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Transitioning from parenteral to inhaled prostacyclin therapy in pulmonary arterial hypertension

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ABSTRACT

Background: Parenteral prostacyclin therapy for PAH has allowed for improvements in functional status, quality of life and mortality. Parenteral therapies however carry an increased risk of line-associated complications. Inhaled prostacyclins are an attractive alternative therapy; however, limited data exists supporting the safety and outcomes after transition.

Methods: We describe a retrospective observational analysis of adults with PAH who were transitioned from a parenteral prostacyclin to inhaled treprostinil at our institution. Endpoints include duration of transition, hospital length of stay, adverse effects during transition, and cardiopulmonary function post transition.

Results: Eight patients were included, all of which were on triple therapy. Seven patients receiving intravenous prostacyclin therapy were transitioned in an ICU setting, while one patient was transitioned from subcutaneous treprostinil as an outpatient. The average ICU and hospital length of stay was 4.1 ± 0.7 days. Patient preference was the most common reason for transition (n = 5), followed by line complication (n = 2), and intolerance to parenteral therapy (n = 1). One adverse event was observed while initiating inhaled treprostinil that only required slowing of the transition process. On follow-up (19.6 ± 11.1 months) functional class did not change, and non-parametric test showed no change in 6MWD after transition (p = 0.62). One patient failed inhaled therapy necessitating transition back to intravenous therapy.

Conclusion: Transitioning patients from parenteral to inhaled prostacyclin therapy can be safely accomplished in specialized centers over a 48–72 h period. Patient preference was overwhelming the most prevalent reason for transition.

1. Introduction

Pulmonary arterial hypertension (PAH) consists of a group of diseases affecting the pulmonary arterioles contributing to a pathological increase in the pulmonary arterial pressures and pulmonary vascular resistance, in the setting of a normal pulmonary artery occlusion pressure [1]. These hemodynamic changes, in turn, increase the load on the right ventricle leading to elevated right ventricle pressure and right-sided heart failure [2]. The advent of intravenous prostanoid therapies in the mid 1990s for the treatment of World Health Organization (WHO) Group I PAH has changed the management of this debilitating disease, with patients experiencing significant improvements in their functional status, cardiopulmonary function, quality of life, and mortality [3,4].

Long-term parenteral therapy, although life-saving, is cumbersome for patients and carries an increased risk of complications associated with the mode of administration, including line associated thrombosis, infections, injection site pain, and inflammation [5–7]. Secondary to the short half-life of the parental prostacyclins, abrupt therapy disruption due to one of the aforementioned complications can precipitate acute pulmonary hypertension [8]. Inhaled treprostinil (Tyvaso®), which received Food and Drug Administration approval in 2002, is an attractive alternative for many patients as its administered four times daily approximately four hours apart via the Tyvaso Inhalational System® [9]. Dosing is initiated at three breaths four times daily titrated to a target dose of

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nine breaths four times daily. A single breath via the Tyvaso Inhalational System delivers 6 mcg of treprostinil®. That being said, limited data exist describing the safety of transition from parenteral to inhaled prostanoid therapy. A multicenter study conducted by de Jesus and colleagues observed a low risk of complications when transitioning eighteen patients from parenteral to inhaled therapy [10]. An additional single center study also reported no complications when transitioning three patients [11].

The aim of this study was to investigate and describe our center's experience with transitioning patients with Group I PAH from parenteral to inhaled prostanoid therapy. We report on the patients' functional and hemodynamic variables pre- and post-transition, and included our detailed protocol used to perform the transitions.

2. Methods

2.1. Patients

University of Florida institutional review board approved the study protocol (UF IRB number 201400983). A single center retrospective observational analysis was conducted in patients over the age of 18 years diagnosed with WHO Group I PAH that were transitioned from intravenous (IV) or subcutaneous prostanoid therapy to inhaled prostanoid therapy treprostinil (Tyvaso®; United Therapeutics Corp, Research Triangle Park, NC, USA) at the University of Florida Health Shands Hospital from August 2011 to August 2014. Patient demographics, WHO functional class, clinical data such as the 6 min walk distance (6MWD), and right heart catheterization (RHC) hemodynamic data were collected pre- and at least three months post-transition when available.

2.2. Study design and transition protocol

All transitions were initiated based on patient request. Prior to commencing transition, all patients were made aware of the limited evidence on performing such transitions and the possibility of returning to parenteral prostanoid therapy. All patients enrolled were in addition already receiving dual oral PAH therapies including an endothelian receptor antagonist (ERA) and a phosphodiesterase-5-inhibitor (PDE5i) at the time of transition. The parenteral prostacyclin dose was titrated down in outpatient setting to a goal dose of 20–25 ng/kg/min, or the minimum dose tolerated without experiencing any decline in symptoms or functional class, prior to transition.

All transitions from IV to inhaled therapy were performed in an ICU setting under the care of a multidisciplinary team experienced in the management of patients with PAH. Patients on subcutaneous prostanoids were transitioned in an outpatient setting.

The patients admitted to the ICU for transition, nebulized treprostinil was initiated at a dose of 3 puffs four times a day. The dose of inhaled treprostinil was increased daily to a goal dose of 9 puffs four times a day. During this period the parenteral prostanoid was decreased simultaneously every 6 h (Fig. 1). If side effects were encountered during the transition, the dose of parenteral therapy was increased to the previously tolerated dose and the transition was delayed for 6 h before resuming the titration.

2.3. Statistical methods

Data are presented as a mean ± standard deviation; categorical variables are expressed as a percentage of all patients in the data set. Comparisons of primary and secondary endpoints, before and after transition, were performed using unpaired t-tests for normally distributed data. A p-value < 0.05 was considered statistically significant.

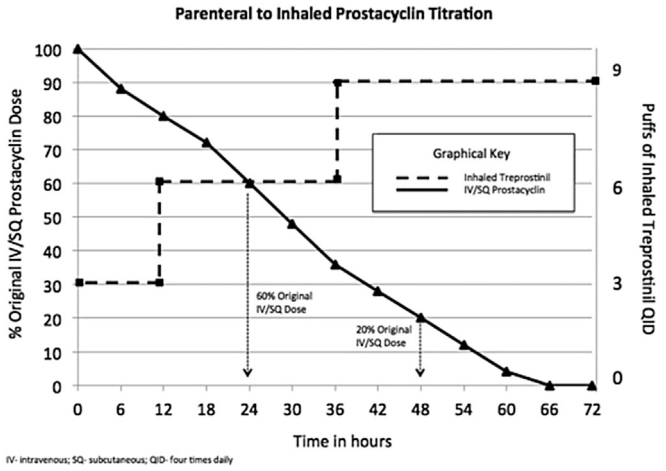

Fig. 1. Graph showing the change in parenteral prostacyclin dose as the patient is transitioned to inhaled treprostinil.

3. Results

A total of 8 patients were transitioned from parenteral prostanoids to inhaled treprostinil, detailed patient demographics and data are presented in Table 1. Prior to initiating the transition, 87.5% (n = 7) of patients were functional class 1 and 2, and 12.5% (n = 1) was functional class 3. Seven patients were on IV epoprostenol while one patient was receiving subcutaneous treprostinil. The average duration of parenteral prostanoid therapy prior to transition was 21.1 ± 12.2 months. Patients with Group I PAH included the following etiologies: idiopathic (n = 5, 62.5%), scleroderma-related (n = 1, 12.5%), secondary to drug abuse (n = 1, 12.5%), or associated with congenital heart disease (n = 1, 12.5%). The most common reason for transition was patient preference related to quality of life (n = 5, 62.5%), followed by line complications (n = 2, 25%), and intolerance to parenteral therapy (n = 1, 12.5%).

RHC hemodynamic parameters, functional class, and 6MWD were analyzed for all patients prior to and after transition when available (Table 2). RHC data was available in 4 patients at least three months after transition. The mean parenteral prostacyclin dose prior to initiating the transition was 22.6 ± 7.7 ng/kg/min. The average ICU and hospital length of stay was 4.1 ± 0.7 days for those transitioned as an inpatient. Only one adverse side effect was observed in one patient during the transition (n = 1, 12.5%), a coughing episode, which required the slowing down of the transition by 6 h.

The average follow up was 19.6 ± 11.1 months, with no difference in the functional class status or the 6MWD when compared to the pre-transition period (406.3 ± 100.8 m versus 418.5 ± 120.9 m, p = 0.62). Follow-up RHC hemodynamics after transition were available for four patients at least three months after the transition period. Only one patient failed inhaled therapy necessitating transition back to intravenous epoprostenol.

4. Discussion

Limited data exists supporting the transition of patients from parenteral epoprostenol therapy to parenteral treprostinil [12–15], inhaled iloprost [16,17], and inhaled treprostinil [10,11]. Currently, there is an ongoing prospective trial evaluating the transition of patients from parenteral to inhaled prostacyclins (NCT01268553).

The non-invasive and convenient method of administering