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Optimal Use of Treprostinil in Pulmonary Arterial Hypertension

A Guide to the Correct Use of Different Formulations

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Abstract

Treprostinil is a synthetic prostacyclin analogue with antiplatelet and vasodilatory properties. It is the only prostacyclin analogue with different options of delivery, i.e. subcutaneous, intravenous, inhaled or oral. Subcutaneous treprostinil has been shown in short- and long-term studies to improve exercise capacity, functional class, haemodynamics and survival in patients with pulmonary arterial hypertension (PAH). Pain at the infusion site has been a major drawback of subcutaneous treprostinil, hampering dose titration, and ultimately leading to increased discontinuation rates. The additional clinical interest in treprostinil as an alternative intravenous prostacyclin has developed due to its favourable properties, including longer half-life, chemical stability, the possibility of intravenous infusion without the need for ice packs, and easy drug preparation. Intravenous treprostinil improves exercise capacity, functional

class and haemodynamics in patients with PAH, over the period of 12 weeks. If patients are switched to intravenous treprostinil, they usually need to double the dose to attain the same efficacy. Whether the effect of intravenous treprostinil remains clinically relevant beyond 12 weeks is not known, and a longer follow-up would be required to investigate this. Inhaled treprostinil is an efficacious treatment in PAH patients who are moderately symptomatic on background oral therapy. Oral treprostinil on top of background therapy did not lead to an improvement in 6-minute walking distance after 16 weeks of treatment.

1. Introduction

Prostaglandin I2, also known as prostacyclin, is the main metabolite of arachidonic acid in the endothelium. Prostacyclin (i.e. epoprostenol) or prostacyclin analogues (e.g. treprostinil, iloprost, beraprost) supplementation counteracts the apparent deficiency in prostacyclin in patients with pulmonary arterial hypertension (PAH).[1,2] The short-term haemodynamic effects of prostacyclin therapy in PAH are attributable to cyclic adenosine monophosphate (cAMP)-dependent vasodilation of pulmonary vascular beds mediated through the prostaglandin I (IP) receptor.[3] The IP receptor acts by inhibiting platelet aggregation[4] and smooth muscle cell proliferation. Furthermore, evidence suggests that prostacyclin may have anti-inflammatory and immunosuppressive activity.[5]

Treprostinil is a tricyclic benzindene prostacyclin analogue with similar antiplatelet and vasodilatory actions to epoprostenol.[6] It has no apparent direct cardiac effects as assessed by indices of contractility and by electrocardiogram, no intrinsic effect on the autonomous nervous system, and no significant effect on respiratory mechanics. Treprostinil tends to inhibit gastrointestinal motility and decrease pentagastrin-stimulated gastric acid secretion, and therefore has gastric anti-ulcer and mucosal protective actions.[7] The safety profile is favourable, in particular it has no reproductive toxicity, and no mutagenic effects.[7]

Treprostinil (Remodulin®, United Therapeutics Corp., Research Triangle Park, NC, USA) is chemically stable in either sterile water or 0.9% sodium chloride at room temperature, not requiring reconstitution and cooling. Treprostinil is rapidly and completely absorbed after subcutaneous administration and has an absolute bioavailability of 100%.[8] The metabolism of treprostinil is hepatic. Treprostinil is eliminated in a biphasic distribution; approximately 79% of the administered dose is excreted in the urine either as unchanged (4%) drug or as an identifiable metabolite (64%).[7] As no clinical studies have been carried out in patients with renal impairment, treatment recommendations are not established for patients with renal impairment. As treprostinil and its metabolites are excreted mainly through the urinary route, caution is recommended when treating patients with renal impairment in order to prevent deleterious consequences related to the possible increase of systemic exposure. Therefore, the use of treprostinil cannot be recommended in patients with cardio-renal syndrome or chronic renal insufficiency or in those being treated with dialysis.

2. Pharmacokinetics of Treprostinil

Continuous subcutaneous infusion of treprostinil results in steady-state plasma concentrations after about 10 hours.[8] Examination of the pharmacokinetic parameters of short-term treprostinil administration (<1 day) in healthy volunteers appeared to indicate modest differences between the pharmacokinetics of intravenous and subcutaneous treprostinil.[9] However, comparison of the pharmacokinetic parameters of long-term (for 72 hours) intravenous or subcutaneous treprostinil showed bioequivalence of the two routes of administration at steady state in 51 healthy volunteers, with similar values for pharmacokinetic parameters between the two routes.[10]

Long-term administration of subcutaneous treprostinil was also found to produce pharmacokinetic effects that were linear with respect to

infusion dose rate.[9] In addition, there were diurnal variations in treprostinil plasma concentration, consisting of two daily peaks and two daily troughs, which were observed across all doses of treprostinil (2.5–15 ng/kg/min).[9] The linear relationship between treprostinil plasma concentration and dose was confirmed in patients with PAH at treprostinil doses up to 125 ng/kg/min (12.1–125 ng/kg/min corresponding to plasma levels of 14.9–18 248 pg/mL).[11] The correlation between plasma concentration and dose of treprostinil was not affected by the route of administration. The addition of treprostinil to warfarin therapy appeared to have no significant effects on the pharmacodynamics or pharmacokinetics of warfarin, and raised no apparent safety concerns.[8]

3. Efficacy and Safety of Subcutaneous Treprostinil

Treprostinil is stable at room temperature, and supplied in 20 mL vials containing either 1, 2.5, 5 or 10 mg/mL of the drug. These characteristics and a relatively long half-life (2–4 hours) make this drug suitable for subcutaneous administration.

3.1 Short-Term Studies

The short-term efficacy and safety of subcutaneous treprostinil has been reported in two pivotal studies, which were undertaken over time periods of 8 and 12 weeks, respectively.[12,13]

In the multicentre, double-blind, placebo-controlled, randomized, 8-week trial, efficacy and safety of subcutaneous treprostinil were evaluated in 26 patients with idiopathic pulmonary hypertension (iPAH). Subcutaneous treprostinil treatment was initiated at a dose of 2.5–5.0 ng/kg/min and could be increased by daily increments of up to a maximum dose of 20 ng/kg/min dependent upon response and tolerability, resulting in a mean ± SD dose of 13.0 ± 3.1 ng/kg/min in the 8th week. Patients in the subcutaneous treprostinil group showed a trend towards improvement in the primary endpoint of 6-minute walking distance (6-MWD) and also a trend towards improvement in haemodynamic variables.

Subcutaneous treprostinil was investigated in a pivotal 12-week, double-blind, placebo-controlled, multicentre trial in 470 patients with PAH, either iPAH or pulmonary hypertension (PH) associated with connective tissue disease (CTD-PAH) or congenital systemic shunts. Compared with placebo, treprostinil improved exercise capacity (assessed by 6-MWD), Borg Dyspnoea Score (BDS), WHO functional class and haemodynamics.[13] Subcutaneous treprostinil was initiated at a dose of 1.25 ng/kg/min, and the dose could be escalated to a maximum infusion rate of 22.5 ng/kg/min by the 12th week, depending on tolerability. The mean dose of subcutaneous treprostinil in the 12th week in the active treatment group was only 9.3 ng/kg/min. The between-treatment-group difference in the median 6-MWD was 16 metres ($p = 0.006$), showing a greater improvement in the sicker patients, independent of the disease aetiology. An improvement of +37 metres was present in patients receiving doses >13.8 ng/kg/min (as assessed by quartile analysis). Dose escalation was limited by protocol to avoid pain at the infusion site (85% of treprostinil-treated patients) and consequently many patients did not receive therapeutic doses. Overall, 18 patients (8%) in the subcutaneous treprostinil group had their treatment discontinued due to intolerable abdominal infusion site pain. Infusion site erythema, induration and infusion site pain related to the subcutaneous route of infusion were the most commonly reported adverse events (AEs). Other AEs, typical for prostacyclin use, e.g. headache, diarrhoea, flushing, jaw pain and foot pain were less frequent than infusion site reaction.

Overall, subcutaneous treprostinil appears to be efficacious for the treatment of patients with iPAH, as demonstrated by the improvements observed in 6-MWD, BDS and Dyspnoea Fatigue Index score in the short-term studies.

3.2 Long-Term Studies

Long-term observations on subcutaneous treprostinil therapy have confirmed findings from short-term studies.

Barst et al.[14] reported on long-term experience with patients treated with subcutaneous

treprostinil for more than 1 year, who were either enrolled in three placebo-controlled trials or were included as *de novo* patients. The primary endpoint was survival, monitored throughout the entire study period of up to 4.5 years. The US–European study, including 860 patients with PAH, has summarized significant benefits of treprostinil treatment in regard to exercise capacity and survival. Survival was 87–68% over 1–4 years for all 860 patients and 88–70% over 1–4 years with subcutaneous treprostinil monotherapy (130 out of 860 patients received additional PAH treatment: 12% bosentan, 3% sildenafil). For patients with iPAH, survival was 91–72% over 1–4 years. In this open-label extension study, 23% of the patients discontinued due to AEs, with 98% of discontinuations due to infusion site pain. However, almost 70% of these withdrawals occurred within the first year. For those patients who continued to receive subcutaneous treprostinil over the 1-year period, the survival rates were 90–79% at 2–4 years. The authors concluded that, while subcutaneous treprostinil may not be the drug of first choice for most PAH patients, having subcutaneous treprostinil available as a therapeutic option may improve outcomes in PAH.

In a retrospective multicentre study, 122 patients with PH of various aetiologies were followed for a mean of 26 months.[15] In this long-term, open-label, multicentre, retrospective study, treprostinil provided sustained improvements in exercise capacity and survival benefits of patients from three European PAH centres. The mean subcutaneous treprostinil dose was 26.2 ng/kg/min after 1 year, and was increased to 31.9 ng/kg/min (after 2 years) and 39.8 ng/kg/min (after 3 years), at which point 6-MWD had improved by +100 metres and WHO functional class had improved from 3.2 to 2.1 on average. Survival rates were 88.6%, 70.6% and 65.6% at 1, 3 and 5 years, respectively, and were comparable regardless of disease aetiology. Infusion site pain was the most frequent treprostinil-related event (82% of patients). The duration of pain was less than 4 days in 71%, and 20% of all patients were pain free. Site pain was unpredictable, unrelated to dose, and appeared less severe in patients within a stable social network. On average, pain started 2–3 days after a change of infusion site, subsided 3–5 days after the site change and then disappeared.

A recently published prospective registry[16] confirmed the efficacy of subcutaneous treprostinil in the longest observation of treprostinil-treated patients reported so far. The objective of the study[16] was to evaluate long-term effects on WHO functional class, 6-MWD, haemodynamics, survival and long-term tolerability of first-line subcutaneous treprostinil in 111 patients with severe pre-capillary PH. Data were collected from patients with WHO functional class III/IV PH (Dana Point groups 1 and 4) and severe haemodynamic dysfunction (mean right arterial pressure >10 mmHg and/or cardiac index <2.2 litres/min/m^2). The main differences in this registry compared with previously published studies with subcutaneous treprostinil were the inclusion of patients with chronic thromboembolic pulmonary hypertension (CTEPH) and a higher percentage of patients in WHO functional class IV (49%). Of 111 patients (treprostinil-treated since 1999), 12% stopped treatment prematurely because of drug side effects, 9.9% underwent double lung transplantation and 44.1% died of any cause (36.9% on treatment, 7.2% after early drug discontinuation). Overall survival rates at 1, 5 and 9 years were 84%, 53% and 33%, respectively. In patients who were able to tolerate treatment for >6 months, survival rates were 96%, 78% and 57% at 1, 5 and 9 years. The authors concluded that the first-line treatment of severe pre-capillary PH with subcutaneous treprostinil is safe and efficacious over many years. If up-titration beyond 6 months is tolerated, effective doses are reached and outcomes are good. The long-term survival of patients in WHO functional class IV appears to be similar to that of iPAH patients treated with first-line intravenous epoprostenol.

Three studies[15-17] reported the beneficial effects of subcutaneous treprostinil in CTEPH. Treprostinil-treated patients demonstrated significant improvements in 6-MWD, WHO functional class, B-type natriuretic peptide (BNP) plasma levels, cardiac output and pulmonary vascular resistance (PVR).[17] The treated patients within this study experienced significantly improved long-term

survival compared with the historical control group at doses between 12.5 and 42 ng/kg/min.[17]

3.3 Optimal Use of Subcutaneous Treprostinil

Treprostinil is indicated for patients with WHO functional class II–IV symptoms to diminish symptoms associated with exercise and for patients requiring transition from epoprostenol.[7] In practice, subcutaneous treprostinil is used in newly diagnosed WHO functional class III patients or/and patients who are deteriorating or not improving despite treatment with one or more oral therapies or an oral and an inhaled therapy. In addition, subcutaneous therapy is initiated in patients who are ineligible for or refuse intravenous therapy, or who desire or require transition from an intravenous to a subcutaneous prostanoid because of catheter-related complications.

Pain at the infusion site has been a major drawback of subcutaneous treprostinil, hampering dose titration and leading to a 10–15% discontinuation rate. The nature of infusion site reactions are highly variable and may include tenderness at the site, mild surrounding erythema, warmth, mild-to-moderate inflammation, mild site bleeding and nodule or induration at the site. In rare cases, the infusion site may develop an abscess, requiring local incision, drainage and antibacterial treatment. The mechanisms that drive infusion site reaction and pain potentially involve inflammation, vasodilation and pain stimulation.[18] Pain appears to decrease over time when patients maintain the infusion site for more than a week, thus deviating significantly from what is recommended by the manufacturer and from the package insert and recommendation of routine use. The key strategy for keeping patients on treatment has been minimizing site changes and maintaining sites for a minimum of 4 weeks, because the initial pain subsides after approximately 5 days.[19]

Treprostinil plasma concentrations correlate with subcutaneous dose of the drug, indicating consistent absorption despite local site reactions in >80% of cases.[17] Furthermore, it has become clear that subcutaneous treprostinil requires up-titration, followed by dose adjustments over time. Our experience[16] suggests that an average of 6 months is required before an effective and stable dose is reached. Long-term practice reveals that a more aggressive titration regimen is feasible and does not lead to premature discontinuation.[19] Moreover, most patients are able to reach a minimal effective dose of approximately 15–20 ng/kg/min within 3 months. Dry catheter pre-placement may reduce the local trauma of subcutaneous infusion by temporally separating the physical disruption of catheter placement from the inflammatory and vasodilatory responses elicited by drug exposure (White JR, personal communication). Current protocols are more likely to include the use of topical therapies such as pluronic lecithin organogel (PLO gel) compounds and/or oral agents. Pain management can be advanced to lidocaine patches, gabapentin and tramadol within the first week of therapy as needed. The use of pain management protocols, a dedicated nursing staff and follow-up of patients by expert PAH centres has resulted in a low discontinuation rate for site pain.[18] Practical and psychological support is an essential component of individualized care for patients receiving subcutaneous infusion therapy because it takes time for them to learn how best to manage their pain and cope with the infusion pump system.[16]

Subcutaneous treprostinil has received approval for the treatment of PAH in Europe, North America and some South American countries. Treprostinil therapy is currently indicated for WHO functional classes III and IV PAH patients (approved for WHO II–IV in the USA).

4. Efficacy and Safety of Intravenous Treprostinil

Additional clinical interest in treprostinil as an alternative intravenous prostacyclin has developed due to its favourable properties, including longer half-life, chemical stability, possibility of intravenous infusion without the need for ice packs, and easy drug preparation. Furthermore, the longer half-life of treprostinil may help to reduce clinical symptoms arising from short-term interruptions to therapy.

Intravenous administration provides an alternative therapy for patients who are unable to continue treatment due to subcutaneous infusion site pain.

4.1 Short-Term Studies

The efficacy and safety of intravenous treprostinil was investigated in a 12-week, double-blind, placebo-controlled, randomized, multicentre trial in 44 patients with PAH, performed in India.[20] The majority of patients were in WHO FC III at baseline. A significant improvement from baseline to week 12 was observed in 6-MWD in patients receiving intravenous treprostinil compared with placebo (N = 30 vs N = 14; median difference of 83 metres; p = 0.008), at the mean intravenous treprostinil dose of 72 ng/kg/min.

Statistically significant improvements were observed in WHO functional class and BDS. Other indicators of clinical improvement included a trend towards survival in patients receiving treprostinil compared with placebo (p = 0.0511), although the study was not statistically powered to assess survival. This occurred despite the presence of an open-label escape strategy to rescue patients in the placebo arm.

AEs, including headache, pain in extremities, diarrhoea and jaw pain, occurred more often with intravenous treprostinil than with placebo. Many of the hospitalizations reported in the study were not related to the progression of PAH but related to travelling times for assessment or catheter-related problems. There was no significant difference in serious AEs attributed to sepsis, infection or PAH between treprostinil-treated and placebo-treated patients. Intravenous treprostinil therapy appears to be efficacious for the treatment of PAH; it significantly improved 6-MWD, WHO functional class and BDS.

An open-label study demonstrated that intravenous treprostinil therapy improved exercise capacity, BDS, WHO functional class and haemodynamics at week 12 compared with baseline in 16 patients with PAH.[21] Continuous intravenous treprostinil at 41 ng/kg/min increased 6-MWD by 82 metres from baseline to week 12 (p = 0.001). The AEs reported in these studies were typical of those associated with prostacyclin use.

Two case studies of the use of intravenous treprostinil to reduce symptoms of PAH in patients requiring organ transplantation have been published. In the first, intravenous treprostinil treatment successfully reduced mean pulmonary arterial pressure (mPAP) in two out of three patients with PAH and end-stage liver disease, enabling them to undergo liver transplantation.[22] In the second, intravenous treprostinil improved 6-MWD, WHO functional class and several haemodynamic parameters in a patient with idiopathic pulmonary fibrosis (IPF) further complicated by the presence of PAH. The improvements in these efficacy parameters allowed the patient to undergo successful single-lung transplantation.[23] No AEs related to intravenous treprostinil therapy were documented in either case study; however, catheter malfunction, catheter-related infection[22] and nausea (when dose escalation beyond 30 ng/kg/min was attempted)[23] were reported.

4.2 Long-Term Studies

In an observational, open-label study, McLaughlin et al.[24] investigated the efficacy and safety of intravenous treprostinil in *de novo* patients (n = 16) and in those transitioning from intravenous epoprostenol (n = 31). At 1 year, mPAP, cardiac index and PVR index were significantly improved. 6-MWD was improved in the *de novo* group; none of these parameters were significantly different from baseline in the transition group. The AEs reported during the study were typical of those associated with prostacyclin use. In conclusion, the efficacy and safety profile of intravenous treprostinil appeared to be maintained 1 year after the start of therapy.

4.3 Transitioning Studies of Prostacyclin Therapy

Transitioning from intravenous epoprostenol to intravenous treprostinil was safe and effective in 31 patients with PAH in a 12-week, open-label study.[25] The intravenous infusion of treprostinil was increased while intravenous epoprostenol was reduced. Treprostinil was dosed on the basis of dyspnoea on exertion as a clinical endpoint, similar to current intravenous epoprostenol dosing recommendations. The 12-week dose of intravenous

treprostinil was greater than twice the dose of intravenous epoprostenol before transition.

The safe transitioning from intravenous epoprostenol to intravenous treprostinil by a direct switch of the medication reservoir (1 : 1 ng/kg/min) from epoprostenol to treprostinil was reported.[26] Subsequently, the dose of treprostinil was adjusted to twice the baseline epoprostenol dose. Most patients reported prostacyclin-related side effects of intravenous treprostinil as less severe than epoprostenol side effects.

The safe transitioning of 13 stable paediatric patients with PAH from intravenous epoprostenol to intravenous treprostinil was reported.[27] There was no change in 6-MWD or WHO functional class after switching. Apart from leg pain, all other prostacyclin-related AEs were less severe following transition.

In conclusion, current data suggest that continuous intravenous treprostinil is an effective treatment option for patients with PAH and may be considered as a safe and effective alternative to intravenous epoprostenol in paediatric PAH patients. The long-term effect of continuous intravenous treprostinil requires further assessment.

4.4 Prevention of Central Venous Catheter-Related Bloodstream Infections with Prostanoid Therapy

The Centers for Disease Control and Prevention (CDC) have conducted a retrospective investigation with the assistance of several state health departments and the cooperation of seven PAH treatment centres to determine the relative rates of bloodstream infections (BSI) in a sample of patients treated with intravenous treprostinil and intravenous epoprostenol during 2003–6.[28] It has been indicated that, based on combined data, pooled mean rates of BSI (primarily Gram-negative BSI) were significantly higher in patients receiving treprostinil than in those receiving epoprostenol. The difference in rates might have been caused by differences in preparation and storage of the two agents, differences in catheter care practices, or differences in the anti-inflammatory activity of the agents. The results do not suggest intrinsic contamination of intravenous treprostinil as a cause of the infections. Similar values were also reported by Kallen et al.,[29] with treprostinil patients reporting a higher incidence of catheter-related (CR)-BSI relating to Gram-negative bacteria than epoprostenol patients (0.81 vs 0.04 per 1000 patient-days, respectively). Potential routes of Gram-negative infection include wetting the infusion system connections during bathing or showering and thus allowing hydrophilic Gram-negative organisms to colonise the delivery system. Patients should therefore avoid wetting these connections. Many components of the delivery system provide potential infection routes, and closed-hub systems may help to minimize bacterial contamination. Different types of needle-free catheter hub connectors may also help reduce the incidence of CR-BSI.

Doran et al.[30] published guidelines, based around those issued by the CDC for the prevention of intravascular catheter-related infections.[31] These specific guidelines for chronic intravenous prostanoid therapy should help to minimize the occurrence of treatment complications/interruptions related to CR-BSI in patients with PAH.

4.5 Optimal Use of Intravenous Treprostinil

Clinical studies have demonstrated that the two prostanoids available for intravenous administration, epoprostenol and treprostinil, improve exercise capacity, dyspnoea and cardiopulmonary haemodynamics in patients with PAH. The safety profiles of epoprostenol and intravenous treprostinil during short-term therapy appear comparable. Potential differences in the biochemical properties of these two drugs may have clinical implications. Whereas long-term data with subcutaneous treprostinil have been published, such data for intravenous treprostinil are not currently available. A major challenge associated with intravenous prostanoid therapy in patients with severe PAH is maintaining the sterility of the drug, infusion set and central venous catheter in order to minimize the risk of CR-BSI. Although long-term intravenous infusion of both epoprostenol and treprostinil has been associated with an increased risk of BSI, the organisms isolated from BSI in patients receiving epoprostenol are pre-

dominantly Gram-positive organisms. The reason for the apparent differences in organisms in the above reports of BSI is not yet clear. Many components of the delivery system provide potential portals for infection, and closed-hub systems may help to minimize the risk of bacterial contamination. The inevitable risk of BSI requires careful attention to aseptic technique during establishment and maintenance of the infusion system.

Patients who require central-line insertion should be counselled and advised about the risks of CR-BSIs and the correct procedures for catheter care in advance of central-line insertion. Other AEs associated with intravenous treprostinil use are typical of those associated with prostacyclin therapy.

5. Inhaled Treprostinil

Difficulties with injection and its relative selectivity for the pulmonary circulation of inhaled therapy led to the development of aerosolized treprostinil therapy for PAH. The ability of modern ultrasonic nebulizers to decrease and control particle size make these devices ideal for delivering prostacyclin analogues to the distal airspaces, which are in close proximity to the resistance pulmonary arterioles. Treprostinil delivered intermittently to the pulmonary circulation, i.e. four times daily via inhalation using an Opti-Neb ultrasonic nebulizer (NebuTec, Elsenfeld, Germany) appears to be an effective treatment for PAH.

5.1 Short-Term Studies

Voswinckel et al.[32] conducted a study to compare the effects of inhaled treprostinil and inhaled iloprost in a crossover design. It was found that both agents resulted in comparable maximal decreases in PVR. However, the peak effect of inhaled treprostinil occurred later than that of inhaled iloprost. The duration of the treprostinil effect (after 60 minutes post-inhalation, PVR was not back to baseline) was longer than the iloprost effect (after 60 minutes post-inhalation, PVR had returned to baseline). The pharmacokinetic studies showed that maximum plasma drug concentration (C_{max}) for the 60 μg (1.59 ng/mL) and 90 μg (1.74 ng/mL) doses were in accordance with previously reported plasma concentrations of subcutaneous or intravenous treprostinil delivery. These data confirmed the potent and sustained nature of inhaled treprostinil as a pulmonary vasodilator.

Channick et al.[33] conducted a pilot, 12-week, open-label trial evaluating the efficacy and safety of two doses of inhaled treprostinil in 12 patients with PAH concurrently receiving bosentan. Acutely, inhaled treprostinil decreased mPAP in a dose-dependent manner. Additionally, the study demonstrated that inhaled treprostinil given chronically was well tolerated, with an acceptable safety profile, with common side effects including transient cough, headache, and sore throat, but no serious AEs. Furthermore, the combination of sildenafil and inhaled treprostinil[34] appeared to be well tolerated and to induce additive, pulmonary-selective vasodilatation in patients with pre-capillary PAH.

Based on the positive results from these pilot studies, a randomized, placebo-controlled trial was conducted (TRIUMPH-I [TReprostinil Sodium Inhalation Used in the Management of Pulmonary Arterial Hypertension]). PAH patients with persistent WHO functional class III and IV symptoms despite receiving oral treatments (bosentan or sildenafil) for at least 3 months ($n = 235$) were randomized to receive either inhaled treprostinil (nine inhalations, 54 μg four times daily) or placebo, delivered via the Opti-Neb nebulizer. At the end of 12 weeks, there was a highly significant ($p = 0.0004$) 20 metre placebo-corrected median improvement in 6-MWD: 52% of patients receiving treprostinil for 12 weeks had improvements of 20 m or more, while 31% of treprostinil-treated patients walked 50 metres or more compared with baseline. Based on the results of the TRIUMPH-I study, inhaled treprostinil received US FDA approval under the tradename Tyvaso® (United Therapeutics Corporation, Silver Spring, MD, USA). Since 2011, Tyvaso® has been indicated for the treatment of PAH (WHO Group 1) to improve exercise ability. While there are long-term data on use of treprostinil by other routes of administration, nearly all controlled clinical experience with inhaled treprostinil has been on a background of bosentan or sildenafil. The controlled clinical experience was limited to 12 weeks in duration.

5.2 Long-Term Studies

Following completion of the 12-week, double-blind phase of TRIUMPH-I, 206 of the original 235 patients transitioned into the long-term, open-label extension trial.[35] Previously reported interim data from these patients showed that exercise capacity as assessed by 6-MWD continued to improve: 31, 34 and 50 metres at 12, 18 and 24 months, respectively, while maintaining a similar adverse event profile.

Due to the longer-acting availability, the potential of transitioning patients from the shorter-acting iloprost to inhaled treprostinil was examined. Data from a 24-month, multicentre, open-label trial[36] of 55 patients provided preliminary evidence supporting the safety of rapid transition from inhaled iloprost to inhaled treprostinil while maintaining exercise capacity and improving quality of life.

5.3 Optimal Use of Inhaled Treprostinil

Inhaled treprostinil is an efficacious treatment in PAH patients who are moderately symptomatic while receiving background oral therapy. Given that the benefits of oral PAH therapies on exercise capacity appear to plateau within 3–6 months, this timeframe seems reasonable to decide whether to add inhaled treprostinil to oral therapy. Based on the efficacy of inhaled treprostinil, coupled with convenience and an acceptable side effect profile, some physicians may be tempted to start using this medication earlier in the course of the disease or as up-front combination therapy with an oral agent.

Tyvaso® is dosed in four separate, equally spaced, treatment sessions per day during waking hours. Initial therapy should begin with three breaths of Tyvaso® (18 μg of treprostinil) per treatment session, four times daily. Dosage should be increased by an additional three breaths at approximately 1–2 week intervals, if tolerated, until the target dose of nine breaths (54 μg of treprostinil) is reached per treatment session, four times daily. If adverse effects preclude titration to target dose, Tyvaso® should be continued at the highest tolerated dose. If a scheduled treatment session is missed or interrupted, therapy should be resumed as soon as possible at the usual dose. Safety and efficacy have not been established in patients with significant underlying lung disease (asthma or chronic obstructive pulmonary disease).

The effects diminish over the minimum recommended dosing interval of 4 hours; treatment timing can be adjusted for planned activities.

The use of inhaled agents reduces the risks and inconveniences associated with infused treatments, and further expand the potential role for prostacyclin therapies. Continued experience with, and evaluation of, inhaled treprostinil, particularly in combination with oral therapies, will help to provide further assessment of its long-term safety and efficacy.

5.4 Transitioning Studies

In a recently published retrospective cohort study,[37] clinical, haemodynamic and functional data from 18 clinically stable patients with PAH from six large national PAH centres were collected. All patients were transitioned from parenteral prostanoids (15 patients receving intravenous or subcutaneous treprostinil, three patients receiving intravenous epoprostenol) to inhaled treprostinil. Although most patients who transitioned to inhaled treprostinil demonstrated no statistically significant worsening of haemodynamics or 6-MWD, a minority demonstrated worsening of WHO functional class over a 7-month period. Although transition from parenteral prostanoids to inhaled treprostinil appears to be well tolerated in clinically stable patients, this strategy is not supported by the current evidence, and should be done under close supervision.

6. Oral Treprostinil

Treprostinil diethanolamine is a salt form of treprostinil designed to release the drug in a sustained-release osmotic tablet for twice-daily dosing. Early pharmacokinetic studies demonstrated that oral treprostinil has an absolute bioavailability of approximately 18% and that plasma treprostinil concentrations achieved fall within a dosing range observed with parenteral treprostinil.[9,38] Additionally, oral treprostinil does not have clini-

cally relevant drug interactions with bosentan[39] or sildenafil.[40] The FREEDOM-C (Oral Treprostinil for the Treatment of Pulmonary Arterial Hypertension in Patients on Background Endothelin Receptor Antagonist and/or Phosphodiesterase Type 5 Inhibitor Therapy) trial[41] was conducted to determine the efficacy and safety of oral treprostinil in patients receiving concomitant oral endothelin receptor antagonist and/or phosphodiesterase type-5 (PDE-5) inhibitor therapy. In this 16-week, multicentre, double-blind, placebo-controlled study, 350 patients with PAH were randomized to placebo or oral treprostinil. At study initiation, patients were administered a 1 mg twice-daily starting dose, with increases in 1 mg increments. Additional tablet doses of 0.5 and 0.25 mg were made available to patients at sequentially later times in the study. Patients for whom all doses were available received oral treprostinil at 0.5 mg twice daily and, if clinically tolerated, received dose increases by 0.5 mg increments every 3 days. Doses were increased from 3 mg to a maximum of 16 mg twice daily over the 16 weeks, depending on AEs and symptoms and signs of PH. If patients escalated therapy but experienced side effects requiring a dose reduction, the 0.25 mg tablets were used at the discretion of the study investigator as an intermediate dose at any time during the 16 weeks. Study drug was administered with the morning and evening doses of background therapy ~10 minutes after breakfast and dinner (at least 500 calories). The primary endpoint of improvement in 6-MWD at week 16 did not achieve significance. There was a statistically significant improvement in 6-MWD at week 12; however, this was not a prespecified endpoint. Patients receiving oral treprostinil did experience a significant improvement in combined 6-MWD and BDS and Dyspnoea Fatigue Index Score at week 16.

There are several factors that could have led to lack of improvement in 6-MWD at week 16. One explanation could be premature discontinuation of the study drug due to AEs associated with higher-dose tablets. A 1 mg twice-daily dose of oral treprostinil is approximately equivalent to 10 ng/kg/min of infused treprostinil, and dose increases of 0.5 or 1 mg were poorly tolerated by most patients. Another explanation for the lack of improvement in 6-MWD is that the patients participating in this study were, on average, receiving background therapy and may have been less likely to deteriorate during a short clinical trial than completely treatment-naive patients.

This study enhanced understanding of oral treprostinil titration and dosing, which has set the stage for additional studies. Importantly, an additional study arm randomizing patients to oral treprostinil monotherapy might have given insight regarding the relative effectiveness of the study drug without background therapy masking its effects. Two more phase III trials are currently underway, including a large-scale trial of oral treprostinil monotherapy (FREEDOM-M) and a second combination study (FREEDOM-C2), both with lower-dose tablets available.

7. Cost Effectiveness of Treprostinil Compared with Other Prostanoids

A recently published study[42] provided a cost-effectiveness and cost-utility comparison of initiating prostacyclin therapy with three different treatment alternatives (inhaled iloprost, intravenous epoprostenol and subcutaneous treprostinil) for patients with PAH. At the end of 3 years, in the base case of the deterministic analysis, initiating prostacyclin therapy with iloprost was the less costly strategy (€132 840), followed by treprostinil (€359 869) and epoprostenol (€429 775) [year 2009 values].[42] Epoprostenol has shown the best efficacy results, followed by iloprost and treprostinil.

In Canada, a cost-minimization analysis was used to compare epoprostenol and treprostinil[43,44] under the assumption that treprostinil and epoprostenol were clinically equivalent. Two cohorts of 60 patients, treated with treprostinil or epoprostenol, were evaluated over 3 years by using a dynamic spreadsheet model. In the base-case analysis (over 3 years), treatment with treprostinil resulted in an expected savings of $US2 610 642. On a per-patient level, treatment with treprostinil resulted in an average annual savings of $US14 504. The greatest savings with treprostinil came from reduced hospitalizations.

In another study, Narine et al.[44] analysed 270 patients who were treated with subcutaneous

treprostinil and intravenous epoprostenol and evaluated over 3 years using a spreadsheet model. In the base-case analysis, treprostinil demonstrated savings of $US22 701 and $US37 433 per patient over 1- and 3-year time horizons, respectively. The greatest saving with treprostinil came from reduced or minimal hospitalizations attributed to the dose titration and treatment of adverse events, such as sepsis, associated with intravenous epoprostenol. Published data support that by initiating and continuing treatment with treprostinil over a 3-year period, economic burden associated with iPAH may be reduced compared with treatment with epoprostenol.

Taken together, in a rare subset of patients using prostanoids (<20% of all PAH patients), within an orphan disease and an incidence of less than 50 per million, costs must be judged on an individual risk/benefit assessment. The only alternative for patients on prostanoids is lung transplantation, associated with even higher costs than any parenteral prostanoid treatments long term.

8. Conclusions

Treprostinil is the only prostanoid that can be administered by several administration routes: subcutaneous, intravenous, oral and inhaled. Parenteral treprostinil (subcutaneous or intravenous) is indicated for patients with PAH in WHO functional class III and IV to diminish symptoms. Pain at the infusion site has been a major drawback of subcutaneous treprostinil. The key strategy has been minimizing site changes and maintaining sites for a minimum of 4 weeks, because the initial pain subsides after approximately 5 days. Inhaled treprostinil is an efficacious treatment in PAH patients who are moderately symptomatic on background oral therapy. Initial therapy should begin with three breaths, with further incremental increases up to nine breaths, four times daily. A large-scale trial of oral treprostinil monotherapy (FREEDOM-M) and a second combination study (FREEDOM-C2) are still ongoing in order to assess the efficacy and safety of oral treprostinil on top of background therapy.

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