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Rethinking PBC Care: Inside the RESPONSE Trial

Announcer:
You're listening to *GI Insights* on ReachMD. Here's your host, Dr. Brian McDonough.

Dr. McDonough:
This is ReachMD. I'm Dr. Brian McDonough, and joining me to discuss the RESPONSE trial and its findings on the role of seladelpar in primary biliary cholangitis management is Dr. Gideon Hirschfield. He's the Director of the Autoimmune and Rare Liver Disease Programme, as well as the Lily and Terry Horner Chair in Autoimmune Liver Disease Research at Toronto General Hospital. He's also a co-author of the study we'll be discussing today. Dr. Hirschfield, welcome to the program.

Dr. Hirschfield:
Thank you, Brian, and thank you for having me today to talk about PBC.

Dr. McDonough:
Starting with the big picture, Dr. Hirschfield, how would you describe seladelpar's role in the current treatment landscape for primary biliary cholangitis, and what makes it distinct from other available or investigational therapies?

Dr. Hirschfield:
So there's been a lot of progress in treating PBC, and we've moved far beyond ursodeoxycholic acid. In the US, obeticholic acid is no longer available, so next-generation PPAR agonists are really very important for patients who get insufficient response to UDCA. Seladelpar is a PPAR delta agonist. It's the only selective PPAR delta agonist dosed at 10 milligrams daily, and it's one of the two approved PPAR agonists in the US and around the world used to treat patients who have insufficient biochemical control of disease and/or ongoing symptoms.

I guess where seladelpar stands out slightly is it's the only of the two PPAR agonists—the new-generation agonists—where in addition to improving biochemistry, there was evidence in the clinical trial of improvement in pruritus at a statistical level in the predetermined analysis plan. So I think it's quite exciting times for patients with PBC, and that's the reason why people are using these new-generation PPAR agonists more and more.

Dr. McDonough:
Let's focus now on the pivotal phase 3 RESPONSE trial, which examined oral seladelpar versus placebo. It found that the percentage of patients who had a biochemical response and alkaline phosphatase normalization was significantly greater with seladelpar than with placebo. How do you interpret these findings, and what could they mean for clinical practice?

Dr. Hirschfield:
Sure. I mean, the way the world is going in PBC, we now have three targets. We want our patients to have a normal bilirubin, a normal alkaline phosphatase, and to have the lowest symptom burden. In this phase 3 clinical trial of 193 patients, seladelpar versus placebo demonstrated significant biochemical response. One in four patients normalized their alkaline phosphatase, and in a key secondary analysis at six months, those patients with moderate-to-severe pruritus had significant improvements in their pruritus scores as measured by a numerical rating scale.

So seladelpar met all of its endpoints as regards to the so-called regulatory endpoint, which is the primary endpoint, and then the intuitive endpoints, which is the normalization rate—alkaline phosphatase—and a symptom parameter. So, for this clinical trial of this new-generation PPAR agonist in PBC, patients had demonstrable benefit with biochemistry and demonstrable benefit statistically with

symptoms.

Dr. McDonough:
Another interesting finding was seladelpar's effect on pruritus, which is notoriously hard to manage in primary biliary cholangitis. Can you walk us through the mechanism and clinical implications here?

Dr. Hirschfield:
That's absolutely true. So we know that PPAR agonists generally have been reported to have antipruritic effects, and we believe that's across the class. What was intriguing in this phase 3 trial is it's the only licensed PPAR agonist which actually met statistical significance in the improvement in pruritus in those patients with moderate-to-severe pruritus at baseline. How this appears to be is probably a number of effects. First and foremost, we do believe that seladelpar is modifying the disease. It's improving the biochemistry, so we believe that there is less cholangitis. And we believe that long-term use of seladelpar—and there are conference presentations and papers on the long-term use of seladelpar—will demonstrate that there is disease modification with this PPAR agonist.

Secondly, there has been some interest in measuring other biomarkers of pruritus. IL-31 as a cytokine has been quite interesting in the world of cholestatic itch and in the world of general dermatology and dermatitis. So IL-31 levels are elevated in cholestatic pruritus, and there is evidence that seladelpar reduces IL-31, and reductions in IL-31 are correlated with reductions in pruritus. IL-31 has been demonstrated to be elevated in other clinical trials of itch in PBC. Itch in PBC remains an unmet need, and there are other sponsors developing drugs that work in different ways. It's therefore intriguing that, in those studies—those studies are of IBAT inhibitors—they've also reported elevated IL-31, and they've also reported at different stages of development that when their drugs improve pruritus, the IL-31 goes down. So there does appear to be quite an interesting new biomarker story around IL-31 in cholestatic pruritus, and it's therefore notable that seladelpar has published data on reductions in IL-31 when treating patients with PBC.

Dr. McDonough:
And touching on safety for a moment, the trial found the incidence and severity of adverse events were similar across the two groups. Why are these results important when we think about the potential utility of seladelpar?

Dr. Hirschfield:
Well, we've been discussing the use of PPARs for a long time in managing patients with PBC, and until recently, there's only been off-label therapies available, and these have generally not been available in the US in particular. Therefore, when introducing a new therapy for people with PBC, particularly when that therapy is likely to be given long-term because the mechanism of action is continued—suppression of bile acids and continued suppression of lymphocytic cholangitis—safety is paramount. The safety of new PPAR agonists is therefore being closely followed. In this pivotal clinical trial, as you point out, the adverse event rates were similar between placebo and treatment. And therefore, this should give reassurance to prescribers as they move to use this new PPAR agonist—licensed PPAR agonist—that there don't appear to be any expected serious or significant adverse events.

From that, there's always been a concern around creatinine and myalgias. And in particular, again, when compared to placebos, seladelpar did not demonstrate any increased adverse event rates. So, all in, although it takes a long time to understand the safety profile of any new drug, at least on the data from this trial and this particular manuscript, it's reassuring for patients and providers that there appears to be a benign safety profile.

Dr. McDonough:
For those just tuning in, you're listening to ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Gideon Hirschfield about the use of seladelpar for primary biliary cholangitis.

So, Dr. Hirschfield, we've talked about the RESPONSE study and its results, which were published early in 2024. I want to ask you, since its publication, what's been happening with research on seladelpar? Are there any new findings or highlights?

Dr. Hirschfield:
I think so. So, with all new therapies, you expect long-term safety data to accrue, and that's no different for the world of PBC and the world of the new licensed therapies in PBC. Specifically to seladelpar, as you asked me, there's an important study called the ASSURE study, where patients who have been in any of the clinical trials of seladelpar to date continue to receive open-label seladelpar at 10 milligrams daily. What this has allowed is a number of conference presentations and a manuscript already—and other manuscripts, no doubt, for the future—to look at durability of response, the rate of normalization over time of alkaline phosphatase, the effects of pruritus over the long term, and safety. There's now over three years—and in some cases nearly four years—worth of data on seladelpar, which has confirmed a very durable biochemical response of the same magnitude reported. It's demonstrated normalization rates—which are now exceeding over 30 to 35 percent at least—for patients on seladelpar in terms of alkaline phosphatase. There's data demonstrating ongoing improvements in symptoms, including pruritus and beyond—and fatigue is another symptom of note for people living with PBC.

And the safety profile continues to be evaluated, and no new information from adverse event monitoring has been reported.

In addition, there's now conference proceedings looking at the stability of liver elastography, and in some cases, the improvement. So that speaks to the idea that when you control the disease biochemically, when you see this normalization rate—which in the ASSURE studies is well over 30 percent—that this is associated with stability and improvements in liver stiffness. And so all in for this molecule and its long-term safety data, there's been a lot of activity and a lot of reassuring information that mirrors the original registration clinical trial.

Dr. McDonough:
As we come to the end of our program, Dr. Hirschfield, how do you see seladelpar fitting into primary biliary cholangitis treatment in the coming years?

Dr. Hirschfield:
I think it's clear that we're being more aspirational in treating people with PBC. As I said, we're aiming for normal bilirubin, normal alk-phos, and normal symptoms. And providers are now given the opportunity to look at the data and to choose the therapy that they think will have the highest chance of normalization and the highest chance of improvement in symptoms for their patients. So I think that we'll see much more use of second-generation—new-generation–PPAR agonists, and the data, as presented in this clinical trial and in the ASSURE study for seladelpar, will reassure prescribers that they're on the right track in really optimizing the care of patients with PBC.

Dr. McDonough:
With those forward-looking insights in mind, I want to thank my guest, Dr. Gideon Hirschfield, for joining me to discuss how seladelpar can impact care for patients with primary biliary cholangitis. Dr. Hirschfield, it was great having you on the program.

Dr. Hirschfield:
Thank you very much for listening.

Announcer:
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