



EDITORIAL

Intravenous iloprost for pulmonary arterial hypertension: still waiting for evidence

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Irrespective of its aetiology, pulmonary arterial hypertension (PAH) is a serious disorder that results in right ventricular dysfunction, functional impairment and, ultimately, right heart failure and death. Over the last 20 yrs, significant advances in our understanding of the disease have led to the development of new, specific treatments. In 1996, a placebo-controlled trial demonstrated significant survival benefit with intravenous epoprostenol in severe idiopathic PAH [1]. Observational studies also suggested epoprostenol was associated with improved long-term outcomes [2, 3]. Subcutaneous treprostinil was subsequently shown to improve exercise capacity in PAH [4]. More recently, *i.v.* treprostinil was approved for use by the US Food and Drug Administration in cases of intolerable subcutaneous infusion site pain based on a bioequivalence study [5] and prospective open-label trials [6, 7]. Finally, randomised placebo-controlled trials documented the efficacy of inhaled iloprost either as monotherapy [8], or in addition to bosentan [9]. These drugs are now part of the recommended treatment algorithm for PAH [10], together with endothelin receptor antagonists and phosphodiesterase type-5 inhibitors.

Conversely, data on clinical efficacy of *i.v.* iloprost in PAH have been scarce. Iloprost is a stable synthetic analogue of prostacyclin [11]. It possesses several pharmacological advantages over epoprostenol including enhanced chemical stability at room temperature and increased half-life, resulting in less frequent reservoir changes and the potential to avoid life-threatening events in case of sudden infusion interruption. Short-term open-label [12] and observational [13] studies suggested *i.v.* iloprost was effective in improving exercise capacity and pulmonary haemodynamics in PAH. However, these studies were limited in size (eight and 13 patients treated with iloprost [12, 13], respectively) and included heterogeneous forms of pulmonary hypertension. Intravenous iloprost was never evaluated in a formal randomised placebo-controlled trial. It is noteworthy that despite a similar mode of action, the demonstration that inhaled iloprost and other parenteral prostacyclins are effective in treating PAH does not mean *i.v.* iloprost is equally effective. Indeed, apart from

differences in pharmacokinetics and pharmacodynamics, the potency and additional effects of prostacyclins appear to be specific to each compound [11]. Consequently, the efficacy of parenteral iloprost for PAH remains largely unknown, and *i.v.* iloprost is not currently recommended for the treatment of PAH [10]. Despite this lack of evidence, *i.v.* iloprost has been approved for PAH therapy in New Zealand and has been widely administered as off-label use in Germany and other European countries. Thus, the demonstration of *i.v.* iloprost efficacy is an important clinical issue in PAH.

In the current issue of the *European Respiratory Journal*, HOEPER *et al.* [14] describe the long-term outcome of a German cohort of World Health Organization functional class III–IV PAH patients treated with *i.v.* iloprost, mainly as rescue therapy following treatment failure with first-line inhaled iloprost. These patients mainly suffered from idiopathic PAH or PAH associated with connective tissue disease. Intravenous iloprost was associated with significant short-term improvements in exercise capacity and pulmonary haemodynamics. However, long-term haemodynamic data were less impressive and the overall survival rates were extremely poor, with 1-, 3- and 5-yr survival rates from the initiation of *i.v.* iloprost of 54%, 31% and 15%, respectively. Moreover, 26% of patients additionally underwent lung transplantation. As Germany has developed a remarkable transplant system with possible urgent listing and transplantation, overall survival could have been even worse in other countries where such a system is not yet established. In the subset of idiopathic PAH patients, the transplantation-free survival was similar to the expected survival on conventional therapy based on the haemodynamic severity at the time of *i.v.* iloprost initiation [15].

As acknowledged HOEPER *et al.* [14], the numerous biases inherent to retrospective studies make the interpretation of the data hazardous. Indeed, the study population probably represents a “negative” selection bias as the patients had extremely severe PAH at the time of *i.v.* iloprost initiation. More importantly, only patients who failed with first-line inhaled iloprost treatment were described [14]. One may also argue, however, that the study population may represent a “positive” selection bias of a larger group as patients who died before *i.v.* iloprost or were not eligible for this more aggressive therapy were not reported [14]. The comparison between the present cohort of second-line “prevalent” patients and the National Institute of Health survival model or the long-term observational series with epoprostenol [2, 3], both based on first-line “incident” cases, is thus problematic. Similar biases

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may also have influenced the long-term haemodynamic results. Finally, it remains unknown whether the long-term outcome of second-line *i.v.* iloprost would be similar in the current treatment era, where endothelin receptor antagonists, phosphodiesterase inhibitors and combined therapies are more commonly used. Thus, it is difficult to draw any firm conclusion from the data presented about the long-term efficacy of *i.v.* iloprost for PAH.

However, the study by HOEPER *et al.* [14] confirms that patients with poor functional capacity on therapy have extremely poor long-term prognosis. Indeed, despite what some may judge as the most advanced therapy to date, severe PAH remains a catastrophic disease with poorer overall survival than most advanced cancers. Importantly, the absence of survival benefit compared to the expected survival based on the National Institute of Health equation does not mean that *i.v.* iloprost is ineffective. In fact, data on efficacy and long-term outcomes with second-line therapies are tragically lacking in PAH. The few series [16–18] describing the long-term outcomes with rescue therapy generally reported better prognosis than in the study of HOEPER *et al.* [14]. Previous studies also documented that the timing of epoprostenol initiation was crucial in determining the long-term prognosis [2, 3, 16]. Whether the poor outcome described in the study by HOEPER *et al.* [14] is related to the initiation of second-line therapy at a later stage of the disease, the transition to a less potent rescue therapy or simply lead-time bias remains unknown. However, it certainly highlights the urgent need to consensually define treatment goals and to properly address the best therapeutic approach following failure to first-line therapy in PAH.

While the study by HOEPER *et al.* [14] is clearly informative regarding the outcome of patients with severe PAH failing on first-line therapy, numerous questions remain. Does *i.v.* iloprost influence the long-term outcomes of PAH? Is *i.v.* iloprost as effective as epoprostenol in end-stage PAH? What is the optimal dose? These unresolved questions highlight the difficulties and ethical issues of performing prospective controlled trials in devastating conditions for which alternative therapies are available. For obvious ethical reasons, long-term placebo-controlled trials to assess the effect of PAH therapies on survival are no longer possible. Short-term placebo-controlled trials would also be considered unethical in end-stage PAH. We would, however, argue that using therapies with very limited evidence of efficacy to treat end-stage PAH is also questionable, given that epoprostenol has been confidently associated with survival benefit in severe PAH [1]. Some study designs, such as switch trials from epoprostenol to *i.v.* iloprost [6] or direct comparison between both drugs, may limit risks for patients and add confidence in using this compound. The potential pharmacological advantages of iloprost over epoprostenol and the preliminary studies with its parenteral form would certainly satisfy the principle of equipoise to justify such a trial. From our point of view, a controlled trial to confirm the clinical efficacy of *i.v.* iloprost in severe PAH is not only feasible but also clearly needed.

Taken together, the study from HOEPER *et al.* [14] certainly raises more questions than answers. It is also a humility lesson as despite recent therapeutic advances that led to improved quality of life and survival for a subset of patients [19], PAH

remains a devastating disease with poor long-term survival and unsatisfactory treatment progresses for many others.

STATEMENT OF INTEREST

Statements of interest for S. Provencher and O. Sitbon can be found at www.erj.ersjournals.com/misc/statements.dtl

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