Safety, Tolerability, and Efficacy of Rapid Inpatient Titration of Intravenous Treprostinil for Pulmonary Arterial Hypertension

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PURPOSE: To describe the protocol and the safety, tolerability, and efficacy of rapid inpatient titration of intravenous treprostinil.

BACKGROUND/SIGNIFICANCE: Treprostinil is a prostaglandin administered by IV or SQ infusion for PAH. In the home setting, SQ treprostinil is initiated following a slow titration protocol by increasing the dose by 1-2 ng/kg/min every 1-3 days. Achieving a higher dose of treprostinil in a shorter period of time has been shown to reduce site pain and improve exercise tolerance, suggesting rapid treprostinil titration is beneficial. In our center, we have over 10 years of experience with approximately 100 patients utilizing a rapid inpatient IV treprostinil titration protocol without serious adverse events.

METHOD: As a prospective analysis, patients were admitted to the ICU with Swan Ganz catheter for hemodynamic monitoring. IV treprostinil was initiated at 2ng/kg/min and increased by 2ng/kg/min every 4-6 hours. Titration was increased until dose limiting side effects occurred, with the goal of titrating to 10-15ng/kg/min before transition to SQ treprostinil. If dose limiting side effects occurred, the titration was held at the current dose or the dose was reduced to the previously tolerated dose. Data collected included hemodynamics, biomarkers, maximum dose achieved, time to target dose, dose-limiting side effects, and treatment of dose-limiting side effects.

FINDINGS: We included six consecutive patients from December 2012 to April 2013. Two had idiopathic PAH, one had CHD-associated PAH, one had CTD-associated PAH, and two had HIV-associated PAH. The mean maximum dose achieved was 12.8 ng/kg/min ± 1.4 ng/kg/min with dose-limiting side effects occurring at 7.9 ng/kg/min ± 2.7 ng/kg/min. Mean time to maximum dose was 30.8 hours ± 10.2 hours (range 17-44 hours). Dose-limiting side effects included headache (100%), nausea (83%), vomiting (17%) flushing (50%), jaw pain (17%), chest pain (17%), and diarrhea (17%). Two patients required down-titration for dose-limiting side effects with subsequent up-titration. Treatment for dose-limiting side effects included antiemetics (83% of patients, 2-13 doses), analgesics (83 % of patients, 2-9 doses), and narcotics (50% of patients, 1-8 doses). Improvements in BNP, SVi, and PVRi were observed. No adverse hemodynamic events occurred. Upon discharge, one patient required narcotics for leg pain that developed after achieving maximal dose. Upon discharge, one patient required narcotics for management of site pain. After discharge, all patients continued up-titration of SQ treprostinil over 3 months to 30 to 50ng/kg/min.

IMPLICATIONS: Rapid inpatient titration of IV treprostinil is a safe, tolerable, and effective alternative to slow outpatient SQ treprostinil titration for patients with PAH. In less than three days, patients were able to achieve doses of treprostinil higher than those achieved over 12 weeks in previous treprostinil studies. While dose-limiting side effects did occur, they rarely led to dose reduction and were effectively treated with antiemetics, analgesics, and minimal narcotics. A cohesive care team involving the physician, nurse coordinator, and specialty pharmacy nurse, as well family members provided consistent daily support to the patient during the titration. Upon discharge, patients had minimal site pain and improvements in hemodynamics and biomarkers were observed.

*Denotes off-label use of medication