Future Treatments for NASH

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New Targets and Treatments for NASH

DR. CUSI: Okay. In this last section, we're just going to give you a little glimpse of what is in the horizon for the treatment of NASH, drugs in development, and different targets that are being considered, to try to reverse this very complex, chronic liver disease. So, moving on, what we have here is a little schema of the potential targets that we have for the management of NASH. So, we're going to go around and just comment on the greatest in the classes that are being studied, and hopefully, this will give you a very quick idea of where the field stands. It's not all comprehensive. There are more than 100 compounds. So, we're going to talk largely of those that are in phase 2 and phase 3, because we wouldn't have enough time to cover all of them at this point.

So, before we dive in to it, there are two. As we briefly mentioned before, there are two major guidelines the FDA and other agencies over the world take in to consideration to approve a drug. A, on the left, is NASH resolution. This focuses on disease activity, see if you can turn off the necrosis and inflammation, necroinflammation that's going on, while at the same time, halting at least the progression of fibrosis. Fibrosis cannot get worse. So, it has to be at least held at bay or improved.

On the right-hand, you see fibrosis improvement. Pretty straightforward. The pathologist says, yeah, there's more than a stage of fibrosis improvement. But, of course, the inflammation cannot get worse. So, same kind of reversing the coin.

With that, again, we're going to talk about our patients, again, and we're going to talk about pharmacological therapy. I put this slide in there to remember ourselves, that really nothing is really going to work, unless our patients also work on their lifestyle, to improve their cardiometabolic health, if they're not overweight or obese, or to lose weight, while they also improve their lifestyles and overall cardiometabolic profile.

So, let's start here with insulin sensitizers and GLP-1 receptor agonists. Very quickly, several agents are trying to take advantage of the observation that pioglitazone improves NASH, but without the undesirable side effects, such as that weight gain of 3-4%, and potential on bone loss.

Again, I'm just going to share with you the data on lanifibranor. There is, just to mention, saroglitazar is a PPAR Alpha-delta that has shown to reduce liver enzymes in a paper published in Hepatology in 2021, and is undergoing biopsy studies, and has had some biopsy studies performed in Mexico and India with promising results. There are other compounds, like from Coherus and Poxel that are near their stages of development. I'm just going to show you one slide with the results of lanifibranor. Again, with the rationale that a compound that could influence and change the behavior of adipose tissue would have far-fetched benefits in these patients.

So, remember, PPAR gamma receptors are very abundant, 10 times higher than in any other tissue, in adipose tissue. So, adipose tissue is clearly not the only, but an important target for PPAR gamma. But there are also PPAR gamma in immune cells that compose a significant portion of the adipose tissue, and macrophages, and also in the Kupffer cells in the liver

that trigger inflammation, and the stellate cells. PPAR gamma turns off the stellate cells that lay collagen, and we think that's maybe another indirect mechanism of benefit.

But, typically, when you take, for example, pioglitazone, you see a reduction of 30% or 40% in free fatty acids, and reverse of steatosis. You also see improved mitochondrial function and improved mitochondrial proliferation, and a number of other mechanistic effects, in addition to an increase in adiponectin.

Similar results have been shown with lanifibranor in a study just published in October. But, before that, I can tell you that the field is pretty complicated, in the sense that, for example, PPAR gamma only, like rosiglitazone, only reduces steatosis, with no effect on inflammation or fibrosis. Or, if you take a PPAR alpha, pure PPAR alpha, like fenofibrate, great effect on lipoprotein metabolism, no effect on insulin sensitivity or in liver fat. If you take a PPAR delta only, seladelpar, some reduction in liver fat, but not significant improvement in NASH or fibrosis. And, lanifibranor, PPAR alpha, PPAR delta, again limited benefit in NASH and was discontinued.

So, again, we have pioglitazone, promising results with saroglitazar, but lanifibranor has shown the greatest benefits on both, on NASH resolution and on fibrosis, so for.

Again, just want to show you one slide here. They used, in a short biopsy study before and after six months only of treatment, at two doses, 800 and 1200, you know the primary reduction was a change in two more points of a SAF score. It's a score that integrates inflammation, ballooning, and fibrosis in a quantifiable way. You saw a clear, significant difference at the higher dose, almost with the lower dose. When you looked at resolution of NASH without worsening fibrosis, both doses were significantly better. And, when you looked at the improvement in fibrosis, again, the other FDA endpoint, the higher dose reached that endpoint. Again, when you look at what they call a dual endpoint, improved resolution of NASH and improved fibrosis, again, both were reached with lanifibranor.

So, this has been very exciting. This was just published in October 2021, and there is now the FDA granted accelerated moving forward to their phase 3 clinical trial, which is starting as we speak. So, very, very promising results. And, again, reaffirms that weight loss, by any means, is important. Changing the biology of fat is also critical. And, this has been a fantastic proof of concept.

Novel GLP-1 RAs for NASH

We're going to talk now about GLP-1RAs, loss of activity. We talked a little bit about the currently available ones for diabetes. Again, semaglutide is also approved for weight loss, same as the high-dose liraglutide. But, what is new in the horizon?

So, what has been new has been the effects of tirzepatide. Tirzepatide is a dual GLP-1, GIP agonist, and this year, was very exciting finding of looking the effects of 5, 10, or 15mg of tirzepatide. In this case, they used as a control diabetes dose of semaglutide. Again, very dramatic reductions in A1c. The question, what does the GIP add to this compound that is also a GLP-1, this dual agonist? The big suspect is it has a huge impact on adipose tissue

metabolism. Again, these results have been very exciting. There are a number of studies by the tirzepatide firm called SURPASS, of different kinds.

I'm going to show you on that did a sub-study looking at liver fat, SURPASS-3, compared tirzepatide to basal insulin. This is very, very important, because it really tells you what to do when the patients fail oral agents. Should we go to insulin? Should we go to a compound like tirzepatide? Many studies have shown that it's better to go to a GLP-1 receptor agonist compared to insulin, because you achieve similar or better glycemic control with weight loss and improvement in cardiometabolic parameters. Same thing here. You see the weight loss going down markedly with no apparent plateau, at least at the higher dose. And, compared to a weight gain with insulin, better seen on the right panel as columns, very important difference.

The question here is what did this do to the liver? So, they did look at liver fat content by MR IMID resonance-based technique, and you see really significant reduction in liver fat, also with insulin. Why is that? Because I think that you reduce free fatty acids coming from the liver, at the same that you're also lowering glucose, which would be a substrate for triglyceride synthesis. Again, if you looked at the intermediate-to-higher doses, led to a 40, to almost 50%, reduction in liver fat. Very impressive results.

This is an example of a patient who had 27% liver fat. Remember that we defined NAFLD or steatosis based on having more than 5.6% of liver fat. This person had 27% liver fat. After tirzepatide treatment, it was 2%, reduced by 90%. So, this is something, again, this is a hyper responder, but this is very provocative result.

Shifting gears, there's also another dual GLP-1 and glucagon receptor agonist. Again, the effects of glucagon are complex, but in this case, believed to contribute maybe to the weight loss observed with the GLP-1 receptor agonist, although not completely well established. What they looked at here in this paper, published in Diabetes Care, also in 2021, was the dose response of cotadutide in patients with diabetes, in this case, and looked at changes in liver enzymes.

You see that there is going from 100 to 200 to 300 and dose response and reduction of AST, ALT, and the FIB-4, that by now you are experts in the FIB-4. There's another score that I didn't talk of, - -, but it over-reads and gives a lot of false positives in people with diabetes, so you can also say here that it wasn't as useful as the FIB-4. Interestingly, this effect is greater than liraglutide 1.8mg daily.

So, again, what is new is a study that was presented at the liver meeting in November 2021, which I want to share with you, the effects on people who had NASH with fibrosis. So, remember, the dose used in the diabetes care trial went up to 300. This went up to 600. Small study, more of a proof-of-concept after 19 weeks and looking at liver fat before and after, but these are adults with biopsy-proven NASH.

So, what you look at is absolute liver fat fraction was greatly reduced with the 600microgram dose. And, in relative terms, it went down by 12 weeks to 42% at the higher dose, and 55% with the extension to 10 weeks. However, the higher dose has a lot of GI side effects. I think the 300mg dose, still a 40% reduction in liver fat is highly provocative.

So, the thing is that the higher side effects of the 600-microgram dose might make it a little bit of a more of a challenge, but this kind of being sorted out as we speak. So, provocative findings. I have to say that there are many dual GLP-1s, with glucagon or GIP or others, that are being tested at this point. But, I just wanted to give you a feeling of where the field is heading, and I'm sure this is rapidly going to be changing soon.

Potential role of FGF-19, FGF-21, and Thyroid Hormone Receptor (THR)-ß-Selective Agonists in Nash

I'm going to show you another aspect of this, which is the role of agents that can alter liver metabolism, like FGF-19, FGF-21, of which there are about seven or eight in development, and thyroid hormone receptor selective agonists for NASH. So, I'm going to show you one or two slides on each. I don't pretend you'll be come experts in this, but just to give you a little bit of a feeling of what's coming.

So, let's start with FGF-19 agonists. I have to say that there's also an A and B kinase activator. Metformin is an indirect activator, ANP kinase. This compound called PXL-770, just recently there was a study published showing a reduction in liver fat of 27%, and this is now being pursued further. Because of time, I can't show you that data, but it was published last year, so go and find it.

So, what I wanted to focus on was this drug, alderman, which is an FGF-19 analog. The mechanism of this is to reduce liver fat, has significant effects on steatosis, and apparently - - no lipogenesis in the liver. What they did with this FGF-19, now there were very exciting findings that it would be able to reduce liver fat and improve NASH, based on significant reductions of liver enzymes, and reductions in liver fat, and what they saw in a small study was some patients also had a reduction in histology.

So, with this paper that was published in Gastroenterology last year, not only improvement in NASH, but improvement in fibrosis. But, again, not statistically significant. But, associated with also biomarkers. You remember we mentioned PRO-C3 being used in clinical trials, a reduction in PRO-C3, again, all signals that were highly promising. This is from data generated and presented in 2019, 2020, and published in 2021.

Well, with this, there was the promising thing that was presented at the study, at the liver meeting. Unfortunately, that approach did not completely work in a study that was just published two months ago. So, most likely, that program is not going to continue.

So, preliminary data was promising, but the trial that was presented two months ago was negative. So, it will not be pursued further, despite the fact that there was about an 80% reduction in liver fat.

So, in summary, what this study that was presented in the 2020 annual meeting of the liver society suggested is this was very promising. In the meantime, they had their FALCON program that was with biopsies. Now, that work was presented at the last meeting of the American Association for the Study of Liver Disease, and what they did was to show the results of a dose-response study with three different doses of FGF-19 and see if this improved histology after 48 weeks. So, a biopsy before and a biopsy afterwards.

In a nutshell, the study was negative. If you look at the number of people that improved fibrosis without worsening of NASH or improved NASH without worsening if fibrosis, this was not significant. And, when you broke it down in to the two individual endpoints that you're now experts, resolution of NASH alone or improvement of fibrosis alone, it was not significant. So, the bottom line is that approach-based and FGF-19 was negative, and it is unlikely that this approach will move forward.

Now, let's move on to thyroid hormone receptor, a ß-selective agonist. There are two that are in the more advanced phase of development, resmetirom and VK2809, by Viking company. The other is being developed by Madrigal. You need to know that there are many such compounds. Again, I'm just going to mention two that had the greatest degree of improvement. Both reduced liver fat and may improve the lipid profile.

Again, resmetirom has been shown to reduce, in a dose-dependent manner, liver fat. This is relative reduction up to 50%, absolute reduction also proportional. Typically, the baseline liver fat is between 15-18% in people with NASH. Again, the interesting thing is that if you looked at the NAS component, the individual components, in general, there is an improvement greater than that with placebo. Again, ballooning did not improve that markedly, but taken together as a score, it was significantly improved, and this is being published. So, again, the larger studies are underway, and this may be a promising approach for patients with NASH.

To finish, FGF-21, there are many kinds of types that bind to different compounds, in terms of how they interact with FGF-21 receptor. FGF-21 has a big role, in terms of liver metabolism, producing lipid accumulation, the LDL uptake, de novo lipogenesis. Has effects in decreasing glucose uptake and lipid disposal in adipose tissue, a number of beneficial effects, potentially, in the heart, etc.

What is important is that there are many, many different approaches. They're not identical. This is important to understand. And, again, this review may rapidly put you up to date on this, because failure of one type of FGF-21 does not mean it's a failure for others

Potential Role of FXR Agonists in NASH

DR. CUSI: So, now, in the last class of agents, I want to share with you what is called FXR agonists. These are very important, one of the earliest agents developed, and there are many kinds, and obeticholic acid has been approved primary biliary cirrhosis and has been under study in NASH for quite some time. So, again, this will be a compound that would be more focused on reversing fibrosis, but also has shown some activity on steatohepatitis. There's a vast biology, again, about the effects of FXR in this complex web of factors that lead, in the end, to liver fibrosis and collagen formation, and, in the end, cirrhosis.

Again, vast number of mechanisms describing animal models, from inflammation, also involving atherogenesis, glucose and lipid metabolism. These compounds have a very powerful impact on bile acid metabolism. Again, the link between cholesterol and bile acid metabolism has been long studied, and remember, we talked about FGF-19 earlier, as

binding to the receptor modulating bile acid metabolism, but together with that lipogenesis, and pursuantly being able to work in NASH. But, that failed.

However, the rationale for FXR agonists is pretty broad, from FGF-19 to direct effects on cholesterol and bile acid metabolism that led to its primary biliary cirrhosis indication, and now on a path to try to get approval for an effect in NASH.

Again, many different mechanisms. It also involves TGR and other gut pathways with vast effects presumably, also, in mitochondrial metabolism, Kupffer cells, TGF1ß. Let's look at the data.

So, the ones that have been most importantly studied have been obeticholic acid. The trial with obeticholic acid did not reach statistical significance. There was a trend for an improvement in fibrosis, but not a significant improvement in steatohepatitis, and the FDA has not approved it yet. Again, there is debate to whether it will. So, rather than focusing on obeticholic acid, I would like to expand on the newer compounds that are being studied so far.

One is tropifexor. But, again, this compound showed effects of a 48-week study that were not as exciting as we expected, although more people did reach lower liver fat at the end, again, also, in a dose-response, meaning there was not a major effect on fibrosis, as you can see, particularly in the right, lower panel, which were also quite disappointing.

So, the idea of what if we combine these agents to improve the modest effect of tropifexor on NASH resolution, and that was a combination of an anti-inflammatory agent called cenicriviroc that was abandoned as a single agent in NASH. But, again, as you can see here, the combination of these two also did not add much more to the mix. So, again, this FXR has not moved forward.

The next approach would be to combine, for example, agents that are known to have an effect, like semaglutide, with other compounds, like an FXR, like cilofexor, and another agent that did not eventually work, but we know now, like firsocostat. But, again, the effect of this combination and liver fat has also been a disappointment. Same in the mean change of liver fat content, again, not significantly better than semaglutide alone.

So, again, this combination of an antifibrotic with an antimetabolic drug did not lead to any great effect. So, the final word on the class is still to be determined.

Summary of Novel Agents for the Treatment of NASH

I want to summarize a lot of information that I gave you in the last half hour in the next three slides. So, the number one message, many drugs in development, so an exciting time and, again, I think the two classes with the greatest promise being insulin sensitizers with some PPAR gamma activity, and GLP-1 receptor agonists as monotherapy or as dual agents, together with a GIP, glucagon and others. Thyroid hormone receptor selective agonists may also play a role, and many others that were discussed earlier.

Of interest, we see that the good news, to some extent, is that agents that are available now can improve steatohepatitis more than other options that have been tested before. Ocaliva is a obeticholic acid. Aramchol, again, works on lipid metabolism in the liver. We see that lanifibranor, semaglutide, great effect on NASH. Again, great effect of pioglitazone, some of vitamin E. So, there are options today that you can use successfully.

Message that's important from this review that we wrote, now a couple of years ago, is that NASH is a progressive disease, where lifestyle intervention has to play a key role. Structured programs are greater in reducing weight and improving cardiometabolic health and should be proposed, if possible, to your patients. And, the key thing is to prevent cirrhosis. We can prevent cirrhosis today, but we need to modify weight. We need to offer patients also some pharmacological therapy.

So, in summary, obesity and diabetes epidemics are going to continue to grow as a public health problem, as sedentary lifestyles and aging are going to be two big factors. We can prevent this. Your mission is to prevent with early diagnosis, with FIB-4, and an imaging test in primary care and endocrine clinics that our patients go untreated. There are many treatments, as we discussed. Lifestyle is key. Don't forget bariatric surgery as a tool. But, again, I think that the agents that are going to reverse obesity and insulin resistance, either like a GLP-1-based therapy or that improve the biology of adipose tissue, like a PPAR-gamma-based therapy, like pioglitazone or lanifibranor, will hold the keys to the future management of the disease, with also many other agents in the pipeline.

So, with this, thank you very much for your time, and I hope this has been a little, in a nutshell, where we stand in the management of our patients with NASH.