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Practical considerations for therapies targeting the prostacyclin pathway

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ABSTRACT Therapies that target the prostacyclin pathway play a key role in the treatment of both early- and late-stage pulmonary arterial hypertension, and provide significant clinical benefits for patients. A number of agents have been approved, which are administered *via* intravenous, subcutaneous, inhaled or oral routes. The use of these therapies is associated with practical challenges, relating to the need for up-titration and their routes of administration. We discuss here a number of measures that can be taken to support patients and healthcare professionals in order to address the complexities of using these therapies and to encourage compliance. Providing patients with timely information and education, together with practical advice on managing their medication and associated equipment, assists patients with day-to-day management of therapy. Referral to patient associations and support groups can be of further benefit. With an effective management plan and an experienced multidisciplinary team, the use of therapies that target the prostacyclin pathway can be optimised.



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Practical support for patients and HCPs to facilitate the use of therapies that target the PGI₂ pathway in PAH <http://ow.ly/468S305Dl6m>

Introduction

The prostacyclin (prostaglandin I₂ (PGI₂)) pathway is an important therapeutic target in pulmonary arterial hypertension (PAH). Reduced levels of PGI₂ are associated with pathogenic changes within the lung vasculature [1, 2] and therapies that aim to restore PGI₂ signalling have been shown to play a key role in PAH management [3]. Evidence to support the use of therapies targeting the PGI₂ pathway was first generated in the 1990s when intravenous epoprostenol, a synthetic version of PGI₂, was demonstrated to provide symptomatic and haemodynamic benefits and to improve survival [4, 5]. As a result, epoprostenol was the first drug to be approved for PAH [5]. A number of other therapies targeting the PGI₂ pathway have since become available, administered by *i.v.* [6, 7], subcutaneous [6], inhaled [8–10] or oral [11–15] routes (figure 1 and table 1) [8, 16–26].

These therapies have demonstrated significant clinical benefits for a broad population of PAH patients, and play a key role in the treatment of both early- and late-stage disease. There are, however, some practical challenges associated with the use of these agents, which may contribute to their underuse in clinical practice [27, 28]. The challenges can be broadly grouped into two aspects. Firstly, these drugs require up-titration to find the clinically appropriate dose for each individual patient. Secondly, for some of these drugs, the physicochemical properties require that they are administered *i.v.*, *s.c.* or by the inhalation route. Due to the importance of PGI₂-targeting therapies, it is critical for the wellbeing of PAH

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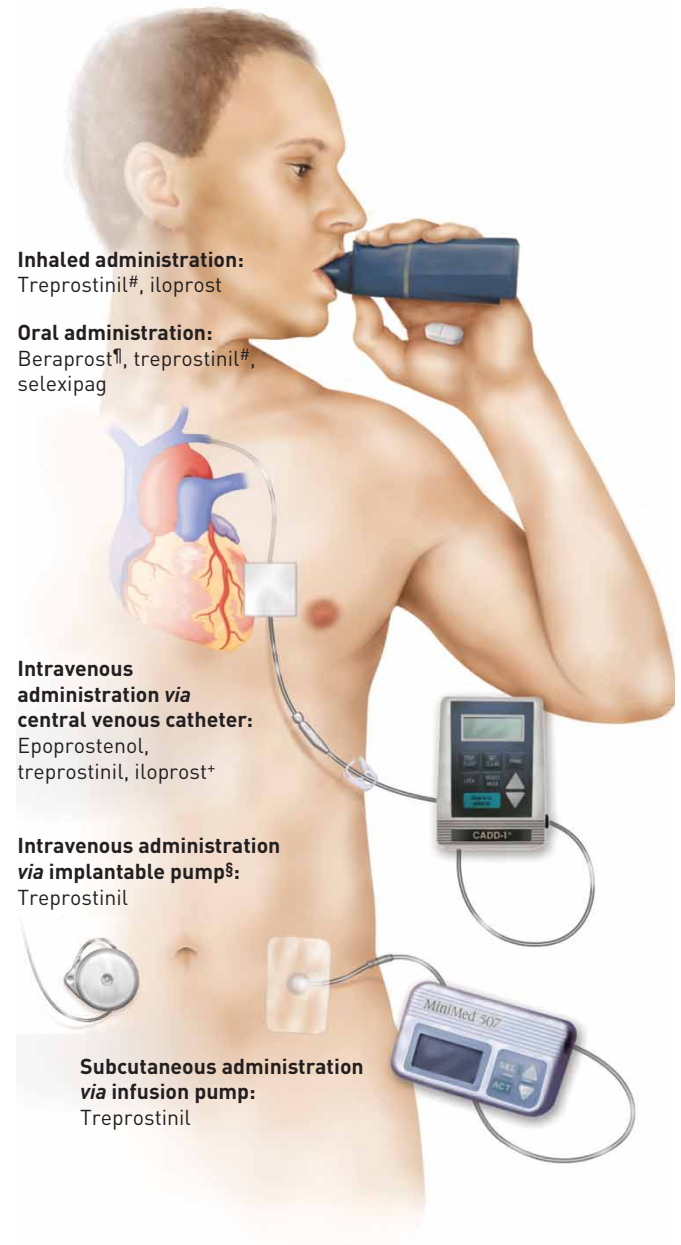


FIGURE 1 Drugs that target the prostacyclin pathway and their routes of administration. [#]: approved only by the US Food and Drug Administration; [¶]: approved only in Japan and South Korea; [†]: approved only in New Zealand; [§]: this pump is under investigation and is not approved in the USA or Europe. Reproduced from [16] with permission from the publisher.

patients that both patients and healthcare professionals (HCPs) are comfortable with their use. In this review, we describe practical ways to facilitate the use of these therapies in PAH, in order to support HCPs and patients. We draw on our own clinical experience, the experience of many other pulmonary hypertension (PH) experts and an expanding literature in this field.

Up-titration of therapies

Therapies that target the PGI₂ pathway require up-titration; the reason for this is two-fold. Firstly, the efficacious dose varies between individuals and the up-titration process allows the clinically appropriate dose for each patient to be achieved. Secondly, up-titration allows patients to initiate therapy at a low dose and increase it gradually, whilst managing potential side-effects associated with activation of the PGI₂ pathway.

Up-titration is performed according to one of three approaches: up-titration to the highest tolerated dose, up-titration to a pre-defined target dose or up-titration until a clinical response is observed. The approach

TABLE 1 Overview of therapies targeting the prostacyclin pathway

PGI ₂ therapy	Approval		WHO FC indication	Mode of administration	Frequency of administration	Half-life	ESC/ERS class of recommendation [#] and level of evidence for use as monotherapy [¶] [3, 17]					
	Europe	USA					WHO FC II		WHO FC III		WHO FC IV	
							Class	Level	Class	Level	Class	Level
Flofan [18] (epoprostenol)	+	+	III–IV	Intravenous	Continuous	<6 min [24]			I	A	I	A
Velettri* [19, 20] (epoprostenol)	+	+	III–IV	Intravenous	Continuous							
Remodulin [6, 21] (treprostinil)	+ ^{##}	+	II–IV	Intravenous	Continuous	34 min [25]			IIa	C	IIb	C
Remodulin [6, 21] (treprostinil)	+ ^{##}	+	II–IV	Subcutaneous	Continuous	85 min [25]			I	B	IIb	C
Tyvaso [8] (treprostinil)	–	+	III	Inhaled	4 times per day, with each inhalation taking up to 3 min [8, 26]	NA			I	B	IIb	C
Orenitram [11] (treprostinil)	–	+	II–III	Oral	2–3 times per day	3–4 h [24]			IIb	B		
Ilomedin[§] [7] (iloprost)	–	–	III–IV	Intravenous	Over 6 h daily	20–25 min [24]			IIa	C	IIb	C
Ventavis [9, 10] (iloprost)	+	+	III–IV	Inhaled	6–9 times per day, with each inhalation taking 3–10 min, depending on dose and nebuliser device [9]				I	B	IIb	C
Dorner^f [15] (beraprost)	–	–	NA	Oral	3–4 times per day	45 min [24]				IIb	B	
Uptravi [12, 13] (selexipag)	+	+	II–III	Oral	2 times per day	6.2–13.5 h ^{¶¶} [12]	I	B	I	B		

PGI₂: prostaglandin I₂ (prostacyclin); WHO FC: World Health Organization functional class; ESC: European Society of Cardiology; ERS: European Respiratory Society; NA: not available. [#]: I, evidence and/or general agreement that a given treatment or procedure is beneficial, useful or effective; II, conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure; IIa, weight of evidence/opinion is in favour of usefulness/efficacy; IIb, usefulness/efficacy is less well established by evidence/opinion; III, evidence or general agreement that the given treatment or procedure is not useful/effective and in some cases may be harmful. [¶]: A, data derived from multiple randomised clinical trials or meta-analyses; B, data derived from a single randomised clinical trial or large nonrandomised studies; C, consensus of opinion of the experts, and/or small studies, retrospective studies or registries. *: known as Caripul in some countries. [§]: approved in New Zealand. ^f: approved in Japan and South Korea [22], a modified-release version is available (Careload [14] and Berasus [23]) and can be administered twice per day. ^{##}: approved in the European Union, except Ireland, Spain and the UK [21]. ^{¶¶}: active selexipag metabolite.

TABLE 2 Protocols for up-titration of therapies that target the prostacyclin pathway

PGI ₂ therapy	Initiation protocol	Up-titration protocol	Target dose and dosing frequency	Dose adjustments	Additional comments
Epoprostenol Flolan [18]	Short-term: 2 ng·kg ⁻¹ ·min ⁻¹ ; if this is not tolerated, a lower dose which is tolerated should be identified [#] Long-term: 4 ng·kg ⁻¹ ·min ⁻¹ less than MTD identified during short-term dosing; if MTD ≤ 5 ng·kg ⁻¹ ·min ⁻¹ , infusion should be started at 1 ng·kg ⁻¹ ·min ⁻¹ [¶]	Increased by increments of 2 ng·kg ⁻¹ ·min ⁻¹ every 15 min or longer [#]	Until maximum haemodynamic benefit or dose-limiting pharmacological effects [#] Administered as continuous infusion ^{#,¶}	Increase: by 1–2 ng·kg ⁻¹ ·min ⁻¹ at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 min [¶] Decrease: gradually in 2 ng·kg ⁻¹ ·min ⁻¹ decrements every 15 min or longer until dose-limiting effects resolve [¶]	Short-term dosing should be conducted in a hospital with adequate resuscitation equipment [#] Abrupt withdrawal of Flolan or sudden large reductions in infusion rates should be avoided due to the risk of potential fatal rebound effects [¶] Except in life-threatening situations, infusion rates should be adjusted only under the direction of a physician [¶]
Veletri [19]	Short-term: 2 ng·kg ⁻¹ ·min ⁻¹ ; if this is not tolerated, a lower dose which is tolerated should be identified [#] Long-term: 4 ng·kg ⁻¹ ·min ⁻¹ less than MTD identified during short-term dosing; if MTD ≤ 5 ng·kg ⁻¹ ·min ⁻¹ , infusion should be started at half the MTD [¶]	Increased by increments of 2 ng·kg ⁻¹ ·min ⁻¹ every 15 min or longer [#]	Until maximum haemodynamic benefit or dose-limiting pharmacological effects are elicited [#] Administered as continuous infusion ^{#,¶}	Increase: by 1–2 ng·kg ⁻¹ ·min ⁻¹ at intervals sufficient to allow assessment of clinical response; these intervals should be at least 15 min [¶] Decrease: gradually in 2 ng·kg ⁻¹ ·min ⁻¹ decrements every 15 min or longer until dose-limiting effects resolve [¶]	Short-term dosing should be conducted in a hospital with adequate resuscitation equipment [#] Abrupt withdrawal of Veletri or sudden large reductions in infusion rates should be avoided due to the risk of potential fatal rebound effects [¶] Except in life-threatening situations, infusion rates should be adjusted only under the direction of a physician [¶]
Treprostinil Remodulin <i>i.v./s.c.</i> [6]	1.25 ng·kg ⁻¹ ·min ⁻¹ for patients new to PGI ₂ infusion therapy; reduce to 0.625 ng·kg ⁻¹ ·min ⁻¹ if 1.25 ng·kg ⁻¹ ·min ⁻¹ is not tolerated	The prescribing information suggests increments of 1.25 ng·kg ⁻¹ ·min ⁻¹ per week for the first 4 weeks of treatment and increments of 2.5 ng·kg ⁻¹ ·min ⁻¹ per week after 4 weeks of up-titration. In clinical practice, the dose is usually increased more quickly, aiming to reach 20 ng·kg ⁻¹ ·min ⁻¹ after 4 weeks [29]	Based on clinical response Administered as a continuous infusion	NA	Avoid abrupt cessation In the case of mild to moderate hepatic insufficiency, decrease initial dose to 0.625 ng·kg ⁻¹ ·min ⁻¹ If transitioning from <i>i.v.</i> epoprostenol, the dose should be increased while simultaneously reducing the dose of <i>i.v.</i> epoprostenol. The transition to Remodulin should take place in the hospital with constant observation of response
Tyvaso [8]	3 breaths (18 µg) per treatment session; if 3 breaths are not tolerated, reduce to 1 or 2 breaths and subsequently increase to 3 breaths as tolerated	Increase by an additional 3 breaths at 1–2-week intervals	9 breaths (54 µg) per treatment session, 4 times daily	NA	Titrate slowly in patients with hepatic or renal insufficiency

Continued

TABLE 2 Continued

PGI ₂ therapy	Initiation protocol	Up-titration protocol	Target dose and dosing frequency	Dose adjustments	Additional comments
Orenitram [11]	0.25 mg twice or 0.125 mg three times daily	Increase by 0.25 or 0.5 mg twice daily or 0.125 mg three times daily, not more than every 3–4 days as tolerated	MTD is determined by tolerability; increase to highest MTD Administered twice or three times daily	If intolerable pharmacological effects occur, decrease the dose in increments of 0.25 mg	If transitioning from <i>i.v./s.c.</i> Remodulin, the dose should be increased while simultaneously decreasing the <i>i.v./s.c.</i> infusion rate In the case of mild hepatic impairment, initiate at 0.125 mg twice daily, increase at 0.125 mg twice daily every 3–4 days Avoid abrupt discontinuation
Iloprost Ilomedin [7]	0.5 ng·kg ⁻¹ ·min ⁻¹ for 30 min	Increase by 0.5 ng·kg ⁻¹ ·min ⁻¹ in 30-min intervals up to 2.0 ng·kg ⁻¹ ·min ⁻¹	MTD within the range of 0.5–2.0 ng·kg ⁻¹ ·min ⁻¹ Administered as an <i>i.v.</i> infusion over 6 h daily	If undesirable side-effects occur, the infusion rate should be reduced until the tolerable dose is found	Should only be used under strict monitoring in hospitals or outpatient clinics with adequate facilities
Ventavis [9]	2.5 µg per treatment session	Increase to 5 µg if initial dose is well tolerated	Administered 6–9 times daily, depending on individual need and tolerability, up to 5 µg per treatment session	In cases of poor tolerability of the 5 µg dose, the dose should be reduced to 2.5 µg per treatment session	In patients with hepatic impairment, special caution should be exercised during initial dose titration
Beraprost Dorner [15]	20 µg three times daily	The dosage may be increased gradually according to symptoms	Maximum daily dose should not exceed 9 tablets (180 µg) If the dose is increased, it may be taken 3–4 times daily	NA	
Selexipag Upravi [12]	200 µg twice daily, 12 h apart	Increased in increments of 200 µg twice daily, at weekly intervals	MTD (can range from 200 to 1600 µg twice daily) Administered twice daily	If the patient reaches a dose that cannot be tolerated, the dose should be reduced to the previous dose level	At the beginning of treatment, and at each up-titration step, it is recommended to take the first dose in the evening If treatment is missed for 3 days or more, Upravi should be re-started at a lower dose and then up-titrated Withdrawal of Upravi should be done gradually, while an alternative therapy is introduced

PGI₂: prostaglandin I₂ (prostacyclin); MTD: maximum tolerated dose; NA: not available. #: short term; ¶: long term.

varies depending on the drug (table 2 [29]). Selexipag is an example of a therapy that is up-titrated to the individual patient's highest tolerated dose, up to a maximum of 1600 µg twice daily [12, 13]. This individualised dosing strategy was employed in the GRIPHON study, in which selexipag showed consistent efficacy when patients were grouped according to whether they received a low, medium or high dose of the drug [30]. These data confirm the validity of titrating to the highest tolerated dose in order to find the efficacious dose [30]. In contrast, inhaled treprostinil is up-titrated with the aim of reaching a target maintenance dosage of nine breaths (54 µg treprostinil) per treatment session, as tolerated [8]. Despite a lack of efficacy data, doses higher than the approved dose of 54 µg treprostinil have been administered in some cases [31]. Intravenous prostanoids and *s.c.* treprostinil are examples of therapies that are usually up-titrated based on clinical response [6, 7, 18]. Clinical response can be assessed using multiple parameters, including haemodynamics, exercise tolerance, World Health Organization functional class (WHO FC), echocardiography and brain natriuretic peptide level. The reasons for the different dose responses between patients are not known, although a number of hypotheses exist. IP prostacyclin receptor density varies among patients and may influence the individual dose required [32–34], as may differences in receptor kinetics or drug metabolism between patients.

Since up-titration is a requirement for the use of therapies that target the PGI₂ pathway, steps can be taken to optimise the process for HCPs and patients. These include taking a flexible approach to the up-titration process, managing side-effects, and providing education and support to patients.

Protocols for up-titration allow flexibility, enabling the process to be tailored according to the needs and preferences of the patient and the treating staff. Titration schemes may be adapted depending on factors such as clinical response, side-effects and experience of the HCP. There is also flexibility for certain therapies regarding dosing frequency; modifying the dosing frequency may help to facilitate successful up-titration [11]. For example, it has been hypothesised that increasing the dosing frequency of oral treprostinil from twice to three times a day improves the pharmacokinetic profile of the drug by reducing peak to trough fluctuations. This may reduce the frequency of dose-limiting side-effects [35–37]; although this has not yet been proven in a randomised controlled trial, it is being evaluated in the FREEDOM-EV trial, which is currently enrolling patients [38].

There is also scope for flexibility regarding where the up-titration process is initiated for certain drugs. Inhaled and oral therapies may in some cases be started at home with adequate supervision and training by a PAH specialist. Subcutaneous treprostinil can be started at home for some patients, while others require hospitalisation for a few days [39] if their disease is less stable and/or side-effects are more severe. In contrast, *i.v.* therapies must always be initiated in a hospital setting with experienced personnel and strict patient monitoring [6, 7, 18].

Prostanoid therapies are associated with several side-effects, including headache, diarrhoea, flu-like symptoms, jaw pain, muscle spasm, flushing and nausea [40]. During up-titration, side-effects may in some cases prevent a patient from reaching an efficacious dose. Informing patients in advance about common side-effects can help to prepare them for the up-titration process. Patients can be reassured that side-effects are more frequent during the up-titration phase and that once the appropriate dose has been reached, the side-effects will improve. Compliance can be improved by explaining to patients that side-effects are often unavoidable to reach an appropriate dose. HCPs can also provide support by advising patients that the dose can be decreased or up-titrated more slowly if side effects are not tolerated. This allows patients to gain a sense of control during the up-titration process.

A number of steps can be taken to proactively manage side-effects. Increasing the dose of *i.v.* prostanoids more aggressively during initiation in the hospital enables patients to experience side-effects in a supportive environment before they are discharged. Providing patients with a supply of analgesics, antiemetics and antidiarrhoeal agents to take home allows them to promptly manage side-effects as they develop. Patients may also take these agents before dose increases if headaches, nausea or diarrhoea have been a problem previously, or to avoid pain/nausea memory.

Despite the importance of up-titrating therapies to an efficacious dose, there may be a reluctance to increase the dose of some therapies. This can be illustrated by *s.c.* treprostinil, where there may be a misconception amongst patients and many HCPs that higher doses cause greater infusion site pain. To counteract this misconception, patients can be informed that infusion site pain is not dose-dependent [41] and higher doses are needed to achieve efficacy [42].

The up-titration process requires patients to be well-informed, with clear explanations about what is involved and that side-effects will abate. By providing support and managing their expectations, patients can be empowered to be involved in their own self-care. Patient engagement and the benefits of involving patients, families and carers in decisions about patient care are discussed further by GAARUP *et al.* [43] in this issue of the *European Respiratory Review*.

Various educational materials on therapies targeting the PGI₂ pathway and the up-titration process are available to patients, such as DVDs, websites and printed information. Patient associations have developed a wealth of information around PAH (e.g. www.ourphlibrary.com). Patients receiving *i.v.* therapies can also access drug-specific web portals that have been developed by pharmaceutical companies to provide information and help with troubleshooting. Using these resources to highlight the benefits of therapy aids motivation to persevere with up-titration. Patients can also learn from the experience of others through patient-directed videos, meeting patient volunteers and attending support groups organised by patient associations. In addition, there are patient chat rooms, including those associated with the Pulmonary Hypertension Association [44]. Introduction to a buddy/patient support system matches individuals to a PAH patient of similar demographics who has been successfully established on therapy, allowing new patients to learn from those with more experience.

To address the complexities of titrating PGI₂-targeting therapies, patients require support from a multidisciplinary team of HCPs. Initiation of these therapies should also be conducted under the guidance of an experienced pulmonary hypertension centre. Successful up-titration not only depends on patient education, but also HCP education, experience and knowledge, both in the hospital and community. As many of the patients will live a significant distance away from their pulmonary hypertension centre, it is advisable that the local community nurses and physicians are aware of possible side-effects and know whom to contact for specialist advice. Nurses play a central role in the multidisciplinary team [45, 46], managing patient expectations, and working with patients to set realistic, measurable and achievable treatment goals [45]. These goals may relate to the patient's symptoms, functional capacity or mortality. Personal treatment goals, such as reaching a particular milestone or life event (e.g. a family wedding), may improve motivation to continue with the titration process. Reassurance and support can be provided to patients by HCPs through regular follow-up, both over the phone and during clinic visits, and provision of emergency out-of-hours contacts. This support is beneficial to the patient, not only during the up-titration phase but also during long-term treatment.

Once patients on therapies that target the PGI₂ pathway have reached their clinically appropriate dose, it is essential they are formally assessed at regular intervals to monitor their clinical status [3]. For those receiving *i.v.* and *s.c.* prostanoids, the intervals between clinic visits are usually shorter since these patients tend to be more unwell, at least initially, and need more attentive follow-up. Tolerance to prostanoids may develop during long-term use [47]. As such, further up-titration may be needed after variable periods of time on the previous efficacious dose. In addition, dose increases may be needed due to disease progression. Regular patient assessment ensures that any necessary dose adjustments can be made in a timely manner.

Considerations relating to the route of administration

There are various challenges related to the routes of administration of therapies targeting the PGI₂ pathway. Taking appropriate action to address these issues is crucial to minimise the impact on patients and carers, and to optimise the benefits that these therapies offer (table 3) [48–50].

Intravenous administration

Several *i.v.* therapies are approved for the treatment of PAH: epoprostenol [18, 19, 26], treprostinil [6] and iloprost [7] (table 1). The European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines cite different levels of recommendation and evidence for each therapy [3, 17], with epoprostenol having the highest level (IA) in patients with WHO FC III or IV disease. Intravenous prostanoids require continuous infusion *via* a central venous catheter due to their short half-lives [6, 18, 39]. This route of administration is complex, and can present challenges for patients, carers and HCPs. In light of this, and given the clear benefits of *i.v.* prostanoids in PAH treatment, steps must be taken to support patients and HCPs (table 3).

Prior to starting therapy, patients can be introduced to the *i.v.* delivery system to help them understand what treatment will entail. As patients need to wear a pump continuously once on therapy [6, 18], providing patients with practice pumps and equipment to take home allows them to get used to wearing and sleeping with the equipment. Only pumps that meet the stringent safety criteria detailed in the prescribing information should be used [6, 26, 51]. For the majority of patients, a battery-operated ambulatory pump is used; an implantable pump for delivery of *i.v.* treprostinil is currently under investigation. The patient is expected to participate in the preparation of the infusion; however, learning the reconstitution process can be lengthy and complicated [6, 7, 18, 52], especially when the patient is unfamiliar with the equipment. Thus, patients will benefit from receiving clear practical advice on this. Practical training allows clinical staff to observe patients, and to assess and identify potential issues with the physical, emotional and cognitive ability of the patient to manage *i.v.* therapy [39]. Staff should consider whether the patient has a suitable home environment and social support system, including a support

TABLE 3 Practical considerations and steps to aid patients on intravenous, subcutaneous, inhaled or oral therapies

Mode of administration	Practical considerations and steps
Intravenous	Provide practice equipment/pumps prior to linking infusion Provide an introduction/education on the <i>i.v.</i> delivery system, the need for a central venous catheter and the up-titration procedure Patient participation in infusion preparation Patient education for managing medication at home and care of <i>i.v.</i> line and sterility Provide patients with a well-defined care plan on hospital discharge, including management of side-effects Provide advice on what to do in case of pump malfunction or a compromised <i>i.v.</i> line Provide advice on practical matters on living with an <i>i.v.</i> line (e.g. showering) Inform local emergency services about the patient's medication in case the patient needs to be seen urgently Use of thermostable epoprostenol [48]
Subcutaneous	Dry siting of the infusion cannula [49] Flexibility about when the site is changed [49] Analgesics [39] Patient education on what to do in case of infusion system malfunction, and the need to carry spare equipment and drug
Inhaled	Educate patients on how to use and look after the devices Written materials including brochures and tools to aid compliance Medication reminders through alarms or apps on smartphones InSight training devices to reinforce effective breathing patterns and check adherence [50] Ensure that the patient understands the basic function of the medication, the importance of regular dosing and what to do if a dose is late or missed
Oral	Support for management of their side-effects Support and tools to aid compliance Medication reminders through alarms or apps on smartphones Ensure that the patient understands the basic function of the medication, the importance of regular dosing and what to do if a dose is late or missed
All routes	Education on the up-titration process Patient associations/support groups Written materials, DVDs and online information

person committed to assisting with care of the infusion if the patient is unable to do so [39, 45]. A specialist team of PAH physicians and nurses is required to deal with the complexities of *i.v.* therapy [39].

Placement and removal of the central venous catheter may require surgery under local anaesthesia and hospitalisation [6, 53], although it is sometimes performed as an outpatient procedure. Once the infusion has been set up and the patient is ready to be discharged, it is essential that a well-defined care plan is in place. Patients also benefit from receiving written materials [54] and other sources of information, such as DVDs and online resources.

Intravenous administration is associated with a risk of catheter occlusion, venous thrombosis [39, 47] or thromboembolism [39], line infections [39], and catheter-related sepsis [18, 55]. Educating patients on how to care for their *i.v.* line is therefore important. Patients must be taught how to maintain sterile conditions when preparing infusion cassettes and syringes, and of the need to keep the cannula insertion site clean and dry. A solution of 2% chlorhexidine in 70% isopropyl alcohol can be used to clean the site [56]; it should be allowed to dry completely before applying a waterproof dressing. Risk of line infection can be reduced by using single-lumen rather than double-lumen catheters [57, 58], and by using closed-hub systems with protected connections [59–61]. Early recognition of potential signs of infection is essential [62], as sepsis from line infections can be fatal. Cases of line/tunnel infection should be treated as a medical emergency using *i.v.* antibiotics, with peripheral blood cultures sent for investigation and the existing line promptly removed once alternative *i.v.* access has been achieved. Less serious side-effects of *i.v.* administration, such as local skin reactions to dressings, may also occur. Testing alternative dressings on the underside of the forearm allows sensitivity to be checked prior to applying the dressing to the infusion site, and sterile application of barrier films below the dressing may help. In some cases, referral to a dermatologist may be needed.

Serious side-effects may occur on interruption or withdrawal of *i.v.* prostanoids [4, 18], which can result from pump malfunctions or if the line is erroneously compromised. A compromised line can lead to cardiovascular collapse [63], which in our experience, can occur within minutes, although this complication is exceedingly rare, especially with appropriate patient education. In the current era, the risk of *i.v.* infusion interruption leading to fatal side-effects may be lower than it was previously, as an increasing number of patients are now taking an endothelin receptor antagonist and/or phosphodiesterase-5 inhibitor, in addition to an *i.v.* prostanoid [64]. Nevertheless, patients must be taught what to do if treatment interruption occurs. It may be helpful to provide patients with information to pass on to their local HCP and emergency facilities regarding how to manage *i.v.* prostanoids. Arranging for the patient to be reviewed in their local hospital allows a clear management plan to be put in place in case of an emergency. Instructing personnel to never turn off the pump is crucial, even in cases of symptomatic hypotension. Information can be attached to the pump itself detailing what to do in an emergency and listing the contact details of the PAH specialist. Instructing HCPs and local emergency personnel not to use the central line to administer other medications is also important, as this can result in a bolus dose of prostanoids and side-effects related to over-dosing, such as hypotension. Patients are encouraged to be assertive to prevent catheters from being used for anything other than prostanoid administration.

Intravenous prostanoids can affect physical, social and emotional aspects of the patient's life, and also the lives of family and close friends. Causes of physical discomfort associated with *i.v.* therapies include the ice packs that need to be used with nonthermostable epoprostenol. These can be avoided by using room temperature-stable epoprostenol [19, 26, 48], which negates the need for frozen gel packs and permits less frequent cassette changes. It also improves convenience by allowing patients to prepare their infusions ahead of time and store the cassettes for up to 8 days before use. Patients on temperature-stable epoprostenol who meet specific criteria may qualify for a programme where the speciality pharmacy ships seven fully-prepared cassettes on a weekly basis to the patient's home. This avoids the step of the patient or carer having to prepare the medicine. It is, however, essential that the patient and carer can prepare the infusion in an emergency situation, and that checks of this capacity are made on a regular basis by their HCPs. Physical discomfort can also be caused by the *i.v.* line itself. For example, patients may have discomfort when driving a car due to the seatbelt rubbing on the tunnelled line. While *i.v.* prostanoid therapies offer improvement in clinical status and exercise tolerance, physical day-to-day activities may be limited. Practicalities of how to undertake activities such as showering, sport or sexual intercourse while wearing a pump need to be considered. Patients benefit from practical advice, preferably in written form [54], on how to live with the *i.v.* line, such as how to shower using waterproof dressings.

Patients need adequate time and a suitable place to prepare infusions, which may affect social and work activities. Proximity to a hospital and PAH specialist is a consideration in case of pump malfunctions. When travelling, patients need to take spare equipment and pumps, requiring extra luggage capacity, and should carry documentation to allow them to take their equipment and solutions through airport security. Intravenous therapies can also impact the emotional wellbeing of the patient. The requirement to wear a pump can be a reminder of being ill and affect the patient's confidence, causing difficulties when forming personal relationships. There may be intimacy and body image concerns, especially for young patients, who may worry about how to conceal the pump in their clothing. Empathetic HCPs and referral of patients to patient associations and support groups can help to address the physical, social and emotional aspects of using *i.v.* therapies. Some patients may also benefit from professional psychological counselling. It is important to acknowledge that *i.v.* therapy leads to added responsibility for families and carers, and that this can also impact their emotional and social wellbeing.

Subcutaneous administration

Subcutaneous treprostinil was first approved for use as a PAH treatment in 2002 [6] and in the current ESC/ERS guidelines it is recommended for use in patients in WHO FC III or IV [3, 17] (table 1). Subcutaneous treprostinil is administered as a continual infusion *via* a *s.c.* catheter [6]. It has a longer half-life than epoprostenol [62] and as a result, the risk of haemodynamic compromise within a short period of time due to rebound pulmonary constriction appears to be lower. It is available in pre-mixed vials [6, 65], is stable at room temperature and can be infused continuously for 72 h without the need for ice packs [6, 62]. Subcutaneous therapies do not require central venous access, utilise only a small syringe pump, and have a low risk of bacteraemia, catheter or venous thrombosis, and thromboembolism [39].

Although the *s.c.* mode of administration offers advantages, the delivery of a continuous parenteral infusion is not without practical challenges. Infusion site pain and reaction were the most common adverse reactions reported in clinical trials, occurring in 85% of patients [6, 42]. Failure to address infusion site pain may lead to discontinuation of treatment [6, 42]. Although site pain is not dose-dependent [65] and is manageable in the majority of patients, local, topical or systemic analgesics may be required [39].

Patients with chronic pain may need referral to a pain specialist. HCPs should consider dry siting of the infusion cannula before the drug is given to allow the patient to get used to the cannula, which itself can be painful [49].

Localised abscess formation at infusion sites may occur [39] and a lack of suitable sites may become an issue with chronic use. Patients who are on *s.c.* treprostinil for 10 years or longer may have skin hardening and no suitable areas to place the catheter. There is scope for flexibility with regard to how frequently the site is changed. Historically, it was suggested that the site should be changed every 3–4 days [49, 65]. However, in current practice, the site does not have to be changed so frequently [49, 66]. As treprostinil can cause significant site pain, which abates after several days, patients often use the same site for weeks or months [67], providing the tissue at the infusion site remains healthy.

Patients, carers and HCPs should be aware of the possibility of infusion system malfunctions. These can lead to adverse events related to symptoms of excess treprostinil, such as nausea, or drug interruption, resulting in a return of PAH symptoms such as dyspnoea [6]. Although these events are uncommon in clinical practice, patients are advised to carry a spare pump, drug vials, necessary consumables and the emergency contact details of their pulmonary hypertension centre at all times.

Inhaled administration

Treprostinil [8, 68] and iloprost [9, 10] are inhaled agents for the treatment of PAH (table 1). The inhaled route avoids the need for *s.c.* or *i.v.* access and the pump delivery systems associated with the infusion of parenteral prostanoids [39], and reduces systemic side-effects [52, 69]. For patients who cannot manage a parenteral infusion, for example those with extensive digital ulcers and limited dexterity, inhaled agents may provide an alternative means of targeting the PGI₂ pathway. Current ESC/ERS guidelines support the use of inhaled therapies for the treatment of WHO FC III or IV patients (table 1) [3, 17].

The use of inhaled therapies can be quite time-consuming as a result of the frequency and length of the inhalations, as well as the time required for drug preparation and device maintenance [8–10, 55, 68]. This may affect patient compliance, ultimately reducing the efficacy of the treatment. Inhaled treprostinil should be administered four times per day [8], with each inhalation taking up to 3 min [68]. Inhaled iloprost can be even more time consuming, requiring six to nine inhalations per day, with each inhalation taking between 4 and 10 min depending on the dose and nebuliser [9, 10]. For both therapies, time must also be spent maintaining the nebuliser by cleaning it daily, with a more thorough clean on a weekly basis [10, 68]. For iloprost, the drug chamber must also be rinsed after every use. A number of practical steps can be taken to aid in the use of inhaled therapies (table 3). Of particular importance is detailed education on the mode of administration, including teaching patients how to use and look after the devices correctly. Written support materials including brochures and tools to aid compliance are also useful. Patients may set up medication reminders through alarms or apps on their smartphones. Pulmonary hypertension centres may use InSight training devices to reinforce effective breathing patterns and check adherence [50].

Inhaled therapies may cause side-effects related to the route of administration, including cough, throat irritation, pharyngolaryngeal pain and risk of bronchospasm [8–10]. As they are not administered continually, patients are not dosed overnight, which is likely to result in sub-efficacious plasma drug levels while sleeping.

The risk of a rebound effect cannot be excluded in case of interruption of inhaled therapies [9]. Therapy should be resumed as soon as possible [8] and an alternative treatment considered in critically ill patients [9]. Providing patients with a back-up device will help in case device malfunction occurs [8].

Oral administration

Oral therapies that target the PGI₂ pathway (table 1) were developed to address the challenges associated with the other routes of administration. Currently, there are three approved oral drugs: beraprost (only approved in Japan and South Korea) [14, 15, 24, 70]; treprostinil (only approved in the USA) [11]; and selexipag (approved in the USA, Europe and a number of other countries worldwide) [12, 13, 71]. Compared with most parenteral PGI₂ therapies, these drugs have a relatively long half-life [12, 20, 22]. As these drugs have not been studied in WHO FC IV patients, the current ESC/ERS guidelines recommend the use of selexipag in WHO FC II and III patients as monotherapy or combination therapy, and state that beraprost and treprostinil may be considered in WHO FC III patients as monotherapy [3, 17] (table 1). In summary, oral therapies should therefore not be seen as substitutes for parenteral therapies in WHO FC IV patients.

Although oral administration is relatively simple compared with the parenteral routes, up-titration is still required. There also remains a need for comprehensive patient education to ensure that patients understand the function of the medication, the importance of regular dosing and what to do if a dose is late or missed. Patients treated with selexipag need to be informed that if they interrupt treatment for 3 days or longer, it is recommended that they restart at a lower dose and re-titrate [12, 13]. The risks of

abruptly stopping parenteral therapy are well-recognised [4, 6, 18]. However, less is known about the impact of interrupting oral therapies that target the PGI₂ pathway. Patients require advice on how to manage their drug regimen if they are going to be nil by mouth due to the need for surgery. In the event of a planned short-term treatment interruption for patients unable to take oral medications, temporary use of *i.v.*, *s.c.* or inhaled therapies may be considered. A recent analysis from the phase III GRIPHON study with selexipag indicated that treatment interruption was generally manageable and well-tolerated [72]. After re-titration, most patients reached similar selexipag doses to those received prior to stopping treatment, indicating that treatment can be successfully restarted [72].

Although oral drugs are more convenient than other routes of administration, patients may neglect to take their tablets and compliance needs to be considered. Data from other disease areas show that compliance for orally administered therapies can be suboptimal [73–75] and it is likely that patients who need to take medication more frequently will be less compliant. HCPs should emphasise the need for medication compliance, and provide support to patients and their carers in order to maximise compliance and ensure that patients receive the full treatment benefits. As for inhaled therapies, patients may set up medication reminders through alarms on their smartphones.

Conclusion

A wealth of evidence exists on the benefits of therapies that target the PGI₂ pathway in PAH. These agents have a good risk–benefit profile and provide significant therapeutic benefits to patients. However, administration is not necessarily straightforward due to the need for titration and considerations regarding route of administration. An important aspect of optimising the use of these therapies is to address the practical challenges associated with their use. Practical advice and support delivered in a timely manner helps patients to overcome their concerns about treatment. With an effective management plan and support from an experienced multidisciplinary team, dealing with the complexities of therapies that target the PGI₂ pathway becomes more manageable.

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