Macitentan Improves Risk Categorization for Liver Transplant Mortality in Patients With Portopulmonary Hypertension: A PORTICO Study Post Hoc Analysis

TO THE EDITOR:

Portopulmonary hypertension (PoPH) is a form of pulmonary arterial hypertension (PAH) associated with portal hypertension, usually caused by liver cirrhosis. Prognosis is poor for patients with PoPH, and 5-year survival from diagnosis is significantly lower compared with patients who have idiopathic or heritable PAH.\(^1\) LT can be a lifesaving option for patients with cirrhosis and PoPH,\(^2\) but pretransplant and posttransplant outcomes depend on their cardiopulmonary hemodynamics. Indeed, by the time patients with PoPH have Model for End-Stage Liver Disease (MELD) scores high enough to be listed for LT, their cardiopulmonary hemodynamics may be too severely impaired for them to withstand the procedure.

The mPAP and PVR are the key hemodynamic parameters used to guide the decision to perform LT. Specifically, mPAP has been associated with the risk of LT perioperative mortality in patients with PoPH, with values \(\geq 50\) mm Hg associated with a 100% mortality rate and those ranging from \(\geq 35\) to \(< 50\) mm Hg with PVR \(\geq 250\) dyn/second/cm\(^5\) associated with a 50% mortality rate.\(^3\) No deaths were reported for patients with mPAP values \(< 35\) mm Hg or for patients with mPAP values \(\geq 35\) to \(< 50\) mm Hg, but with PVR \(< 250\) dyn/second/cm\(^5\).\(^3\) Given this, the International Liver Transplant Society guidelines recommend that PoPH patients with mPAP \(> 35\) mm Hg initiate PAH-targeted therapy to improve their hemodynamics prior to LT and state that mPAP values \(\geq 45\) mm Hg are an absolute contraindication for LT.\(^4\)

In the United States, a MELD exception rule (based on mPAP and PVR) was introduced for patients with PoPH to address the fact that the MELD score alone does not appropriately reflect the candidate’s medical urgency for LT. This exception allows PoPH patients demonstrating adequate hemodynamic response to PAH therapy (posttreatment mPAP \(< 35\) mm Hg and PVR \(< 400\) dyn/second/cm\(^5\)) to be ranked higher on the transplant waiting list than their calculated MELD score would ordinarily allow. Similar MELD exception rules have also been implemented in a number of other countries. However, it has been reported that even for PoPH patients with an approved MELD exception, the overall mortality rate is approximately 23% while awaiting transplant, and PVR has been identified as an independent predictor of wait-list mortality.\(^5\)

The recently completed PORTICO study evaluated the effects of macitentan, an endothelin receptor

### Abbreviations:
- CI: confidence interval
- IQR: interquartile range
- LT: liver transplantation
- LVEDP: left ventricular end diastolic pressure
- MELD: Model for End-Stage Liver Disease
- mPAP: mean pulmonary arterial pressure
- mRAP: mean right arterial pressure
- OR: odds ratio
- PAH: pulmonary arterial hypertension
- PVR: pulmonary vascular resistance
- SD: standard deviation

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antagonist, in PoPH patients and was the first randomized controlled trial of a PAH therapy specifically conducted in this patient population.\(^6\) In the PORTICO study, macitentan treatment resulted in improvements in PVR and mPAP as compared with placebo, and was well tolerated by most patients, with similar overall and hepatic safety profiles to those observed in trials of macitentan in patients with other PAH etiologies.\(^6\) We conducted this post hoc analysis to evaluate the implications of the hemodynamic changes obtained during macitentan treatment with respect to patients’ risk of LT perioperative and wait-list mortality.

**Patients and Methods**

PORTICO (clinicaltrials.gov, NCT02382016) was a multicenter, double-blind, placebo-controlled, prospective study that explored the efficacy and safety of macitentan in patients with PoPH.\(^6\) The study has been described in detail elsewhere.\(^6\) Briefly, adults with confirmed PoPH were randomized to receive blinded treatment with either 10 mg of macitentan or placebo for 12 weeks, followed by 12 weeks of open-label treatment with macitentan. Patients with severe hepatic impairment, defined as Child-Pugh class C liver disease or a MELD score ≥19, were excluded from the study. Patients could be receiving a stable dose of background PAH therapy (phosphodiesterase type 5 inhibitor, soluble guanylate cyclase stimulator, or inhaled prostanoid).

Exploratory post hoc analyses were conducted on the full analysis set (all randomized participants) for the double-blind treatment period. Changes were analyzed descriptively by treatment group using shift tables from baseline to week 12 for the following patient data:

1. Perioperative mortality risk, as determined by mPAP and PVR: low risk, \(\text{mPAP} < 35 \ \text{mm Hg} \) or \(35 \ \text{mm Hg} \leq \text{mPAP} < 45 \ \text{mm Hg} \) with \(\text{PVR} < 240 \ \text{dyn/second/cm}^5\); intermediate risk, \(35 \ \text{mm Hg} \leq \text{mPAP} < 45 \ \text{mm Hg} \) with \(\text{PVR} \geq 240 \ \text{dyn/second/cm}^5\); and high risk (contraindication to LT), \(\text{mPAP} \geq 45 \ \text{mm Hg} \).\(^3,4\)

2. LT wait-list mortality risk category based on PVR criteria from DuBrock et al.\(^5\): low risk, \(\text{PVR} \leq 450 \ \text{dyn/second/cm}^5\); and high risk, \(\text{PVR} > 450 \ \text{dyn/second/cm}^5\).

An exact logistic regression with factors for treatment and risk category at baseline was used to compute the odds ratio (OR), 95% confidence interval (CI), and \(P\) value (macitentan versus placebo) for improvement to a better risk category at week 12. The number of patients improving from ineligible to eligible for LT MELD exception (mPAP <35 mm Hg and PVR <400 dyn/second/cm\(^5\)) from baseline to week 12 are reported by treatment group.

**Results**

A total of 85 participants were randomized to receive either macitentan (\(n = 43\)) or placebo (\(n = 42\)). Baseline demographics and disease characteristics are shown in Table 1.\(^6\) With respect to perioperative mortality risk, 7 patients were classified as low risk (macitentan, \(n = 3\); placebo, \(n = 4\)), 36 as intermediate risk (macitentan, \(n = 15\); placebo, \(n = 21\)), and 42 as high risk (macitentan, \(n = 25\); placebo, \(n = 17\)) at baseline. For wait-list mortality risk, 30 patients were classified as low risk (macitentan, \(n = 13\); placebo, \(n = 17\)), and 55 were classified as high risk (macitentan, \(n = 30\); placebo, \(n = 25\)) at baseline (Tables 1 and 2).

After 12 weeks, 20 (47%) macitentan-treated and 6 (14%) placebo-treated patients had improved their risk category for LT perioperative mortality (Table 2; Fig. 1), and the OR for improvement in risk category was 4.9 (95% CI, 1.6–17.7; \(P = 0.004\)) in favor of patients on macitentan. At week 12, 11 (26%) macitentan-treated and 3 (7%) placebo-treated patients had transitioned to the low-risk category for LT perioperative mortality (Table 2). Of these, patients achieving mPAP <35 mm Hg included 6 (14%) in the macitentan arm and 3 (7%) in the placebo arm; 5 (12%) patients in the macitentan arm and 0 in the placebo arm.
arm achieved 35 mm Hg ≤ mPAP < 45 mm Hg with PVR < 240 dyn/second/cm².

For wait-list mortality risk, 18 (42%) macitentan-treated and 3 (7%) placebo-treated patients who were in the high-risk wait-list mortality group at baseline had moved to the low-risk group by the end of week 12 (Table 2; Fig. 1). The OR for improvement in risk category was 10.5 (95% CI, 2.4-66.8; \( P = 0.001 \)) in favor of patients on macitentan.

Based on mPAP and PVR, patients who would not have been eligible for an LT MELD exception at baseline but who achieved eligibility criteria at week 12 included 6 (14%) macitentan-treated and 2 (5%) placebo-treated patients.

### Discussion

Results from the PORTICO study showed that treatment of PoPH with macitentan leads to an improvement in mPAP and PVR without adversely affecting liver function. Both of these are linked to LT perioperative and wait-list mortality risk in this patient population. A variety of therapies...
TABLE 2. Change From Baseline to Week 12 in LT Perioperative and Wait-List Mortality Risk Categories

| Baseline Risk Category | n | Low Risk | Intermediate Risk | High Risk | Missing | OR for Improvement (95% CI)* | P Value |
|------------------------|---|----------|-------------------|-----------|---------|-----------------------------|--------|
| Change from baseline to week 12 in LT perioperative mortality risk category | | | | | | | |
| Macitentan (n = 43) | | | | | | | |
| Low risk | 3 | 2 (5) | 0† | 0† | 1 (2) | 4.9 (1.6-17.7) | 0.004 |
| Intermediate risk | 15 | 7 (16)† | 6 (14) | 0† | 2 (5) | 20 (47) |
| High risk | 25 | 4 (9)† | 9 (21)† | 11 (26) | 1 (2) |
| Placebo (n = 42) | | | | | | | |
| Low risk | 4 | 2 (5) | 2 (5)† | 0† | 0 | | |
| Intermediate risk | 21 | 3 (7)† | 13 (31) | 5 (12)† | 0 | 6 (14) |
| High risk | 17 | 0† | 3 (7)† | 13 (31) | 1 (2) |
| Change from baseline to week 12 in LT wait-list mortality risk category | | | | | | | |
| Macitentan (n = 43) | | | | | | | |
| Low risk | 13 | 11 (26) | — | 1 (2)† | 1 (2) | 10.5 (2.4-66.8) | 0.001 |
| High risk | 30 | 18 (42)† | — | 9 (21) | 3 (7) | 18 (42) |
| Placebo (n = 42) | | | | | | | |
| Low risk | 17 | 14 (33) | — | 3 (7)† | 0 | | |
| High risk | 25 | 3 (7)† | — | 21 (50) | 1 (2) | 3 (7) | | |

NOTE: Data are given as n (%) unless otherwise noted. Numbers in bold are patients who improved risk categorization from baseline to week 12. LT perioperative mortality risk categories: low, mPAP <35 mm Hg or mPAP between ≥35 and <45 mm Hg with PVR <240 dyn/second/cm²; intermediate, mPAP between ≥35 and <45 mm Hg with PVR ≥240 dyn/second/cm²; and high, mPAP ≥45 mm Hg. LT wait-list mortality risk categories: low, PVR ≤450 dyn/second/cm²; high, PVR >450 dyn/second/cm².

*OR in favor of macitentan-treated patients.
†Improved from baseline.
‡Worsened from baseline.

have been used and reported to improve mPAP in patients with PoPH. However, the potential beneficial effects of such therapies have been based largely on retrospective studies and successful outcomes, with the limitations inherent to these types of studies hindering the ability to draw strong conclusions. Data from this post hoc analysis reveal the extent of these hemodynamic changes was enough to reduce the potential LT perioperative mortality risk category of almost half, and the wait-list mortality risk category of over 40%, of patients receiving macitentan treatment.

In PORTICO, patients with MELD ≥19 or Child-Pugh class C liver disease were excluded, yet the mean mPAP was 45.1 mm Hg, indicating severe PoPH. In this context, it is worth noting that 64% of patients were already receiving PAH treatment at the start of the study. At baseline, almost half of the patients in PORTICO had mPAP values ≥45 mm Hg, which would prevent them from being considered for future LT without effective PAH treatment. In addition, it is conceivable that without management of their PAH, patients with less impaired hemodynamics at baseline would experience substantial further PAH progression by the time they were in need of LT, thus increasing their likelihood of being contraindicated for the procedure and/or increasing their risk of wait-list and perioperative mortality.

The LT wait-list mortality for PoPH patients granted a MELD exception is approximately 23%, with a median time on the waiting list of almost 1 year (344 days) and a quarter of patients remaining on the waiting list for 2 years or more. Given that 1- and 2-year survival for patients with PoPH has been reported at 85% and 67%, respectively, it is an important clinical goal to improve hemodynamics with targeted and efficacious treatments to reduce the risk of wait-list mortality and enable LT.

One limitation of the current work is the post hoc nature of these analyses. Because the PORTICO study was not designed to investigate these endpoints, the required sample size was not determined. However, PORTICO has the strength of the data being obtained in the only double-blind, prospective, randomized controlled trial performed in patients with PoPH and that
it used objective hemodynamic parameters as endpoint measures. With respect to the wait-list mortality analysis, the PVR cutoff of 450 dyn/second/cm² was chosen based on survival analyses presented in the article by DuBrock et al. The authors chose this cutoff value because it was the median initial PVR of patients in that study, and as such, it is somewhat arbitrary. Despite this, the value is, in fact, close to the median baseline PVR of 491 dyn/second/cm² observed in PORTICO. Finally, our data show that macitentan improves LT wait-list and perioperative mortality risk based on established hemodynamic thresholds. However, further studies are required to establish if this translates into improvements in mortality in the real-world setting.

Conclusions

In conclusion, on the basis of hemodynamic criteria, treatment with macitentan significantly improved patients’ risk category for LT perioperative mortality and markedly decreased the number of patients in the high-risk category for wait-list mortality. Macitentan was generally well tolerated in PORTICO and did not lead to further adverse liver conditions in this hepatically impaired population.

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