CHEST

Treprostinil Administered to Treat Pulmonary Arterial Hypertension Using a Fully Implantable Programmable Intravascular Delivery System

Results of the DelIVery for PAH Trial

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BACKGROUND: The use of systemic prostanoids in severe pulmonary arterial hypertension (PAH) is often limited by patient/physician dissatisfaction with the delivery methods. Complications associated with external pump-delivered continuous therapy include IV catheter-related bloodstream infections and subcutaneous infusion site pain. We therefore investigated a fully implantable intravascular delivery system for treprostinil infusion.

METHODS: A multicenter, prospective, single-arm, clinical trial (DelIVery for Pulmonary Arterial Hypertension) was conducted by using an implantable intravascular delivery system. The implanted pumps were refilled percutaneously at least every 12 weeks. The primary end point was the rate of catheter-related complications using the new model 10642 catheter compared with a predefined objective performance criterion of 2.5 per 1,000 patient-days based on the literature.

RESULTS: Patients (n = 60) with severe PAH (World Health Organization group 1) receiving a stable dose of IV treprostinil for at least 4 weeks received an implant device and were followed up for 12.1 ± 4.4 months. Six catheter-related complications occurred, corresponding to a complication rate of 0.27 per 1,000 patient-days. The 97.5% upper one-sided confidence bound of 0.59 was less than the predefined criterion of 2.5 per 1,000 patient-days ($P < .0001$). Plasma treprostinil levels at 1 week postimplantation were highly correlated with baseline levels ($r = 0.91$; $P < .0001$). The delivery system management time as reported by the patients was 2.5 ± 1.7 hours per week preimplantation, and this time decreased to 0.6 ± 0.8 hour per week at 6 months' postimplantation ($P < .0001$). All patients rated overall satisfaction with the implantable system as good, very good, or excellent at 6 weeks and 6 months. There were no catheter-related bloodstream infections or catheter occlusions.

CONCLUSIONS: The implantable intravascular delivery system delivered treprostinil to patients with PAH with a low rate of catheter-related complications and a high rate of patient satisfaction.

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ABBREVIATIONS: 6MWD = 6-min walk distance; CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; EQ-5D = European Quality of Life-5 Dimensions; FACIT-TS-G = Functional Assessment of Chronic Illness Therapy Treatment Satisfaction general questionnaire; NYHA = New York Heart Association; OPC = objective performance criterion; PAH = pulmonary arterial hypertension; QoL = quality of life

The development of targeted therapies for pulmonary arterial hypertension (PAH) has led to improved symptoms and outcomes.[1,2] Parenterally administered prostanoids are indicated in advanced PAH; however, prostanoid therapy is underused due to reluctance from patients and physicians. In a report by Farber et al,[3] 61% of patients with PAH whose condition deteriorated to New York Heart Association (NYHA) functional class IV were not receiving parenteral prostanoid therapy 90 days after their deterioration, despite an indication for this therapy based on guideline recommendations. In addition, indwelling central venous catheters increase the risk of bloodstream infections, which can be fatal.[4] Subcutaneous administration is associated with significant infusion site pain, which may preclude continued administration.

Limitations with current prostanoid delivery systems prompted a clinical trial (DelIVery for Pulmonary Arterial Hypertension) to determine if a fully implantable, programmable delivery system could safely administer treprostinil (Remodulin, United Therapeutics Corporation) to patients with PAH. Treprostinil was chosen because it is stable at body temperature[5] and has a longer plasma half-life (~4 h[6]) than epoprostenol.

Patients and Methods

DelIVery for Pulmonary Arterial Hypertension was a multicenter, prospective, single-arm clinical trial using an investigational implantable drug delivery system conducted at 10 US centers. The implantable drug delivery system consisted of the model 10642 Implantable Intravascular Catheter,[5] the model 8637 SynchroMed II implantable drug delivery pump, and the model 8840 N'Vision programmer (Medtronic, Inc). A key design intent of the model 10642 catheter was to prevent occlusion while delivering treprostinil at low flow rates.

Patients

Patients included in this trial had stable PAH (Word Health Organization group 1)[7] and were receiving continuous IV infusion of treprostinil by using an external infusion pump. Eleven patients (18%) were prescribed subcutaneous treprostinil within 3 months of pump implantation and were switched to IV treprostinil 41 ± 12 days (range, 30 to 71 days) prior to implantation. All patients were in stable condition, defined as NYHA functional class I, II, or III with no change in treprostinil dose for at least 4 weeks and no additional PAH treatment for at least 2 months before enrollment. The exclusion criteria included: age < 18 years; NYHA functional class IV; a recent (within 3 months) infection; unresolved infection; increased susceptibility to infection; chronic renal disease; an implanted pacemaker, implantable cardioverter-defibrillator, or spinal cord stimulator; or an existing external catheter that would remain in place after implantation of the system. Patients were also excluded if their body habitus was unacceptable for an 80-cm catheter or abdominal subcutaneous pump implantation.

This study was conducted in accordance with the amended Declaration of Helsinki. The institutional review boards at each center approved the protocol, and written informed consent was obtained from all patients (e-Table 1).

Study End Points

The primary end point was the rate of catheter-related complications per 1,000 patient-days using the implantable system compared with an objective performance criterion (OPC) of 2.5 complications per 1,000 patient-days. A complication was an adverse event that required an invasive intervention (e-Table 2). In addition, because pneumothoraces are known complications due to venous access and/or central venous catheter placement,[8] these were conservatively included as part of the primary end point. The OPC was calculated based on published complication rates in populations with PAH that included central venous catheter systemic bloodstream infections (0.43-1.13 per 1,000 patients-days[9,10]), site infections (0.26-0.87 per 1,000 patient-days[11,12]), and complications from catheter thrombosis, mechanical dysfunction, or catheter dislocation in the general central venous catheter population (0.36-0.51 per 1,000 patient-days[8,13,14]). The sum of the upper rates for these three complications was used as the OPC (2.5 per 1,000 patient-days). An independent Adverse Events Advisory Committee reviewed all adverse events and deaths to determine their relatedness to the study procedures or system components. Adverse Event Advisory Committee structure and duties are shown in e-Tables 1 and 2.

The ancillary end points included changes from baseline in plasma treprostinil levels, 6-min walk distance (6MWD), NYHA functional class, quality of life (QoL), treatment satisfaction, and delivery-system management time. QoL was assessed by using the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), a PAH-specific questionnaire.[15] Generic health status was assessed with the European Quality of Life-5 Dimensions (EQ-5D) Summary Health Score.[16] Treatment satisfaction was assessed with the Functional Assessment of Chronic Illness Therapy Treatment Satisfaction general questionnaire (FACIT-TS-G).[17] Delivery system management time

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