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EXPERT REVIEWS

Inhaled iloprost for therapy in pulmonary arterial hypertension

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Iloprost (Ventavis®, Bayer Schering Pharma, Germany) is a synthetic prostacyclin that is used in its inhalative form for the therapy of pulmonary arterial hypertension. Long-term therapy can increase exercise capacity and quality of life. The use of modern nebulizers especially designed for the administration of iloprost guarantees the pulmonary deposition of the required doses and systematically minimizes side effects. Regarding existing data, inhalative iloprost acts in effective and safe combination with other classes of medication; indeed, such combination therapy is frequently necessary in pulmonary arterial hypertension.

Keywords: inhaled iloprost • PAH • prostanoids • side effects of therapy • therapy algorithm

Pulmonary arterial hypertension (PAH) summarizes a group of diseases that are characterized by increased pressure in the pulmonary circulation system. They are diagnosed by invasive right heart catheterization.

Until the middle of the 20th Century, studies on PAH primarily involved animal and anatomical studies. The essential research findings that brought about a better understanding of this disease and its pathophysiology were obtained within the last several decades. The epidemic occurrence of PAH in Europe during the 1960s was associated with the appetite-suppressant drug aminorex, which prompted the WHO to initiate the first expert meeting about PAH to determine clinical and diagnostic standards. This first meeting was followed by many international conferences. The last conference took place in 2008 in Dana Point, CA, USA, resulting in an update of the classification of pulmonary hypertension (PH) as well as of diagnostic and treatment algorithms [1,2]. The drugs that have been developed within the last years focus on class 1 PAH only (**Box 1**). The current hemodynamic definition of PAH requires precapillary PH (defined as mean pulmonary arterial pressure ≥25 mmHg, pulmonary wedge pressure ≤15 mmHg and a normal or reduced cardiac output) and includes several different diseases with similar changes within the lung vessels. International therapy algorithms and national specified recommendations have been developed.

The current European algorithm was approved in 2009 through the cooperation of the European Society of Cardiology, the European Respiratory Society and the International Society of Heart and Lung Transplantation [3].

In addition to addressing specific medications, the algorithm refers to several additional measures that should be addressed, such as recommendations for travel, physical activity, rehabilitation, birth control, infection prevention, psychosocial support and supportive therapies such as oral anticoagulants, oxygen and diuretics.

Classes of specific PAH medications include prostanoids (beraprost, epoprostenol, treprostinil and iloprost), endothelin-receptor antagonists (bosentan and ambrisentan), phosphodiesterase-5 inhibitors (PDE-5; sildenafil and tadalafil) and calcium channel blockers (CCBs; only for so-called 'vasoreactive patients' in idiopathic PAH [IPAH], heritable PAH and PAH due to anorexigens in functional classes I–III). Different modes of administration exist for prostanoids; for example, treprostinil can be injected intravenously, subcutaneously and inhaled, iloprost can be inhaled or injected intravenously, while epoprostenol is only administered intravenously. Beraprost is only given as oral medication. The current guidelines also suggest that an early combination therapy can be considered if clinical improvement under monotherapy is not satisfactory, which was previously only considered for functional class IV.

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Box 1. Clinical classification of pulmonary hypertension.

Class 1: Pulmonary arterial hypertension
1.1. Idiopathic pulmonary arterial hypertension
1.2. Heritable:
1.2.1. Bone morphogenetic protein receptor type 2
1.2.2. Activin receptor-like kinase type 1, Endoglin
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4. Associated with:
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anaemia
1.5 Persistent pulmonary hypertension of the newborn
1´ Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis
Class 2: Pulmonary hypertension owing to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
Class 3: Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive patterns
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
Class 4: Chronic thromboembolic pulmonary hypertension
Class 5: Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Adapted from [1].

It must be mentioned that the approval for the endothelin-receptor antagonist, sitaxentan, was withdrawn by the US FDA in December 2010 because of some sudden deaths assumed to be associated with sitaxentan.

Iloprost

Chemistry

Iloprost is a synthetic analogue of the endogenous prostacyclin PGI_2. It has a high affinity for the prostacyclin receptor and a high molecular stability. The differences between iloprost and PGI_2 are that the molecule has a methyl group at C_{16} and that the atomic orbitals of the C_{18} and C_{19} carbon atoms are sphybridized, which in turn leads to the formation of a triple bond. The longer half-life of iloprost results from the fact that the enol oxygen in the upper ring structure of PGI_2 has been replaced by a methylene group (Figure 1).

Pharmacodynamics

Iloprost stimulates adenylate cyclase by binding to specific membrane receptors (IP-receptors) and other receptors that are localized on the cell surface or in the nucleus (prostaglandin E receptor, peroxisome proliferator-activated receptor). The result is an increase in cAMP level. This in turn leads to a strong inhibition of platelet aggregation and all reactions related to it. A similar process takes place with respect to vasodilatation. An increase of the 'second messenger' cAMP in the muscle cells activates the calcium pumps and thus makes calcium stream out of the cytoplasm. In addition, it opens the potassium channels, which in turn causes hyperpolarization. The increased intracellular cAMP level inhibits the myosin kinases. In the end, this results in vasorelaxation, with a reduction of vessel resistance and increased blood flow.

The prostanoid system thus closely interacts with systemic hormonal and neuronal factors as well as with the interior of cells. This means that the intracellular ion concentration (e.g., Ca^{2+}), as well as enzyme activities (e.g., adenylate cyclase and/or guanylate cyclase), have a decisive influence on the volume of endogenous prostanoid synthetase.

Regardless of structural differences, iloprost has a pharmacological profile similar to endogenous PGI_2 [4]. This has been demonstrated by tests on several animal species, in healthy test subjects and in patients. A comparison of the platelet-inhibiting effect proved that iloprost is up to ten-times more potent than PGI_2 [5].

Iloprost inhibits thrombocyte activation in all stages, and it inhibits platelet activation, regardless of the kind of stimulus.

Aggregation inhibition is reversible and returns to the original value approximately 1 h after the end of the infusion. The inhibition of thromboxan release by iloprost has been demonstrated during the infusion of 1 and 2 ng/kg/min of iloprost [6]. Vasodilatation in healthy test subjects was proven indirectly by preventing vasoconstriction induced by cold [7]. It has been possible to prove that *in vitro*, iloprost inhibits the growth of the smooth muscle cells of the human pulmonary artery [8,9]. During the past several years, many other effects of iloprost have been found, including its effect on macrophages, monocytes and T cells (acting as a mediator) [10]. Therefore, iloprost has a protective influence on the integrity of the endothelium; it inhibits inflammatory processes and thus influences vessel remodeling *in vitro*. In addition, it causes immunomodulatory effects [11].

Pharmacokinetics & metabolism

After intravenous application of iloprost, the plasma level drops in two phases. The first drop after 2.8 ± 1.6 min depends on the distribution of the agent in the body. The second half-life of 26 ± 7.2 min shows how it is metabolized. Iloprost is completely metabolized by β-oxidation. Approximately 70% of the main metabolites are eliminated through the kidneys as glucuronic acid and/or sulphuric acid conjugates [12].

The pharmacokinetic profile of iloprost in the alveolar compartment has been investigated with isolated, blood-free, perfused rabbit lungs with two different deposition dosages (75 and 900 ng). The decisive difference involved absolute intravascular bioavailability (by definition, the bioavailability is 100% for intravenous application). An absolute intravascular bioavailability of 63% for an inhalative deposition dose of 75 ng has been found; for the dosage of 900 ng, this value was only 14%. A significant increase in the inhalative dosage did not lead to an adequate increase in the perfusate level. The dosage-related reduction of the passage of iloprost from the alveolar to intravascular space might be caused by processes of inhibited perfusion or carrier-related transportation processes that have not yet been fully clarified. Furthermore, it has been shown that the inhalative application of iloprost leads to faster metabolization by β-oxidation than its intravascular application [13].

Pharmacokinetic calculations concerning the inhalative application of iloprost in humans have been studied by comparing three nebulizers [14]. The effectiveness (i.e., the reservoir or nebulized dose inserted into the mouth) varied between 13 and 25% such that for the purposes of the investigation, an adjustment was made to 5 µg of iloprost at the mouthpiece. Inhalation times ranged from 10 to 12 mins; after only a few minutes, detectable levels were measured in the serum. The maximum serum concentration measured after inhalation was shown to range from 65 to 300 pg/ml. This value was reached at the end of inhalation and dropped quickly, with a half-life ranging from 6.5 to 9.4 min.

Hemodynamic efficacy of inhaled iloprost

As compared with intravenous administration, the advantage of the inhalative administration of vasodilatative drugs in PAH therapy is a lower incidence of side effects because of the organ-specific action in the pulmonary vessels. This advantage was also shown in a study that compared intravenous epoprostenol with inhaled nitric oxide (NO) in patients with PH [15].

In a pilot study, inhalative NO, inhalative and intravenous epoprostenol, and inhalative iloprost were compared in six patients with PAH. Both inhalative prostanoids showed comparable hemodynamic effects. The effects mediated in this study by inhalative epoprostenol lasted up to 30 min, while the iloprost effect lasted up to 120 min [16]. The application device for iloprost was a jet nebulizer (IloNeb with Aerotrap reservoir [produced by Nebutec, Elsenfeld, Germany] with Pulmocar battery compressor [produced by Sanesco Medizintechnik, Vienna, Austria] with a fluid flux 0.15 ml/min; mass median aerodynamic diameter of particles 2.9 ± 3.1 µm). During one inhalation, 1.5 ml from a 10-ml solution (100 µg iloprost/10 ml in 0.9% NaCl) were nebulized for 10–15 min.

Another study compared the acute hemodynamic effect of one inhalation of NO (40 ppm) and iloprost (14–17 µg) in 35 patients with IPAH [17]. The study was carried out with the aforementioned jet nebulizer (IloNeb with Aerotrap reservoir with Pulmocar battery compressor). Iloprost was more effective at decreasing the pulmonary arterial pressure and vascular resistance, and it produced a significantly greater increase in the cardiac output as compared with NO. The hemodynamic changes after iloprost inhalation showed significant differences from the initial values to an average of 45 mins.

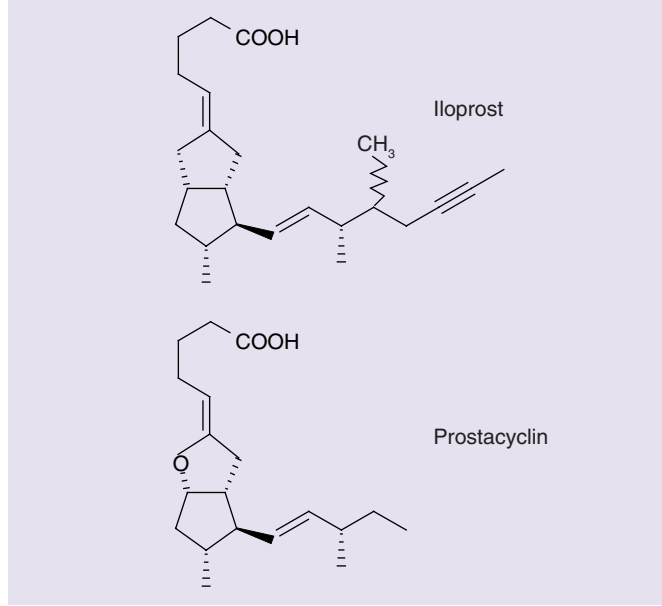

Figure 1. Iloprost and prostacyclin.

Over time, several new inhalation devices have been developed [18], and clinical studies of the efficiency of these devices have been conducted [14,19]. Today, the older jet nebulizers are less frequently used in favor of newer ultrasonic devices that deliver more constant doses of iloprost at the mouthpiece per inhalation (that is, 2.5 or 5.0 µg). Modern devices also offer features such as inhalation-triggered drug release, which contributes to achieving an optimum efficiency. Both the European (Venta-Neb [NEBUTEC med. Produkte Eike Kern GmbH, Germany]; HaloLite AAD [Respironics Germany GmbH, Germany], Prodose AAD [Respironics Germany GmbH] and I-neb AAD [Respironics Germany GmbH]) and the American (I-neb AAD and Prodose AAD) regulatory authorities recommend several devices for drug application. To charge these devices with iloprost, 20-µg (2 ml) and 10-µg (1 ml) vials are currently available. In the USA, a higher concentrated solution, 20-µg (1 ml), has been approved for administration in patients with long inhalation times.

Several reviews summarize the results of existing studies about inhalative iloprost [18,20] and provide additional information regarding the treatment of PAH in children [21]. Throughout these review studies, iloprost is shown to have an equivalent or better acute effect on hemodynamics as compared with other vasodilatory medication.

By combining inhalative iloprost with PDE-5 inhibitors, the hemodynamic effects can be amplified and prolonged. In 11 patients (eight with IPAH), the hemodynamic effects of an inhalative application of iloprost (1.4 µg at the mouthpiece) were observed for a period of 2 h [22]. After the acute iloprost effect had decayed, a dual PDE-5 inhibitor (tolafentrin) was applied. Tolafentrin itself did not produce any hemodynamic effect, but a subsequent second iloprost inhalation led to an increased and prolonged response as

compared with iloprost alone. The enhanced and prolonged effect of inhalative iloprost after the application of a PDE-5 inhibitor has also been shown in five patients with IPAH [23]. Various doses of sildenafil were given, but an increase beyond 25 mg of sildenafil did not result in additional benefit. This aspect was investigated further in another study with 30 patients (ten with IPAH and 13 with chronic thromboembolic PH). After testing doses (12.5 and 50 mg) for sildenafil and inhaled iloprost (2.8 µg at the mouthpiece) monotherapy, both drugs were combined, and the greatest reduction in pulmonary vascular resistance was achieved with a combination of iloprost with 50 mg of sildenafil [24]. Additive effects for inhalative iloprost have also been demonstrated in the case of pre-existing epoprostenol therapy. In a study with eight IPAH patients pretreated with intravenous epoprostenol (12–30 ng/kg/min), additional iloprost inhalation (30 µg within 15 min with a pressure nebulizer) led to an improvement in hemodynamics [25].

Clinical efficacy of inhaled iloprost

A subgroup of PAH patients have benefited from CCB therapy, but before CCB therapy can be used, patients must be tested to see if they are positive for a so-called CCB responder status. Patients responding to CCBs in most cases show a decrease in mean pulmonary arterial pressure below 40 mmHg after the administration of a test dose of CCB [26]. To avoid augmentative and prolonged reactions and thus ensure the safety of patients, responder status is not detected by testing with CCBs. Over the years, it was established that CCB responders could be identified by testing patients during right-heart catheterization with intravenous adenosine, inhalative NO or intravenous epoprostenol. The criteria that define a positive responder status based on the hemodynamic answer to the test drug have been published [27], and these recommendations have been confirmed by an analysis of existing study data for patients with IPAH [28] and PAH [29]. Iloprost can also be applied in vasoreactivity testing [30] prior to CCB therapy. A current review summarizes existing data about vasoreactivity testing prior to CCB therapy [31].

Chronic treatment with inhalative iloprost

In an uncontrolled, monocentric trial, 24 IPAH patients were treated for 12 months with 100–150 µg of inhalative iloprost filled into a jet nebulizer per day [32]. In this study, the inhalative iloprost treatment resulted in a significant improvement in hemodynamics as well as in the results of a 6-min walk test. By contrast, we investigated the data for 15 out of 18 IPAH patients who had received a comparable dose of inhalative iloprost for 12 months; we found no improvement in hemodynamics [33].

In another uncontrolled, multicenter study with 81 PAH patients (64 IPAH), 51 patients were treated with inhalative iloprost for up to 24 months. It was shown that the majority of patients achieved a clinical stabilization despite existing functional limitations [34].

Motivated by these findings, another small study investigated whether other classes of PAH patients benefit from inhalative iloprost. In a study with 12 patients (seven CTEPH, four PAH and one IPAH), an inhalative iloprost therapy (100–150 µg/day) with a mean treatment period of 10 ± 5 months (range: 2–19 months) did not lead to clinical improvement. The majority of patients terminated therapy because of deterioration in hemodynamics or clinical worsening [35].

Alternatively, one study investigated the use of inhalative iloprost with 19 PH patients (12 IPAH) with acute right heart failure. After initial clinical stabilization, iloprost therapy was continued (100–200 µg per day) over the following month. In the first 3 months, hemodynamic parameters as well as the results of a 6-min walk test improved, and four patients (21%) died [36].

In a multicenter, double-blind, randomized, placebo-controlled pivotal study with inhalative iloprost, 203 patients (IPAH, PAH associated with collagenosis and chronic thromboembolic PH) were involved. Patients were treated with six to nine inhalations daily (2.5 or 5.0 µg of iloprost at the mouthpiece vs placebo). The primary end point was an increase in 6-min walk distance (6MWD) of at least 10% and an improvement in the New York Heart Assocciation (NYHA) functional class in the absence of deterioration of the clinical condition or death within the 12-week period of the study [37]. Iloprost therapy led to a significant improvement in this combined end point in comparison to the placebo group. According to a logistic regression model, the probability of reaching the end point was not dependent on the form of PH. The IPAH group showed the greatest increase in 6MWD.

Many uncontrolled therapy studies using inhalative iloprost have been published, but it is not always possible to compare the results of these studies because of the different nebulizers and different patient populations that are used.

An overview of the literature on inhalative long-term therapy with iloprost is given in Table 1.

Supplementary studies that investigate combination therapies with inhalative iloprost as one of the combination therapies have also been published.

In 20 patients with IPAH, nine of whom had been previously treated with inhalative iloprost, an additional application of bosentan was added. The combination was shown to result in a significant improvement of parameters for cardiopulmonary exercise and in 6MWD [38].

In another investigation of 16 PH patients (ten with PAH) who showed clinical worsening under prostanoid therapy (i.e., ten patients with inhalative iloprost for more than 12 months), those receiving bosentan showed a significant improvement with respect to their clinical situation, different echocardiographic signs and 6MWD [39].

In a study from 2003, 14 out of 72 PAH patients who experienced deterioration under inhalative iloprost monotherapy were switched to a combination therapy with sildenafil. Under the combination therapy with iloprost and sildenafil, all of the patients showed hemodynamic and clinical improvements [40].

Similar results in terms of improvements in clinical status and 6MWD were found in a study published in 2006 with PH patients; this study investigated inhalative prostanoids in combination with other PH medication [41].

Of particular interest from a methodological standpoint is one study involving 23 patients with congenital heart disease; the study employed an initial combination therapy of two drugs. Oral PGI_2

was titrated up to the maximum tolerated dose and combined with inhalative iloprost (20 µg daily). After 12 months, 6MWD and NYHA class improved significantly [42].

A fifth double-blind, randomized, placebo-controlled combination so-called 'STEP' study involving inhaled iloprost included 67 clinically stable PAH patients (37 had IPAH) undergoing bosentan therapy. For 12 weeks, either a placebo or iloprost was inhaled. After 12 weeks of receiving the combination therapy, improvement in 6MWD had not reached statistical significance ($p = 0.051$), but secondary end points (e.g., improvement of NYHA class and time to clinical deterioration) showed significant benefits for the patients who received combination therapy [43].

A so-called 'Combi' study investigated a combination of inhalative iloprost and bosentan in an open-label controlled study. The study was terminated prematurely after 40 patients with IPAH had been randomized. This was due to an interim analysis that revealed that the primary end point (i.e., improvement in 6MWD) could not be reached with the planned number of patients [44].

Another current publication presents 2 years of data on 63 PAH patients (40 with IPAH) under inhalative iloprost therapy [45]. The study design included a 3-month randomized period (with or without iloprost), followed by an observation period of up to 24 months.

In the first 3-month period, the premature discontinuation was equal in both groups (i.e., seven patients each). Subsequently, 36 out of 52 patients were included in the long-term phase and completed the 24-month iloprost treatment period. Frequent explanations for discontinuation were related to drug inhalation (n = 6) or other reasons (n = 6). Only two patients died during the long-term phase of the study and two other patients required transplantation. The statistically estimated 2-year survival rate on iloprost monotherapy was 91% for IPAH patients and 62% for the other PH group that included associated PAH, lung and chronic thromboembolic disease. For 31 patients, significant improvements in 6MWD and hemodynamics were observed after 24 months.

Table 1. Long-term trials with inhaled iloprost as the first-line therapy.

Patients	Characteristics	Ref.
76 IPAH patients	Uncontrolled study for a mean of 12 months	[48]
22 children (4–18 years of age, 12 with IPAH and ten with PAH associated with CHD)	Uncontrolled study for a median of 9 months	[47]
63 PH patients (17 with IPAH, 15 with CTEPH, 12 with CTD, 11 with CHD and 11 with lung diseases)	Uncontrolled study over 3 months	[46]
13 patients with PoPH	Retrospective study for up to 36 months	[51]
Five PAH patients (CREST syndrome)	Uncontrolled study for a mean of 13 months	[52]
Five PH patients (four with PAH)	Uncontrolled study for up to 19 months	[53]
12 patients with PoPH	Uncontrolled study for up to 12 months	[54]
12 PAH patients (five with IPAH, six with CTD and one with PoPH)	Uncontrolled study for a median 20 months	[55]
21 PH patients (PH due to sarcoidosis)	Uncontrolled study for 4 months	[56]

CHD: Congenital heart disease; CTD: Connective tissue disease; CTEPH: Chronic thromboembolic pulmonary hypertension; IPAH: Idiopathic pulmonary arterial hypertension; PAH: Pulmonary arterial hypertension; PH: Pulmonary hypertension; PoPH: Portopulmonary hypertension.

Safety & tolerability

Based on these existing studies, when used as a monotherapy or in combination with other PAH drugs, inhalative iloprost is safe and the side effects that occurred were clinically acceptable.

None of the existing studies reported on relevant changes in laboratory tests (i.e., chemistry, hematology or urinalysis) caused by inhalative iloprost. Typical side effects were coughing during inhalation, flushing, headache, jaw pain at the end of the inhalation, dry mouth and chest pain or palpitations. Syncopes were reported, which are often a symptom of PAH itself; therefore, syncopes were not viewed as caused by inhalative iloprost. Most side effects were moderate, and therapy interruption due to severe coughing or bronchial obstruction was rare [30,46]. Nevertheless, lung function studies showed bronchial obstructions in children (4–17 years of age) after iloprost inhalation [47]. In some cases, bronchial obstruction developed late, and iloprost therapy could be continued after starting anti-obstructive medication with inhaled corticosteroids and β-agonist agents.

Regulatory affairs

Based on the pivotal study data on inhaled iloprost regulatory approval was granted by the EMA in September 2003 for the treatment of IPAH functional class NYHA III patients. The US FDA approved the drug in 2004 for patients with PAH functional class NYHA III and IV. The Australian Therapeutics Good Administration granted approval for treatment of patients with moderate or severe forms of IPAH and associated forms of PAH as well as inoperable forms of chronic thromboembolic PH in 2004.

Conclusion

Iloprost is a synthetic analogue of endogenous prostacyclin with a broad spectrum of pharmacological effects. After inhalative application, it shows a predominantly selective effect on pulmonary vascular hemodynamics for up to 2 h.

Besides its role in the treatment of PAH and acute right heart failure [18], it is used for testing pulmonary vasoreactive patients during right heart catheter procedures. This is an important and recommended component of the diagnostic process used for PH to detect patients that might benefit from CCB therapy.

In patients with PH, repetitive daily inhalation with iloprost can improve pulmonary hemodynamics, exercise capacity and quality of life. Yet, in Europe, this medication is only legally approved

to treat a selected group of patients with PH (i.e., idiopathic or familial PAH) in functional NYHA class III.

Regarding current guidelines and local health authority regulations, inhalative iloprost can be used for monotherapy in PAH patients [3].

There are also several studies that suggest that iloprost can be safely and effectively combined with other PAH medication [34,48].

Moderate flushing, headache and coughing are frequently reported side effects, but a cessation of iloprost medication because of these side effects seldom occurs.

Expert commentary

Inhalative iloprost, particularly its role as a PH medication, has been developed since the middle of the 1990s, especially by German workgroups. Beside inhalative iloprost, there are other prostanoids for PH therapy, such as intravenous epoprostenol and orally available beraprost. One advantage of inhalative iloprost is a lower rate of side effects. Note that this method of administration was facilitated by the development of modern nebulizer devices that guarantee a constant dosing as well as easy and safe handling by the patients.

Given the increasing availability of oral PH medication, inhalative iloprost is today more often a second-line combination partner. Despite the wide range of possible applications of inhalative iloprost discussed in the literature, its regulatory approval, especially in Europe, is rather limited. Even its use for pulmonary reactivity testing or in acute right-heart failure must be regarded as an off-label use in Germany.

Five-year view

Because of their lower rates of systemic side effects and their pulmonary vascular selectivity, inhalative prostanoids are expected to play a role in a selected group of PH patients.

One barrier that limits the wider use of inhalative iloprost is the restrictive regulations policy (use is limited to NYHA class III and only for IPAH patients) of local health authorities in Europe.

There are other inhalative prostanoids such as treprostinil with a longer drug half-life that are playing an increasing role in the US market. However, approval by the EMA for the European market is not expected soon [49].

There are new PH drugs in development that focus on new targets, such as antiproliferative effects. With this in mind, it is not possible to determine the role inhalative iloprost will play in the future. An existing cost–benefit analysis from the USA of inhalative iloprost falls behind other existing oral PH medication [50].

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Key issues

- Iloprost is a synthetic analogue of the endogenous prostacyclin PGI_2. It has a high affinity for the prostacyclin receptor and a high molecular stability.
- The use of modern nebulizers especially designed for the administration of iloprost guarantees the pulmonary deposition of the required doses and systematically minimizes side effects.
- Published data show that repetitive daily inhalation with iloprost in patients with pulmonary hypertension, can improve pulmonary hemodynamics, exercise capacity and quality of life.
- For inhalative iloprost the regulations policy of local health authorities is restrictive and includes in Europe only New York Heart Assocciation (NYHA) functional class III idiopathic pulmonary arterial hypertension patients and in the USA less specific pulmonary arterial hypertension functional class NYHA III and IV patients.
- Existing data show that inhalative Iloprost can be safely and effectively combined with other pulmonary arterial hypertension medication.

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