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Treatment Strategies for Nonalcoholic Fatty Liver Disease: Part 2

Dr. Buch:
Welcome to GI Insights on ReachMD. I'm Dr. Peter Buch, and this is the second and final part of our two episode series focused on treatment strategies for nonalcoholic fatty liver disease. Joining me in this discussion is Dr. Sidney Barritt, who's an Associate Professor of Medicine and the Director of Hepatology at the UNC Liver Center at the University of North Carolina.

Dr. Barritt, welcome back!

Dr. Barritt:
Thank you very much for having me, Dr. Buch.

Dr. Buch:
Now moving on to therapeutics for nonalcoholic steatohepatitis, NASH, which is a subcomponent of nonalcoholic fatty liver disease, which patients with this condition should be considered for vitamin E therapy or pioglitazone? And are there any concerns when using these medications?

Dr. Barritt:
Well before I specifically address vitamin E and pioglitazone, I'd like to take a step back, and this is a conversation that I have with my patients. When we think about the whole patient with NASH and we look at the all-cause mortality for this population, the number one risk for morbidity and mortality is cardiovascular disease, followed by number two, cancer, and number 3 is liver disease. And if there's a silver lining to this process, we can address these risks in a complementary manner with some of our currently available therapies. And it's important to know that this is a situation where the gastroenterologist or the hepatologist is really on the same page and the same team as the cardiologist, the oncologist, the endocrinologist, and the primary care physician. I worry that too frequently in modern medicine, you'll get two different specialists who tell the patient to do the complete opposite intervention, but fortunately, here we're all on the same page.

And since there are no FDA-approved medications for the treatment of nonalcoholic fatty liver disease, we have to start with risk factor control. And so by that I mean addressing the risk factors of the metabolic syndrome. Patients with diabetes need to have their diabetes well-controlled. Patients with dyslipidemia, meaning high LDL, low HDL, high triglycerides, these patients need to have their lipids controlled, and that includes using statins. Statins are safe in liver disease. And additionally, patients need to control their high blood pressure as well too. And all of these factors—diabetes, dyslipidemia, and hypertension—all get better with weight loss and weight management.

And we talk a lot about weight management in nonalcoholic fatty liver disease because we've found that weight loss is really the cornerstone of therapy for the vast majority of our patients, and if we compare weight management and weight loss to many of the investigational drugs that have come down the pipeline over the past couple years, weight loss is still a superior intervention. And what we found is that approximately 5 percent weight loss can begin to reverse fat in the liver, and a 7 percent weight loss can begin to reverse inflammation in the liver, and a sustained 10 percent weight loss can start to reduce fibrosis or scar tissue in the liver.

So when it comes to vitamin E or pioglitazone, I go by the American Association for the Study of Liver Disease guidance, and in highly selected patients with biopsy-proven NASH without diabetes, I may use vitamin E. My experience with vitamin E is not a great one, however. If you look at the PIVENS trial, the PIVENS trial went for 96 weeks. And my experience with vitamin E is since this is an over-the-counter supplement, patients may take it for a little while and then forget about it and take it for a little while, and sustained use over a long period of time isn't always something that happens for many of my patients. My other concern is that we've tried vitamin E for

everything under the sun over the past 30 years. You may recall back in the mid '90s vitamin E was part of a lung cancer prevention trial, and the vitamin E arm had more lung cancers. Vitamin E has also been used in a prostate cancer prevention trial, and the vitamin E arm had more prostate cancers. And vitamin E along with a variety of other supplements had to be subject to Cochrane review, and the Cochrane review found that the vitamin E and supplement-containing arm suffered greater all-cause mortality. So while I may use vitamin E, I'm usually restricting it to nonsmoking younger women, for all of those reasons that I just mentioned.

When it comes to pioglitazone, I'm okay with pioglitazone if it's already a part of a patient's diabetic regimen or if a patient has underlying diabetes. One of the concerns that I have with pioglitazone is the weight gain that comes along with it, and this is something that's been shown in a variety of studies, but it was also highlighted in that same PIVENS trial back from 2010 where the patients in the pioglitazone arm had sustained weight gain that persisted after the end of the study when the pioglitazone was withdrawn. And so in a disease process where weight management is the cornerstone to therapy, it's a little challenging starting them on a medication that may cause weight gain, and so I don't use a tremendous amount of pioglitazone for that reason.

Dr. Buch:
Dr. Barritt, just to clarify for our audience, if you can just discuss a little bit more about statin use in nonalcoholic fatty liver disease.

Dr. Barritt:
Sure. So the statin class of medications have been out for 25 years or more now, and when they first came out, there was a signal of elevated liver enzymes in the clinical trials, and there can be this rare but isolated significant elevation in LFTs with some statin use; but whether or not patients have underlying liver disease doesn't influence that, and so it's a idiosyncratic, idiopathic drug-induced liver injury. And so whether or not a patient has underlying fatty liver or has no liver disease whatsoever doesn't change that rare idiosyncratic reaction that patients can get with statin-based therapies.

And so if we're thinking about the big picture, if we're thinking about cardiovascular risk reduction, if we're thinking about cancer risk reduction and if we're thinking about risk factor control for the metabolic syndrome, I consider statins part of that therapy. You just have to monitor them like you'd monitor anybody else. And so since many of our patients may be starting with an abnormal ALT, we'll tolerate perhaps a three times elevation from whatever their baseline may be before we pull off the medication. And more than often I've found that a patient may have a slight transient rise in their ALT, and then it comes back down with time. In many other cases I've been referred patients for an elevated ALT who have fatty liver, and the first thing that happened was the statin was removed and their ALT didn't get any better because it wasn't the statin causing the abnormal ALT but their underlying fatty liver instead.

Dr. Buch:
This is a question I get all the time, and I'm sure you do as well. Are statins alone useful for treating nonalcoholic fatty liver disease if a patient doesn't have hyperlipidemia?

Dr. Barritt:
Yeah. So for the a priori use of treating only fatty liver disease, no, they're not indicated, but the vast majority of our patients do wind up having an indication for a statin use. Many of our patients have underlying diabetes, and our LDL thresholds for statin use in patients with diabetes are lower. Interestingly, we did a study out of one of our real world cohorts, the TARGET-NASH study sponsored by Target Real World Evidence, and in that we found that in patients with an indication for a statin, a large proportion of those patients were not taking a statin, so I'm much more concerned about statins being underutilized than I am about statins being overutilized. But all that said for the a priori treatment of NASH without a dyslipidemic indication, no, I wouldn't use it in that setting.

Dr. Buch:
For those just tuning in, you're listening to *GI Insights* on ReachMD. I'm Dr. Peter Buch, and I'm speaking with Dr. Sidney Barritt about managing patients with nonalcoholic fatty liver disease or NAFLD.

Dr. Barritt, can you discuss newer therapeutics for weight loss? And even more importantly than that, does weight loss always equilibrate with improvement in nonalcoholic fatty liver disease?

Dr. Barritt:
So that's a great question. So there are a variety of medications that are now available that help with both diabetes control and weight loss, and these are the GLP-1 receptor agonists, and these medications have been studied; of course, they've got an indication for diabetes, they have been shown to reduce cardiovascular outcomes, and they have actually been studied in NASH as well too. So if you go back to 2016, there was the LEAN study liraglutide used for NASH, a small study, a Phase 2, but did show improvement in NASH in 39 percent of patients versus only about 9 percent of placebo. And we had secondary outcomes of improvement in ALT and secondary outcomes of weight loss, and so that left us with a reasonable signal that we may be able to improve some of the inflammatory factors of NASH, meaning steatosis in the liver and inflammation in the liver as well too.

This led to a more recent study, semaglutide in NASH, that was published in *The New England Journal*, I think in 2021 that again showed NASH resolution in almost 60 percent of patients versus only about 17, 20 percent of placebo patients. However, there was no difference in fibrosis between semaglutide and placebo, so here we have this little bit of odd juxtaposition where we are improving markers of inflammation, markers of steatosis with some of these drugs, but not yet improving scar tissue in the liver.

There are even newer combinations of weight loss drugs that incorporate GLP-1 receptor agonists and some glucose-dependent insulinotropic polypeptides, and this is the medication that was recently released—goes under the tradename Mounjaro. And there was a *New England Journal* paper last summer that showed remarkable weight loss in obese patients. Now, these weren't NASH patients. These were obese patients. But some of our medical weight loss therapies are approaching the success that we see with bariatric surgery.

We are hopeful that weight loss will improve NASH. There's always going to be some proportion of patients that don't get an improvement. Like I mentioned, in the semaglutide trial there was a 60 percent NASH resolution. Well, that means 40 percent didn't have NASH resolution, so it doesn't work for everybody, and why it works for some people but not others, we've yet to tease out.

Dr. Buch:
So before we conclude, Dr. Barritt, are there any studies or therapies we can look forward to for our patients with nonalcoholic fatty liver disease?

Dr. Barritt:
So while there have been a number of studies that have sort of washed up on the rocks in Phase 2 or Phase 3, there are two drugs that have posted positive interim results in their Phase 3 clinical trials, and one of those is obeticholic acid, which is a medication that's already FDA approved for a different liver indication, a disease called primary biliary cholangitis, and it's now being looked at in NASH. And that Phase 3 trial is ongoing and in long-term follow-up now.

The original interim results were published in 2019 that showed about a 23, 25 percent improvement in fibrosis without worsening of NASH, and that's compared to about a 12 percent placebo response and so those data were consistent both in the 2019 interim release and the 2022 interim release. And so these are promising in that we've got a statistically significant improvement in fibrosis compared to placebo. However, only 23 percent of the study population benefitted. So what I'd really like to know is what's going on with the other 77 percent here and what's the difference between those who got benefit and those who didn't.

Another drug that's potentially coming down the pipeline is resmetirom, which is a thyroid hormone beta receptor agonist. And this is a medication that's being produced by Madrigal and they released interim results about a year ago that showed positive interim results in terms of reduction in liver fat, reduction in LDL, and reduction in triglycerides. And so this is another potentially promising drug that's currently in Phase 3 clinical trial with positive interim results. Neither of these are FDA approved as of yet, but they're the ones that are closest to market if they can get across the finish line.

Dr. Buch:
Well, this has been an eye-opening review of nonalcoholic fatty liver disease. And I want to thank my guest, Dr. Sidney Barritt, for sharing his insights.

Dr. Barritt, it was great speaking with you again.

Dr. Barritt:
Well, thank you very much for having me. I enjoy talking about this topic a lot, so thanks again.

Dr. Buch:
For ReachMD, I'm Dr. Peter Buch. To access this and other episodes in this series, visit ReachMD.com/GI Insights where you can Be Part of the Knowledge. Thanks for listening and see you next time!