Current Treatments for NASH: A Deeper Dive

Kenneth Cusi, MD, FACP, FACE,

Professor of Medicine

Chief, Division of Endocrinology, Diabetes and Metabolism

University of Florida,

Gainesville, United States

Current Treatments for NASH: An Introduction

DR. CUSI: What we're going to be talking about now are the current pharmacological treatments for people with NASH and try to understand what the rationale for the use, what can be accomplished with them, keeping in mind that tomorrow you can help your next patient prevent their progression of the disease to cirrhosis. These are my disclosures.

We discussed in the prior section that we have divided our patients based on their risk of potential cirrhosis on the basis FIB-4, the elastography test, and potentially a liver biopsy in those who qualify. We typically would reverse a liver biopsy to those that we suspecting that have indeterminate or higher risk based on FIB-4, remember between 1.3 and 2.67, or in those with higher risk greater than 2.67. And also based on transient elastography, a number above 8 puts you into this intermediate to high risk. But if it's greater than 12, now we're really beginning to worry. Again, the hepatologist will assess the patient and decide what is the need for a liver biopsy. And what we really understood clearly that what we're trying to do is incorporate lifestyle therapy, weight loss if the patient is overweight or obese, and trying to reduce cardiovascular risk with the use of statins. But it is really with the diabetes medications where we can do major impact in addition to that associated with changing the lifestyle.

Role of Lifestyle Modifications in NASH Resolution

Let's first discuss in a nutshell, because I know that Dr. Mantzoros already mentioned about lifestyle modification leading to weight loss, and see, just in a couple of studies, what this can do for your patients. This is a classic study by Dr. Promrat et al. And they looked at people who had NASH on a biopsy and they randomized them to lose, with a target of 10 percent of their body weight, against just lifestyle advice and monitoring. The lifestyle intervention had a duration of six months. And the main result was that that group lost 9.3 percent on average compared to 0.2 percent in the control group, after again intensive work over, in this case, 48 weeks. And, again, 40 percent in the lifestyle group achieved about equal or greater than 10 percent of weight loss.

And here's where you see it. If you look at the weight change, this is weight loss from mild weight gain, down to almost more than 25 percent of weight loss. In blue triangles, those who were in the control group, the lifestyle are the red circles. And this is the improvement in NASH. This is better; this is worse. This is a histological scale. You see that most people who lost weight improved. But you see that there's a huge variability in this change. Somebody who lost a little bit of weight improved as much as somebody who lost a lot. Some individuals didn't lose so much weight and improved even move. Huge variability, that we hope that with the addition of medication can be translated into a consistent improvement in your liver histology. Keep that in mind as something important. What I highlight into two boxes is basically this person improved the same with 7 percent weight loss, compared to this one at 27. But, again, in general, and this what we learned a lot from bariatric surgery studies, the more weight loss, typically the steatohepatitis improves in proportion to the amount of weight loss.

DR. CUSI: In this study by Dr. Vilar-Gomez and colleagues, down in Cuba, what they found was that one year of intervention led to significant weight loss in a majority of patients.

About 20 percent lost 7 percent or more. This data is showing you the relationship between weight loss, this is more weight loss, this is less weight loss, and the changes in fibrosis. And the first thing that this apparent is that whether you're in the worst, stable, or better group, there is a lot of variability. In those that are better, some lost a little bit of weight or no weight, and others lost more. And you can see that the changes in fibrosis are highly variable. In general, the more weight loss, the better fibrosis gets. But, again, this variability indicates the importance of adding pharmacological therapies to our therapies in NASH.

The other important concept is that we've done pretty well with diabetes medications in managing the cardiometabolic complications, particularly nephropathy, with SGLT2 inhibitors, but also GLP-1 receptor agonists with cardiovascular disease. But it is time that we incorporate the liver in what I like to call a triangle of care, as these medications help also in reducing liver fat and steatohepatitis. But we don't usually think about this benefit when we choose our agents. You should know that there are drugs like pioglitazone, GLP-1 receptor agonists. Even SGLT2 inhibitors have shown a reduction in liver fat with these medications, and that's what we're going to be talking about in the next 15 minutes.

Again, back to our slide to remind you how important this is. Again, let's now dive into these diabetes medications that have shown a benefit. Now I have to clarify before moving forward, that no diabetes medication has an FDA label for approval. When we recommend that you use it for somebody with diabetes, what we are really saying is that if you have diabetes and need a diabetes medication, choose a diabetes medication that can also help the liver. The current indication is for diabetes in the setting of NASH, because you will have two important targets, hyperglycemia and steatohepatitis or fibrosis. Again, the key concept here that I want you to remember this that you learned from the lecture by Dr. Mantzoros on the pathophysiology of NASH, it is dysfunctional adipose tissue that hypertrophies, that beings secreting a number of cytokines that promote insulin resistance adipose tissue and other tissues, ectopic fat deposition. It is in this setting that we think that it's critical to change the biology of adipose tissue. There are two things you can do. Number one, with loss. If you lose degree of adipose tissue mass, for example, with GLP-1 receptor agonists or bariatric surgery or significant lifestyle changes, that adipose tissue begins behaving, again, in a more normal fashion. The other approach is to change the biology of fat with agents that change the DNA messages, like you can do with PPAR-gamma agonist like pioglitazone.

Let's look at these two agents and how both are targeting. They have a myriad of targets. But they both reverse the function of adipose tissue and make it normal, to again restore biology adipose tissue, reverse lipotoxicity, and prevent this fat attack on the liver. We talked about this. Again, now I'm going to give you a different angle and tell you how the pharmaceutical companies have approach the problem of NASH. Conceptually, there are two Approaches. Although every pharmaceutical agent that has been tested has an effect on both, on fibrosis, to some extent and on steatohepatitis. One approach is focused on let's treat fibrosis, because fibrosis is what's going to, in the end, lead to end organ damage and cirrhosis. Unfortunately, the drugs that are focused on fibrosis have not been, so far, successful. The second approach is to say, well, let's do a more upstream approach. Since the intrinsic mechanisms of NASH are not known in humans, let's do what I like to call a

shotgun approach, where we reduce fat mass or we reverse its dysfunction with pioglitazone and see how the liver responds. That what I'm going to show in the next minutes.

The paradigm is as follows. When you gain weight from overnutrition, you cause or worsen insulin resistance. You increase significantly your visceral adipose tissue. And, again, obesity will lead to significant abnormalities like lower adiponectin secretion that's critical to reduce ectopic fat in the liver. And you're going to have a high flux of fatty acid to the liver. You're going to promote diabetes, you know that. And you're going to promote higher cardiometabolic risk.

Role of GLP1-RA and SGLT-2s in NASH Resolution

Let's look at the approach that GLP-1 receptor agonists and SGLT-2 inhibitors can offer in patients with NASH. We know weight loss, by different mechanisms, refer these three aspects: insulin resistance, type 2 diabetes, and cardiometabolic risk. Let's look at the data that we have.

Recently Dr. Chavez is a fellow in our program at the University of Florida and Dr. Kadiyala is an assistant professor, soon to be associate professor. We wrote a little summary. And we discussed in there that there are several GLP-1 receptor agonists that have shown benefit. These are some studies with dulaglutide that showed benefit on liver enzymes or benefit on liver fat. However, dulaglutide has been the GLP-1 more broadly studied. And these are the controlled studies of 24 weeks duration or more. Again, not all have been controlled studies, but they've been the larger studies here, a couple have been open label. But the results are typically consistent in promoting weight loss and reducing liver fat. However, there have been only two studies with liver histology, one is the LANDMARK study by Dr. Armstrong with liraglutide, small study, very provocative, but it showed some resolution of NASH. And then Dr. Newsome in a study that I also participated in, showing semaglutide showing significant benefit. And I think Dr. Mantzoros might have mentioned this. Again, very important because, A, two-thirds of the patients had diabetes, which is the highest risk of developing cirrhosis down the line. And two-thirds also had moderate-to-advanced fibrosis, stage F2 or F3. The formulation was a daily injection with the aim of delivering more drug with reduced side effects. But in the end, the amount of side effects is comparable to the obesity dose of semaglutide 2.4 weekly. That is probably what is going to be used in the future.

But I just want to show you in a nutshell the metabolic effects, which I think you might be very familiar. Significant impact on the hemoglobin A1C. And more important was the effect on the liver. At the higher dose, almost 60 percent of the patients had an improvement in steatohepatitis. And you say, what is this, no worsening fibrosis? Well, that is an endpoint as to be met by the FDA, the Food and Drug Administration. That means I wanted to improve inflammation, and it counts as something good, as long as fibrosis is not making progress, too. Basically you have to resolve the inflammation, turn off the disease, without fibrosis containing to progress. It has to be the same or better. And that was reached again in 58.9 percent of the patients, compared to 17.2 on placebo. There's another endpoint by the FDA that is just improvement in fibrosis. That was not met. There was improvement numerically, but it did not reach statistical significance. However, why that has happened, we don't know. But the real key message I think is that progression of

fibrosis was significantly reduced. If you look at those at the higher dose, only about 5 percent of the patients had progression, compared to almost 20 percent on placebo. This was a 72-week trial. If you translate this year and a half into 10 or 15 years, these findings are going to be highly significant, if they remain in this short period of time.

Shifting gears, SGLT2 inhibitors have been another class of agents broadly used in the diabetes field. They cause a little bit of weight loss. And here I'm summarizing for you the key studies that were published until about a year and a half ago of at least 24-weeks duration. And, again, you see these are uncontrolled studies in the top, controlled studies in the bottom. We did a little study with canagliflozin. Again, typically compared to placebo, that's a placebo is always favoring SGLT2 inhibitor, 2, 3 percent of weight loss. Reduction of liver enzymes when elevated. In these studies, liver enzymes in patients were not elevated. But, again, with a consistent reduction in liver fat. This is very promising because any weight loss is of value. And more importantly, studies are underway to look at the effect on liver histology. Again, the amount of weight loss is about between 15 to 20 percent, placebo-subtracted.

This is the canagliflozin study that I was telling you. Again, this is the relative change in intrahepatic triglycerides plotted by body weight. You can see that those in green on canagliflozin, the green squares, more people are able to lose weight and reduce liver fat than those on placebo. But, again, there you have somebody on placebo who decided to really lose weight and was the champion of the group. It's nothing specific, we think. It's largely weight-loss related. That could be other mechanisms that we may discover as we discover so many on the kidney. But, again, useful, but we still need more data.

Role of Pioglitazone in NASH Resolution

Now we're going to shift to pioglitazone. That has been the agent most studied for the longest time, and that is of great value in this field. Again, we talked about weight gain, worsening insulin resistance, diabetes, and worsening cardiometabolic health. Now we talk about weight loss reversing everything. And then we talk about the mild weight gain with PPAR-gamma agonists. And we're going to talk about pioglitazone. And in the next stretch of future agents, I'll tell you about lanifibranor, another pan-PPAR gamma alpha and delta. And surprisingly, despite some weight gain, which is the range between 1 to 4 percent, things get better.

And this has been studied in several studies. Dr. Belfort was a fellow working with me. We published this in 2006. Again, two studies later followed in people without diabetes with similar results. We published a three-year study in *Annals of Internal Medicine.* It involved people without diabetes, but with prediabetes or type 2 diabetes. And then we combined it with vitamin E, which is an agent that you can see in that *New England p*aper in 2010, the trial by Sanyal and colleagues called PIVENS showed benefit. But vitamin E did not have benefit on its own in this single small study. But pioglitazone had as significant benefit. There was really no additive effect. That's why in people with diabetes, I would be inclined to use pioglitazone.

Now this is the summary of studies available. Again, for steatohepatitis, there is significant benefit, which is similar in direction in all the studies. This is a study also published by the

Institute for Clinical and Economic Review. Again, these were small effects, although the right direct, most of the time, on average, not significant, but we do have individual patients that can significantly improve their fibrosis, and there are meta-analysis showing that if you just take those with F3, F4, like Dr. Moussa (Phonetic) published in JAMA 2016, it is significant.

So, we tried to really look in to why this happens, and we just published last year a detailed study about this. What we can tell you is that what is very apparent is that when you used pioglitazone, you shrink not only their fat, but visceral fat tends to decrease, but the fat now is deposited in the subcutaneous tissue, which is metabolically less harmful, and that would prevent it from getting in to tissues like the liver, causing harm, or the muscle, promoting insulin resistance.

So, long story short, I'm just going to show you one patient, and I'll guide you to read the paper. This is the typical patient that we looked at that was treated, in this case, for six months. Glucose goes down. A1c improved. They gained some weight, about 3% of body weight. But, you see that visceral fat is decreasing. Subcutaneous fat increasing. We wouldn't like any weight gain to happen, but again, we think that combining with agents like SGLT2 inhibitors or GLP-1, you can prevent that weight gain.

Again, when we looked at the histology of these patients, we improved. Again, this is data from the early pioglitazone trial in the New England. You see that NASH improved, and also fibrosis improved. So, it's clearly that the redistribution of fat plays an important role, and we did a specific analysis here. I don't want to put you to sleep, but there are two factors that played a big role, changes in adiponectin and changes in visceral fat. Both predicted the histological response in these people, using this partial least squared discriminate analysis. Also, to some degree, improvement in insulin sensitivity during an OGTT.

Furthermore, what most people have forgotten is that pioglitazone reduces cardiovascular disease. So, these, I'm just putting the titles of classic studies. In the PROACTIVE, the primary outcomes were not reached, but there was a reduction in myocardial infarction and reduction in stroke. CHICAGO and PERISCOPE were two other studies with - - vascular ultrasound. And, finally, the IRIS study in people with a stroke clearly showed benefit after five years of pioglitazone. And, there've been a number of analysis in those people. Again, what pioglitazone does is you reverse each one of these factors that trigger atherosclerosis and cardiovascular disease.

Regarding heart, there's always this view that it causes heart failure. And, that comes from the initial study, the PROACTIVE study here that showed that there were more people having lower extremity edema and heart failure. In that study, with 5000 people, they gave the drug to many people with baseline heart failure. In all the studies then afterwards, in which the medication was not given to people with heart failure, there was no increase in the rate of heart failure in people given pioglitazone or placebo.

So, very important to remember, this is the data from PROACTIVE showing the reduction in MACE overall. The combination of cardiovascular death, stroke, and myocardial infarction, that is frequently forgotten. This is the effect on stroke on the left panel and myocardial

infarction on the right panel. Huge decreases that are really important to keep in mind in your treatment strategy.

Regarding the IRIS study, I'm just going to show these are the results of the main trial. Fairly large study, using 45 mg as the target dose. What they showed after five years was a significant improvement in the event-free survival, and again, this comes hand-in-hand with the findings from the other two studies, the J SPIRIT and the PROactive study, that all went in the same direction.

So, important to remember, and improvement in the first stroke was clearly also seen in that study. So, remember this is really important, because it's information that can be important for your patients.

Finally, the last sub-analysis of the IRIS study. What they looked at was what was the impact of the medication in people who really took it. So, they divided in two groups, those who had an adherence of greater than 80%, and you can choose your parameter. Stroke was reduced by 36%. Acute coronary syndrome by more than 50%. New-onset diabetes, almost greater than 80%. Again, medications work better when you take them. Again, look at the low numbers needed to treat. Again, if you didn't take it, of course, that diluted the effect overall.

But, the take-home message is that pioglitazone will be an effective strategy for secondary prevention of stroke.

I mentioned to you earlier that after that first study, the PROACTIVE study, all other trials that have later given pioglitazone in clinical trials have not seen an increase in heart failure. So, this is critically important to remember, that don't give your medication to somebody with heart failure. And, if you don't, typically, you're going to be able to not only treat the liver, but also prevent cardiovascular events.

Another issue that has been important with pioglitazone is this controversy on bladder cancer. It should be important, and I'm just going to make it very short. This came out from this study from Lewis that said that there was a cumulative greater risk of bladder cancer of about the magnitude, overall, of 20% for exposure greater than four years. Again, this created a lot of alarm in many studies. Lewis later did a 10-year study that did not see that effect. If this pioglitazone would be the offender, you would see a greater effect. That was not the case, and most studies have been largely negative.

So, most studies have been negative. Five positive studies that have been criticized for a number of study design flaws. But, even if you take them at face value, you would need to treat for three years, between 877 to 4500 patients, depending on the study, to cause one bladder cancer. Okay? So, again, something to think about, but again, don't give the medication to somebody with a history of bladder cancer or with hematuria. So, always check that when see your patients.

Finally, the issue of osteoporosis or bone loss. This is the data that has also been shown from the IRIS study. There is greater bone loss with pioglitazone compared to other agents. We've noticed that if you give vitamin D, prevent them from being vitamin D deficient, the

effect can be blunted, but that's something you want to consider in your patients. The best data is from the IRIS study, where there was a significant increase in bone loss.

So, how to use pioglitazone? Think of its effects beyond glycemia. This is the choice you make for people with diabetes. I avoid it if you're BMI is already very high, for obvious reasons. I don't give it if there's any edema at baseline. Also, amlodipine causes edema, and between both agents, you're putting yourself at a greater risk of developing edema. If you're on a high-dose of insulin, insulin, by itself, causes edema and causes weight gain, so I don't think that is also a great setting, unless you just use a lower dose of 15mg. Again, check for the potential for heart failure. If needed, you can do an NT-BNP or an echocardiogram, or consult cardiology. Usually, you can do it based on the history or a physical exam. Then, the risk of osteoporosis.

If you start at 15mg, weight gain with 15mg is very low. Then, you check on the next visit and consider if there's any ankle swelling, shortness of breath, or anything of that kind. Then, you can increase to 30 or continue just with 15mg.

Now, 15mg is been dose-effective in type 2 diabetes. But, not still tested on histological outcomes in NASH. But, I'm going to show you, before moving on, the process to try to prevent weight gain in patients on pioglitazone. So, one is using low-dose pioglitazone. The other is combination with other agents.

So, there have been many studies with 15mg. These are the studies that have compared 15 to 30mg. These three have been done in the United States. This is from India. You see that the reduction in A1c is quite significant. There's also an improvement in lipids that with lowering of triglycerides and increase in HDL, and the weight gain is just about 1-2%. So, keep that in mind as an approach. Then, eventually, you can increase it if patients have not gained additional weight.

I just want to share this study. It was published in 2021 from an Italian group, looking at the effects of low-dose on patients with NAFLD. What you can see here is quite simple and straightforward. Baseline in blue, one year later in red, or dark red. Liver enzymes go down, both ALT, GGT, and it doesn't matter which was the dose that you used. The reductions were very comparable. Liver fat also went down, and a specific NASH Index also went down in all groups, with being significant at the lower dose, particularly.

The other approach, rather than low-dose pioglitazone, could be combining it with an SGLT2 inhibitor. There have been many studies in the diabetes realm. I'm just going to share one from a classic study, like EMPA-REG EXTEND, in which they added empagliflozin to people on pioglitazone. What you see is this additional 0.6, 0.7 reduction in A1c, without causing weight gain. So, you see that on pioglitazone alone, after 72 weeks, you gained a kilo. Here, you lost a kilo. So, the add-on of empagliflozin is very useful.

The other approach is using semaglutide. As we showed, this works very well to treat NASH. Again, you have this additional greater reduction in A1c than the SGLT2 inhibitor. You see this added the weight loss. The brighter blue is 0.5, the darker blue is 1mg semaglutide. When you take all the people who meet these three criteria of getting to the A1c of less

than 7, no weight gain, and no hypoglycemia, you see the majority of people reached that. So, this is something that needs to retested with NASH outcomes.

In the end, you are familiar with the glucose-lowering medications. I hope that in 2022 we incorporate a sub-group of those with NASH, and again, neither pioglitazone or semaglutide or liraglutide or other diabetes agent is approved by the FDA or other European or other country regulatory agents for NASH. The point is that in the same way we treat somebody with heart failure and diabetes with an SGLT2 inhibitor, we would choose GLP-1 or pioglitazone to treat people with diabetes and NASH.

With that, this is going to be the end of the current therapy. I hope that you leave with this thinking, that we're going to treat not only the kidney and the heart of people with our diabetes medication, but several of our diabetes medications can have a huge impact on the liver, and you would have the potential to prevent cirrhosis in many of your patients already with advanced fibrosis. So, keep that in mind. And, in the next presentation, let's see what's in the pipeline.

Thank you very much.