Respiratory Medicine 196 (2022) 106806

Contents lists available at ScienceDirect

Respiratory Medicine

journal homepage: www.elsevier.com/locate/rmed

# Practical considerations in the management of inhaled prostacyclin therapy for pulmonary hypertension associated with interstitial lung disease (WHO group 3)

Charlie Lee [a,*], Joan Hamlyn [b], Julie Porcelli [c], Ann Schmit [d]

[a] Brigham and Women's Hospital, USA
[b] University of Louisville, USA
[c] New York Presbyterian Hospital, USA
[d] Ascension St. Vincent Medical Group, Indianapolis, USA

ARTICLE INFO

*Keywords:*
Pulmonary hypertension
Interstitial lung disease
Inhaled treprostinil
Administration
Titration
Tolerability
Adverse event management

ABSTRACT

Pulmonary hypertension (PH), as a consequence of lung disease or hypoxia, has been classified as Group 3 PH by the World Symposium on Pulmonary Hypertension. The most common lung diseases associated with Group 3 PH are chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). PH in ILD (PH-ILD) is associated with reduced exercise capacity, greater supplemental oxygen needs, decreased quality of life, and earlier death compared to ILD alone. Several agents have been evaluated in clinical trials for the treatment of Group 3 PH, but only one treatment has been recently approved by the FDA as conclusively demonstrating efficacy for the treatment of pulmonary hypertension in this group. In the INCREASE study, treprostinil inhalation solution (Tyvaso) demonstrated significant clinical benefit for patients with PH-ILD. The inhaled route of administration may be associated with cough, throat irritation, pharyngolaryngeal pain and risk of bronchospasm and are important considerations upon initiation of therapy. Here we provide a practical review of inhaled prostacyclin therapy and suggestions for healthcare professionals to optimize the management and outcomes for the treatment of WHO Group 3, PH-ILD patients. Recommendations include up-to-date practical considerations pertaining to the entire care team and encompass patient education and communication, monitoring, titration methods and mitigation of side effects.

## 1. Introduction

Pulmonary hypertension (PH) is defined as an elevation in mean pulmonary arterial pressure (mPAP) of >20 mmHg, accompanied by a pulmonary vascular resistance (PVR) of ≥3 Wood Units [1]. The World Symposium on Pulmonary Hypertension has categorized PH into five groups, based on characteristic pathophysiology, etiologies, clinical presentation, hemodynamic characteristics, and therapeutic management. Group 1 describes pulmonary arterial hypertension (PAH) and includes diverse diseases that all result in similar pathological changes within the pulmonary vasculature. Group 1 PAH is noted as being particularly aggressive in nature, with poor survival [2]. PH, as a consequence of lung disease or hypoxia, has been classified as Group 3. The most common lung diseases associated with Group 3 PH are chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD), the latter characterized by inflammation, marked scarring or fibrosis in the lungs, resulting in arterial thickening and PH. PH in ILD (PH-ILD) is associated with reduced exercise capacity, greater supplemental oxygen needs, decreased quality of life, and earlier death compared to ILD alone [3,4].

Until very recently, there have been no approved therapies for the treatment of Group 3 PH patients. Although several agents had been previously evaluated in clinical trials for the treatment of Group 3 PH patients, none had conclusively demonstrated efficacy for the treatment of pulmonary hypertension in this group [5–12].

In April 2021, the United States Food and Drug Administration (FDA) approved treprostinil inhalation solution (Tyvaso, United Therapeutics Inc.) to improve exercise ability for patients who have PH associated with ILD (PH-ILD) based on results of the INCREASE study, which demonstrated significant clinical benefit to this patient group.

* Corresponding author. Brigham & Women's Hospital, Cardiology Division, 75 Francis Street, Boston, MA, 02115, USA.
*E-mail address:* clee39@bwh.harvard.edu (C. Lee).

https://doi.org/10.1016/j.rmed.2022.106806
Received 4 November 2021; Received in revised form 12 February 2022; Accepted 6 March 2022
Available online 12 March 2022

Treprostinil is a chemically stable tricyclic analogue of prostacyclin, which promotes direct vasodilation of pulmonary and systemic arterial vascular beds and inhibits platelet aggregation [13]. Inhaled treprostinil was originally approved in 2009 for the treatment of WHO Group 1 PAH. Based on nearly a decade of experience in PAH patients, the pivotal INCREASE study was designed to evaluate inhaled treprostinil in 326 adult patients with Group 3 PH-ILD [14]. Inhaled treprostinil was well tolerated and patients experienced significant improvements in exercise capacity as early as 8 weeks, with a placebo-corrected improvement from baseline in peak 6MWD of 31 m at 16 weeks. Additionally, patients treated with inhaled treprostinil demonstrated improvements in other clinically meaningful outcomes, including significant reductions in NT-proBNP, clinical worsening events, and lung disease exacerbations compared to placebo. Exploratory analyses also demonstrated inhaled treprostinil resulted in improvement in percent predicted FVC at week 8 (1.79%; $P = 0.01$) and week 16 (1.80%; $P = 0.03$) [14].

As observed in the INCREASE study, there are potential side effects associated with the inhaled route of administration, including cough, throat irritation, and pharyngolaryngeal pain [14]. Often, healthcare professionals are tasked with supporting patients through the side effects and practical challenges related to inhaled treprostinil therapy and its administration. In 2011, Poms and Kingman published an insightful review on the use of inhaled treprostinil in Group 1 PAH patients including recommendations for practical management of side effects in these patients [15]. A few years later, Farber and colleagues shared their experience and practical suggestions for supporting patients and healthcare professionals in addressing the complexities of PAH treatment with prostacyclin therapies to encourage compliance and optimize outcomes [16]. The previous work related to PAH treatment provided a valuable foundation for the current understanding of inhaled treprostinil treatment in PH-ILD. In light of recent advancements in inhaled treprostinil therapy, an update to the practical guidance for implementation of inhaled therapy into clinical practice is timely and essential to optimize effectiveness.

Four healthcare professionals were approached to aid in the development of clinical pearls and practical guidance to optimize therapy with inhaled treprostinil. These clinicians represented varying healthcare disciplines from different geographies and were selected based on their experience using inhaled treprostinil in patients with PAH and PH-ILD and patient enrollment into the INCREASE trial. After selecting these clinicians and confirming their interest, two virtual interview sessions were conducted to reflect on published literature and share best practices and real-life experience with inhaled treprostinil. A question/answer session was included as part of each virtual meeting. Clinicians discussed their first-hand experience with the methods applied and management experience of PAH and PH-ILD patients in pulmonary hypertension care centers and major PH programs in their respective areas. Based on the discussions during the interview sessions, a summary of recommendations was drafted and circulated to the clinicians for review.

Based on the published literature and the authors' expertise and experience with inhaled treprostinil delivery, we provide important considerations for the management of inhaled prostacyclin therapy in PH-ILD in WHO Group 3 patients. Recommendations include up-to-date practical considerations affecting the entire care team and encompass patient education and communication, monitoring, titration methods and mitigation of side effects.

### 1.1. Setting up for success - onboarding

Some of the most important factors in successful inhaled treprostinil administration occur prior to the patient's first dose. Studies have demonstrated that patient instruction plays a central role in disease management and that effective education can have a significant impact on disease control [17]. Patient education about the device, dosing, safety, and efficacy of treatment and setting expectations related to side-effects and outcomes are critical to success. Equally important is ensuring patients are familiar with other potential members of their care team, including their specialty pharmacy.

PH-ILD patients presented with the potential benefits of inhaled treprostinil as a new treatment option may be apprehensive about starting any treatment that is new to them, or that has been recently approved. It can be helpful to advise patients that although inhaled treprostinil has been recently approved for PH-ILD, the medication has successfully been administered via nebulization to treat other patients for over a decade. Reinforcing that the treatment is not new, but that studies have now shown that it can be beneficial for this patient population can help to instill confidence in the PH-ILD patient. This, combined with the support of the care team in being able to offer a new treatment option, may alleviate patient apprehension.

When starting therapy with inhaled treprostinil, it is important to emphasize the potential benefits and side effects of treatment, while underscoring the commitment required on behalf of the patient. Commitment to treatment and perseverance during titration will enable patients to reach a target dose that can improve their symptoms and functional status. Learning the appropriate breathing technique, the frequency of treatment, and the daily preparation of medication and assembly and cleaning of the device may seem daunting at first, but as the patient's comfort level with the device improves, so does their confidence to continue. Patients can expect the best opportunity for clinical improvement with this treatment if they are able to commit to the process and dosing regimen.

### 1.2. Practical considerations of administration

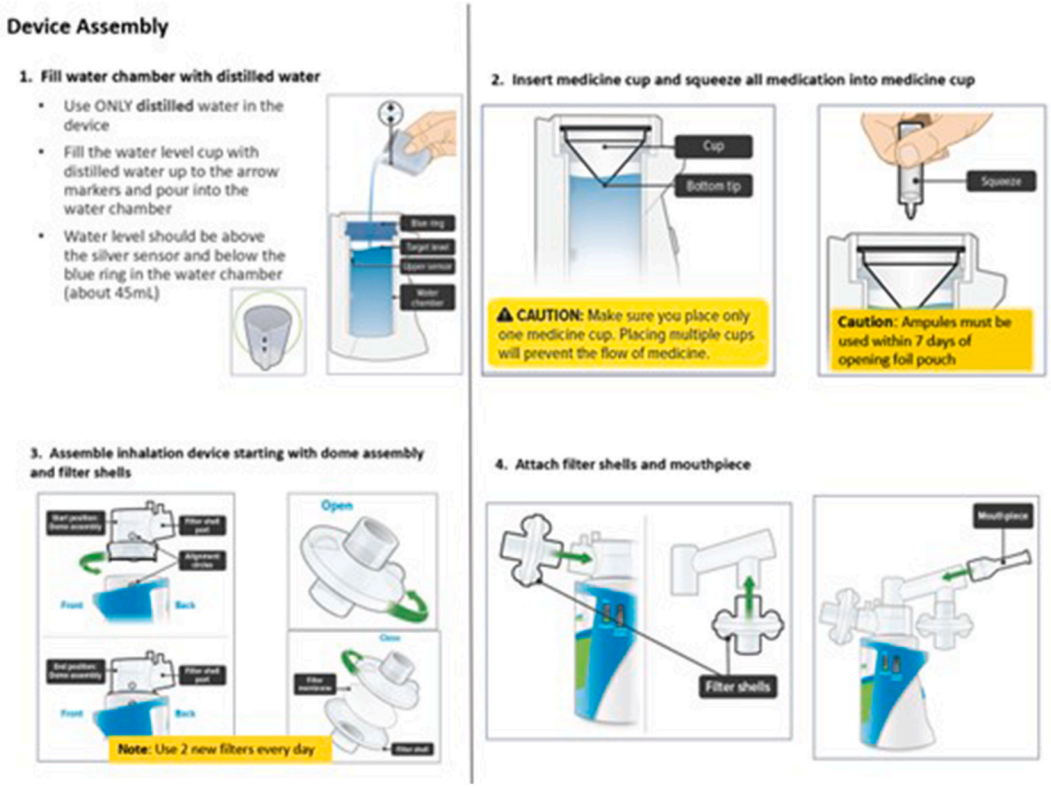
Inhaled treprostinil solution is dosed using the Tyvaso Inhalation System, which consists of an ultrasonic, pulsed delivery device and accessories (Fig. 1). An important foundation for success is teaching the correct use of the device and mastering the technique of taking proper breaths. The patient may not understand that the device will be different than an inhaler or nebulizer that they have used in the past and be surprised by the differences in breathing technique. Patients are advised to take in a normal, full breath lasting approximately 3 s, and then exhale with their mouth removed from the mouthpiece. It is important to remind patients that treatment only takes a few minutes, not up to 20 min that is typical of other nebulizer therapies [18] and that once the device is set-up in the morning it can be used for every treatment session that day (see Fig. 2).

Treprostinil dosing is measured in breaths and one breath is equivalent to approximately 6 mcg of treprostinil. Inhaled treprostinil solution should be administered four times daily, with treatment sessions scheduled approximately 4 h apart, during waking hours. The standard titration schedule begins with an initial dose of 3 breaths (18 mcg) per treatment session and may be increased gradually, by an additional 3 breaths per session at approximately 1–2 week intervals based on tolerability of side effects [19]. If side effects occur, the titration schedule can be adjusted as needed to 1–3 breaths per session every 3–14 days. In the INCREASE study, patients up-titrated on average by 1 breath per session, as often as every 3 days, until they reached a target dose of 9 breaths with most patients achieving it by week 8 [14]. Although the target dose was 9 breaths, many patients achieved the maximum dose of 12 breaths by week 16. Target doses are consistent with the INCREASE study, typically 9 to 12 breaths per treatment session, four times daily. The device allows for titration increments of one breath. Target dosing and up-titration are individualized, however, based on the patient's ability to tolerate the associated side-effects and assessed clinical benefit.

### 1.3. Communication and the care team

Delivery of inhaled treprostinil to PH-ILD patients requires open lines of communication among the entire care team, including patients,

A




B

**Fig. 1.** Inhaled treprostinil device (A) and assembly and medication preparation (B).

caregivers, clinical coordinators and specialty pharmacy that dispenses medications and provides virtual and in person nursing support (Fig. 3, Table 1). There is considerable evidence that suggests that patient engagement improves outcomes. Specific to pulmonary disease, patients who feel well-informed and receive comprehensive guidance, find it easier to cope with their disease and have demonstrated better outcomes [20,21]. If patients develop side-effects, it is essential that they know who to contact to help guide them through dose adjustments or help manage adverse events. The presence of a family member or caregiver during clinical discussions and education sessions is an additional resource that may aid in retention of information about the disease and treatment plan [22].

It is important that patients feel supported during the entire treatment journey and have a network of resources to address their questions or concerns. These may include online connections, in-person support groups, patient volunteers or other patients with treatment experience, often organized by patient advocacy groups or medical associations.

Maintaining good communication between all members of the care team is integral in providing consistent and optimized care to the patient. Often at the initiation of therapy all members of the care team are very involved with the patient and each other, however as the patient becomes more stable, interactions may become less frequent. The patient may have communication regarding therapy with one member of the care team, such as the specialty pharmacist, however this communication may not be relayed to the entire team, leaving some unaware of a patient's challenges or changes in therapy. Establishing a communication plan between all members of the care team, particularly between the specialty pharmacy and clinical team, is fundamental to delivering

**Fig. 2.** Clinical pearls for proper breathing technique for inhaled treprostinil solution.
Take a normal, full breath for 3 s. Do not hold breath once medication is inhaled. Use start/stop button to pause as needed for coughing or treatment interruptions. Keep the Tyvaso device level during treatment to direct the flow of medication into the airway.

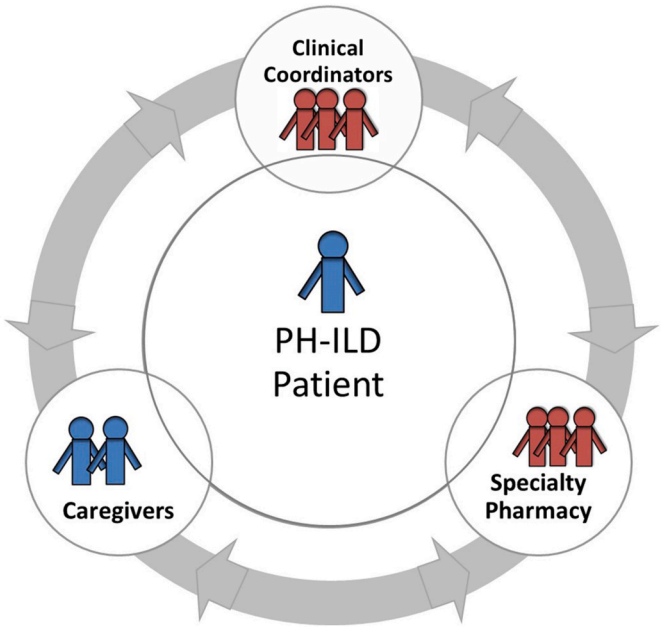



**Fig. 3.** Team members involved in the care of the PH-ILD patient.

the best possible consistent level of care. Utilization of specialty pharmacy resources such as appointed pharmacy liaisons, weekly patient reports and provider portals may help to ensure that all team members have access to all patient-related communication. The specialty pharmacy generated patient roster may include trackable updates related to medications, dose changes, preauthorization status, and patient-reported issues.

Based on the studies that established the effectiveness of inhaled treprostinil in patients with PAH and PH-ILD, the dosing target is 9–12 breaths per treatment session, 4 times daily [19]. The effectiveness of inhaled treprostinil is a function of up-titration and the ability to achieve the maximum tolerated, clinically appropriate dose for each individual

**Table 1**
Roles of the care team.

| Care Team Member | Care Team Role |
|---|---|
| Clinic Staff (physicians, advanced practitioners, nurses, medical assistants, clinic pharmacists, etc.) | ● Responsible for prescription, referral, and prior authorization submission for inhaled treprostinil<br>● Educate on disease and medications<br>● Provide tools to assist with management of medication side effects<br>● Manage mediation titration to reach optimal stable dose<br>● Serve as point of contact between patient and specialty pharmacy |
| Specialty Pharmacy (specialty pharmacy nurses, pharmacists, and pharmacy technicians/liaisons) | ● Process initial referral and contact insurance company to determine and verify coverage<br>● Provide initial drug/device training and ongoing support<br>● Serve as liaison between clinical staff and patient<br>● In collaboration with clinical team, assist with side effect management and medication titration<br>● Arrange for follow-up and ongoing shipment of supplies |
| The Patient/Caregiver | ● Caregiver provides patient support<br>● Participate in device training, set-up, and management<br>● Communicate treatment issues to clinical staff and specialty pharmacy team<br>● Notify clinical staff and specialty pharmacy of insurance changes or financial needs |

Treatment Regimen and Titration.

patient. Results from the INCREASE study demonstrated that achieving higher doses was associated with improved clinical effect, specifically improvements in 6MWD and clinical worsening [14 suppl]. Additionally, in a post-hoc analysis of INCREASE study data, there has been an observed link between higher doses and decreased rates of clinical worsening and death [23]. For PAH patients, up-titration by 3 breaths per session is recommended, at approximately 1–2 week intervals and for those with PH-ILD, up-titration of 1 breath per week is recommended.

It is important that patients understand that treatment with inhaled treprostinil is individualized and progresses in a stepwise manner. The care team should establish treatment goals at the onset of therapy and emphasize flexibility in dosing. For example, if a patient is not able to tolerate the starting dose of 3 breaths, it can be reduced to 1 or 2 breaths and subsequently increased to 3 breaths, as tolerated [19]. Making titration adjustments on a regular weekly schedule may simplify the regimen and improve patient adherence. Achieving the target of 9–12 breaths per treatment session is quite common, and further increases may be considered on an individual basis. As patients gain experience and success with inhaled treprostinil, the treatment goals can be re-evaluated, and the plan adjusted accordingly.

### *1.4. Compliance*

Follow-up visits provide the opportunity to assess the patient's progress and impression of therapy, as well as emphasize key teaching points. Reinforcing device positioning and breathing technique will help to ensure that the patient is performing the breathing maneuvers appropriately. If the patient's scheduled treatment occurs during their appointment time, the team member can observe their technique and provide helpful feedback, if necessary, and also assess the patient's compliance with therapy. Non-compliance may be related to side-effects, but it is also important to consider that patients may feel they

are too busy to adhere to the recommended schedule. Non-compliance may also occur because patients are perhaps feeling better or more comfortable, resulting in sub-optimal compliance with treatment. Many patients have success adhering to their recommended treatment schedules by setting reminders or alarms on their phones or smartwatches. Adherence may be assessed by checking Specialty Pharmacy records or by simply asking the patient if they are having any difficulties managing their prescribed number of treatments per day. Patients may be reluctant to acknowledge missed treatments, therefore the tone of the conversation needs to be positive and supportive with the goal of helping the patient optimize their outcomes on inhaled treprostinil therapy.

Compliance can also be assessed by comparing results of objective clinical measurements and non-invasive testing across previous visits. If a patient has worsened compared to a prior visit, this may signal a compliance issue. Presenting the worsening measurements to the patient creates an opportunity to discuss potential compliance challenges and how to address them.

### 1.5. Side-effects: expectation and mitigation

In the INCREASE study, 43.6% of patients treated with inhaled treprostinil solution experienced cough, 27.6% experienced headache, 12.3% reported throat irritation and 15.3% reported some nausea; similar to the side effects reported in Group 1 PAH trials, although treatment discontinuation due to side effects was shown to be relatively low and comparable to the placebo group [14,24]. It is important that patients understand that if these side effects occur, it does not mean they are having a "bad reaction" or are allergic to treatment. These side effects are related to the medication and the route of delivery and can often be managed with assistance from their care team.

In addition to being aware of the potential side-effects, discussing the severity and duration of side-effects can be helpful. Patients need to be aware that they may not feel well during the first few days following a dosing adjustment or up-titration but the side effects may lessen or completely resolve with time. Keeping close contact and directing the patient to communicate with their care team if they are not improving will provide an opportunity to adjust dosing or provide supportive intervention. It is important that patients feel comfortable and ready to up-titrate even if this means taking additional time to manage side-effects. The goal is to support the patient through the titration period as they reach their stable dose.

Cough is a primary complaint with inhaled treprostinil therapy and needs to be at the forefront of any side effect discussion. Many PH-ILD patients have a baseline cough, which may worsen with administration of inhaled treprostinil. It is important to emphasize cough associated with inhaled treprostinil tends to only occur around treatment time and does not persist throughout the day. Patients on inhaled treprostinil should be advised to be proactive and pre-treat whenever possible.

For patients experiencing a treatment-related cough, it is recommended that the first step be to review treatment administration technique. Often, simple adjustments to breathing technique or to the positioning and holding of the device can reduce the severity of or alleviate the cough. If cough persists, aids such as swallowing a small amount of yogurt, honey, peanut butter or drinking something cold or warm to sooth the patient's throat prior to treatment may be beneficial. Short acting bronchodilators, including albuterol, an inhaled beta agonist, can relax bronchial smooth muscle and open the airway, while throat pain relievers, such as Chloraseptic spray act as temporary analgesics.

If patients develop worsening dyspnea, they should be reevaluated for any clinical changes such as volume status, oxygenation and/or underlying airways disease as a potential cause. Additionally, during treatment sessions, patients may experience temporary shortness of breath, particularly as the number of breaths per session increases. If dyspnea occurs during treatment, patients can briefly pause their session, by pressing the stop/start button on the device, to catch their breath and then resume inhalations to complete the treatment session.

Other common side effects associated with inhaled treprostinil therapy include gastrointestinal issues and headache. If a patient experiences nausea following treatment, the first step should be to re-evaluate the position of the device to ensure it is being held level and medication delivery is being directed toward the airway. Incorrect holding of the device/placement of the mouthpiece results in medication being deposited on the tongue and subsequently swallowed, which can cause can nausea and potentially diarrhea. If nausea persists following a treatment session, it is recommended that patients swish their mouth with water and spit to remove any remaining medication from the mouth. Loperamide is used to help manage the symptoms of diarrhea. Acetaminophen is recommended for headache (Table 2).

Patients that are on multiple medications should receive special consideration and simultaneous onboarding of different medications should be avoided, when possible, to lessen side-effects. Concomitant medications, such as antifibrotics, may lead to an increase in gastrointestinal-related side effects, emphasizing the need to preemptively manage these side effects to the extent possible [25].

### 1.6. Treatment outcomes

It is important to present the benefits of inhaled treprostinil therapy and ensure that patients are well educated about what they can expect in relation to their PH symptoms. They may need to be reminded that they did not arrive at their current degree of symptoms overnight, and therefore it is not reasonable to expect a dramatic improvement in their symptoms in a short period of time. Naturally, patients will want to know when they can anticipate noticeable improvement. It is recommended to frame these discussions around their baseline symptoms. For example, advising patients that they may experience shortness of breath less often, recover more quickly or feel less exertion moving from room to room or from the bed to the commode. Setting patient-specific benchmarks may help them to recognize functional capacity improvements, such as walking to the mailbox with less shortness of breath. Family members or caregivers can also be helpful in identifying small improvements, and over time, building toward bigger improvements. The key is to set realistic expectations based on the patient's current abilities and exercise capacity and set long term goals appropriately.

### 1.7. Future directions

Most recently, the results of a study evaluating a treprostinil dry powder inhaled formulation using a small portable inhaler for patients with PAH was released. The device and formulation have the potential to provide improved convenience and thus better compliance with treatment. The BREEZE study included 51 patients with Group 1 PAH already on nebulized inhaled treprostinil (Tyvaso) who transitioned to the dry powder formulation and device [27] (Fig. 4). They demonstrated that the transition was safe and well tolerated with significant improvements in 6MWD (+11.5 m), device preference and satisfaction, and patient reported outcomes after only 3 weeks of treatment [27]. Similar to previous inhaled treprostinil studies in patients with PAH, 35% experienced cough, and 16% reported headache.

### 1.8. Conclusions/summary

Being well versed on inhaled treprostinil, both the medication and the device, the realistic benefits and expected side effects, is crucial to success of treatment. Including the patient in all the discussions and establishing the clear lines of communication with frequent touch points will provide the best opportunity for patients to meet their treatment goals. This is particularly important during the initial dosing and titration process. Encouraging the patient to continue with treatment at their own pace and assisting them through up-titration will give them the best opportunity for improvement.

**Table 2**
Possible adverse events associated with inhaled treprostinil solution and interventions for mitigation.

| Adverse Event | Frequency of Occurrence in INCREASE study [14] | Suggested Interventions for Mitigation |
|---|---|---|
| **Cough** | 43.6% (n = 71) | ● Re-evaluate breathing technique<br>● Slow breathing pace or pause between breaths<br>● Drink warm or very cold water prior to treatment<br>● Eat a spoonful of yogurt, peanut butter or honey prior to treatment<br>● Cough medicine (over the counter or by prescription), but cough drops should be avoided due to increased aspiration risk<br>● Short-acting bronchodilator<br>● Oral phenol-based analgesic sprays (Chloraseptic)<br>● Consider adjusting or optimizing airway medications |
| **Headache** | 27.6% (n = 45) | ● Anti-inflammatory medication or acetaminophen<br>● May resolve over time without mitigation<br>● Slow titration schedule if severe headache persists<br>● Decrease dose and attempt re-titration once headache has subsided |
| **Dyspnea** | 25.2% (n = 41)<br>*31.3% in placebo group | ● Reevaluate for any clinical changes such as volume status, oxygenation and/or underlying airways disease<br>● For dyspnea during treatment, use the start/stop button to temporarily pause inhalations and resume when shortness of breath resolves |
| **Dizziness** | 18.4% (n = 30) | ● Decrease and/or slow down inhaled treprostinil dose titration<br>● Re-evaluate breathing technique: normal breathing pattern, no deep breath or breath hold, utilize device pause button between breaths<br>● Monitor BP and fluid intake and adjust other blood pressure lowering medications as appropriate |
| **Nausea** | 15.3% (n = 25) | ● Re-evaluate breathing technique to ensure level holding of the device<br>● Anti-nausea medications<br>● Swish mouth with water and spit out after treatment<br>● Eat a small meal prior to treatment |
| **Fatigue** | 14.1% (n = 23) | ● Reevaluate for any clinical changes i.e., worsening volume status, oxygenation and/or disease progression<br>● Evaluate other causes for fatigue |
| **Diarrhea** | 13.5% (n = 22) | ● Dietary - BRAT diet (Bananas, Rice, Applesauce, Toast)<br>● Anti-diarrheal agents |
| **Throat irritation** | 12.3% (n = 20) | ● Oral phenol-based analgesic sprays (Chloraseptic) prior to treatment |
| **Oropharyngeal pain** | 11.0% n (=18) | ● Drink warm or cold water prior to treatment<br>● Anti-inflammatory medication |

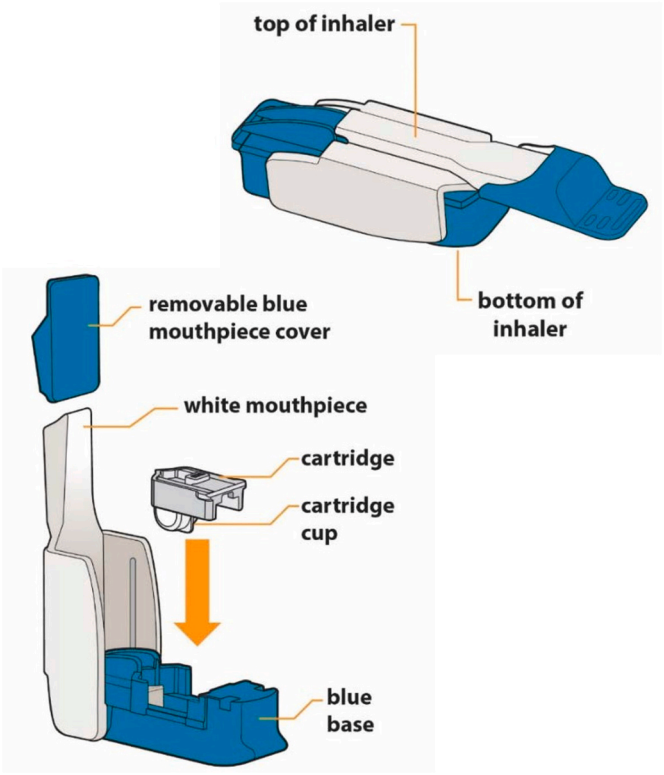



**Fig. 4.** Dry powder formulation of treprostinil and a small, portable, dry powder inhaler [26].

As new inhalation devices and therapies become available, providing the patient with resources and information in conjunction with an educated and engaged care team establishes the foundation critical to successful treatment.

## Funding

This work was sponsored by United Therapeutics Corporation.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence what is reported in this paper.

## References

[1] G. Simonneau, D. Montani, D.S. Celermajer, C.P. Denton, M.A. Gatzoulis, M. Krowka, P.G. Williams, R. Souza, Haemodynamic definitions and updated clinical classification of pulmonary hypertension, Eur. Respir. J. 53 (1) (2019 Jan 24) 1801913, https://doi.org/10.1183/13993003.01913-2018.
[2] S. Sahay, Evaluation and classification of pulmonary arterial hypertension, J. Thorac. Dis. 11 (Suppl 14) (2019 Sep) S1789–S1799, https://doi.org/10.21037/jtd.2019.08.54.
[3] S.D. Nathan, Pulmonary hypertension in interstitial lung disease, Int. J. Clin. Pract. Suppl. (160) (2008 Jul) 21–28, https://doi.org/10.1111/j.1742-1241.2008.01624.x.
[4] S.D. Nathan, P.M. Hassoun, Pulmonary hypertension due to lung disease and/or hypoxia, Clin. Chest Med. 34 (4) (2013 Dec) 695–705, https://doi.org/10.1016/j.ccm.2013.08.004.
[5] Idiopathic Pulmonary Fibrosis Clinical Research Network, D.A. Zisman, M. Schwarz, K.J. Anstrom, H.R. Collard, K.R. Flaherty, G.W. Hunninghake, A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis, N. Engl. J. Med. 363 (7) (2010 Aug 12) 620–628, https://doi.org/10.1056/NEJMoa1002110.Epub2010May18.
[6] T.E. King Jr., J. Behr, K.K. Brown, R.M. du Bois, L. Lancaster, J.A. de Andrade, G. Stähler, I. Leconte, S. Roux, G. Raghu, BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis, Am. J. Respir. Crit.

Care Med. 177 (1) (2008 Jan 1) 75–81, https://doi.org/10.1164/rccm.200705-732OC.
[7] J.R. Seibold, C.P. Denton, D.E. Furst, L. Guillevin, L.J. Rubin, A. Wells, M. Matucci Cerinic, G. Riemekasten, P. Emery, H. Chadha-Boreham, P. Charef, S. Roux, C. M. Black, Randomized, prospective, placebo-controlled trial of bosentan in interstitial lung disease secondary to systemic sclerosis, Arthritis Rheum 62 (7) (2010 Jul) 2101–2108, https://doi.org/10.1002/art.27466.
[8] T.E. King Jr., K.K. Brown, G. Raghu, R.M. du Bois, D.A. Lynch, F. Martinez, D. Valeyre, I. Leconte, A. Morganti, S. Roux, J. Behr, BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis, Am. J. Respir. Crit. Care Med. 184 (1) (2011 Jul 1) 92–99, https://doi.org/10.1164/rccm.201011-1874OC.
[9] T.J. Corte, G.J. Keir, K. Dimopoulos, L. Howard, P.A. Corris, L. Parfitt, C. Foley, M. Yanez-Lopez, D. Babalis, P. Marino, T.M. Maher, E.A. Renzoni, L. Spencer, C. A. Elliot, S.S. Birring, K. O'Reilly, M.A. Gatzoulis, A.U. Wells, S.J. Wort, BPHIT Study Group, Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia, Am. J. Respir. Crit. Care Med. 190 (2) (2014 Jul 15) 208–217, https://doi.org/10.1164/rccm.201403-0446OC.
[10] G. Raghu, J. Behr, K.K. Brown, J.J. Egan, S.M. Kawut, K.R. Flaherty, F.J. Martinez, S.D. Nathan, A.U. Wells, H.R. Collard, U. Costabel, L. Richeldi, J. de Andrade, N. Khalil, L.D. Morrison, D.J. Lederer, L. Shao, X. Li, P.S. Pedersen, A. B. Montgomery, J.W. Chien, T.G. O'Riordan, ARTEMIS-IPF Investigators, Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial, Ann. Intern. Med. 158 (9) (2013 May 7) 641–649, https://doi.org/10.7326/0003-4819-158-9-201305070-00003.
[11] Available from: Clinicaltrials.gov. Bethesda (MD): National Library of Medicine https://clinicaltrials.gov/ct2/show/NCT02138825?term=RISE-IIP&rank=1. NCT02138825.
[12] S.D. Nathan, J. Behr, H.R. Collard, et al., Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study, Lancet Respir. Med. 7 (2019) 780–790.
[13] L.H. Clapp, J.H.J. Abu-Hanna, J.A. Patel, Diverse pharmacology of prostacyclin mimetics: implications for pulmonary hypertension, in: T. Nakanishi, H. Baldwin, J. Fineman, H. Yamagishi (Eds.), Molecular Mechanism of Congenital Heart Disease and Pulmonary Hypertension, Springer, Singapore, 2020.
[14] A. Waxman, R. Restrepo-Jaramillo, T. Thenappan, A. Ravichandran, P. Engel, A. Bajwa, R. Allen, J. Feldman, R. Argula, P. Smith, K. Rollins, C. Deng, L. Peterson, H. Bell, V. Tapson, S.D. Nathan, Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease, N. Engl. J. Med. 384 (4) (2021 Jan 28) 325–334, https://doi.org/10.1056/NEJMoa2008470.
[15] A. Poms, M. Kingman, Inhaled treprostinil for the treatment of pulmonary arterial hypertension, Crit. Care Nurse 31 (6) (2011 Dec) e1–10, https://doi.org/10.4037/ccn2011153.
[16] H.W. Farber, W. Gin-Sing, Practical considerations for therapies targeting the prostacyclin pathway, Eur. Respir. Rev. 25 (142) (2016 Dec) 418–430, https://doi.org/10.1183/16000617.0083-2016.
[17] J. Scullion, The nurse practitioners' perspective on inhaler education in asthma and chronic obstructive pulmonary disease, Cancer Res. J. (2018 Aug 5) 2525319, 2018.
[18] M. Sockrider, Nebulizer breathing treatments at home, Am. J. Respir. Crit. Care Med. 202 (3) (2020 Aug 1) P7–P8, https://doi.org/10.1164/rccm.2023C7.
[19] Tyvaso, Prescribing Information, United Therapeutics Corp, 2017. www.tyvaso.com/hcp/pdf/TYVASO-PI.pdf. (Accessed 21 October 2021).
[20] B. Ivarsson, B. Ekmehag, R. Hesselstrand, G. Rådegran, T. Sjöberg, Perceptions of received information, social support, and coping in patients with pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension, Clin. Med. Insights Circulatory, Respir. Pulm. Med. 8 (2014 Oct 23) 21–28, https://doi.org/10.4137/CCRPM.S18586.
[21] W. Gin-Sing, Pulmonary arterial hypertension: a multidisciplinary approach to care, Nurs. Stand. 24 (38) (2010 May 26-Jun 1) 40–47, https://doi.org/10.7748/ns2010.05.24.38.40.c7802.
[22] J. Graarup, P. Ferrari, L.S. Howard, Patient engagement and self-management in pulmonary arterial hypertension, Eur. Respir. Rev. 25 (142) (2016 Dec) 399–407, https://doi.org/10.1183/16000617.0078-2016.
[23] V.F. Tapson, S.D. Nathan, M. Fisher, H. Ford, J. Gagermeier, J. Parambil, A. Raina, D. Zwicke, A. Gerke, E. Shen, P. Smith, D. Lee, Y. Rao, A. Waxman, Dose-response analysis of inhaled treprostinil in pulmonary hypertension associated with interstitial lung disease and its effects on clinical worsening, Pulm. Vasc. Dis. 160 (4 Suppl) (2021) A2279–A2280, https://doi.org/10.1016/j.chest.2021.07.1995.
[24] V.V. McLaughlin, R.L. Benza, L.J. Rubin, R.N. Channick, R. Voswinckel, V. F. Tapson, I.M. Robbins, H. Olschewski, M. Rubenfire, W. Seeger, Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial, J. Am. Coll. Cardiol. 55 (18) (2010 May 4) 1915–1922, https://doi.org/10.1016/j.jacc.2010.01.027.
[25] A. Waxman, V.F. Tapson, L. Satterwhite, M. Antkowiak, M.R. Lammi, E. Shen, C. Q. Deng, P. Smith, S.D. Nathan, Tolerability of inhaled treprostinil in patients with pulmonary hypertension associated with interstitial lung disease: a post-hoc analysis of the INCREASE study, in: PHPN Symposium, 2021.
[26] P.M. Smith, C.B. Watkins, J. Scoggin, C.Q. Degn, An open-label, clinical study to evaluate the safety and tolerability of treprostinil inhalation powder (TreT) in patients with pulmonary arterial hypertension (BREEZE study), in: PHPN, 2019. Poster 1027. PHPN 2019.
[27] L. Spikes, BREEZE: Open-Label, Clinical Study to Evaluate the Safety and Tolerability of a Treprostinil Dry Powder Inhaler in Patients with Pulmonary Arterial Hypertension Currently Using Tyvaso, European Respiratory Society, 2021. Poster 1928.