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Subcutaneous treprostinil in pulmonary arterial hypertension: Practical considerations

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Treprostinil, which is available for subcutaneous (SC) and intravenous (IV) administration, has demonstrated efficacy in increasing exercise capacity, reducing signs and symptoms of pulmonary arterial hypertension (PAH), and improving cardiopulmonary hemodynamics in patients with PAH; however, the infusion site pain commonly experienced with SC treprostinil has limited its use. Prospective and observational clinical studies have shown that the dose of SC treprostinil can be escalated at a higher rate than described in early clinical trials to achieve symptom relief, in part because of favorable tolerability of treatment and the apparent dose independence of site pain. In addition, pain management protocols that include non-pharmacologic and pharmacologic (i.e., topical and systemic) approaches provide analgesic relief from infusion site pain. With experience, physicians and patients have recognized that some infusion sites are better than others, and the frequency of site rotation can be reduced to improve tolerability. Dosing to achieve rapid onset of efficacy and proactively managing infusion site pain enhance the likelihood for a patient with PAH to maintain and derive benefit from SC treprostinil therapy.

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Pulmonary arterial hypertension (PAH) is characterized by pulmonary arterial vasoconstriction and remodeling, aberrant vascular endothelial cell proliferation, and thrombosis in situ.[1,2] Prostacyclin, implicated in PAH pathogenesis, is produced by the vascular endothelium and has vasodilatory, anti-proliferative, anti-thrombotic and anti-inflammatory properties.[1] Epoprostenol was the first PAH-specific therapy to demonstrate a survival benefit as compared with conventional therapy.[3] The efficacy of epoprostenol, however, is tempered by its cumbersome treatment regimen—the instability and short half-life of epoprostenol (<3 to 5 minutes)[1] necessitates the use of ice packs and administration through an indwelling central venous catheter. Moreover, because of the short half-life, interruptions in drug infusion as a result of pump failure or dislocation of central venous catheter may lead to cardiopulmonary collapse and death.[4,5] These and other considerations led researchers to develop more stable prostanoids for administration via alternative routes (i.e., subcutaneous [SC], inhaled and oral).

Treprostinil is a tricyclic benzindene prostanoid that was approved for SC administration by the U.S. Food and Drug Administration (FDA) in 2002. Stability at room temperature, a half-life of ~4 hours[6] and a neutral pH allow treprostinil to be administered by either continuous SC or intravenous (IV) infusion. Treprostinil has demonstrated efficacy in the treatment of PAH when administered by either route[5,7–17]; however, infusion site pain, a common side effect associated with SC treprostinil, has limited the appeal of SC treprostinil to patients and physicians. Clinical experiences at PAH specialty centers have provided new insight regarding dosing and management of infusion site

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pain, which has led to improved clinical benefit from SC treprostinil. These PAH centers provide patients with experienced physicians who have extensive expertise with this complex disease; specially trained nurses to assist in management of the complicated therapies; and a multidisciplinary approach to care, including pulmonologists, cardiologists, rheumatologists, hepatologists, hematologists and transplant physicians, as well as psychologists and social workers. The nurse clinicians are an integral part of the long-term outpatient management of therapies such as SC treprostinil, providing competent education, triage, emotional support and ongoing medical assessments. They also provide frequent telephone contact, especially during initiation of therapy, as well as during periodic follow-up evaluation of treatment. The goal of this article is to provide insight into the day-to-day management of PAH with SC treprostinil utilizing expertise from representative PAH specialty centers.

Clinical profile of SC treprostinil

Subcutaneously administered treprostinil is rapidly and completely absorbed, with 100% bioavailability.[18] The pharmacokinetics of SC treprostinil (steady state) were demonstrated to be dose proportional over a range of 2.5 to 15 ng/kg/min in healthy volunteers and 10 to 125 ng/kg/min in patients with PAH (Figure 1).[19,20] Among healthy volunteers administered treprostinil 10 to 15 ng/kg/min, plasma concentration rose rapidly and reached maximum plasma concentration within 2 to 3 hours after administration of SC treprostinil.[19,21] The elimination half-life after chronic SC administration of treprostinil to healthy volunteers was 2.9 to 4.6 hours.[19,21]

The efficacy and safety of SC treprostinil were first described in a pivotal 12-week, placebo-controlled study, wherein 470 patients with PAH were randomized to receive SC treprostinil or placebo in addition to conventional therapy (Table 1).[12] Change from baseline to Week 12 in the primary efficacy end-point, 6-minute walk distance (6MWD), was significantly greater with treprostinil than with placebo (between-group difference in median 6MWD = 16 meters; $p = 0.006$). The apparent dose response observed in this study with respect to dose and improvement in 6MWD has also been observed in a long-term study (Figure 2).[8] The most common adverse events reported for treprostinil and placebo in the 12-week study were infusion site pain (85% and 27%, respectively), infusion site reaction (83% and 27%) and infusion site bleeding/bruising (34% and 44%).

Long-term benefits of targeted therapy in the treatment of PAH were initially established with IV epoprostenol treatment.[22,23] Chronic IV epoprostenol administration has demonstrated improvement in long-term clinical outcomes including survival, delaying or even obviating the need for lung transplantation in patients with severe PAH.[23] Long-term outcomes for SC treprostinil were evaluated in two studies that included a total of 982 patients.[7,8] In a large study of 860 patients with PAH who received SC treprostinil monotherapy for up to 4.5 years, Kaplan–Meier estimates for survival at 1, 2, 3 and 4 years were 88%, 79%, 73% and 70%, respectively (Figure 3).[7] In addition, patients in a better functional class (FC) at study entry lived longer, with the highest survival rates among patients who were in Class II. Although all the patients in this study were started on SC treprostinil monotherapy, 11% switched to an alternative prostanoid during the course of the study, and 12% and 3% received bosentan and sildenafil, respectively, as add-on therapies. A recent single-center study demonstrated 10-year efficacy of SC treprostinil treatment.[24]

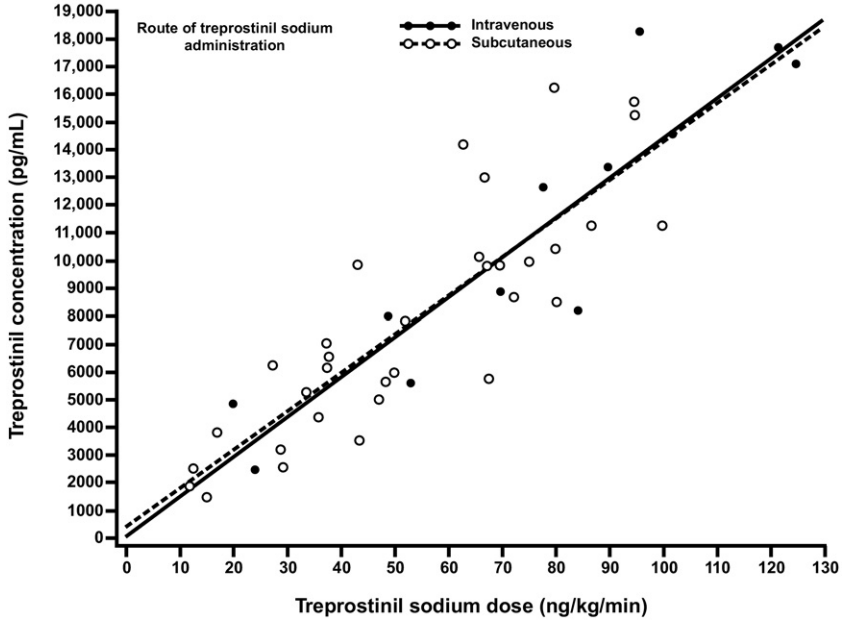

Figure 1 Plasma treprostinil concentration vs treprostinil sodium dose curve for patients with pulmonary arterial hypertension ($n = 47$) administered subcutaneous or intravenous treprostinil.[20] Reprinted with permission from Sage Publications.

Table 1 Clinical Trials With SC Treprostinil

Study	Design	Study population	Primary outcome	Secondary end-points
Data from Simonneau et al[12]	12-week, multicenter, double-blind, placebo-controlled trial	$N = 470$	Change from baseline 6MWD: 16-m difference from placebo ($p = 0.006$) (greatest difference among severely ill patients [baseline 6MWD <150 m])	Improvement compared with placebo in: • Borg dyspnea score ($p < 0.0001$) • Hemodynamics ($p \leq 0.002$)
Data from Lang et al[8]	Long-term, open-label follow-up of participants in RCTs and other eligible participants	$N = 122$; PAH ($n = 99$), CTEPH ($n = 23$)	Event-free survival rates of 83% and 69% at 1 and 3 years, respectively	Improvement in: • 6MWD (305 ± 11 m to 445 ± 12 m, $p = 0.0001$) • NYHA functional class ($p < 0.05$)
Data from Barst et al[7]	Long-term, open-label follow-up of participants in RCTs and other eligible participants	$N = 860$; Class II ($n = 128$), Class III ($n = 654$), Class IV ($n = 78$)	1-, 2-, 3- and 4-year survival: overall: 87%, 78%, 71% and 68%; Class II: 91%, 84%, 79% and 74%; Class III: 88%, 79%, 72% and 70%; Class IV: 71%, 62% and 52%	Documentation of additional or alternative treatments
Data from Sadushi-Kolici et al[24]	Long-term (10-year), single-center, retrospective study	$N = 79$; first-line SC treprostinil ($n = 65$); switch to SC treprostinil from oral therapy ($n = 14$)	Survival rates of 92%, 75%, 74% and 69% at 1, 3, 5 and 10 years, respectively	
Data from Rubenfire et al[11]	8-week, randomized, placebo-controlled study transitioning IV epoprostenol to SC treprostinil	$N = 22$	Clinical deterioration; SC treprostinil 7%, placebo 88%	Improvement compared with placebo in: • 6MWD ($p = 0.0041$) • Borg dyspnea score ($p = 0.0017$)
Data from Feldman et al[17]	12-week, multicenter, open-label study of SC or IV treprostinil added to existing oral PAH therapy	$N = 20$; ERA monotherapy ($n = 7$), PDE-5I monotherapy ($n = 6$), ERA+PDE-5I ($n = 7$)	Significant improvements in 6MWD from baseline (35 ± 24 m; $p = 0.04$)	

CTEPH, chronic thromboembolic pulmonary hypertension; ERA, endothelin receptor antagonist; IV, intravenous; 6MWD, 6-minute walk distance; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; PDE-5I, phosphodiesterase type 5 inhibitor; RCT, randomized, controlled trial; SC, subcutaneous.

The efficacy and safety of SC treprostinil have also been assessed in patients who transitioned from other prostanoids.[11,16,25] In an 8-week, multicenter, placebo-controlled, withdrawal study, patients with stable PAH and currently receiving epoprostenol (mean dose: 22.3 ± 3.3 ng/kg/min) were transitioned to SC treprostinil (maximum dose: 32.2 ± 4.9 ng/kg/min) with practically no clinical deterioration (13 of 14 patients transitioned without clinical deterioration).[11] The results of this trial facilitated an FDA amendment of this agent to include patients transitioning from epoprostenol treatment to treprostinil therapy. Combination therapy with addition of the phosphodiesterase type 5 inhibitor sildenafil or the endothelin receptor antagonist bosentan to an existing SC treprostinil regimen resulted in clinical improvements in two small studies and was well tolerated.[5,25] Treprostinil has also demonstrated efficacy when added on to an oral therapy regimen.[17]

Treatment considerations with SC treprostinil

Patient selection

Treatment decisions are based on clinical measures as well as physician and patient preference, financial considerations (insurance/reimbursement) and experience of the PAH center. Treprostinil is indicated for patients with New York Heart Association Functional Class (FC) II to IV symptoms to diminish symptoms associated with exercise and for patients requiring transition from epoprostenol.[26] In practice, SC treprostinil is used in newly diagnosed FC III patients 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, SC therapy is initiated in patients who: are ineligible for or refuse IV therapy; desire transition from an IV to an SC prostanoid; or require

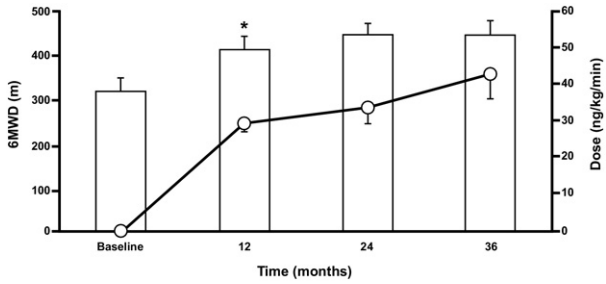

Figure 2 Mean change from baseline in 6-minute walk distance (6MWD) over time in patients with idiopathic pulmonary arterial hypertension or chronic thromboembolic pulmonary hypertension treated with subcutaneous treprostinil.[8] ∗Improvement in 6MWD and New York Heart Association functional class occurred by 12 months. Adapted and reprinted with permission from the American College of Chest Physicians.

transition from IV prostacyclin therapy because of catheter-related complications, such as infection, sepsis or thrombosis. In addition, careful consideration must be given regarding the presence of reliable caregiver support for patients, especially those with dexterity and cognitive impairments, before initiating SC therapy.

From a patient's perspective, SC therapy may be appropriate for patients with sub-optimal family support, those living in rural areas or far from emergency services, those who are active or travel and desire a less complex medication regimen, and those who refuse a central line because of body image or invasive therapy concerns. Patients with a low pain threshold based on on-site nurse assessments may not be suitable for SC therapy. In some cases, patients may need to transition to IV prostanoid therapy should SC therapy fail. Therefore, careful consideration is necessary for patients desiring to transition from IV to SC prostanoid therapy.

Dosing

Although the optimum target doses and rates of dose increase have not been clearly delineated with parenteral prostanoid therapy, prostanoid dosing is typically initiated at a low starting dose and is up-titrated to achieve reductions in signs and symptoms of PAH while maintaining an acceptable tolerability profile. In the pivotal studies, SC treprostinil was initiated at 1.25 ng/kg/min and up-titrated slowly, with a maximum dose of 22.5 ng/kg/min that resulted in a low, potentially sub-therapeutic average dose over the 12-week study period (9.3 ng/kg/min).[12] This regimen is consistent with the Remodulin label, which recommends starting SC treprostinil at 1.25 ng/kg/min in patients without hepatic insufficiency and up-titrating 1.25 ng/kg/min per week for the first 4 weeks and 2.5 ng/kg/min per week for any subsequent titrations.[26]

The rationale for starting low and up-titrating slowly with SC treprostinil was based on concern about the potential for dose-related side effects, particularly infusion site pain. In the pivotal studies, infusion site pain did not appear to be dose related; however, there was a perceived correlation between site pain and rate of dose increase.[12] Subsequent studies have confirmed that infusion site pain is not related to dose and, in fact, rapid titration appears to have a favorable effect on infusion site pain.[6,8,27] A recent randomized, prospective study directly compared a slow versus a rapid dose-escalation protocol in 23 consecutive patients with PAH.[6] Patients in the slow-escalation group initiated SC treprostinil at 2 ng/kg/min, and the dose was increased by 1.25 to 2.0 ng/kg/min weekly. Patients in the rapid-escalation group initiated SC treprostinil at 2.5 ng/kg/min, and the dose was increased by 2.5 ng/kg/min twice in the first week, with an additional increase of 2.5 ng/kg/min every 1 or 2 weeks. At Week 12, the mean dose had reached 12.9 $\pm$ 2.7 ng/kg/min in the slow-escalation group and 20.3 $\pm$ 5.8 ng/kg/min in the rapid-escalation group. Notably, improvements in exercise capacity at Week 12 were significantly greater in the rapid-escalation group compared with the slow-escalation group ($p = 0.03$). Moreover, infusion site pain was more common in the slow-escalation group (82%) compared with the rapid-escalation group (58%; $p = 0.04$).

Experience has shown that higher doses than those reported in early clinical trials are needed to achieve therapeutic benefit. Soto and colleagues reported on dosing and clinical experiences with patients under "real world" conditions.[27–30] After rapid dose escalation in 24 patients, a mean SC treprostinil dose of 40.6 ng/kg/min was attained within 7.8 months.[27] Review of data from 33 patients who had received long-term SC treprostinil at this same center revealed a mean peak treprostinil dose of 44 ng/kg/min (range 26 to 72 ng/kg/min) at 12 months.[30] These doses are notably higher than the 26 ng/kg/min reported at 1 year in long-term SC treprostinil clinical studies.[7,8] Among a population of de novo patients ($n = 24$), the peak SC treprostinil dose was 43.3 ng/kg/min during a mean follow-up period of 19 months.[29] Soto and colleagues attributed their success in achieving clinical benefits with low discontinuation rates (6% to 8%) to a combination of rapid dose escalation, achieving higher doses than initially recommended, and strong nursing support.[27,30] By allowing the patient to experience the therapeutic benefits of treprostinil

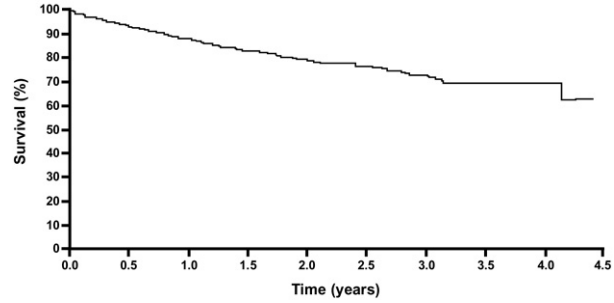

Figure 3 Kaplan–Meier survival curve for patients maintained on subcutaneous treprostinil monotherapy ($n = 860$). Patients were censored when additional pulmonary arterial hypertension therapies were added to the treatment regimen. Estimated survival rates at 1, 2, 3 and 4 years were 88%, 79%, 73% and 70%, respectively. Data obtained from Barst et al.[7] Reprinted with permission from the European Respiratory Society.

quickly, the patient may be more likely to tolerate side effects experienced during the initial phases of treatment. This group has successfully escalated the SC treprostinil dose in the range of 10 to 16 ng/kg/min within 3 to 4 days.[28]

In the current era, at experienced PAH centers, SC treprostinil treatment is commonly initiated at 2 ng/kg/min, in the clinic, during a short inpatient stay, or at home. The dose is increased by 2 ng/kg/min daily, then weekly and biweekly according to clinical efficacy and tolerability, such that a dose range of 40 to 80 ng/kg/min is attained by 6 months of therapy. Also, SC treprostinil dose increases and the frequency of dose adjustments are individualized based on the initial severity of PAH and subsequent prostanoid side effects. Importantly, infusion site reaction and site pain do not limit dose escalation. Patients with more severe disease or impending right heart failure may require hospital admission with more rapid dose escalation. The treatment success rates in these expert centers are in part related to rapid dose escalation and higher treatment doses than those recommended in the product information for treprostinil.[26]

Managing infusion site pain

Infusion site pain is the most commonly reported treatment-emergent adverse event with SC treprostinil. Up to 5% to 23% of treated patients discontinue long-term treatment because of site pain.[7,8] Infusion site pain typically reaches an apex 2 to 5 days after starting a new infusion site, usually subsides 5 to 7 days after site change, and generally improves after several months of therapy and with effective pain mitigation techniques. In clinical studies, infusion site pain and discontinuations because of site pain have diminished over time as healthcare professionals have become more skilled in managing site pain.[7,14] 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 topical antibiotic treatment. The mechanisms that drive infusion site reaction and pain potentially involve inflammation, vasodilation and pain stimulation. Although prostanoids have demonstrated anti-inflammatory activity,[31,32] depending on the physiologic circumstances, these agents can act to inhibit or promote inflammation.[33,34] Combinations of these actions likely underlie the site pain experienced with SC administration as well as the jaw pain, extremity pain and headache experienced with prostanoids in general.

As PAH centers have gained experience with the use of SC treprostinil, strategies have been developed and refined for managing infusion site pain. Use of a preferred site, such as the abdomen, upper buttocks, lower flanks, backs of upper arm and outer thighs, and avoiding sites with stretch marks, scar tissues, bruises and sites of edema is important for managing infusion site pain/reactions. Site rotation was historically recommended every 72 hours, although more recent experience indicates success for sites maintained for up to 4 weeks or more.[8,14] Indeed, less site pain was experienced by patients who changed the infusion site less than once per week compared with those who employed more frequent site rotation.[6,8] Patients should be encouraged to maintain pain- and reaction-free sites for a longer period of time by changing medication, syringe and tubing every 72 hours to ensure sterility and stability of the medication and to abandon unfavorable sites quickly. Therapy is commonly initiated on the abdomen to allow for self-monitoring and self-administration of topical remedies.

Other recommendations for reducing site pain include rapid dose titration,[6] removing medication droplets from the end of the needle after priming, keeping the pump rate low ($\leq$0.020 ml/h) to reduce the infusion volume, pre-treatment with anti-inflammatory agents and pre-placement of a dry catheter. Dry catheter pre-placement may reduce the local trauma of SC infusion by temporally separating the physical disruption of catheter placement from the inflammatory and vasodilatory responses elicited by drug exposure. The use of medications (pre-treatment with anti-inflammatory agents in addition to oral H1 and H2 [histamine receptors] antagonists) or the use of a dry catheter pre-placement method was explored in a recently completed study of SC treprostinil.[35] Both methods appear to be effective in managing site pain.

Myriad topical and systemic therapies have been used singly or in concert to manage infusion site pain (Table 2). In early clinical studies, site pain management techniques were not described and, in one long-term study, systemic pain medication was discouraged.[8] Current protocols are more likely to include the use of topical therapies such as pluronic lecithin organogel (PLO gel) compounds and/or oral agents.[6,14,27,36] In reference to these therapies, PAH specialty centers will commonly begin with remedies including ice and acetaminophen as first-line options. They often advance to lidocaine patches, gabapentin and tramadol within the first week of therapy as needed. Alternative therapies such as massage, acupressure, acupuncture and relaxation techniques are also viable pain management options. Centers where SC treprostinil use is routine often follow pain management protocols and may partner or consult with a palliative care specialist or pain service, particularly when considering systemic agents. Using a pain management protocol that included the use of thin Duoderm (ConvaTec, Inc., Skillman, NJ) patches with PLO gel, oral agents and psychologic support of patients and their families, one study was able to achieve 0% SC treprostinil discontinuation among 12 patients in a 16-week trial.[36] These data compare favorably with the 5% to 23% discontinuation rates due to infusion site pain/reaction reported in earlier studies of SC treprostinil.[7,8]

The use of pain management protocols, a dedicated nursing staff and follow-up of patients by expert PAH centers has resulted in a low discontinuation rate for site pain. Pain management protocols may include aggressive pre-therapy counseling, minimal site changes (every 4 to 8 weeks) and up-front local and systemic options for pain control. Before therapy initiation in some centers, patients are requested to commit to SC treprostinil for a minimum of 3 months. The patients are contacted via phone at least once a week for the

Table 2 Local, Topical and Systemic Options to Manage Infusion Site Pain

Mode of action	Medication	Comments
Local/topical options:		
First-line remedies	Ice, warm bath with Epsom salt, aloe vera gel, arnica oil, capsaicin cream	First-line options to relieve site reaction or pain
Anesthetic agents	Lidocaine 5% patches, lidocaine/prilocaine cream, Caladryl[a] lotion/cream (pramoxine), Icy Hot[b] (menthol/methyl salicylate)	Analgesic and anti-pruritic effects; used during initiation phase of new subcutaneous site
Vasoconstrictive agents	Hemorrhoid ointment	Anti-pruritic and relieves discomfort
Corticosteroids	Hydrocortisone cream, triamcinolone acetonide, fluticasone propionate nasal spray, clobetasol propionate cream	Anti-pruritic and anti-inflammatory; relieves erythema and dryness
Calcineurin inhibitors	Pimecrolimus cream	Second-line option in patients who have failed to respond adequately to other topical prescription treatments
Histamine H1 receptor antagonists	Diphenhydramine HCl, topical	Anti-pruritic and anti-inflammatory
Histamine H1 and H2 antagonist	Doxepin cream	Anti-pruritic and anti-inflammatory
Combination of multiple drug classes	PLO gel compounds[c]	Anti-pruritic and anti-inflammatory; extensively used (for current and old sites), often as first-line option
Systemic options:		
Non-opioid analgesics	Ibuprofen, acetaminophen	First-line options
GABA analogs	Gabapentin, pregabalin	Second-line option after non-opioid analgesics
First-generation anti-histamine	Hydroxyzine pamoate	Anti-pruritic and anti-inflammatory (for severe cases)
Histamine H1 receptor antagonists	Loratadine, fexofenadine HCl, cetirizine HCl	Anti-pruritic and anti-inflammatory
Histamine H2 receptor antagonists	Ranitidine HCl, famotidine	Anti-pruritic and anti-inflammatory
Opioid analgesics	Tramadol HCl, fentanyl patch, hydrocodone with acetaminophen	For severe pain
Antidepressant	Amitriptyline HCl	Used as analgesic for chronic pain

NSAID, non-steroidal anti-inflammatory drug; PLO gel, pluronic lecithin organogel.
[a]Johnson & Johnson, New Brunswick, NJ.
[b]Chattem, Inc., Chattanooga, TN.
[c]Contain ketoprofen, lidocaine and gabapentin and may also contain ketamine, amitriptyline and clonidine.

first several weeks after initiation to troubleshoot site pain and to encourage them to stay on therapy. Telephone follow-up by a specialty pharmacy or PAH center nurses is essential to modify or escalate management strategies for site reaction or other side effects. In a single-center study with a once per 3- to 4-week site-change protocol for patients on SC therapy, the treatment was well tolerated with a low incidence of complications.[37]

Patient support has been cited as a key component for success in treating patients with SC treprostinil.[27,36] Patients have access to multiple sources of support, including family members, caregivers, healthcare providers, support groups (e.g., the Pulmonary Hypertension Association, Patients Exchanging Experience with Remodulin network) and specialty pharmacies. Educating patients about their disease and its management, setting expectations about the treatment regimen and any anticipated side effects, developing a plan for managing side effects, and maintaining frequent contact are important in a successful SC treprostinil treatment plan.

SC treprostinil and other available prostanoids

Currently, three different prostanoids (epoprostenol, treprostinil and iloprost) are approved for clinical use in the USA, and several are under active investigation. The FDA has approved IV epoprostenol, SC treprostinil, IV treprostinil, inhaled iloprost and inhaled treprostinil for the treatment of patients with PAH (FC II to IV).[38] Thus far, no head-to-head formal comparative studies of these agents have been conducted; therefore, the efficacy and safety of these agents can be compared only in a general way.

Although epoprostenol is the most chemically unstable and has the shortest half-life necessitating continuous IV infusion, it remains a "gold standard" for treatment of severe PAH (FC IV).[38] Epoprostenol has been shown to improve exercise capacity, FC and hemodynamics in patients with PAH.[3] It also appears to improve survival, according to results from a 12-week, randomized trial[3] and two longer-term, open-label studies.[22,23] Based on bioequivalence to SC therapy, the use of IV treprostinil was

approved by the FDA.[21] Studies have demonstrated the efficacy and tolerability of IV treprostinil in the treatment of PAH in de novo patients[15,39] and patients who transition from epoprostenol.[5,13]

Iloprost is another chemically stable prostanoid with a relatively longer half-life (20 to 30 minutes) than epoprostenol, which allows for an inhaled route of delivery.[40] Inhalation of prostanoids permits more targeted drug delivery to the small arterioles of the lungs, which provides selective pulmonary hemodynamic effects and potentially less systemic side effects.[41] Inhaled iloprost, which is approved for FC III and IV patients in the USA, has been shown to improve a composite end-point of FC, exercise capacity and freedom from clinical worsening.[42] Recently approved inhaled treprostinil has also been shown to be safe and well tolerated and to elicit acute, selective pulmonary vasodilation without undue systemic side effects.[43] Recent studies have demonstrated that inhaled treprostinil treatment adjunct to bosentan and sildenafil therapies improved exercise capacity and hemodynamic effects in patients with PAH.[44–46] Inhaled treprostinil has a practical advantage in the ease of delivery because its longer half-life allows drug administration for approximately 2 to 3 minutes 4 times a day compared with inhaled iloprost, which is administered 6 to 9 times a day with each inhalation requiring an average of 4 to 10 minutes.[40,47] Although the advantages of inhaled prostanoid therapy are evident, long-term mortality benefits of this therapy are not as well established as those of parenteral therapies.

Despite the recent approval of a number of novel therapies for PAH, extensive clinical experience has shown that the prostanoid class of drugs is considered to be the most potent treatment for PAH. Among the different routes of prostanoid administration, SC therapy offers continuous, reliable prostanoid delivery without the need for a central venous line and attendant risk, while allowing for increased patient autonomy and quality of life.

In conclusion, subcutaneous treprostinil is an important treatment option in PAH, providing improvements in exercise capacity, signs and symptoms of PAH and cardiopulmonary hemodynamics. Success in maintaining patients on SC treprostinil and improving its benefits has been achieved by rapidly increasing the treprostinil dose to provide therapeutic improvement earlier in the course of treatment, as well as in proactive management of infusion site reaction. Data suggest that rapid dose escalation may also reduce the prevalence of infusion site pain. By combining improved dosing, better infusion site selection, analgesic care (both pharmacologic and non-pharmacologic) and patient support, infusion site pain can be managed and discontinuations due to site pain can be minimized.

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