Clinical Education Initiative
Support@ceitraining.org

HCV AND HIV MANAGEMENT UPDATE FOR HIV PRIMARY CARE PROVIDERS

Speaker: Andrew Muir, MD MHS

2/8/2017

HCV and HIV/HCV Management Update for HIV Primary Care Providers
[video transcript]

00:00:00

Welcome to Physicians' Research Network. I'm Jim Braun, the course director of the monthly meetings of PRN in New York City. Since our beginning in 1990, PRN has been committed to enhancing the skills of our members in the diagnosis, management, and prevention of HIV disease as well as its co-infections and complications.

00:00:19

We hope this recording of Andrew Muir's presentation "HCV Monoinfection and HIV/HCV Co-infection Management Update for HIV Primary Care Providers" will be helpful to you in your daily practice and invite you to join us in New York City for our live meetings in the future.

00:00:36

PRN is a not for profit organization dedicated to peer support and education for physicians, nurse practitioners, and physician assistants. And membership is open to all interested clinicians nationwide at our website prn.org.

00:00:50

And now allow me to introduce Andrew Muir, professor of medicine, chief in the division of Gastroenterology, and director of the gastroenterology and hepatology research group at Duke University School of Medicine in Durham, North Carolina.

00:01:06

I am delighted to be here and thank you very much for the invitation. This is a great group. I'm not going to take you through every day regimen tonight. I think this group I could tell from the survey is active in the treatment of patients and you know one of the great things is the number of regimens we have right now and the fact that I've been in practice for 15 years and the dramatic change that's happened has been amazing. We now have all these therapies that cover most of the genotypes very very well. And what I really wanted to do was focus on some of the stuff that's coming just so you're prepared and sort of understand how that fits into what we, building upon what we have in the future.

00:01:45

This is a slide that I've been using for several years. And so, in 2016 we had the addition of elbasvir/grazoprevir and then SOF/VEL. And then in 2017 we think we expect later this year that we'll have the addition of two more regimens, the G/P regimen and what we call SOF/VEL/Voxin. And so, another pangenotypic regimen in G/P and then a regimen that will also help out people who are failing the current best standard therapies. And so, we really are getting to the point where I can look every patient in the eye and feel very confident that one way or another I'll be able to cure their virus for Hep C.

00:02:24

All right so I'm going to talk a little bit about SOF/VEL/VOX here. So, this is sofosbuvir, which you all know very well with velpatasvir, which you've probably already been using, with voxilapravir, which is a protease inhibitor, all combined into one. The studies are from the program called POLARIS. There were a couple of different ways that this regimen was evaluated. One was for patients who never had had a direct acting anti-viral before. And there they're looking at an eight-week duration. Genotype 3 was broken out because that's just continued to be a separate issue for us. But also, the people who had already had a DAA regimen with focusing on the NS5A regimens and also on the non-NS5A regimens. And those people had a longer course of therapy.

00:03:08

This is a summary of the overall program. And part of the reason I put it is because I'm not going to go through all the studies in detail. The studies are on the left, POLARIS-2 and POLARIS-3 are the patients who were DAA naive. And if you see, the new regimen of SOF/VEL/VOX is in blue and SOF/VEL is in red. And it's tough to beat SOF/VEL and you see that in the studies. And so, the addition of a third drug doesn't really gain anything. So, we don't expect that to be how this regimen will be used. We expect this regimen to be more used how it's sitting on the right side of the slide, which is having nice responses in patients who have failed DAA regimens. And so that's what I want to expand more on tonight.

00:03:54

This is POLARIS-1, which was a phase 3 study. It's a randomized placebo controlled study. Only the genoype 1 patients were randomized though and the other genotypes all received the regimen of SOF/VEL/VOX. They did stratify by cirrhosis. Again, all genotypes are in here. They failed NS5A regimens. They had to have compensated cirrhosis and I would take a brief minute to talk about compensated cirrhosis. That was one of the things in one of the questions I did was because this regimen and the next regimen I'm going to talk about both have a protease inhibitor. And protease inhibitors we don't use those in people with decompensated cirrhosis. So, if you have a patient who has had one of the complications of portal hypertension and by that I mean they've had ascites, they've had encephalopathy, they've had variceal hemorrhage. These regimens are not going to be recommended for them. We get buildup of the levels of the protease inhibitors and they're not going to be safe. For anybody who was involved in the early days of telapravir, that was one of the issues there. And so, these regimens are really going to be for those people who have compensated cirrhosis. So, your patient who had ascites but is now controlled on diuretics, that patient is still decompensated. That liver crossed a line and so I would still call that patient decompensated and that was the example I had in the little quiz. The patient who had encephalopathy but now is well-controlled with Rifaximin that's also somebody who was decompensated. So you really have to think about these patients and are they going to be eligible for these medications? And that's going to be a key point. That decompensated group, we won't have anything new for necessarily.

00:05:34

So, back to the data. So 12 weeks here. These are the patients you see that this was SOF/VEL/VOX against placebo here. The placebo patients did later receive treatment but mostly genotype 1, as you see, we have 30 percent genotype 3 and we have them all there.

00:05:52

This shows you what they failed before. So, they failed some combination of NS5A inhibitor and a protease and a polymerase and different aspects of it. And you see that about 39 percent of them had received two or more regimens there.

00:06:08

And these are the SVR rates. And I won't read them all off to you but it is to see that every genotype did very well here. And just remember we're talking about that small group of patients who failed our current therapies and then we're getting these kinds of response rates when we treat again. So that's why my confidence has risen in being able to reassure patients that the treatments are very effective and we're seeing these across and so we're very hopeful. And again, this is under FDA review. We hope it to be approved later this year and then available for patients. I don't know how well that's projecting.

00:06:46

This is what we do at our research meetings now. We spend so much time talking about the few patients who failed and trying to understand them and teasing them out and getting a little bit geeky about them. And if there are trends here or observations if you will genotype 3 comes up a little bit in these folks but also cirrhosis overall. It was a 93 percent cure rate in cirrhosis it was 99 percent without cirrhosis. And so I have a feeling kind of like we've seen in the last few years with a number of different regimens that genotype 3 cirrhosis will probably continue to be a bit of a struggle. But again, we're getting great results.

00:07:27

This is looking at their baseline resistance patterns and getting a sense of did that predict things. And as you see in the slide, whether it was to the NS3, the NS5 or to both, the response rates are very high. And so one of the questions is will we use resistance testing? Will that that guide us? And that's something that will be interesting to watch and how the FDA handles that and the data. But you could argue that the data are so high here that won't really change your management necessarily. But that is something I think to watch for to see how that comes out when the FDA goes through the data from the program in great detail.

00:08:00

All right. I also want to mention POLARIS-4. This is the other phase 3. This is in four patients who failed the DAA regimen that didn't include an NS5A regimen. So, this includes some of our older regimens and this looked at SOF/VEL/VOX against SOF/VEL for 12 weeks.

00:08:19

These are the genotypes. It was randomized for one through three but not for the others.

00:08:24

And this is the previous regimens. So, there's a lot of simeprevir/sofosbuvir folks in here, sofosbuvir alone regimens as well.

00:08:36

And this is looking at SOF/VEL/VOX in blue against the SOF/VEL in red and you see that we do see small differences but we see higher rates with the SOF/VEL/VOX. So, again just showing across the different previous failures that we get great responses with this. So again, very encouraging data.

00:08:56

This is looking the same thing and looking at the base high resistance and you know when you do have results that are so high everybody does very well. One of the other key questions here is safety. We are adding a third drug. I mentioned there were issues in protease inhibitors in the past. Every protease inhibitor gets a lot of scrutiny because of some of the issues that we've seen with that class of agent. One of the things I always look for closely in these studies is how many patients discontinued for an adverse event.

00:09:23

You see here in the placebo group it was three patients and it was just a small number of patients in general. There was not an obvious clear safety signal that emerged here. We think of the protease inhibitors as adding a little bit more headache and fatigue and diarrhea. But again, there is perhaps a slight difference there, but all in all, very well tolerated the patients completed the therapy.

00:09:47

The other thing we've seen in the past had some increases in liver enzymes and this was looked for as well. Again, we saw some changes in the placebo group. They went to great detail to reassure us as I have there at the bottom that the one patient who had an increase in bilirubin probably was that was going on already and really didn't see an issue here. All right. So, I'm going to move on to the other regimen. I'm actually going to show a lot more data about this regimen. Again, because this is an update, at our recent European liver meeting, many studies were presented about this regimen so that's why if there appears an imbalance between the two, the SOF/VEL/VOX regimen was at their fall liver meeting and this one was really at the recent European meeting.

00:10:28

This is Glaceprevir and Pibrentasvir, so the protease inhibitor within an NS5A inhibitor. And this is going to be one tablet but the patients will take three tablets in the morning but they'll take it once daily. It's 100 milligrams and 40 milligrams and they take three of them together. A key thing here is minimal renal elimination. Kind of like we've seen with elbasvir/grazoprevir and as also we saw with the prod (?) regimen, there are some benefits over sofosbuvir-based regimens, particularly around patients who have chronic kidney disease and leading into end stage renal disease. That was also in one of the questions I had because we don't have head to head trials with these things and we're not really expecting them in large part. But that is a key factor I think if your patient has significant kidney disease

then if the GFR is less than 30 you're going to go away. I recommend you go away from the sofosbuvir regimens as per the package insert and you head towards some of these other regimens that also work very well. So, in this program they looked at eight up towards 16 weeks. They looked at compensated disease, they looked to chronic kidney disease, and they looked at co-infection.

00:11:43

This is ENDURANCE-1. This is their big phase 3 study. This had patients who were naive or experienced as long as there wasn't an NS5A so there was a very small number of patients who received some early sofosbuvir regimens. Nobody had cirrhosis here. You could have co-infection but it ends up being a small group and it's looking at eight versus 12 weeks. The HIV/Hep C patients, I think it's pretty standard for the co-infected trials. They could be naive if their viral load was low or their CD4 count was over 500. If they were on antiretroviral therapy it needed to be undetectable HIV RNA with a CD4 count above 200. And this is one thing I will be looking for in this regimen I showed you here the antiretrovirals are included I think I've not seen a full analysis around what drugs are going to go for this and that's something that we'll learn more when the FDA has completed their analysis and comes up with a package insert.

00:12:41

Just to give you a sense of who the patients are in this big study, look it's 351 and 352 patients in each of the groups so a very big study. Mainly male, mainly white. Notice it's 85 percent F0 -F1, these are not a lot of patients with cirrhosis. And a small number of patients, four to five percent of each arm who are co-infected. And a very small number had received sofosbuvir.

00:13:06

This is the co-infection group. Again, as you see, I listed the regimens that they are getting their median CD4 counts as we often see in these studies are quite high.

00:13:16

And these are the SVR12 rates and you see the eight weeks in green the purple is twelve. And it's very impressive. I separated out by the small number of co-infected patients and it's very high. I'm impressed by all these studies all these companies that run these studies to make sure these patients show up and get these last visits. It's a tour de force and very impressive. But again, we have a protease inhibitor here, how are we doing for safety?

00:13:43

And you see the discontinuations for adverse events were very small, a small number of serious adverse events. And the more common adverse events were headache and fatigue. But again, a very well-tolerated regimen.

00:13:59

Also at the European liver meeting, they did present a study that was just focused on co-infected patients. Very similar concepts. And as far as the population of patients who had HIV/Hep C, they could

have cirrhosis. In this study if they did not have cirrhosis they would receive eight weeks of treatment. If they had cirrhosis, it was 12.

00:14:21

And this is the antiretroviral regimens again that were included there, a little bit broader than in the study that I showed you before. I have a feeling this likely more mimics what we're going to see in the package insert. But again, I don't know the details on that of course. And that is something that we'll just have to watch for as well.

00:14:40

These are the patients again mainly male, mainly white. Over 60 percent of them are genotype 1 but we do have some genotype 3 patients in here as well and over 80 percent of them are treatment naive for Hep C.

00:14:54

Again, this sort of shows you the mixture of the different regimens that we see separating between the patients who do not have cirrhosis versus those who did. And I probably didn't highlight well enough on the earlier slide, but notice it's only 16 patients with cirrhosis. So, we're not getting a wealth of experience here about co-infected patients with cirrhosis. I really think of this as a non-cirrhotic study.

00:15:17

How did these folks do? So, all patients intention to treat is 98 percent. And in the patients without cirrhosis all of them were cured. In the patients with cirrhosis they did a modified intention to treat which was 14 out of 15. Basically again, we focus on the failures. That's what we do. We're so negative in hepatitis C now. There was one breakthrough. This was a genotype 3A patient with cirrhosis. That's kind of a predictable story. One poor patient had a stroke and that patient discontinued and there was one patient who had undetectable virus SVR4 but was lost to follow up. But that patient also looked encouraging. But again, the co-infected group doing extremely well here with this regimen.

00:16:01

How about their safety profile? Also looked very similar to what we saw with the mono-infected group. Very impressive.

00:16:11

I'm going to go through some of these other studies a little bit more quicker, but I wanted them in the slide set for you. I know you had to download them and I think you can reflect on it later. I'm happy to expand on them in the question and answer but I won't go through everything in tremendous detail but I'll give you the highlights of them.

00:16:28

Because genotype 3 is such a challenge for us, this study particularly looked at genotype 3 patients. It did exclude people with HIV. And they looked at the G/P regimen for 12 weeks versus

declatavir/sofosbuvir for 12 weeks, which has been a very popular regimen around the world. Then after the trial had begun because of the good findings with their G/P regimen at eight weeks they added in another arm. I realize for the purists of clinical trials this is not good. I'm just reporting what they did.

00:17:04

And so these are the patient characteristics in the three arms. It was mainly white again and again mainly a low fibrosis group here.

[00:17:17] And these are the SVR12 rates. So, it's 95 percent with G/P for 12 weeks. It's 97 percent with SOF/DAC for 12 weeks and we're over at 95 percent in that additional arm that was added of G/P for eight weeks. The relapses are coming up in the G/P group there and that's what we expect to see. I would not call these numbers statistically significant by any stretch. I would again argue that all of these regimens are effective and excellent. I'd be curious to see again how the FDA handles it. If the FDA has had a pattern when they've looked at these drug regimens that they really want to minimize the relapses. I think that there's caution around that particularly as we move out to clinical practice. So I think their tolerance for relapses is not great. So, I expect that will likely go longer. They did look at resistance here. There were five of them who had the resistance substitution combination of A30K and Y93H. That combination leads to a 69 fold resistance to pibrentasvir. If it was just Y93H at baseline, all five patients responded with eight weeks of treatment. So, again I think we're talking about we do know there are some there are some substitutions that will matter but overall the response rates remain very high.

00:18:40

SURVEYOR-II. So, this was a study of genotype 3 uncompensated cirrhosis that I just want to highlight and show you how this group did.

00:18:52

98 percent and 96 percent. This sort of shows you for that treatment experience group genotype 3, again this regimen, this was a smaller study but this regimen can be quite effective.

00:19:05

EXPEDITION-1 here was focused on cirrhosis. I think we saw similarly with the elbasvir/grazoprevir study program, I think they did a great job with that program because it was a protease inhibitor in the past history of protease inhibitors that was a nice big study in patients with compensated cirrhosis that demonstrated that that was very effective and safe.

00:19:27

We see the same thing here with this protease inhibitor regimen and this is an open label single arm study. All the patients are getting 12 weeks of treatment here with all the genotypes except three. And you see that again as we expect they're mainly genotype 1 patients but we do have a smattering of all the genotypes, which is nice to see. Seventy-five percent of them were naïve. There were more patients

in here who had had some exposure to sofosbuvir, at 31 percent, but sofosbuvir with ribavirin or sofosbuvir with peginterferon and ribavirin.

00:20:00

And you see again the genotypes types all do very, very well here. So, very impressive. And even in the group that's cirrhotic.

00:20:12

But again, I think one of the key things about this study was the safety profile. So how did they do from a safety perspective? Discontinuations for adverse events were zero, which was nice to see. These are patients with cirrhosis, they did have some serious adverse events. In the opinion of the investigator, there were zero of these events that were thought to be treatment-related. There was one death and there were two cases of liver cancer and we're going to talk about that at the end of my talk tonight in more detail. But overall again, headache was 14 percent, fatigue 19 percent, very well-tolerated. And again, in this patient group with cirrhosis did they have any increase in liver tests? Did they have any issues with liver toxicity? That was one of the questions. They did not see that in this study. All right so, I'm describing to you a really potent regimen. It's pangenotypic. And one of the questions will be can you can you use it in patients who failed other DAAs?

00:21:16

And I will tell you this study is by no by no means definitive because it's small but it is sort of interesting to see what it shows. So this is a Phase 2 study. It was not part of what was submitted to the FDA is my understanding. It's a randomized open label study. It has patients with genotypes 1, 4, 5, and 6. You could have compensated cirrhosis in here but not HIV. And so I put the drugs that some of these patients had received. So they had protease inhibitors that included paritepravir, simeprevir, asunaprevir, telaprevir, and boceprevir. And the NS5A inhibitors included daclatasvir, ledipasvir, and ombitasvir. So, some of these patients you can piece together from those drugs also received sofosbuvir. So some of the sofosbuvir combinations are in here. And they received the G/P regimen for either 12 or 16 weeks.

00:22:08

And it was 44 patients in the 12-week group, 47 in the 16 week group. Again, most of them are genotype 1, 1a, especially that's where we're going to see more of our failures as well.

00:22:21

This to give you a sense of who are these people and do they mimic my patients? So, the top line there is patients who had failed a protease inhibitor and an NS5A inhibitor regimen, so they're about a third of them. About a third of them are people who had an NS5A only so often that's going to be along in combination with sofosbuvir. And then there's about a third of them who had an NS34A only. And I think the resistance pattern here is going to matter a lot. This is looking at baseline resistance in this group. About 30 percent of the patients had no resistance as measured to the threshold here. The most common thing we see is over 50 percent have the NS5A. And that's just one thing again I highlighted

that in one of the questions about that's the most common resistance pattern that is an issue for us and hepatitis C now when we usually when we see resistance to the protease inhibitors those usually go away. The patient reverts to the wild type within a relatively short period of time. It's the NS5A resistance that's extending out for a much greater period of time. And so that's at least in this current era. I'm not sure if I can say era when our drugs change every year but in our current time we think about that. I've already shown you data that suggest the response rates are going to be so high that again I'm not sure how much this is going to matter. But this is this is something that all these regimens are studying and even the next couple that you'll hear about probably next year are looking at the same kinds of questions. So, I think it's important for me to see that this study did include patients who had NS5A resistance in there so we could see how the regimen would do with it so I was glad to see that. I was particularly glad to see that with the patients did well.

00:24:14

Here they were at 39 out of 44, 89 percent with the 12 weeks and we're at 43 out of 47 and 91 percent. I realize when we're not at 99 or 98 or 100 you all are disappointed and ready to throw it out. I just I got to remind you this is a Phase 2 study and I think we'll see more about understanding this regimen and its role with some of these patients. And I think this is where we probably need more data larger sets and understanding the patients a little bit more. But that will be something to watch for I think as this regimen comes forward. What would its role potentially be with it? Because clearly on the one hand is great. We're going to have a small number of patients who are going to fail but we're going to know what's the right strategy to do with them. We do have another regimen under investigation which does have a polymerase inhibitor in addition to an NS5A and protease that will be again you'll hear more about that probably at the upcoming meetings. We are going have this window where we're going to have these regimens to think about how to strategize for these patients. This just kind of highlighted how we did it based on the different things and you see that this group of patients that had failed protease and NS5A they looked a little bit lower. But it's tough for me to make too much of those data when we're talking about really small patient groups. So, I'm going to stop showing you a bunch of graphs of different things but I hope that was helpful. I really mainly wanted you to have the slide set so that you could go through the data when you're really thinking about those different agents.

00:25:52

There's been some other issues that have come up in Hepatitis C that I think are important and that we need to be thinking about.

00:26:00

The first one is Hepatitis B reactivation. So, this is an announcement that came out in October of 2016 and the FDA warned us about the risk of Hepatitis B reactivating in some patients treated with direct acting antivirals. And what they highlighted in their announcement was that there were patients who had severe serious liver problems and death. So, I want to get into a little bit more about where that came from and kind of how our field is thinking about this right now.

00:26:31

When you go through some of the other stuff the FDA has released, this is what they're telling us, recommending us, to do. Screen all patients who have hepatitis C for hepatitis B surface antigen and hepatitis B core antibody. And we all should be doing that anyway. I think we all probably have been. That's just sort of standard because of the similar transmission factors. In patients with evidence of hepatitis B infection, so that would include your patient who has negative surface antigen and positive core antibody. I have had a lot of people like this in my practice, so in that group of patients they recommend we measure Hepatitis B DNA prior to initiation of the DAA therapy. And then we monitor those patients who either have current infection so surface antigen positive or my core antibody folks during DAA treatment and in the post-treatment follow up. And by that they mean monitoring surface antigen, DNA, and AST/ALT. So, they recommend that we're doing that. So why are they recommending this?

00:27:31

This is a report that was presented at the American Liver Society meeting back in October. This was one of those posters at the late breaker poster session. So, they had 29 cases and these were cases from all over the world by the way they were not all American cases and this was a combination of the FDA reporting system and also looking at cases all around the world. And so please keep in mind in these cases they have limited data. I mean they have some they have a lot of information, in some they're really piecing together different pieces. And so that's one of the issues. So but as best as I could tell from these cases, the Hepatitis B flares were temporally related to DAA initiation. And it seemed to occur within four to eight weeks and a mean time 53 days. And it wasn't clear with the data they had, and I will tell you the data was incomplete, about how often it was a Hepatitis B surface antigen patient versus core antibody or both. What they were concerned about and what made them act was that decompensation happened in three of these patients including death in two patients and a liver transplant in one. They did observe that hepatitis B treatment was given but only in 16 of these 29 cases. And that was concerning to them. And they were concerned that when they did get to see some information about the patients that the treatment was delayed. And so they felt like it was their obligation to highlight this and encourage us all to monitor this more closely and to treat the patients more aggressively for it. So that was shocking to everybody. And in the aftermath of that there's been a lot more looking at it and particularly in some countries of Asia for example where there be a lot of Hepatitis B patients. Sort of like why are we not seeing more of this? But also, as we expand Hepatitis B treatment there's been concern what will we see? I'm involved in a program in Myanmar and another one in Rwanda where there's going to be a lot of hepatitis B and how aggressively we go about treatment, we want to make sure that we're not hurting people. So, now you can imagine in the follow-up scientific meetings we've had there's lots of things about hepatitis B. I'm going to show you a couple of them. This is an observational prospective study out of China.

00:29:47

327 patients. And they looked at hepatitis B DNA and surface antigen every two weeks during the DAA therapy and then four weeks post-treatment out to week 12. So, they had 10 patients who met the criteria for hepatitis and with elevated liver enzymes. In three of them it was from hepatitis B reactivation and it was all in patients who had a positive surface antigen. So not in patients who were

surface antigen negative and core antibody positive. There's a number of slides on other studies that have shown similar results. And I will tell you in most of the panels I'm in, the experience of most of the people have busy hepatitis C clinics is that we've not seen this to the same degree in the patients who are surface antigen negative core antibody positive. So, our guidelines group from members of ASLD and IDSA came up with these recommendations for hepatitis B surface antigen positive patients.

00:30:45

That's somebody who is going to have chronic hepatitis B infection. If they're not already on antiviral therapy for hepatitis B then it's recommended that we do monitor their levels during and immediately after they start their hep C therapy and use the criteria that we have for hepatitis B antiviral therapy to decide if they should be treated. Thankfully, hepatitis B therapy is very effective, it's well-tolerated and it could get somebody under control if that were to happen. And I would be very aggressive in such a case. I'd have a very low threshold to have somebody on hepatitis B therapy before I started their hepatitis C therapy. I don't have a slide for you about what ASLD IDSA says around Hepatitis B core antibody positive when it's surface antigen negative because they said there's not data for it. They don't have a recommendation around it. So, we really just haven't seen other evidence to suggest that such a problem-- and I must say I do worry that that's a lot of monitoring to add to patients. And so I have followed what ASLD IDSA have done. I have not personally for those core antibody positive surface antigen negative patients been doing the hepatitis B DNA during treatment. If they were to have an increase in liver enzymes, I definitely would. I would react to it. I follow my patients that way. But I've not been doing this systematically to every patient. I'm happy to talk about that more in Q&A.

00:32:09

My next controversy is do DAAs increase the risk of liver cancer, hepatocellular carcinoma?

00:32:16

This is a study that almost, you know-- so many talks on hepatitis C, I showed it to the medical students last week and we tell people that one of the reasons we're treating them for Hepatitis C is to reduce their risk of liver cancer. So, this is a wonderful study. Please recall this is all from the interferon era here. Okay? So, these are patients who were treated in the interferon era, five centers in Europe and Canada. These are all people with advanced fibrosis or cirrhosis followed for a median of 8.4 years. And this is the study that was quoted that showed that improvement in all-cause mortality, improvement in liver-related mortality, in need for transplant, and lower rates of HCC. So interferon, we know it reduced it and it motivated us to treat people.

00:33:03

Last year, we had this study that came out of Europe. Retrospective cohort study, single center. And they looked at all their patients who were treated in 2014 and 2015. And they started off with 103 patients They did exclude people who were treated with interferon, people who had HCC after their DAA therapy, or a lack of follow up on imaging. And so, this is not new cases this is recurrence. And so, what they saw was a higher than expected rate of recurrence in their patients who'd had HCC and then

got hepatitis C therapy. And so they shared these data and were very concerned about them. This was soon followed by another study out of Italy.

00:33:52

This is multiple Italian centers we're now talking about 344 patients. And these are people with cirrhosis. They had an excellent response rate as we've seen 91 percent. There was the patients who had no prior history of of liver cancer, they developed it in nine out of 285 cases or 3 percent. And if the patients did have prior history of HCC, they got it 17 out of 59 or 29 percent. And I think this shows you sort of how we got there. So, they felt they were seeing similar concerns around recurrence and also around occurrence as well. So, the French cohorts, and we're lucky that there are some really impressive cohorts that have been developed in Europe to track these patients to learn from them. How we use them is one of the controversies right now.

00:34:44

The French had three cohorts that they were looking at. They have a cohort of patients with hep C and hep B and they're tracking them. And this includes patients who've had liver cancer to see what their recurrence rates are. When they looked at their DAA treated patients versus the no DAs, they did not see a difference in recurrence. They also have a middle cohort there that is the patients who they have a group of patients who all had biopsies that showed cirrhosis. And they tracked them and again looked at DAA versus no DA. Again, they couldn't see a difference in recurrence. And they also have in the red there they have a group of patients who've had liver transplants with recurrence in DAA therapies and some of those patients would have the liver transplant for hepatocellular carcinoma, that was in 330. They did have recurrence in seven of the patients. In six of seven it was (?), which means that was localized and it was 70 months after liver transplant. So, the overall opinion of the French investigators was that they were not seeing a significant increase. I'm part of a study that is taking all the patients from the Gilead program who've been treated and following them through.

00:35:58

And this was a poster we had last year at the Liver Society meeting. I will say this is still early because a lot of these patients are still within that 12 to 24 months period out. I care a lot more about how these patients are going to do over more years and we need patients to be followed longer. What we did seem to see here was that we had quite a low rate of the patients had compensated cirrhosis at the time of their DAA therapy versus the patient who had decompensated. And we expect that patients who have more advanced liver disease have a higher risk of cancer. And so that's one of the potential things that we're seeing as we move forward with our hepatitis C therapy. We're treating sicker patients. We're treating different-- that VanderMeer paper from those five centers in the interferon area, those were not decompensated people. We couldn't give them interferon. We would have killed them. And so we are studying different people in some of those respects.

00:36:56

There was a meta-analysis. Daniel's already told us that he doesn't like these, but I will proceed. But this was done by an Australian group looking at both the occurrence and recurrence and this was presented on a Liver Society meeting. They looked at this is a broad array of data from 2000 to 2017.

00:37:19

The methods I thought were quite good.

00:37:22

They start off with 6715 references and they end up with 26 in one arm and 15 in the other so they did a rigorous job of getting down to the key pieces of data.

00:37:37

And they also again looked at occurrence, so new cases, versus recurrence of disease. And they divided up between the DAA and the interferon group. And I would just point out a couple of things. So, the DAA patients older, we're treating older people in general. With our therapies we're able to treat older people. Notice that the CHOP (?) UA on the bottom left there the second from the bottom. 66 percent of the patients are CHOP UA in the DAA and it's 100 percent in interferon. We're treating more decompensated patients with the DAAs. And the follow up is a lot longer with the interferon era as well.

00:38:17

This is the graph to sort of again show you what the occurrence is looking and these are in rates per 100 person years. And we see that with interferon, it was 1.14 for a hundred person years. It's 3.09 in the DAA era, so that is a higher number and was examined more closely.

00:38:38

They used an analysis, a meta-regression and taking some of these factors including the severity of liver disease, the age, the treatments that were done. And as part of that evaluation, they did not see, that's what you're seeing in the boxes in red is the adjusted relative risk, which was not different and was not increased. So, their conclusion from this wealth of data was that there's not evidence of differential HCC occurrences and it's more again this issue that we're treating different people now, we're studying different populations and we shouldn't be comparing it that way, is sort of an issue. But so, where are we now? So, you know, my take on it is that the strongest data are from the interferon era still. We have not had patients in the DAA era out for this number of years to be definitive about what the risk the risk of cancer is. None of the above was where I was headed. And I can tell you it's an ongoing controversy about this. I was telling these guys that I just finished scoring abstracts for our liver society meeting and there were so many abstracts about this that are going to be shown in the fall. Everyone's looking at their databases around this question and trying to understand. We know it's an issue for our patients. Those who have educated themselves well about the field will be aware of this and may talk to you about it. I still personally come back to some of those early findings that we are helping their liver situation. I personally think we can translate the clearance of virus that we saw with Interferon in the DAAs. There will be beneficial outcomes to these patients for their liver status, including complications of portal hypertension as well as liver cancer, but I do think because of some of these data it's

imperative that these studies continue and we understand this and can talk about it with our patients as well.

00:40:38

And my last thing that I wanted to talk to you about, actually Jim asked me to. He said that this had been raised a little bit was this recent Cochrane review that was published and I guess made the New York Times and The Guardian.

00:40:53

And they were looking at, using the Cochrane methodology, about whether DAAs benefited people with chronic hepatitis C. They looked at multiple generations of DAA regimens in this in a very detailed way. They had 138 trials randomizing 25,232 patients. And this is I don't know how many of you all have been involved in any GRADE methodology analyses but they use that and I'll go in a little bit more.

00:41:26

And then these are the tables that they came up with looking at the various outcomes. So, they looked at all-cause mortality at maximum follow up and they looked at those studies where there was placebo or no intervention and risk with DAAs. You see the relative effect is 3.72, but the confidence intervals are very broad. So, across this one (?) and so therefore you can say that there's an effect. And the quality evidence, you'll notice there's a trend. They were very critical of the quality of evidence in hepatitis-C trials. That's putting it mildly. Now the next line they look at the proportion of patients with one or more SAEs and when they look at this for placebo versus DAAs, they did not see a difference, but again they felt the quality was very low. And when they looked at SVR, the proportion with no SVR the relative risk is .44 from the 6,886 patients, but again the quality is very low. So, what did they say?

00:42:27

They laid off from a safety perspective saying that the DAAs have no effect on the risk of serious adverse events. And then I just put this in quotes. "In all remaining analyses we could neither confirm or reject that DAAs had any clinical effects," which kind of hurts my feelings. And they said I should have put this in quotes: "DAAs seemed to reduce the risk of no SVR," which seems kind of backwards. So, and then, "Clinical relevance of the effects of DAAs on no SVR is questionable." "All trials and outcome results were at high risk of bias, so our results presumably overestimate benefit and underestimate harm." "The quality of the evidence was very low." And there's footnotes about how low they thought the quality of evidence was. And again, if you've been involved in the GRADE methodology, they did use that and our trials maybe our trials didn't follow some of the things particularly around randomization, the methods of randomization, blinding, we had open label studies. Remember I mentioned the one study where they add in the third arm? They would hate that, right? So, it's not as rigorous. And I'll say I hadn't noticed it before. I've done another thing with GRADE around elastography for our GI society, but the fact that they were all industry-sponsored studies was a big negative. And I understand maybe it would be in an ideal world, these would not be industry-sponsored but I'm a pragmatist about this and to be quite frank without the movement of industry, all this wouldn't have happened and we'd be in a very different place today. So, I understand purely from a methodologic view why they made the conclusions

they did. I would hope that would not impact a patient's decision around the treatment. I particularly around this issue about SVR and mortality, the clinical trials I evaluated were not designed to look at mortality. The slow, natural history of liver disease is such that they couldn't do that. So that's pretty easy to explain that part of it away. An SVR is a surrogate endpoint but you know we dealt with that with the FDA very early. But again, for the purists around methodology, that's why this came up as a big negative. So, I can understand from their perspective why they say it that way. I'm personally not concerned that I need to rethink how my patients are thinking about their hepatitis C therapy, but I'm glad Jim mentioned it, I think it's a good thing because if patients do bring it up, I think it would be good to at least be aware of it and be able to talk to it. And so that's my little tour through tonight. Like I said, we've got I'm very hopeful these two regimens are under FDA review. We've actually got a couple more that are still going on. We'll have more developments in the next few years as we only have more options to help with hepatitis C. And thank you very much.

[Video End]