

November 2013 Tucson Pulmonary Journal Club: Macitentan

Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, Mittelholzer CM, Perchenet L, Sastry BK, Sitbon O, Souza R, Torbicki A, Zeng X, Rubin LJ, Simonneau G; SERAPHIN Investigators. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med*. 2013;369(9):809-18. [\[CrossRef\]](#) [\[PubMed\]](#)

Treatment of pulmonary arterial hypertension (PAH) with endothelin receptor antagonists (ERA) has been shown to improve exercise capacity and functional status, but not mortality. A recent systematic review found uncertainty regarding ERAs' effects on mortality (1). Macitentan, a new molecule structurally similar to bosentan, targets endothelin-A and endothelin-B receptors, offers greater tissue penetration, and has more sustained receptor binding.

SERAPHIN was an industry-sponsored, double-blinded, randomized controlled trial which examined the effect of long-term macitentan use on PAH morbidity and mortality. Between May 2008 and December 2009, 742 patients in 39 countries were randomized to placebo, macitentan 3 mg daily, or macitentan 10 mg daily. Participants had to be ≥ 12 years of age with Group 1 PAH confirmed by right heart catheterization and have WHO functional class II, III, or IV heart failure. Participants taking intravenous or subcutaneous prostanoids were excluded, but other concomitant treatments were allowed. The composite endpoint of worsening of PAH (initiation of intravenous or subcutaneous prostanoids, lung transplantation, or atrial septostomy) or death from any cause was the primary endpoint. Secondary outcomes included the composite outcome of hospitalization or death due to PAH, change in 6-minute walk (6MW), improvement in WHO functional class, and adverse events.

As compared to placebo, both the 3 mg and 10 mg daily dose of macitentan were found to reduce the composite endpoint of worsening PAH or death with hazard ratios of 0.70 (CI 95% 0.52-0.96) and 0.55 (CI 95% 0.32-0.76), respectively. Both also improved the composite endpoint of hospitalization or death due to PAH, 6MW and WHO functional class. The proportions of participants with elevated liver enzymes were comparable across the 3 groups (1-5%); however, participants in the 3 mg and 10 mg macitentan groups were more likely to experience anemia, 8.8% and 13.2%, respectively, than the 3.2% of participants in the placebo group.

Treatment with macitentan significantly decreased the composite endpoint of worsening PAH or death. The major driver of this reduction was fewer instances of worsening of PAH rather than fewer deaths. Similar to previous trials, SERAPHIN fails to clearly demonstrate that ERA use reduces all cause or PAH-specific mortality. While macitentan use did appear to result in meaningful reductions in symptom burden and hospitalization, the effect on 6MW is smaller than that previously reported for other ERAs (1). Macitentan use does appear to be safe with a slightly higher risk of anemia being observed. The incremental benefit of macitentan over existing treatments is unknown.

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Reference

1. Liu C, Chen J, Gao Y, Deng B, Liu K. Endothelin receptor antagonists for pulmonary arterial hypertension. Cochrane Database of Systematic Reviews 2013, Issue 2. Art. No.: CD004434. DOI: 10.1002/14651858.CD004434.pub5. [\[CrossRef\]](#) [\[PubMed\]](#)