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Tolerability and clinical efficacy of inhaled treprostinil in patients with group 1 pulmonary arterial hypertension

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Abstract

Background: Treprostinil is a prostacyclin analogue that directly vasodilates pulmonary and systemic arterial vascular beds. The United States Food and Drug Administration approved inhaled treprostinil in July 2009 for the treatment of group 1 pulmonary arterial hypertension. Inhaled treprostinil avoids issues with continuous infusion prostanoids. This study describes a single institutional experience with inhaled treprostinil.

Methods: This was a retrospective review of group 1 pulmonary arterial hypertension patients receiving inhaled treprostinil from July 2009 through September 2015. Patient demographics, vital signs, prognostic indicators, pulmonary arterial hypertension assessments, treprostinil dosing, pulmonary arterial hypertension medications, and physician assessment were collected. Prognostic indicators and the physician assessment were used to assess treatment response. A modified Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) risk score was calculated prior to and after initiation of inhaled treprostinil.

Results: The mean time on inhaled treprostinil for the 16 patients was 21 ± 17 months. A total of 31% discontinued treatment. The New York Heart Association Functional Class, right ventricular size, and right ventricular function improved after inhaled treprostinil. Directional improvement in B-type natriuretic peptide, 6-minute walk distance, right arterial pressure and mean pulmonary artery pressure were also observed. The mean modified REVEAL risk score (RRS) was 7 ± 3 at baseline. The RRS decreased in 7 of the 11 patients that improved and remained stable in 2 patients.

Conclusion: The majority of patients in this consecutive series receiving inhaled treprostinil tolerated treatment. Most patients remained on therapy for over 12 months. Clinical assessments of disease severity all changed directionally toward improvement and the overall risk assessment was improved or stable in 56% by the RRS.

Keywords: treprostinil, pulmonary arterial hypertension

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Introduction

Treprostinil is a prostacyclin analogue that directly vasodilates the pulmonary and systemic arterial vascular beds and inhibits platelet aggregation. In patients with coexisting pulmonary disease, evidence indicates that inhaled treprostinil potentially reduces the risk of systemic vasodilation and ventilation-perfusion mismatch.[1,2] The duration of the reduction in pulmonary vascular resistance has been shown to be dose dependent.[3] Treprostinil is available in injectable, inhaled, and oral formulations. The injectable formulation requires administration as a continuous intravenous (IV) or subcutaneous (SC) infusion. Several undesirable issues can occur with use of the injectable formulation due to its short half-life. Additionally, there is the potential for blood stream infections.[4]

Inhaled treprostinil was approved by the United States Food and Drug Administration (US FDA)

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in July 2009 for the treatment of pulmonary arterial hypertension (PAH). Inhaled treprostinil avoids the administration issues associated with IV or SC infusion.[4,5] The inhaled formulation is available as a 0.6 mg/ml solution. The initial dose is three breaths (18 μg) administered in four separate treatment sessions each day approximately 4 hours apart, during waking hours. The dose is then increased by an additional three breaths at approximately 1–2-week intervals as tolerated to a target maintenance dosage of nine breaths or 54 μg per treatment session, as tolerated.[6]

Several monotherapy and combination studies have shown that inhaled treprostinil improves symptoms along with the 6-minute walk distance (6MWD).[7–11] Improvement in exercise capacity (i.e. the 6MWD) has been the primary endpoint employed in efficacy studies for most of the currently approved PAH therapies. Additional or secondary endpoints have often included New York Heart Association (NYHA) functional class (FC), hemodynamics, and clinical worsening in support of US FDA approval as therapy for PAH.[12–14]

The TRIUMPH trial involving 235 PAH patients, provided evidence for the approval of inhaled treprostinil in NYHA FC III PAH patients. In this trial, patients on bosentan and sildenafil were randomized to placebo or inhaled treprostinil titrated up to 54 μg four times daily. The patients in the inhaled treprostinil group demonstrated improvement in the primary endpoint of the 6MWD with an increase of 20 meters at 12 weeks. Quality of life (QOL) measures and N-terminal pro b-type natriuretic peptide (NT-proBNP) improved in the active therapy arm; however, there were no improvements in other secondary endpoints (PAH signs/symptoms, NYHA FC, Borg Dyspnea Score, and time to clinical worsening). The authors determined that exercise capacity and QOL improved when inhaled treprostinil was added to the regimen for patients who remain symptomatic on bosentan or sildenafil. Overall, the treatment was well tolerated with the most common side effects including cough, headache, nausea, dizziness, flushing throat irritation, pharyngolaryngeal pain, and diarrhea.[10]

To assess long-term benefits of inhaled treprostinil an extension trial of the TRIUMPH-1 study was completed. The open-label extension trial of the TRIUMPH-1 study included 206 patients and demonstrated that PAH patients received continued benefit from inhaled treprostinil for up to 24 months.[7] Objective results included improved 6MWD and survival rates, as well as lack of clinical worsening. The most common adverse events in the extension trial were no different than those commonly encountered with prostanoid therapy (headache, nausea, vomiting) or were as a result of the administration route (cough, pharyngolaryngeal pain, chest pain).

The Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) is the largest and most comprehensive registry of patients with PAH.[15] A prognostic equation and risk score calculator were developed from the REVEAL data to predict 1-year survival in PAH patients.[16,17] The REVEAL risk score (RRS) calculator was developed from 2716 World Health Organization (WHO) group 1 PAH patients enrolled in the REVEAL registry.[16] An algorithm used for predicting survival was created based on the identification of predictors of short- and long-term survival.[16] The REVEAL PAH risk score assigns points based on criteria: WHO diagnostic group 1 classification, demographics and comorbidities, NYHA FC, vital signs, 6MWD, B-type natriuretic peptide (BNP), echocardiogram (ECHO), pulmonary function test, and right heart catheterization (RHC). Points are added to or subtracted from a starting score of 6 based on the patient's values (see Methods).

The RRS score calculator was validated in a cohort of 504 newly diagnosed PAH patients and the authors noted that the REVEAL prognostic equation and risk calculator could be used to aid in determining when to initiate therapies and adjust therapies based on the patient's risk level .[17]

A number of studies have validated the REVEAL risk model in PAH patients.[18,19] In particular a study by Benza and colleagues determined that changes in the RRS of PAH patients occur over a 12-month period for most patients and can predict survival.[20] Therefore, RRS can be calculated periodically in PAH patients to determine if there are any changes in the disease progression and if modifications to the treatment regimen are needed. Nonetheless, there are currently no data on the use of RRS in assessing patients on inhaled treprostinil. The purpose of this study was to describe the use of inhaled treprostinil and patient outcomes with routine clinical use at a pulmonary hypertension (PH) center. The objective of this

study was to determine characteristics of patients that improved, failed, and did not tolerate treatment with inhaled treprostinil.

Methods

After Mayo Clinic Institutional Review Board (IRB) approval (study ID 15-007270) and informed consent was waived by IRB, a retrospective review of the electronic medical record and PH Clinic database was performed. Consecutive patients with group 1 PAH receiving inhaled treprostinil from July 2009 through September 2015 were identified. Data collected included patient demographics, vital signs, and prognostic indicators such as NHYA FC, BNP, 6MWD, and ECHO PAH assessment. The degree of right ventricular size and function were defined based on the American Society of Echocardiography guidelines. Inhaled treprostinil dosing, concomitant PAH medications, and a subjective physician assessment of patient's clinical status (stable, improved, or worse) at the time of the outpatient visit were also collected. Prognostic indicators and the physician's assessment were used to assess treatment response while on inhaled treprostinil. The modified RRS was calculated prior to and after initiation of inhaled treprostinil. All patients did not have routine follow-up lung function or RHC may not have been performed. The RRS scoring system is provided below.

1. WHO diagnostic group: + 1 point if PAH is in a setting of connective tissue disease or +2 points if there is portal hypertension or familial;
2. Demographics: +1 for renal insufficiency and +2 points if male and >60 years of age;
3. NYHA FC: −2 points if FC I, +1 if FC III, and +2 if FC IV;
4. Vital signs: +1 if systolic blood pressure < 110 mmHg and +1 if heart rate > 92 beats/min;
5. 6MWD: −1 if distance ⩾ 440m and +1 if distance < 165 m;
6. BNP: −2 if BNP < 50 pg/ml and +1 if BNP > 180 pg/ml;
7. Pericardial effusion: +1 if present;
8. % predicted diffusing capacity of lung for carbon monoxide (Dlco): −1 if Dlco ⩾ 80% and +1 if Dlco ⩽ 32%;
9. RHC: +1 if mean right arterial pressure (mRAP) > 20 mmHg and +2 if pulmonary vascular resistance (PVR) > 32 Wood units.

The sum of the total points added to 6 will determine the risk score. Calculated risk scores range from 0 (lowest risk) to 22 (highest risk).[16]

A score of 7 or lower is considered low risk. Of note, RHC was used to confirm the diagnosis of group 1 PAH; however, the baseline and follow-up pulmonary artery pressures were by ECHO not RHC (unavailable at follow up). Descriptive statistics were used to describe the data.

Results

A total of 16 consecutive patients with group 1 PAH treated with inhaled treprostinil were included in the study. Their baseline characteristics are described in Table 1. The majority of the patients were approximately 60 years old, and over two-thirds were female. Overall, 15 of the 16 patients were group 1.1 idiopathic PAH and 1 patient was group 1.4.1 PAH associated with connective tissue disease. The mean time from PAH diagnosis to inhaled treprostinil initiation was 41 ± 40 months. The mean time on inhaled treprostinil was 21 months. Baseline NYHA FC was primarily FC III. The mean BNP, 6MWD, RAP, and mean pulmonary artery pressure (MPAP) are listed in Table 1. Baseline right ventricular (RV) size was moderately or severely enlarged in the majority of patients. Baseline RV function was moderately or severely depressed in the majority of patients.

Prior to starting inhaled treprostinil, 13 patients (81%) were maintained on other PAH medications. Overall, two patients were on a three-drug regimen consisting of a prostacyclin analogue, bosentan, and sildenafil. There were six patients on two-drug regimens; the majority of the two-drug regimens consisted of an endothelin receptor antagonist (ERA) with a phosphodiesterase type 5 (PDE5) inhibitor. The two patients on inhaled treprostinil did not have additional PAH medications on their regimens. The baseline PAH therapy prior to inhaled treprostinil can be divided into the following categories: 8 patients (50%) on an ERA, 10 patients on a PDE5 inhibitor (62.5%), 2 patients (12.5%) on a calcium channel blocker (CCB), and 2 patients (12.5%) on an IV or SC prostacyclin analogue.

While on maintenance inhaled treprostinil, the majority of patients remained on concomitant PAH medications. Overall, one patient was receiving three PAH medications concomitantly

Table 1. Characteristics at baseline and after inhaled treprostinil.

Variable	Baseline	After inhaled treprostinil
Age (years)	58 ± 15	
Female	81% (13)	
NYHA functional class (number of patients)	I–0	I–1
	II–2	II–7
	III–13	III–7
	IV–1	IV–1
6MWD (meters)	322 ± 95	341 ± 127
Brain natriuretic peptide (picogram per milliliter)	326 ± 446	241 ± 304
Right arterial pressure (mmHg)	10 ± 6	8 ± 5
Mean pulmonary artery pressure (mmHg)	52 ± 15	47 ± 19
Right ventricular size (number of patients)	Normal-2	Normal-5
	Mild-1	Mild-2
	Moderate-7	Moderate-3
	Severe-6	Severe-6
Right ventricular function (number of patients)	Normal-3	Normal-6
	Mild-1	Mild-4
	Moderate-7	Moderate-4
	Severe-5	Severe-2

6MWD, 6-minute walk distance; NYHA, New York Heart Association

with the inhaled treprostinil and six patients were receiving two PAH medications in addition to inhaled treprostinil. The breakdown of additional PAH medication while on inhaled treprostinil was: 9 patients on an ERA, 10 patients on PDE5 inhibitor, and 3 patients on a CCB.

A total of seven patients were titrated to doses greater than nine breaths, four times daily.

The NYHA FC shifted toward improvement with 88% FC III–IV at baseline compared with 50% at follow up (Table 1). Similar improvements were demonstrated with RV size (81% with moderate/severe enlargement *versus* 56% at follow up) and function (75% with moderate/severe systolic dysfunction *versus* 38% at follow up). Directional improvement in the absolute values was observed for BNP, 6MWD, RAP and MPAP. As a group, the modified RRS were 7 ± 3 both at baseline and at follow up. Examined for each individual patient, the RRS decreased in 7 of the 11 patients that improved and remained stable in the other 2 patients (RRS 5 and 6, respectively). Follow-up RRS were available in four of the five patients considered as nonresponders and worsened in three of four. Discontinuation of treatment occurred for the following reasons: adverse effects, two patients (12.5%) and patient preference, two patients (12.5%). Overall, one patient discontinued against medical advice and did not return for follow up.

Discussion

A number of new PAH therapies have been approved in the past 5 years. Nonetheless, the

prostacyclin analogues remain a major player in the therapy for PAH. The most recent European PH guidelines provide a Ib recommendation for WHO FC III and IIbC for WHO FC IV when used as monotherapy in PAH. For sequential combination therapy, inhaled treprostinil is recommended to be added to sildenafil or bosentan (IIaB recommendation for WHO FC II and III; IIaC recommendation for WHO FC IV).[21]

Overall, prostacyclin usage remains stable at approximately 20%, however the use of IV or SC infusions has been decreasing while the use of inhaled prostacyclin has increased.[22]

The majority of the group 1 PAH patients in our consecutive series, single-center experience tolerated inhaled treprostinil, and remained on therapy for over 12 months. All clinical assessments changed directionally toward improvement and the overall risk assessment was improved or stable in 9 of 16 (56%) by the RRS.

In our study, adverse effects resulted in discontinuation of therapy in two patients (12.5%). Adverse effects experienced by our patients included cough, headache, and general miserable feeling. In a study by Zamanian and colleagues that enrolled 1333 WHO group 1 PAH patients, 666 PAH patients treated with inhaled treprostinil and 667 controls were treated with US FDA-approved PAH therapy other than inhaled treprostinil. A total of 61% of patients (n = 403) in the inhaled treprostinil group reported respiratory-related adverse effects.[23] The most commonly occurring were cough, throat irritation, nasal discomfort, and hemoptysis. Overall 18% of patients reported experiencing a cough in the Zamanian study, 54% in TRIUMPH, and 33% in the TRIUMPH open-label extension.[7,10,23] Fewer than 1% of patients in the TRIUMPH and Zamanian studies discontinued treatment due to respiratory-related adverse effects.[7,10,23]

Overall, seven patients in our study were titrated to 12–15 breaths, four times daily. Dosing outside of the US FDA-approved maximum range has been described in the literature. Dosing of inhaled treprostinil up to 12 breaths (72 μg) four times daily and has been shown to be well tolerated.[7,24,25] In the study by Parikh and colleagues[25] that evaluated high-dose inhaled treprostinil, common side effects occurring with drug initiation were cough, headache, and throat irritation; however, side effects improved at follow up. Approximately 25% of patients in the Parikh study discontinued inhaled treprostinil.[25] There is limited information on dosing above 12 breaths four times daily. Overall, four of our patients were titrated to 15 breaths four times daily. There were two patients that were transitioned off the inhaled to SC. There was one patient that required a dose decrease to 12 breaths four times per day and was eventually transitioned to SC. Overall, one patient remained on 15 breaths four times per day for 32 months until she died.

The RRS has not been evaluated for use as a treatment-response monitoring tool.[17] In our study we were able to calculate a modified RRS and utilize it to assess whether the patient's predicted survival changed after addition of inhaled treprostinil. In our study, we calculated a modified RRS prior to and after initiation of inhaled treprostinil to evaluate whether the addition of inhaled treprostinil improved predicted 1-year survival.

Prospective studies provide useful information for strict patient groups; however, our study is able to provide real-world experience on the use of inhaled treprostinil in the setting of routine clinical care. Through this study we are able to describe inhaled treprostinil use in the clinical environment. All patients receiving inhaled treprostinil during the study time frame were included, therefore confounding variables were not limited. Limitations of this study include the retrospective design and limited number of patients. The patients included in this study had limited exposure to the newer PAH medications (macitentan, riociguat, and oral treprostinil) which were approved in 2013. Additionally, the study predates the US FDA approval of selexipag.

Conclusion

Our study characterizes the outcomes of inhaled treprostinil in group 1 PAH patients from our single-center experience. To our knowledge, this is the first study to report an institution's experience with inhaled treprostinil in routine clinical care and discuss the use of RRS to assess the improvement in PAH patients receiving inhaled treprostinil.

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Conflict of interest statement
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