Update on the SEATTLE II Clinical Trial

A prospective, single-arm, multicenter trial of the EkoSonic endovascular system with Activase for acute pulmonary embolism.

BY KEITH M. STERLING, MD

In June 2012, 17 sites across the US started enrolling patients in a trial to evaluate the safety and efficacy of catheter-directed ultrasound-enhanced thrombolysis with alteplase (Activase, Genentech, San Francisco, CA) in acute massive and submassive pulmonary embolism (PE). Sixty-six patients have been enrolled to date in the SEATTLE II trial. In this trial, patients with extensive PE and evidence of right heart dysfunction receive a low-dose 24-mg infusion of alteplase via either one or two EkoSonic catheter systems (Ekos Corporation, Bothell, WA), depending on dominant unilateral or bilateral PE. Subjects must have noninvasive evidence of right heart strain based on a right ventricular (RV) end diastolic diameter compared to the left ventricular (LV) end diastolic diameter (RV/LV) ratio of ≥ 0.9.

TRIAL BACKGROUND

The interest in such a trial stemmed from multiple factors, including suboptimal alternative treatments for patients with acute massive PE and poor clinical outcomes in patients with submassive PE whose right heart dysfunction was unresolved. Patients with PE and severe RV dysfunction experience higher rates of adverse events, including hemodynamic collapse, respiratory failure, cardiac arrest, and death. Specifically, when the RV/LV ratio is ≥ 0.9, patients had a fourfold increase in in-hospital mortality.[1] In the most severe cases, patients presenting with systemic hypotension or signs of shock (massive PE) may be candidates for therapies such as a thoracotomy with pulmonary embolectomy or systemic administration of alteplase for a total dose of 100 mg via continuous infusion over 2 hours. The former option is rarely performed, due to the fact that it is not widely available. The latter therapy is associated with an intracranial hemorrhage rate of 1% to 3% and a major bleed rate of up to 20%. These complications are believed to be dose related; therefore, a safe and effective alternative is desired.

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Patients with submassive PE are those who are normotensive despite having RV dysfunction and an

extensive degree of thrombus. This patient population comprises approximately 40% of all PE cases. They are typically treated with standard anticoagulation; however, due to their right heart strain, they have a 21% mortality rate at 3 months[2] and a 44% incidence of chronic pulmonary hypertension at 1 year.[3] Patients without right heart strain will have a 40% lower mortality rate over the same time course.[2]

THE EKOSONIC SYSTEM

Due to the poor outcomes in patients with RV dysfunction who are treated conservatively or inadequately, consideration has been given to more aggressive treatment to resolve clot burden, reverse RV dysfunction, and prevent progression to long-term sequelae and mortality. Catheter-based technologies, which mechanically fragment or macerate the thrombus, have shown efficacy in restoring pulmonary circulation with or without the use of adjuvant thrombolytics; however, they possess a high complication rate with regard to distal embolization, hemolysis, and hemoglobinuria.[4] The EkoSonic system is a catheter-directed technique, which employs ultrasound to facilitate the delivery of thrombolytics into the thrombus. The ultrasound accelerates the thrombolytic process by disaggregating fibrin strands, thus increasing permeability of lytic drug into thrombus and driving the infused drug into the thrombus via the acoustic pressure waves. This mechanism does not cause hemolysis or mechanically fragment the thrombus.

CONCLUSION

Enrollment in the trial has exceeded expectations. More than half of the patients approved for the trial have been enrolled within 4 months. The investigators look forward to sharing the results of this potentially revolutionary treatment approach to this vulnerable PE patient population in the coming months. ■

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