Transcript Details

This is a transcript of a continuing medical education (CME) activity. Additional media formats for the activity and full activity details (including sponsor and supporter, disclosures, and instructions for claiming credit) are available by visiting:
https://reachmd.com/programs/cme/the-treatment-pipeline-for-primary-biliary-cholangitis-sorting-out-the-ppars/16649/

Released: 01/26/2024
Valid until: 01/31/2025
Time needed to complete: 55m

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

The Treatment Pipeline for Primary Biliary Cholangitis: Sorting Out the PPARs

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

Dr. Rabiee:
Hi, this is CME on ReachMD, and I'm Dr. Atoosa Rabiee. Here with me today is Dr. Kris Kowdley.

We're going to be discussing the results of PPAR [peroxisome proliferator activated receptor] clinical trials and how they impact PBC treatment.

Dr. Kowdley?

Dr. Kowdley:
Thank you, Atoosa. So we have a number of different therapies that are in development right now and several therapies that have already been used for many years without FDA approval. So let me start by the PPAR agonists that are specifically in clinical trials.

So seladelpar is a PPAR-delta agonist. This was studied in 2 clinical trials, and the first was the ENHANCE trial, which is a phase 3 trial which was stopped after 3 months due to some concerns about liver safety that turned out to be not an issue subsequently. And in that study 78% of patients actually achieved the so-called POISE criteria, named for the POISE original obeticholic acid trial. And that is achieving an alkaline phosphatase of less than 1.67 times the upper limit of normal, along with maintaining a normal bilirubin with at least a 15% reduction.

The RESPONSE trial was the phase 3 trial that was completed and just presented as a late-breaker at AASLD, and in this study 61% of patients treated with seladelpar compared to 20% of patients treated with placebo actually achieved the same response. What's attractive about seladelpar is that both in ENHANCE and in RESPONSE, in patients who had moderate to severe pruritus, there was also a significant improvement in pruritus in addition to achieving the biochemical response. So seladelpar, very promising, successful phase 3 trial.

Saroglitazar is PPAR-alpha/gamma dual agonist, and this is now in phase 2 trials, and a phase 2b/3 trial is currently underway. And saroglitazar also has shown very high rates of biochemical response and, in fact, some of the higher rates of alkaline phosphatase normalization we've seen thus far.

Elafibranor is a PPAR-alpha/delta dual agonist, and a phase 2 trial showed similar promising results. And a phase 3 trial called ELATIVE, that I had the opportunity to be first author of a *New England Journal* paper that is just out, examined elafibranor compared to placebo. And again, with the same goal of alkaline phosphatase 1.67 times the upper limit of normal or lower, 15% reduction, and bilirubin normal. And here, we saw a response of 47% difference between placebo and treatment arm, with a 51% versus a 4% difference in treatment versus placebo achieving the biochemical response.

Elafibranor did not meet the prespecified exploratory endpoint of improvement in itching in those who had a score of greater than 4 but showed a trend towards improvement in other measures of quality of life and itching.

So we now have two phase 3 trials with both a PPAR-alpha/delta dual agonist and a PPAR-delta agonist that have achieved their results and shown promising outcomes without an unfavorable effect on pruritus. So I think we are excited about these agents potentially being available in the clinic.

There are other fibrates – fenofibrate, pemafibrate, and bezafibrate – that have also been studied. Most of the data exists with bezafibrate. This is some people call it a pan-PPAR agonist. And the most robust data come from Japan where a hazard ratio of 0.3+, so a 70% risk reduction of liver-related serious adverse events such as liver transplantation or death were shown in a large Japanese database. A trial in Europe also showed a very high rate of alkaline phosphatase normalization, although in this study patients started off with lower levels of alk/phos than what we saw with the seladelpar and elafibranor trials. So bezafibrate, another very promising agent, and being used off-label in Canada and Europe.

Dr. Rabiee:
To me, one of the important takeaways is that we are now being able to have agents that not only control the biochemical response but also affect patients' symptoms such as pruritus.

Thank you for those insights, Dr. Kowdley, and thank you to our listeners. I hope you learned something today.

Announcer:
You have been listening to CME on ReachMD. This activity is provided by Prova Education.

To receive your free CME credit, or to download this activity, go to ReachMD.com/Prova. Thank you for listening.