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/selexipag-for-the-treatment-of-chronic-thromboembolic-pulmonary-hypertension-cteph/14833/

Released: 04/29/2022
Valid until: 04/29/2023
Time needed to complete: 1h 59m

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

Selexipag for the Treatment of Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCME 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. Channick:
Hello, my name is Dr. Richard Channick, a Professor of Medicine at UCLA Medical Center in Los Angeles, and Co-Director of the Pulmonary Vascular Disease Program. Today, I'd like to discuss a recently published study on selexipag for the treatment of chronic thromboembolic pulmonary hypertension or CTEPH. This study comes out of a Japanese group led by Dr. Takeshi Ogo. It was published in the European Respiratory Journal this year. As you know, CTEPH is a serious condition characterized by non-resolved and organized thrombus as a result of prior pulmonary embolism that if significant enough can lead to progressive pulmonary hypertension, right heart failure, and even death. Historically, treatment of CTEPH has consisted of surgical intervention with a pulmonary endarterectomy. And that's still considered the first line of treatment for patients who are candidates for this operation. In addition, balloon pulmonary angioplasty has emerged as a potential alternative option for patients who are ineligible for pulmonary endarterectomy. Currently, there's only one approved medication for CTEPH which is riociguat, a guanylate cyclase stimulator, and that's approved for patients with inoperable CTEPH or those who have residual pulmonary hypertension following PEA or BPA.

So because we have limited options for some of these patients, it's natural that we should be looking at other medications that may have benefit in patients with inoperable CTEPH. Previously, there have been a proof of concept study suggesting a hemodynamic effect of selexipag in patients with CTEPH. As you know, selexipag is a prostacyclin receptor agonist which acts on the IP receptor, increasing cyclic AMP leading to vasorelaxation. So the study that I'm discussing today was a placebo-controlled double-blind study examining the safety and efficacy of selexipag in patients with inoperable CTEPH or those who had persistent PAH after PEA or BPA. The methods of this study were fairly standard. These patients had been confirmed to have CTEPH based on imaging and hemodynamics using standard criteria such as mean pulmonary artery pressure of at least 25 millimeters of mercury, wedge pressure less than 16 millimeters of mercury, PVR over 360 dynes, and imaging that confirmed the diagnosis.

These are patients who could not undergo surgery due to either peripheral or distal thrombus and also included patients who were not candidates for surgery due to comorbidities and age, et cetera. Some of the patients in the study were patients who had had a procedure, either PEA or BPA, but had persistent pulmonary hypertension. Patients cannot have been on a previous prostacyclin, but they could be on riociguat for at least 90 days prior to enrollment in the study.

The study design is shown here and it's fairly typical. The primary endpoint was PVR measured at 20 weeks. And then there were a whole host of secondary endpoints, hemodynamic endpoints as we'll discuss briefly, as well as endpoints including six-minute walk distance, quality of life, dyspnea scale, and NT-proBNP. And then safety was looked at. The dosing of selexipag is similar to what is done in clinical practice with pulmonary arterial hypertension and it's an escalating dose regimen based on tolerance and side effects, starting at the lowest dose of 400 micrograms per day, it's 200 micrograms b.i.d., up to a maximum of 3,200 micrograms per day. And then patients would maintain on the dose, the maximally tolerated dose, again ranging anywhere from a low of 400 micrograms per day

up to 3,200 micrograms per day. Hemodynamic analysis was performed, as I mentioned, and the methodology is shown here where the primary analysis of the efficacy endpoint was performed on the full analysis set.

And in addition, other parameters, other hemodynamic parameters, functional class parameters were looked at as well. And the imputation scheme was last observation carry forward or worse value, if a patient was having pulmonary hypertension worsening. This shows the disposition of the patients where 100 patients were eligible, 26 were excluded for various reasons, mainly not meeting inclusion criteria, and then 78 were randomized. And you can see there, 39 assigned to selexipag, 39 to placebo. Most of the patients completed the treatment. A handful of patients discontinued. Baseline data is shown here and again is fairly well-matched between the groups. These are patients who tend to be older as CTEPH patients are compared to PAH patients with baseline six-minute walk distance in the high 300s to low 400s and one can see here the breakdown where the majority of patients were not candidates for intervention due to distal organized thrombus. Some patients were deemed to be too high risk for surgery, and then a smaller number had persistent pulmonary hypertension after PEA. And then we see that there was significant percentage of patients, over half of patients who had had a previous BPA and still had pulmonary hypertension. Over 60% of patients were on background therapy with riociguat and then a small number of patients were also on either ERA, an endothelin receptor antagonist, or a PDE5 inhibitor. And these patients had had a relatively long time since diagnosis, over four years for the group randomized to placebo and over two years for the group randomized to selexipag. This is the primary endpoint of pulmonary vascular resistance. And as you can see on the graph, there clearly was a very significant improvement in pulmonary vascular resistance or decrease in the selexipag group with no change in the placebo group, giving a statistically significant effect on pulmonary vascular resistance. And the numbers are shown here in patients who couldn't undergo PEA 'cause of distal organized thrombus. The difference in PVR between the groups was 135 dynes per second per centimeter minus fifth.

In fact, when we look at this data, it does show that that group of patients who were not surgical candidates due to distal thrombus had the best or greatest effect on pulmonary vascular resistance. When we look at the effect of dose on the decrease in pulmonary vascular resistance, there does appear to be a dose-dependent effect. So patients who ended up on the higher dose range of selexipag 2,400 to 3,200 per day had a higher, a greater reduction in PVR compared to those patients who ended up on a lower dose. In addition, and this is maybe not surprising, patients who were treatment naive, in other words were not on any other pulmonary hypertension medications, had the larger decrease in PVR compared to patients who were on a concomitant medical therapy. This is a big table showing a whole host of secondary endpoints, hemodynamic, six-minute walk, and you can see here, the statistically significant treatment effects are circled there on the right. And you can see there are a number of benefits to the secondary endpoints, from other hemodynamic values like cardiac index, mixed venous saturation, and then Borg dyspnea score improved to a greater degree in the selexipag group.

If you look at subgroup analysis, it's shown on its force plot, and you can look and get a sense that the treatment effect was fairly homogenous throughout various subgroups, gender, age, whether a patient had had a PEA or a BPA, and whether there were concomitant use of riociguat. So it's a consistent effect or benefit that we see with selexipag in the subgroup analysis. Adverse events were present and certainly mirror what we see with selexipag and other prostacyclin pathway drugs, including headache, diarrhea, some nausea, jaw pain. Those were seen more commonly in patients who got selexipag versus placebo. So nothing unique or surprising with these adverse events from this drug. So this study concluded that selexipag did improve hemodynamics in patients with inoperable CTEPH or persistent or recurrent PH after PEA or BPA compared with placebo, although we did not see in this study an improvement in exercise capacity. This is a small study. So the drug met the primary endpoint. And interestingly, additionally, we see that background therapy probably did reduce the PVR and therefore the addition of selexipag might have less of a further effect. To the secondary endpoints, six-minute walk and functional class did not significantly improve.

But again, the study was not powered to show those differences in those endpoints. And importantly, the study did show that selexipag is well-tolerated and safe. And in fact, it did improve hemodynamics in these patients. This, I think, is important information and provocative information in this group of patients for which we're looking for additional therapies. There's certainly some limitations. There's a shorter treatment period than what we obviously use in clinical practice. This was a small study, under 100 patients, randomized, and it's a single study conducted in Japan. Whether these data can be extrapolated to a wider patient population where things like criteria for surgical intervention may be different or varied, we don't yet know. But nevertheless, I think we have a very interesting study that although not necessarily practice changing, certainly should whet our appetites for looking at this agent in more detail in this group of patients. Thank you.

Announcer:
You have been listening to CME on ReachMD. This activity is jointly provided by Global Learning Collaborative (GLC) and TotalCME, Inc. and is part of our MinuteCME curriculum.

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