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Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH, Mayer E, Simonneau G, Wilkins MR, Fritsch A, Neuser D, Weimann G, Wang C; CHEST-1 Study Group. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. **N Engl J Med. 2013;369:319-32.** **[CrossRef]** **[PubMed]**

Chronic Thromboembolic Disease (CTED) leading to pulmonary hypertension has an incidence of 5000 cases per year. It is estimated that up to 3% of all patients with pulmonary embolism develop CTED within 2 years of initial pulmonary embolism event.

The diagnosis of CTED is made through a ventilation perfusion scan detecting chronic thromboembolic disease. Treatment of CTED centers on anticoagulation and surgical thromboendartectomy. Thromboendartectomy is a unique procedure offered only in a few specialized centers throughout the country. Pharmacologic agents in the treatment of CTED have been ineffective except for bosentan. Bosentan, an endothelin receptor antagonist, has been shown to decrease pulmonary vascular resistance but not improve 6 minute walk time. Riociguat is a soluble guanylate cyclase stimulator, which works by increasing levels of cyclic GMP levels, resulting in vasorelaxation.

This study is a randomized double blind placebo controlled 16 week phase 3 trial evaluating the efficacy and safety of riociguat. The study was performed between 2009 – 2012 within 26 countries and 89 centers. A total of 261 patients were included in the study. Patients were excluded if they were pharmacologic agents used in the treatment of pulmonary hypertension. The primary outcome of the study was the improvement in 6 minute walk distance. Secondary outcomes included changes in pulmonary vascular resistance, N terminal BNP levels, WHO functional classification, and dyspnea severity. Medication side effect profiles were also noted.

Patients were divided into 2 groups, 88 subjects in the placebo group and 173 subjects in the treatment group. The discrepancy in sample size was based on needing 173 subjects within the treatment arm to reach a power of 90%. The dose of riociguat was adjusted between 0.5 mg to 2.5mg three times a day based on tolerance to side effects. This dose adjustment was done over the first 8 weeks and then a stable dose maintained for the next 8 weeks. At the end of the 16 weeks outcomes and safety profiles were measured.

The results showed that riociguat improved 6 minute walk distance by a mean of 39 meters as opposed to a decline of 6 meters within placebo. Secondary outcomes were also favorable showing an improvement in cardiac output while decreasing the pulmonary vascular resistance and pulmonary pressures.

The side effects included right ventricular failure in 3% and syncope in 2% of the subjects, both of which were the same in the placebo group. Two percent of patients stopped the drug due to nausea, vomiting and headache and another 2% developed hemoptysis. Two patients died in the treatment arm secondary to drug related heart failure and acute renal failure.

The study demonstrated that riociguat may offer benefit in patients ineligible for thromboendartectomy. Further studies to evaluate longitudinal benefits and safety profiles are needed.

Manoj Mathew, MD FCCP MCCM