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The Continually Improving HCV Treatment Landscape

Dr. Muto:

Hello, Dr. Fried. Welcome to our program.

Dr. Fried:

Thank you. It's a pleasure to be here.

Dr. Muto:

Dr. Fried, can you talk about the treatment of hepatitis C and how it's evolved over the past few years?

Dr. Fried:

Certainly. The treatment of hepatitis C has evolved remarkably over the last several years. Early on, we only had injectable interferon-based treatment regimens that had a tremendous number of side effects and only cured, at most, 50% of the patients that were treated. Many patients weren't even eligible for those treatments because they had other comorbidities that could have been exacerbated by interferon or ribavirin-based treatments. Over the last several years, we've seen the introduction of what we call direct-acting antiviral agents and these are combination oral regimens for the treatment of hepatitis C. What's remarkable about them is that, if you take your medications for durations ranging from 8 to 12 to 24 weeks, depending on certain patient and virological characteristics, you're almost guaranteed to have a sustained virological response in the range of 90 to 95%. Sustained virological response is defined as having undetectable HCV RNA in a blood test 3 months after treatment is discontinued. So this has been used as a surrogate marker for cure of hepatitis C infection, and indeed, with very long-term followup of these patients, if they get to that 3-month post-treatment milestone with undetectable HCV RNA, we know that that is analogous to cure of hepatitis C infection.

Dr. Muto:

That's really amazing. That's probably one of the biggest breakthroughs in treatments of an infectious disease in a very long time.

Dr. Fried:

As far as we know, as far as I can recall, this is truly the only viral infection that once it's chronic we can actually establish that it's now cured with treatment. So yes, it has a successful outcome of therapy, has just a tremendous impact on patients' lives, not just in terms of how they feel, but there's also data accumulating that when you achieve a sustained virological response or cure of hepatitis C, you're not only decreasing liver-related mortality, risk for hepatocellular carcinoma, but, interestingly, all-cause mortality seems to improve as well. So, there are some systemic effects of hepatitis C that are now being more recognized.

Dr. Muto:

Wow! That's really great and exciting. Can you tell me how the primary care provider can identify patients who would benefit from treatment?

Dr. Fried:

So, in the United States, believe it or not, most patients who have hepatitis C still have not been diagnosed. So, there's a big interest in trying to identify those patients. Certainly anybody with a risk factor for hepatitis C such as having ever experimented with intravenous drugs, or ever having had a blood transfusion prior to 1992, or anybody with an abnormal liver enzyme, for example, should all be tested for hepatitis C. But with a better understanding of the epidemiology of hepatitis C in the United States, most infections occur in people who were born between 1945 and 1965, the so-called baby-boomer generation. Approximately 85% of all people who are currently infected with hepatitis C were actually born between those years. So, the CDC recently recommended that, without necessarily inquiring about what kind of risk factors a person may have, which sometimes can be uncomfortable for both the provider and the patient, just looking at their birth year is a good surrogate for recommending testing for hepatitis C. So, anybody born between 1945 and 1965 should have a one-time anti-HCV antibody test for hepatitis C and then be channeled into appropriate care.

Dr. Muto:

If the primary care providers should work with the presumption that almost every patient is considered a candidate for treatment, what steps then should one take to help identify those patients who are ready or motivated for treatment?

Dr. Fried:

Well, I firmly believe that almost everyone who has hepatitis C is a candidate for treatment. The current therapies, as I mentioned, are incredibly effective. They have very few side effects, and they can really be life-changing for patients who have suffered with this disease for 20, 30, and 40 years. So, therefore, it really, as I mentioned before, it's really incumbent upon the primary care physician to really do the appropriate testing and then get the patients the treatment that they could definitely benefit from. Now, in terms of who is a candidate, really, in the absence of any real contraindications to therapy for hepatitis C with current medications, almost every patient would potentially qualify. So, in addition to appropriately screening patients for the potential diagnosis of hepatitis C, once the diagnosis of hepatitis C is established, primary care physicians can also have a major impact on helping the patient understand the context of hepatitis C, that there are curative therapies, and they can provide great reassurance to the patient with this new diagnosis. Since most people with hepatitis C have no symptoms, it often comes as a tremendous shock to patients that they've been infected with this disease and the healthcare provider who is on the frontline who has made the initial diagnosis can really help that patient tremendously deal with that new diagnosis. So, for example, it's important to reassure the patient that hepatitis C is not easily transmitted to family members or loved ones. There are common-sense precautions that are recommended in terms of direct-blood contact and things like that, but in general, there are no changes to sexual practices that must occur for someone who is infected with hepatitis C relative to their partners. In addition, there is virtually no risk to family members through routine household contact. And this can go a long way to reassuring patients in how they deal with their disease. There are a few things that, if you do have a patient with hepatitis C, they do recommend that their spouse or partner get tested on one occasion, more for peace of mind, and similarly, because there's a pretty low risk of mother-to-child transmission, they do recommend that children born to mothers with hepatitis C do get tested on one occasion for the disease.

Dr. Muto:

Are there any other things that primary care providers should be counseling their HCV patients about, or other testing that might be beneficial?

Dr. Fried:

Yes, definitely. Because alcohol is a cofactor in the progression of liver disease toward cirrhosis, patients with hepatitis C should be cautioned about the impact of drinking while they have hepatitis C infection. Certainly patients who have been identified with cirrhosis should not drink at all and patients with mild forms of liver disease should certainly minimize their alcohol intake, since no one really knows what is the minimal amount of alcohol that is problematic for those with hepatitis C infection. So, trying to get an idea of how much your patient drinks and counseling them appropriately is very important and we spend a lot of time with our patients trying to get them to understand those issues. In addition, patients with hepatitis C should be appropriately vaccinated for hepatitis A and hepatitis B, if they are still susceptible. Finally, patients who have underlying cirrhosis that's identified should routinely have hepatic imaging, such as with an ultrasound, approximately every 6 months, in order to screen for the development of hepatocellular carcinoma, for which they remain at high risk.

Dr. Muto:

What else should primary care providers be counseling their HCV patients about?

Dr. Fried:

So, in addition to alcohol cessation that we discussed, we're seeing a great number of patients now who have concomitant non-alcoholic fatty liver disease. So, this is a liver disease that's associated with a metabolic syndrome that, by itself, can contribute to the progression of liver disease, even in patients whose hepatitis C has been cured. So, patients should also be counseled about maintaining good control over blood glucose and making sure their lipid profile is within normal limits. In addition, maintaining ideal body weight is very important to minimize the risk for non-alcoholic fatty liver disease. So all of these things together will contribute greatly to maintaining liver health.

Dr. Muto:

Dr. Fried, what type of monitoring is recommended for patients with hepatitis C in those pursuing treatment and in those not pursuing treatment?

Dr. Fried:

I sincerely hope that most patients with hepatitis C are going to pursue treatment because, as I mentioned, the outcomes are quite remarkable and there are very few side effects associated with this. For those who are planning on treatment, I think the things that I mentioned before, to prepare them for therapy, making sure they're able to be adherent to the medication regimen. Fortunately, the regimens are fairly simple overall, ranging from one to just a few pills a day, taken for a relatively short period of time, anywhere from 8 to 12 or sometimes 24 weeks, depending on prior treatment experience and whether or not the patient has evidence of underlying cirrhosis. So, overall, the treatment regimens are quite simple, but patients still need to be in the right frame of mind that now is the time for me to be treated because once you start therapy you don't want to interrupt it for anything in order to maximize the chances of curing hepatitis C. And, as I said, if you take your medication properly, you're almost guaranteed to have a sustained virological response.

Dr. Muto:

That's really exciting and quite different from years of the past.

Dr. Fried:

Oh yes, it's really amazing. I always say that my clinic now is the happiest place on earth because I've had patients we've been following for 15, 18 years, who have lived with this disease who have tried multiple iterations of treatments that were state-of-the-art at the time, but they just weren't effective for them. And now, with such a short course of all-oral regimens, they're cured from this infection that has burdened them for so long. It's just, it has a tremendous impact on patients' lives that you can't even describe, but that we hear these stories every single day. Now, for monitoring during treatment, again, because these medicines are fairly well tolerated, most regimens don't have any specific requirements for monitoring during treatment. If patients are using a ribavirin-containing regimen, of course we want to monitor their blood counts on a regular basis, because ribavirin induces hemolysis that will cause anemia, sometimes rather severe in some patients. Certain regimens also require periodic monitoring of liver enzymes because there is a small risk of increased liver enzymes with treatment. I also feel it's important to have several touch points during the course of treatment, again, to encourage the patient to be adherent, we happen to check an HCV RNA at week 4 which is a good way to get an idea that the viral load has decreased dramatically during the course of treatment. And again, if the patient is taking the medications, that's virtually assured. It also reinforces to the patient just how effective these medications are, which I think also goes a long way to helping them maintain adherence for the remainder of their treatment course. So, I think how individual practitioners can accomplish these things is really specific to their own practices, but having some touch points during the course of treatment, I think, are still important. I wouldn't just write a prescription to the patient and say, "Here, please come back in 3 months after you take this medication, for followup." I also think that it's important to have some pre-treatment education about. Well, we discussed about the importance of adherence, to also review about the potential for drug-drug interactions. Certain regimens do have a greater potential for drug-drug interactions than others. And I would advise that anyone prescribing these medications be familiar with various websites that can help evaluate drug-drug interactions. Patients should be aware that if they start new medications during the course of treatment, they should check with their provider who is managing their hepatitis C to make sure that those are acceptable within the guidelines.

Dr. Muto:

If you are just tuning in, you are listening to CME on ReachMD. I'm your host, Dr. Muto, and today I am speaking with Dr. Michael Fried, Professor of Medicine and Director of Hepatology at the University of North Carolina, UNC Liver Center in Chapel Hill. We are speaking about the treatment of hepatitis C.

Dr. Fried, when thinking about treatment, what patient characteristics influence treatment choice?

Dr. Fried:

Fortunately almost every patient that we see in our clinics now has at least one and often several options for treatment. You know in the past, when these regimens had substantial side effects, the actual number of patients who were eligible for treatment was rather small. But now, virtually 100% of patients that we see do have some kind of treatment option. For example, patients who already had cirrhosis, particularly those with decompensated cirrhosis in the era of PEG-interferon and ribavirin, we would not even consider treating those patients because of the high chance of causing further harm and worsening their decompensation. With the current regimens for hepatitis C, we are able to take decompensated cirrhotic patients and treat them with effective and fairly safe regimens. We still have to be aware that patients with hepatic decompensation, of course, because of the natural history of their disease, can get worse during the course of treatment, and there have been an association of certain regimens that should not be prescribed in patients with already decompensated cirrhosis. But, nevertheless, we still have choices and can usually cure the hepatitis C infection. Even in those patients, the sustained virologic response rates are in the high 80s to low 90s with a relatively short duration of treatment to achieve sustained virological response. The big question we have about treating those patients is what are the long-term outcomes? We know we can eradicate the infection. Will it lead toward sustained improvement in their MELD score, and obviate the need for liver transplant in the future? So, we still need long-term followup to understand what the implications are of treating patients with decompensated cirrhosis. Another group in the past that never had great treatment options were those patients with renal impairment, such as those on hemodialysis. Now we have regimens that are not metabolized through the kidney and therefore have demonstrated safe and effective treatments for this population and those with advanced, chronic kidney disease. So, almost every patient that we see will have some option for treatment. Now we have to weigh the risk and benefits of treating individual patients when they have many comorbidities, because at the end of the day, we still want to treat patients who have the highest chance of achieving success, as well as having meaningful improvement in their quality of life.

Dr. Muto:

So, how do you decide, like what are the key factors to consider when choosing appropriate therapy for each individual patient?

Dr. Fried:

So, as we've gotten more choices, we have to take into consideration a number of factors. So, the choice of a regimen, the treatment duration that we'll use, and whether or not ribavirin is included in the mix, really depends on a number of factors. We have regimens for genotype 1A versus genotype 1B as well as regimens for genotypes 2-4 which are less commonly seen here in the U.S. than genotype 1. We have to take into account things such as what their prior treatment experience is. Have they ever been treated for hepatitis C, or is this their first course of treatment? And then we look to see whether or not... what they were treated with. Were they treated just with peginterferon and ribavirin, or have they previously been treated with, say a first-generation protease inhibitor, or possibly one of the recent NS5A inhibitors, or possibly even one of the nucleoside polymerase inhibitors that they may have gotten in an earlier iteration of these medicines? We also have to determine whether or not the patient has cirrhosis and treatment regimens differ on whether a patient has compensated cirrhosis, such as a Child-Pugh A cirrhotic, versus those that we talked about with decompensated cirrhosis already. We're starting to understand that for certain treatment regimens that involve an NS5A inhibitor, the presence of a baseline resistant associated variant can have an impact on treatment. And if we understand the presence of those, prior to starting therapy, we can adjust the treatment regimen to substantially impact the likelihood of hepatitis C cure. And, as we talked about before, there is also some potential for drug-drug interactions that we may want to take into account and think about what regimen might be best for this patient, if they're on certain drugs that they just have to continue.

Dr. Muto:

Sounds like a lot of this work parallels the work that was with HIV and the antiretroviral assessments and strategizing for patients. You know, I'm glad to see that now there are so many options and that great people are out there figuring out what works best for each patient.

Dr. Fried:

I'd like to mention that, I mentioned a whole lot of things that are factored into treatment choices, and fortunately, as you said, we have a great resource that your listeners should take a advantage of and that is the AASLD/IDSA Hepatitis C Treatment Recommendations, we found at HCVGuidelines.org and it really digests all of the things that I have said and provides a tiered listing of recommended treatment options for those particular kinds of patients. So, it's a great resource that we refer to in our clinic all the time.

Dr. Muto:

That sounds great. It sounds like some of that work might have come out of programs that have been already cited or recent evidence that offers insight into primary care driven HCV treatment. Do you want to talk about some of those?

Dr. Fried:

Sure. In the U.S. the estimates range between 3 and 5 million people have hepatitis C. There certainly are not enough hepatologists, gastroenterologists, or infectious disease physicians alone, or other healthcare providers, to treat all those patients. So, there has been some interest that in considering whether primary care physicians could successfully treat patients with hepatitis C, and I think the evidence is starting to point to the fact that they certainly can. And I think this has a large part to do with the fact that the treatments have become safer and highly effective, and of a relatively short duration. So, for a lot of reasons, I can understand why interested primary care providers would do well with treating patients for hepatitis C, and there are a number of examples of this. A recent study that was just presented at CROI in 2016 was actually interesting. It came out of the Baltimore/Washington area and they took GI specialists, infectious disease specialists, primary care physicians, and nurse practitioners who were all interested in treating hepatitis C. They provided some baseline level of education about hepatitis C and liver disease and then assigned 600 patients to be treated amongst these various groups and then compared their outcomes. And what they showed was that these very different types of physicians and healthcare providers actually achieved remarkable success with these patients. Over 95/96% sustained virological response rate very similar to the Phase III clinical trials' results that have been published. So, I think, this is the first formal look to see how well a diverse group of treating healthcare providers could do with providing therapies for a large group of patients. Now, there have been other examples in the literature, Sanjeev Arora, has been a big proponent of the ECHO model that is sort of a telementoring concept where clinicians will work sort of in a hub-and-spoke format. Clinicians in the community will work with specialists, in the case of Sanjeev, at the University of New Mexico, to be mentored in managing patients with hepatitis C and over time they become quite expert at recognizing underlying liver disease, managing cirrhosis, as well as treating patients with a variety of agents. Interestingly, Sanjeev started this during a period of time when treatment regimens had a substantial number of side effects, and he also was able to show that, with the proper mentoring, primary care physicians had excellent outcomes that compared favorably to those at a university practice. We're actually doing this in North Carolina. I have a couple of interested physicians working at a Federally-Qualified Health Center and we're doing a modified version of ECHO and they're also treating many patients with hepatitis C with tremendous outcomes as well. And they utilize us as a resource for backup for patients with very severe liver disease or those who have experienced unusual complications during the course of treatment. So, I think, that the short answer is yes. I think that at some point, interested providers in the primary care field who are willing to get appropriate and additional educational opportunities to learn more about liver disease and treatment of hepatitis C, I think they'll be a very valuable resource for treating this disease in the future.

Dr. Muto:

How do you see the role of primary care providers evolving in the coming years in HCV treatment and management?

Dr. Fried:

So, I think that first and foremost, since a large percent of patients who are infected with hepatitis C are not aware of it. It's important for primary care physicians to improve screening and identifying patients with this disease. We talked about the simplicity of birth year cohort screening, and I think we, over the last several years, we're definitely seeing the impact of that as it's being adopted by professional societies and it's being publicized by the CDC as how important that is. So, we're definitely seeing an influx of patients newly diagnosed with hepatitis C and the primary care provider should discuss that with all their patients and once they do identify a patient with hepatitis C, we discussed the importance of sending the right messages early on, so that it sets the tone for how a patient can deal with and understand the disease. The tone and the message have to be incredibly hopeful that we can cure your hepatitis C and that it's not a death sentence, by any means, as has often been conveyed in the past. We mentioned that as the treatments become simpler, shorter duration, more streamlined, less side effects, that they're opening up to all patient types. I could see where primary care physicians, again, with appropriate additional training, and they also have to have an interest in doing this, would be a good resource for treating patients in the community, without having to go to specialty services, because again, we just don't have enough subspecialists to manage all of these patients.

Dr. Muto:

Dr. Fried, I want to thank you for being our guest and thank you for helping us to understand HCV treatment. I am your host, Dr. Muto, and thank you all for listening.