Treatment Decisions for Patients with HCV and CKD

CMEO Podcast Transcript

Nancy Reau:

Hello and welcome. On behalf of CME Outfitters, thank you for joining us for today's CMEO briefcase titled ''Treatment Decisions for Patients with Hepatitis C Virus and Chronic Kidney Disease''. Today's program is supported by the educational grant from Gilead Sciences. I am Dr. Nancy Reau from Rush University and Medical Center in Chicago. And I'll be the moderator for today's briefcase.

Anthony Martinez:

Hi, I'm Dr. Tony Martinez, associate professor of medicine at the Jacobs School of Medicine at the University of Buffalo and medical director of hepatology at Erie County Medical Center in Buffalo, New York.

Nancy Reau:

The goal of today's educational activity is to empower learners to implement screening guidelines in practice to improve the detection and diagnosis of hepatitis C. Let's get started. Dr. Martinez is going to tell us about Ahmed.

Anthony Martinez:

Thank you, Nancy. Let's take a look at Ahmed. He's a 51 year old male, and he's coming into his primary care to establish care. So this is a new visit in a completely new clinical setting. So he complains of arthralgias, and he's also got some burning sensation in his bilateral feet, and he complains of fatigue.

Anthony Martinez:

Now, he's got a past history of type 2 diabetes, hypertension, hyperlipidemia, and he recalls that he's been told in the past that his kidney function was off. But he can't give any more specifics and he's really had no follow-up since. He drinks socially. He doesn't smoke and he doesn't use any narcotics.

Anthony Martinez:

Now on exam, he has an old tattoo on his shoulder. His abdominal exam is relatively benign. And on his bilateral legs, he has some lower extremity edema. But he also has this bilateral purpuric rash. And he tells us that this rash has been there forever.

Anthony Martinez:

So initially, we get some baseline labs. And his CBC, his albumin, his total bilirubin and INR are all within normal limits. His AST and ALT are elevated at 55 and 89. His BUN and creatinine are also elevated at 39 and 2.9. In his urinalysis we find that he has some RBCs and he has proteinuria. Now he is on the usual medications that we

would expect for somebody with his comorbidities. And these include lisinopril, aspirin, metformin, and atorvastatin. Nancy, is this somebody that you would screen for hepatitis C?

Nancy Reau:

Thanks, Tony. I think that's an excellent question because if you look at this individual, our intrinsic bias is that he probably has fatty liver disease. His liver test numbers are elevated. He's on a bunch of medications that can cause liver enzyme abnormalities. And he certainly is above his ideal body weight. And these things certainly predispose a person to having fatty liver disease. And you might even say maybe he drinks more than what he's admitting. So he now has two additional reasons to have an increased liver test numbers, but our guidelines are pretty clear. Not only should we look at Ahmed for making sure that he doesn't have fatty liver, he doesn't have iron overload, as we would think about people with fatty liver disease and diabetes, but what reversible things, it's one thing to miss something you can't treat, but you definitely do not want to miss a treatable condition that impacts his prognosis. And luckily we have a bunch of guidelines that help us identify patients appropriate for screening. So I'm going to let you get to that a little bit, but Tony, what else about Ahmed really screams hepatitis C here?

Anthony Martinez:

He's got a couple of risk factors. On his physical exam, he does have that old tattoo. The rash may also be a tip-off. This is something that we frequently see in our patients with hepatitis C. And the more you treat, the more prevalent that this may be that you're seeing. Additionally, he complains of fatigue and joint pain. And we know that hepatitis C is primarily asymptomatic, but if patients do have symptoms, fatigue and arthralgias are two of the big ones. In addition, we take a look at his labs and you mentioned his transaminases are obviously elevated. There could be other reasons for that, but certainly hep C screening is indicated there. And it's important to identify that he does have some clear-cut renal disease here, and that in and of itself can also be a reason to assess a patient for hep C.

Nancy Reau:

So when we consider our guidelines, one thing about guidelines is there are multiple, multiple, societies that produce them. But uniquely hepatitis C testing is actually pretty uniform. Whether you're looking at AASLD, the CDC, the WHO, WGO, EASL, they all clearly state that there is now near-universal recommendations for hepatitis C screening. Tony, you want to go through some of those fine details?

Anthony Martinez:

Yeah. I think that one of the biggest changes that we've seen relates to the CDC guidelines. And more recently they've made a move toward universal screening. So they now recommend that we screen all adult individuals over age 18. Now that doesn't replace risk-based screening, and don't forget Ahmed has that old tattoo. So we have individuals who are under age 18 that may have some high risk behaviors or high risk practices that might put them at increased risk for requiring hep C. So we still have to screen based on risk. We're clearly doing almost universal screening based on age. And then we have continued periodic screening for our patients that may have been treated and cured, but continue to have high risk behavior.

Anthony Martinez:

Now, the Kidney Disease: Improving Global Outcomes also has a set of guidelines. And this recommends that we screen all HCV positive patients for kidney disease and vice versa. They recommend that we screen all patients with CKD for hepatitis C as well. And they recommend that we utilize either nucleic acid testing alone, or an immunoassay, like an antibody test with NAT reflex to assess for HCV RNA.

Nancy Reau:

Yeah, I think that our nephrologists are very well aware of screening for hepatitis B especially, because it's important for dialysis placement, but hepatitis C is probably a little bit under-recognized. So it's nice to see that the guidelines are clearly identifying CKD alone as a risk factor. So let's go back to Ahmed. I think we've highlighted some reasons that you really should have heightened awareness of hepatitis C, but what we need to discuss next is what are you going to do to screen hepatitis in Ahmed? Are you going to follow those kidney guidelines and get a nucleic acid test right off the bat? Or are you going to maybe go closer to the CDC algorithm where you might do antibody screening? All right. Tony, I do want you to talk about that, but before, let's poll our audience. So what additional laboratory tests would you order for Ahmed?

Anthony Martinez:

Honestly, Nancy, I'd probably get all of these tests in one shot. Just based on his symptoms and based on some of his baseline labs. And that's exactly what happened here with Ahmed. So he had a positive antibody test and hopefully we're utilizing, or we have the ability to utilize a reflex test. So that would mean that if his antibody's positive, they'll automatically run an HCV RNA, so that gives us that critical piece of information that we need that tells us that he's viremic.

Anthony Martinez:

Now, there's also a test that can reflex the viral load to the genotype. And it turns out that Ahmed is genotype 3, and there's six types of hepatitis C, multiple subtypes, but it really doesn't matter in this day and age as the new regimens are pangenotypic. And we'll talk about that more in a minute. Now we calculate Ahmed's eGFR and it's around 25, which indicates that he has more advanced kidney disease. So we did in fact, get those other labs and he has a positive rheumatoid factor. His C3 and C4 are both low, and he has a positive cryocrit, it's 7%. Now frequently, a lot of hepatitis C patients, when they complain of arthralgias, have a rheumatoid factor that gets done as part of that workup and their misdiagnosis is actually having rheumatoid arthritis. But as we'll see, that may not be the case in somebody like Ahmed. So he wants to know Nancy, did his hepatitis C cause his kidney disease?

Nancy Reau:

So Tony, I think that's a really complicated question because he obviously has clear reasons, independent of hepatitis C, to have CKD, namely as diabetes, which may not be ideally controlled. But as you outlined, there is a strong association between hepatitis C and renal disease. Even if we're ignoring the cryoglobulinemia or the other extra hepatic manifestations of hepatitis C, we recognize that CKD is increased in individuals with hepatitis

C infection. And when they do modeling studies, hepatitis C infected individuals with diabetes have worse in renal function, over individuals with diabetes who do not have hepatitis C. So we see that hepatitis C is impactful, even when we say that there's another reason for advanced renal problems. On top of that, we strongly know that extra hepatic manifestations of hepatitis C can include kidney problems as well as skin problems. And so I would say that Ahmed probably has two reasons to have CKD.

Anthony Martinez:

Yeah, it's most likely it is. I agree with you that it's probably multifactorial. And like you said, there's a clear-cut association with hep C and kidney disease. We know that hep C positive patients have a 23% greater risk of presenting with CKD. And end-stage renal disease is actually seven times higher in HCV positive patients versus HCV negative individuals. We also know that dialysis in and of itself can be an independent risk factor. And the time on dialysis can be important. So individuals who are on dialysis for a period of time, that's greater than 20 years, the prevalence increases to about 58%. Now a lot of that maybe has to do with some older risk factors like blood transfusions before 1992 or nosocomial transmission via dialysis itself. And what about kidney transplant? Were people at risk, maybe back in the old days, of acquiring hep C via a transplant?

Nancy Reau:

Yeah, I think that we recognize that iatrogenic exposure of hepatitis C is pretty common. Whether it's kidney transplant or blood transfusions, or patients that have sickle cell or thalassemia, or hemophilia, but there are, before you knew what Hepatitis C was and we were certainly doing renal transplant before that, we could have easily given a person hepatitis C with anything that exposed them to blood and body parts.

Anthony Martinez:

So safe to say that it's a much lower risk in this day and age, but for patients who may have had a transplant prior to, say 1992, it was obviously a bigger risk factor.

Nancy Reau:

And now we're actually taking advantage of that by giving hepatitis C exposed organs to patients and then trying to cure them afterwards. So we do not consider hepatitis C a contraindication to transplant, even if we might have accidentally given individuals hepatitis C with transplant long ago.

Anthony Martinez:

Let's go back to Ahmed for a minute here. What is the most likely cause of his purpuric rash?

Nancy Reau:

Well, I'm going to let you talk a little bit about those skin manifestations of, or extrahepatic manifestations of hepatitis C. I think one of the strongest clues here is the testing that you ordered. You got the complements, you got the cryocrit. This is all strongly screaming that his hepatitis C is causing some mischief and likely causing that rash. Although we do see a lot of edema and brown in our patients with diabetes who have had chronic venous

stasis, but it's important not to mislabel something as venous stasis when there's another much more identifiable explanation.

Anthony Martinez:

Yeah, exactly. And one of the big things that we really should kind of jump out at us, is the fact that 90% of mixed cryoglobulinemia is actually caused by HCV. And this initially begins as a benign lymphoproliferative disorder. And what happens is these abnormal immune complexes or cryoglobulins, they deposit in the small- or medium-sized blood vessels, and this can actually evolve into a non-Hodgkin's lymphoma. Now the typical triad that patients will present with, is this palpable purpura, like we see with Ahmed, arthralgias and weakness. And this is the symptoms that he was complaining about. Now you can have multi-organ mixed cryo syndrome, and this can affect the skin or the kidneys, the joints. So it's this compendium of symptoms that a patient can present with.

Anthony Martinez:

Now one thing that we also saw in Ahmed's labs is that he had some RBCs and proteinuria in his urinalysis. And that may be reflective of MPGN, which 70 to 90% of cases are associated with type II mixed cryo. We commonly think of hep C as just being a liver disease, but really it's a systemic disease. And we've talked about some of these hematologic and derm associations. We've talked about some of the renal stuff, but we also have to think about the fact that hep C is a chronic inflammatory condition, and it can actually worsen cardiovascular disease, things like atherosclerosis or CAD. And there's also a correlation with diabetes and can exacerbate that. We know when patients get treated in curative, their HCV, we'll actually see improvements in their glycemic control and even see reductions in their hemoglobin A1c.

Nancy Reau:

So Tony, I think it's interesting because a lot of the extrahepatic manifestations of hep C are bickered over. There are clear things like the dermatologic and the renal associations. And because of that, this is a disease that crosses multiple subspecialties. But when we talk about some of the other possibly associated injuries, there's a lot less confidence that hepatitis C is causing this. But I think one of the strongest messages is that we have consistently seen in populations that if you cure hep C, there is an improvement in all-cause mortality, not just liver related mortality and morbidities. You're not just preventing cancer and preventing decompensation and liver disease. You're actually decreasing non-liver related malignancies. You're decreasing cardiovascular events. You're decreasing those events from diabetes, so that pro-inflammatory condition is very easily treated and has a strong impact on longevity for our patients.

Anthony Martinez:

Speaking of treatment Nancy. Ahmed, now here he is newly diagnosed, he's got genotype 3, HCV, stage 4 CKD. He has type II mixed cryo. He wants to know, what are his treatment options? With the chronic kidney disease, does he have treatment options? Does it look different than somebody who didn't have CKD?

Nancy Reau:

Oh let's turn to our audience here. So what is the top treatment priority for managing Ahmed's new diagnosis? Well, Tony, I would venture to say that he may not be ready for dialysis or kidney transplant with CKD 4. So would you next turn to the hepatitis C or would you aim for controlling the cryoglobulinemia?

Anthony Martinez:

No. I think that I would probably come in and treat the HCV. And there's a couple reasons for that. Treatment for HCV has gotten really easy. It's essentially down to two regimens. The first of which is called SOF/VEL. This is a combination, single tablet taken once daily for a period of 12 weeks. Now in a small subset of patients, patients who were actively hepatically decompensated, we'd add something called ribavirin, which some people watching this may remember from the previous interferon-era of hep C treatment. But that's, again, a very small subset of patients.

Anthony Martinez:

Now, the other regimen that's available to us is called GP or GLE-PIB. Now this is a combination regimen that's a little bit different, in that it's three pills. It's still once daily dosing and it's taken with a small snack or a meal. And that's given for eight weeks. Now the only group of individuals that we can't use GP in, are patients who are actively decompensated or have a history of decompensated cirrhosis in the past. And we also can't use GP with medications, such as atazanavir or rifampin. So we've got a couple of good options here. Both of these regimens have cure rates or SVR rates greater than 95%. And both of these regimens are indicated for patients with CKD, including individuals who might be on dialysis.

Nancy Reau:

So Tony, it's interesting. You would think that this cryoglobulinemia would be so significant you would go right towards that. Why did you choose to treat the hepatitis C first?

Anthony Martinez:

Actually Nancy, the reason is because we know that when the hep C falls under control, that will actually improve the cryoglobulinemia. So if we take a look at this study from Italy, this included 44 patients that were previously treated with interferon-based regimens. The regimens failed, and they were retreated with these more modern DAA regimens. And if we take a look at this, patients at baseline who had cryocrits that were elevated, and the average here was about 7%, you can see that over the course of treatment, and finally at the end of treatment or SVR12, there were significant improvements. The cryo actually fell from about 7% down to about 3%. And then if you followed things out to an SVR24 or 24 weeks, it ultimately fell to under 2%.

Anthony Martinez:

So you see a significant reduction, not only in the cryos, but you can see a clear improvement in the complement, in the C4. You can also see a reduction in the rheumatoid factor behavior. So you see a baseline, it

starts out somewhere around 140, and by the end of treatment, it's under 50 and it stays relatively suppressed. You see a little bit of a bump up at SVR12, but you see some clear improvements here and you can see by the SVR24, a 100% of the patients had a clinical response, in terms of the vasculitis. Now, 36% had a full response, 41% had a complete response and 23% had a partial response.

Nancy Reau:

So Tony, if a person had not responded, it really implies from this study that most of our patients are going to have a significant improvement, but if they hadn't improved, is hepatitis C a contraindication to using rituximab or other immune suppressants?

Anthony Martinez:

Well, if we did it with the new DAAs first, it's highly likely that the HCV is going to be cured. We're talking about somewhere between a 95 to a 98% SVR rate. So hopefully the hep C is gone. We don't have to worry about that anymore. And then we could probably come in with Rituxan once the hep C is done. If the patients still required therapy, we could come in with the Rituxan at that point.

Nancy Reau:

Excellent. And there's no risk of late relapse of hepatitis C, at least it does not seem to be a significant risk, correct?

Anthony Martinez:

Yeah. The bigger thing would be, in our patients that maybe were hep B exposed, that if they had a positive core antibody, or, we'd likely know if they were chronically infected with HBV, but those are patients that we'd probably more closely monitor while they're on Rituxan. But in terms of the hepatitis C, this is very, very low risk.

Nancy Reau:

Excellent. And his kidney disease. So you've made his skin better. Did you improve his kidneys by curing his hep C?

Anthony Martinez:

Yeah, I think we probably will. Take a look at this study here. This comes to us from Taiwan. Now, this looked at a large body of patients. It looked at 1400 patients who had both hep C and diabetes that underwent therapy. And then there was a separate group of 1400 patients with hep C and diabetes who were not treated. And then there was a control arm of about 5600 patients that didn't have hep C at all. And if you pay attention to end-stage renal disease here, and you look at the split between the patients who were untreated for their hep C and those who were, you saw that there was a reduction in the progression of end-stage renal disease.

Anthony Martinez:

And we also know that in patients with cryo, once we treat their hep C and we get them cured, you do see improvements in their renal function. You might see some reductions in both the BUN and the creatinine. You see the urinalysis might improve as well. This also cuts across some of the other comorbidities that we've discussed previously. We know that when we treat patients and we cure their HCV, there's significant reductions in the cumulative incidents of having an ischemic stroke or an acute coronary event. You can see there's very clear delineations here between patients who get treated and cured versus those who don't.

Nancy Reau:

Tony, you already went over a lot of the characteristics of our new DAA therapy. So let's pull our audience, which DAA therapy would you choose for Ahmed for treatment? All right. So Tony, we've got our audience's responses. Do you have a preference in therapy for this patient?

Anthony Martinez:

No I think you have a good option with either GP or SOF/VEL. Both of them, keep in mind, are indicated for his genotype, both are indicated for his level of kidney disease. So we could go with either option. I think it would probably come down to doing an assessment of any potential drug-drug interactions, assessing his level of baseline hepatic fibrosis. It doesn't appear that he's cirrhotic and doesn't appear that he has any history of decompensation. So I think really we could choose either one of these regimens and get Ahmed cured.

Nancy Reau:

Wonderful. Well, I want to thank you, Dr. Martinez for your insights today. I think we've all learned something and we're going to pull together with our SMART goals to apply in practice. So after today, we hope that our participants will screen all indicated patients for hepatitis C infection according to our recommended guidelines, recognize extrahepatic manifestations of hepatitis C infection in clinical practice and appropriately treat hepatitis C infection with DAA therapy to improve both hepatic and extrahepatic outcomes. Be sure to check out the next two activities in this CMEO briefcase series, mitigating progression of liver fibrosis and HIV hepatitis C co-infection and treatment selection in a patient with decompensated cirrhosis. These activities, as well as many other educational resources for clinicians and patients can be found online at the CME Outfitters Infectious Disease and Virtual Education Hubs. To receive continuing education credit, and a printable certificate for completing today's activity, participants must complete the post-test and evaluation online. Thank you all for participating and providing the best care for your patients. Take care.