitis B under control.”

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Miniature Microscope Making Big Impact in GI Therapeutics

Probe-based confocal laser endomicroscopy (pCLE) has recently entered the field of gastroenterology, taking diagnostic and treatment devices to a new level of precision and speed. The new technology, known as Cellvizio, is essentially a miniature microscope – just under several millimeters in diameter – mounted on a catheter that can be introduced through a scope into the lumina of the GI tract, whether it is the esophagus, stomach, duodenum, rectum, or colon. It can also be used in the bile and pancreatic ducts.

Frank G. Gress, MD, Clinical Chief of the Division of Digestive Diseases at NewYork-Presbyterian/Columbia University Medical Center, and Michel Kahaleh, MD, Chief of Endoscopy at NewYork-Presbyterian/Weill Cornell Medical Center, have been proponents of the approach, applying pCLE to GI and biliary abnormalities with great success. “Physicians began using Cellvizio in clinical decision-making about two years ago,” says Dr. Gress, a specialist in interventional endoscopy. “This is a significant

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Dr. Frank G. Gress

Transforming the Paradigm of Treatment for Hepatitis C (continued from page 1)

Approximately 170 million people are infected with hepatitis C worldwide and 350,000 people die each year from the disease. Federal statistics indicate over three million people in the United States are infected with hepatitis C. And tens of thousands of people in the U.S. are estimated to acquire the disease annually.

According to Dr. Jacobson, the problem with hepatitis C is that it usually results in chronic infection and as the decades go by there is a greater likelihood of scar tissue accumulating in the liver, leading to cirrhosis. “Complications range from internal bleeding to liver failure, and one of the most dreaded – hepatocellular carcinoma,” says Dr. Jacobson. “Hepatitis C is now the leading cause of liver cancer in this country because the consequences of hepatitis C-induced liver disease initiated 20, 30, and 40 years ago by acute infection have now come to fruition.”

Many Reasons for Optimism

In spring 2013, clinical trials of a new drug, sofosbuvir, revealed dramatic cure rates for hepatitis C patients with two subtypes of the infection – genotype 2 and 3, which account for approximately 25 percent of the country’s hepatitis C infections.

“The sofosbuvir therapy offers a much-needed alternative to standard therapy with interferon, which can cause significant side effects for hepatitis C patients,” says Dr. Jacobson, lead investigator on the Phase 3 international clinical trial called POSITRON that contributed to the drug’s FDA approval in December 2013. In one study, after 12 weeks of combined therapy with sofosbuvir and the antiviral drug ribavirin, the patient response rate for those with genotype 2 was 93 percent, and 61 percent in patients with genotype 3. Results were published in *The New England Journal of Medicine* as were those of another trial showing significantly improved cure rates in patients with genotype 3 treated for 24 weeks. Sofosbuvir works by interfering with the ability of the hepatitis C virus to replicate. The drug also confers a high barrier to developing the complication of drug resistance.

“We have dreamed for years of being able to eliminate interferon from our hepatitis C regimens and these and other studies have brought us to the realization of that goal,” adds Dr. Jacobson, who estimates that up to

half of patients with hepatitis C infection either can’t use interferon or don’t want to use it. This mirrored the 207 patients enrolled in the POSITRON trial, who either did not respond to interferon, could not tolerate it, or were unwilling to use it despite the fact that there were no other treatment options available to them. “This new treatment represents a paradigm shift in the way hepatitis C can be treated. The study showed that we were achieving the same or higher cure rates in many patients with sofosbuvir, compared to interferon, and we were doing it in half the time with a drug that has a remarkable safety profile.”

“These new regimens have everything imaginable going for them – far greater levels of efficacy and relatively benign toxicity profiles.”

— Dr. Ira M. Jacobson

With the new oral interferon-free therapies in hand and others on the horizon, Dr. Jacobson and his colleagues are optimistic that in the upcoming years there will be a substantial decline in the number of hepatitis C patients who will ever arrive at a point of cirrhosis or its complications.

“Cures rates are now 95+ percent across a broad spectrum of patients, including treatment-naïve patients and those who have failed to respond to previous therapies, as well as patients with advanced scar tissue – which is very important,” says Dr. Jacobson. “The durations of therapy are much shorter than with traditional interferon-based therapy – 12 weeks appears to be the upcoming standard, and some preliminarily successful eight-week regimens are undergoing ongoing investigation.

“In addition, the toxicity profiles are much more benign with ribavirin and sofosbuvir. Side effects are relatively minor, seldom result in the need to discontinue therapy, or have an impact on the quality of life remotely resembling that of interferon,” says Dr. Jacobson. “It’s been remarkable for me to see patient after



Dr. Ira M. Jacobson

patient in numerous trials that we’ve been conducting at Weill Cornell state that they can barely tell that they’re on anything, yet their virus becomes profoundly suppressed and ultimately disappears.”

Dr. Jacobson and his colleagues in the field anticipate that the next big quantum leap will be in genotype 1 therapy in late 2014, with the expected approval of very effective oral antiviral regimens for these patients, too.

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For More Information

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Miniature Microscope Making Big Impact in GI Therapeutics *(continued from page 1)*

advance in our ability to diagnose gastrointestinal conditions. Unlike an endoscopy procedure, which only captures images of the surface of tissue, Cellvizio makes it possible for us to see the microcellular structure of the GI tract in high definition thus allowing optical biopsy for real-time analysis. We particularly look at the mucosa to determine if dysplasia or cancer is present. Based on what we see, we can make decisions on the spot about an abnormal finding. In the days prior to pCLE, we would image with our scope, take a biopsy, and then wait several days for the results. We can do all of this – from evaluation to biopsy to interpretation to treatment – in one session now.”

The microscope magnifies tissue up to 1,000 times so that physicians can detect disease in real time, often making it possible to determine an immediate diagnosis. Optical biopsy uses the properties of light to enable physicians to make a diagnosis at the time of endoscopy. Prior to this technology, diagnosis could only be made using histological or cytological analysis.

Approved by the FDA for use in the GI tract and in the lung, the device is designed to improve detection and provide faster treatment of pre-cancerous conditions and other digestive diseases. “It is currently being used for patients with Barrett’s esophagus – with and without dysplasia, early esophageal and gastric cancers, and indeterminate biliary strictures,” says Dr. Gress. “Cellvizio has the potential to detect more malignant lesions through better sampling, especially in areas that appear normal under endoscopic examination. We can often confirm the presence of cancer by real-time visual analysis without removing tissue thus avoiding risks associated with surgical biopsy, including infection, scarring, and poor diagnostic results based on insufficient tissue collection. It can also help us to detect disease more accurately, therefore reducing the need for repeat procedures.”

A growing body of published clinical data provides evidence that adding Cellvizio to gastrointestinal endoscopy procedures often enables physicians to differentiate cancerous and pre-cancerous changes in tissue as the images are presented. “Certain criteria indicative of cancer are easily identifiable when cells are analyzed at the microscopic level,” says Dr. Gress. In some cases,



Dr. Michel Kabaleh

with a microscopic view providing improved understanding of the tissue, physicians have been able to perform minimally invasive treatments for conditions that traditionally required major surgery. And recovery after an optical biopsy procedure is fast; most patients resume usual activities and diet immediately.

Dr. Gress notes that Cellvizio can also be used to guide management. “There are other therapeutic tools that can guide us on removing a lesion,” says Dr. Gress. “If we see a suspicious, let’s say esophageal lesion, we will remove it using endoscopic mucosal resection. We can use pCLE to outline the border when looking for the suspicious areas. It will help to better define what we’re going to remove, where we’re going to remove it

from, and confirm that we’ve removed all of it. It looks at the margins of resection as well.”

Dr. Gress and his colleagues are currently collecting pathology data to compare the data to the images collected during probe-based CLE procedures. “Because this technology is so new to us, part of our research is to verify that the images seen during the procedure correlate with the tissue pathology samples,” says Dr. Gress. “This work will allow us to independently verify the positive outcomes that others have experienced with pCLE.”

Addressing Biliary Irregularities

Confocal laser endomicroscopy may also offer a significant advantage for patients with chronic pancreatitis, pancreatic cysts, pancreatic and bile duct strictures, and patients with family history of pancreatic cancer or intraductal papillary mucinous neoplasm.

“CLE can be put through our scope into the bile duct or pancreatic duct and used to see any abnormal tissue in the duct lining,” says Dr. Gress. “In the case of pancreatic cysts, we have not been able to predict with very high accuracy if a cyst is malignant or not, so patients have had to come for regular follow-up in order to be vigilant about any potential cancers. The ability to characterize cells with CLE is a game changer, enabling us to determine whether cells are malignant or not by looking at them rather than extracting samples. It is also very helpful for targeting areas to biopsy; for now we are still taking tissue biopsies and using CLE to validate the findings, but in the future, we hope to be able to make determinations without taking tissue.”

A research team led by Dr. Kahaleh has found that pCLE can immediately and more accurately detect biliary cancers than the current diagnostic techniques, which include biopsies and CT and MRI scans. “This new technique is very important because it provides to patients a one-stop-shop option,” says Dr. Kahaleh, whose research group is focused on interventional endoscopy and the use of new devices to diagnose and treat biliary and pancreatic diseases. “Unlike with biopsy, the results are immediate and allow physicians to proceed with treatment. The procedure is 89 percent accurate in its diagnosis, compared to 72 percent using other methods.”

Benefits of Probe-based Confocal Laser Endomicroscopy*

- Detecting more cancers and pre-cancerous conditions
- Triggering instantaneous intervention
- Picking the right treatment modality
- Prescribing the right drug
- Delineating resection margins
- Monitoring treatment response
- Assessing completeness of resection
- Managing recurrent or residual disease

**As demonstrated by numerous clinical studies of optical biopsy*

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Miniature Microscope Making Big Impact in GI Therapeutics *(continued from page 3)*

Reaching Consensus on pCLE Use and Interpretation

Both Drs. Gress and Kahaleh agree that while pCLE offers great potential for detecting cancer in hard-to-reach areas of the body, it is critical that doctors using the new technology be in agreement over what they are seeing.

“When you have a new technology to search for cancer, you always want to make sure that you’re speaking the same language while using it,” says Dr. Kahaleh. Having found in an earlier study by his research team that there was great variability of interpretation – ranging from diagnoses of cancer to inflammation, Dr. Kahaleh, joined by Dr. Gress and other colleagues around the country, recently undertook a study to assess interobserver agreement and diagnostic accuracy upon completion of a pCLE training session.

The researchers sent 40 video clips of indeterminate biliary strictures to five endoscopists at four tertiary care centers for scoring. Observers subsequently attended a teaching session by an expert pCLE user that included 20 training clips and rescored the same pCLE video clips, which were randomized and renumbered. They found that pre-training interobserver agreement for all observers was “fair” and diagnostic accuracy was 72 percent (55-80 percent). Post-training interobserver agreement for all observers was “substantial” with diagnostic accuracy at 89 percent (80-95 percent.)

With the increasing success of Cellvizio in a number of clinical

arenas, coupled with the recent study finding that a single training session in pCLE for the bile duct can greatly improve both accuracy rates and agreement among practitioners, the research team recommends that more doctors become proficient with the tool.

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