

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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## Treatment of Portopulmonary Hypertension With Macitentan in Patients With Cirrhosis



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**G&H** What is the current understanding of the relationship between pulmonary hypertension and cirrhosis?

**MK** Any liver disease or vascular problem in the liver can cause an obstruction to blood flow within the liver (portal hypertension). This obstruction causes dilation of the mesenteric vessels and facilitates the development of other vascular pathways (eg, esophageal/gastric varices) so that blood from the intestines circumvents the normal metabolism within the liver. This process results in at least 2 important events: first, a high flow state (increased cardiac output) is created; and second, certain factors or mediators bypass the normal metabolism within the liver, traversing it, and can adversely affect the pulmonary arterial bed. Increased cardiac output alone is not a problem and can cause pulmonary hypertension simply due to high flow, as there is no obstruction to the flow. When mediators or other factors come into play, there may be an evolution of the obstruction to pulmonary artery flow by vasoconstriction and proliferation of the endothelium/smooth muscle. It is not possible to predict when, why, or in whom this will occur. Most experts lean toward circulating endothelin as one of the potential mediators. The term portopulmonary hypertension (POPH) was coined to describe this development (ie, pulmonary artery hypertension due to portal hypertension), which is now known to usually develop months to years after the diagnosis of portal hypertension.

It is important to think of these patients as having 2 different disease processes (one in the liver and one in the lungs) that are occurring simultaneously. However,

the relationship between the severity of these diseases is unclear. For example, a patient can have severe liver disease and no POPH, or mild liver disease and very severe POPH.

**G&H** How has POPH traditionally been treated in cirrhotic patients?

**MK** Up until this past year, most cirrhotic patients with POPH were using drugs approved for treating Group 1 pulmonary artery hypertension. The drugs most commonly used in POPH have been prostacyclins (via intravenous, subcutaneous, or inhaled formulations), oral endothelin receptor antagonists such as bosentan (Tracleer, Actelion) or ambrisentan (Letairis, Gilead), and phosphodiesterase inhibitors such as sildenafil or tadalafil. Treatment was essentially empiric use with trial and error reported by case reports and small case series. Based on these experiences, people realized that these drugs were having a beneficial effect on POPH by reducing mean pulmonary artery pressure (mPAP) and pulmonary vascular resistance (PVR). Finally, a multicenter, randomized, placebo-controlled, prospective study (PORTICO) was proposed to study the safety and efficacy of the endothelin receptor antagonist macitentan (Opsumit, Actelion) for the treatment of POPH in patients with mild to moderate cirrhotic or noncirrhotic liver disease.

Only one previous randomized, placebo-controlled trial in pulmonary artery hypertension included patients with POPH. This was the PATENT trial, which studied riociguat (Adempas, Bayer), a guanylate cyclase stimulator,

in 13 patients who had POPH. A post hoc subgroup analysis showed a significant improvement in PVR.

### G&H What is the mechanism of action of macitentan?

**MK** There are 2 basic types of endothelin receptors found in vascular endothelium: endothelin A receptors and endothelin B receptors. Stimulation of endothelin A receptors results in vasoconstriction of blood vessels, whereas stimulation of endothelin B receptors causes relaxation of blood vessels. Macitentan is thought to primarily block endothelin A receptors. However, the actual mechanisms that cause POPH likely go beyond just vasoconstriction because the obstruction to flow is likely also caused by a proliferation of certain cells in the blood vessel wall. It is possible macitentan has an effect on this as well.

### G&H What was the design of the PORTICO trial?

**MK** PORTICO was a multicenter, placebo-controlled, randomized trial whose centers were located primarily in Europe, the United States, and Brazil. There was a total of 85 patients in the study (43 in the treatment arm and 42 in the placebo arm). The diagnosis of POPH was established by right heart catheterization (RHC). Patients had to be older than 18 years of age; able to walk at least 50 meters during the 6-minute walk test; and have, via RHC, a baseline mPAP of greater than 25 mm Hg, a pulmonary artery wedge pressure (PAWP) of less than 15 mm Hg, and, importantly, a PVR of greater than 4 Wood units (normal is <3). Any liver disease diagnosis could be included, and background pulmonary hypertension therapy was allowed as long as it was not modified in the 3-month period prior to enrollment. Macitentan was given at a daily dose of 10 mg. An analysis was made at the end of 12 weeks of treatment, and then there was a 12-week extension for patients who had received placebo instead of the drug. Another analysis was performed at 24 weeks. The data from the first 12 weeks of treatment were presented at 2 recent national meetings: the European Respiratory Society meeting last September and the American Association for the Study of Liver Diseases (AASLD) meeting in November.

### G&H What were the study findings that you presented at the AASLD meeting?

**MK** The primary endpoint involved the assessment of PVR at the end of 12 weeks compared to baseline. PVR is a calculation based upon RHC measurements ( $PVR = [mPAP - PAWP] / \text{cardiac output}$ ). Thus, at baseline

and at the end of 12 weeks, all of the patients underwent RHC for comparative purposes. A favorable primary endpoint result was noted with the mean PVR dropping by 35% from baseline to the end of 12 weeks of treatment. Secondary results were favorable in that the mPAP decreased and the cardiac output increased. The PAWP was unchanged. Functional class and the distance walked in 6 minutes, which were secondary measurements, were also unchanged.

### G&H How safe was this drug in cirrhotic patients? Were there any significant side effects?

**MK** The most significant side effect was peripheral edema, which occurred in approximately 25% of patients. Some patients experienced a drop (usually approximately 1 g) in their hemoglobin level, but this was not a serious side effect. No patients had to stop treatment because of this side effect, and no bleeding problems resulted. In addition, no patients had to stop the drug because of toxicity to the liver. One patient had an increase in liver enzymes but not to the degree that required dropping out of the study.

### G&H How do these safety findings compare with those of similar drugs?

**MK** The safety findings from the PORTICO study were very favorable. There was no difference in any type of liver toxicity between the placebo group and the treatment group. Likewise, no significant safety issues have been reported with the endothelin receptor antagonist ambrisentan. This drug is also effective for the treatment of POPH. The main difference between ambrisentan and macitentan lies in the difference in how they are metabolized by the liver.

In contrast, hepatic toxicity has been reported with the initial endothelin receptor antagonist bosentan, which led to a black box warning from the US Food and Drug Administration.

### G&H Should macitentan be avoided in any patients?

**MK** It is unclear whether this drug can be safely given to patients with the most advanced liver disease, such as patients with a Child-Turcotte-Pugh C score and patients with a Model for End-Stage Liver Disease (MELD) score higher than 19. These groups of patients were excluded from the PORTICO study.

### G&H What follow-up care is needed in cirrhotic patients taking this drug?

**MK** Follow-up care depends on whether the patient is to be considered for liver transplantation. Routine follow-up in a nontransplant situation would usually include complete blood counts, liver function tests, and a transthoracic echocardiogram every 6 months. Follow-up in a potential liver transplant candidate is more complicated and depends on the severity of the baseline RHC measurements.

### G&H Why does liver transplantation require a low mPAP?

**MK** Untreated moderate to severe POPH (mPAP >35 mm Hg) is associated with significant morbidity and mortality with attempted liver transplantation. The goal is to decrease the mPAP to less than 35 mm Hg before transplantation is attempted. In that situation, pulmonary hemodynamics should be checked approximately every 3 months by echocardiography and RHC prior to transplantation. If it can be demonstrated that macitentan or another medication does improve hemodynamics (ie, the mPAP decreases to <35 mm Hg), the patient can receive a higher MELD score (because of the MELD exception process) and, thus, higher priority for liver transplantation. A patient's native MELD score reflects the severity of liver disease and is determined by a formula that includes total bilirubin, international normalized ratio, creatinine, and sodium. However, this score does not correlate well with the severity of POPH; thus, an exception process exists. If a patient has moderate to severe POPH and has a relatively low MELD score (<15), a liver transplantation may be desirable in an attempt to resolve the POPH before it worsens. For patients with a MELD score over 15, the goal is to facilitate a safer transplantation by improving pulmonary hemodynamics and right heart function with POPH treatment.

If the mPAP is too high (usually >35 mm Hg, but certainly >45 mm Hg), the patient will be denied a liver transplantation because of the risk of right heart failure (and possible death) during the operation. When patients with POPH are treated and their pulmonary artery pressures are brought down, the right side of their heart functions better. If they go on to a liver transplantation and survive the procedure, approximately one-half can stop their treatment, and the other half may require less medication to control their POPH. Thus, with liver transplantation and treatment, POPH is completely reversible in some patients, and certainly improvable in others. However, it is not possible to predict which patients will fall into which category.

### G&H Has there been any research on the use of macitentan in patients with very advanced liver disease?

**MK** There has been no formal research on the use of this drug in patients with very severe liver disease. Nevertheless, some doctors have occasionally used the drug in this setting. My colleagues and I have used it carefully in a few such patients, either alone or in combination with other pulmonary hypertension medications, and no adverse effects have been found to date, nor have we needed to discontinue macitentan for any reason.

### G&H What are the next steps in research in this area?

**MK** We need to continue to try to identify circulating biomarkers that correlate with POPH severity and outcomes. In addition, rather than performing another prospective study for a particular drug, a large registry should be established nationally to follow patients using different regimens so that physicians can draw conclusions over time. Prospective studies exclude patients and do not offer an accurate reflection of real-world experiences, whereas any patients who have been diagnosed with POPH could be placed into a registry. Having accurate follow-up data would be very helpful when deciding what could help or not help treatment of these patients. My colleagues and I are currently in tentative discussions with Actelion, which supported the PORTICO study, to consider establishing such a registry.

*Dr Krowka was on the Steering Committee for the PORTICO study.*

### Suggested Reading

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