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A single-centre, placebo-controlled, double-blind randomised cross-over study of nebulised iloprost in patients with Eisenmenger syndrome: A pilot study

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH), is a rare and progressive disease with a high morbidity and mortality. Prostanoid pulmonary vasodilators are the most effective treatment for idiopathic and connective tissue associated PAH. Nonetheless, data examining their safety and efficacy in patients with Eisenmenger syndrome the most severe form of PAH, that is, related to cyanotic congenital heart disease (CHD-PAH) remains limited.

Aim: To evaluate safety and the clinical efficacy of nebulised iloprost in patients with Eisenmenger syndrome who are on maximum background oral PAH therapy.

Methods: This pilot study was a randomised, double-blind, placebo-controlled, cross-over study. Patients were randomised to receive nebulised placebo or iloprost for 12 weeks and were then crossed over, with a 7–14-day washout. The primary endpoint was a change in 6-minute walk distance (6MWD).

Results: Sixteen patients (11 females, aged 47.3 ± 9.8 year) were recruited, twelve completed the study. All were in WHO-FC III, with a resting oxygen saturation of 84 [81–87] % and a median 6MWD of 290 [260–300] m. There was no significant difference in the primary endpoint between nebulised iloprost (0[−4–9]m) and placebo (10 [−15–51]m), $p = 0.58$. There were no safety concerns with nebulised iloprost.

Conclusions: Our pilot study provides preliminary evidence that the addition of nebulised iloprost to maximum oral PAH therapy did not improve the primary endpoint of 6MWD. Nebulised iloprost was well tolerated with no significant safety concerns in CHD-PAH.

1. Introduction

Pulmonary arterial hypertension (PAH) describes a heterogeneous group of conditions sharing similar pulmonary arterial vasculopathy, resulting in right heart failure and premature death. PAH may be idiopathic, heritable, related to exposure to drugs or toxins, or associated with conditions such as connective tissue diseases or congenital heart disease (CHD). The prevalence of PH in patients with CHD is approximately 5–10%, which is likely to rise as patients with more complex defects survive to adulthood [1]. Eisenmenger syndrome (ES) is the most severe form of CHD-PAH, a multisystem disorder characterised by chronic hypoxemia due to a persistent or unrepaired defect, culminating in a right -to left shunt. Treatment of ES with targeted PAH therapy has resulted in improvements in exercise tolerance, quality of life (QoL) and mortality [2,3]. However, controlled data in ES is limited compared to other PAH aetiologies. Thus far, five randomised control trials, testing the use of phosphodiesterase type 5 inhibitors (PDE-5i) or endothelin receptor antagonists (ERAs), as a single or combined therapy, have been completed in patients with ES [4–8]. The latest, the MAESTRO study, testing macitentan, a novel dual receptor ERA, was safe and well tolerated; however, the primary endpoint, namely 6MWD, was no different in the macitentan vs the placebo arm [8]. It is common practice to treat patients with CHD-PAH, including ES patients, with combination oral therapy (endothelin receptor antagonist (ERA) and a phosphodiesterase type 5 inhibitor (PDE-5i)). However, the question whether to consider triple therapy, with the addition of a prostanoid, the third line and most effective PAH therapy, is limited to non-randomised control data.

The aim of our study was to test the hypothesis that the inhaled prostanoid, iloprost, would be safe and provide additional benefit in patients with ES, who had inadequate control on oral combination therapy.

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2. Methods

2.1. Study design and patient selection

This was a single-centre, randomised, double-blinded, placebo-controlled (1,1, iloprost: placebo), cross-over study to evaluate the safety and efficacy of nebulised iloprost in patients with ES, on maximal tolerated oral PAH therapy. Study participants were recruited between December 2014 and November 2015, provided they were over 18 years of age, in WHO functional class III or more, with documented resting oxygen saturations of <90% and a 6-minute walk distance (6MWD) of <400 m, or a deterioration of 30 m within 1 year on dual oral therapy for at least 3 months, or not tolerating oral therapy.

Important exclusion criteria were trisomy 21, obstructive lung disease (FEV1/FVC <60%), a resting systolic blood pressure of <85 mmHg, patients with decompensated heart failure, or a myocardial infarction within the last six months. Patients were also excluded if they had started or stopped specific treatment for PAH within one month of screening (excluding anticoagulation), were on an active organ transplant list, taking other investigational drugs/devices, were using other prostanoids such as epoprostenol or treprostinil or had a planned surgical intervention during the study period (full inclusion/exclusion criteria are shown in Appendix 1).

All patients consented and recruited to the study were allocated a subject number in sequential order during their baseline visit. Randomisation allocation was predetermined and generated manually by the study statistician prior to the investigational medicinal product (active and placebo) being packaged and labelled by the manufacturer. Patients, study recruiters and care providers were blinded during the study.

Recruited patients were asked to return for a baseline inpatient visit within 35 days of the outpatient screening visit. At baseline visit, patients were randomised to either nebulised iloprost or placebo, and then up titrated from 2.5 to 5 μg six times/day for a 12-week course of treatment. This was followed by a 1-week (±7 days) washout period after which time patients returned for the cross-over inpatient visit and received the alternative treatment for another 12 weeks, Fig. 1. At each visit, patients had a full assessment and quantification of their WHO functional class (WHO-FC), 6MWD, QoL score (emPHasis-10 questionnaire), trans-thoracic echocardiogram, hematological and biochemical laboratory testing were performed (Appendix 2). Patients who completed the randomised trial were offered nebulised iloprost on an open-label basis for a further 3 years, with masking of their treatment allocation during the randomised phase preserved until completion of the study.

The study was performed in accordance with the Good Clinical Practice guidelines, and the guiding principles detailed in the Declaration of Helsinki. Ethical approval was obtained from the nationally approved Research Ethics Committee (14/LO/1182) and local R&D approval. All patients gave fully informed written consent to participate. The study complied with the regulatory requirements of the European Union. Adverse events were reviewed by experienced staff who were blinded to treatment allocation, to verify classification and potential association with treatment. An independent data safety monitoring board reviewed safety data at regular intervals throughout the study. The trial is registered with the European Clinical Trials Database (**Eudra CT number**: **2014-000091-25**).

2.2. Study drug and compliance

The study drug ventavis/iloprost trometamol and placebo was supplied by Bayer PLC. Treatment was administered by inhalation via an I-Neb® adaptive aerosol delivery (AAD) system, six times a day. The initial dose was 2.5 μg and, with medical supervision, up titrated to 5 μg six times a day for 12 weeks. Patients were asked to keep a compliance diary and return all unused vials of the study drug at the end of each treatment arm. Patients who missed >20% of doses of the study drug were excluded from the study.

2.3. Study endpoints

The primary endpoint was a change in 6MWD after 12 weeks of therapy. The secondary endpoints were: a change in oxygen saturations at rest; WHO FC status; change in serum B-type natriuretic peptide (BNP); emPHasis-10 score; change in pre-defined echocardiographic parameters (Tricuspid annular plane systolic excursion (TAPSE), E/e', right ventricular effective systolic to diastolic duration ratio (RV S:D ratio), right atrial area (RA) and left atrial area (LA)), after 12 weeks of therapy.

The main safety endpoints were determined to be the proportion of patients with significant (>5%) decrease in oxygen saturation at rest and the proportion of patients not tolerating therapy and requiring discontinuation of treatment.

2.4. Statistical analysis

Statistical analyses were performed using R version 3.4.3 (R: A Language and Environment for Statistical Computing, http://www.R-project.org/). Using a cross-over design, a sample size of 12 was calculated using the level of significance as 0.05, the power as 0.84, the estimated standard deviation (of 6MWD) as 40 m and the minimal detectable difference in 6MWD as 50 m. To account for potential drop-outs 16 patients were planned for enrolment. Only patients completing the trial were included in the analyses.

Descriptive statistics were presented as numbers for categorical data and mean ± standard deviation (SD) or median [interquartile range(IQR)] for continuous variables. Continuous variables were tested for normality using the Kolmogorov-Smirnov test. In case of normal distribution comparison was performed using the paired two-tailed *t*-test and Welch-test in case of unequal variances (assessed using F-test). For data with a non-normal distribution, the Wilcoxon signed rank test was used. Patients who were withdrawn from the study before completion of both arms of the investigational drug were by default excluded from the analyses. No substitution rules were used for missing data in our analysis. Endpoints were assessed using Wilcoxon signed rank test or Fisher test as appropriate. Safety outcomes were reported as rates in the randomisation groups, using McNemar's test to assess the differences of patients' distribution using a two-sided *p*-value of <0.05 as a cut off for statistical significance.

3. Results

A total of 16 patients were recruited and followed up between December 2014 to March 2018. During the study, 2 patients were withdrawn following documented serious adverse events (SAEs; placebo =2). A further 2 patients were withdrawn, one following a serious adverse reaction in one (SAR; placebo = 1) and the other for failing screening at their baseline visit. In total, 15 patients were randomised at baseline visit. Overall, 12 patients completed the main study and 5 patients continued into the open label phase after completion of the study. Patient randomisation and retention is summarised in appendix (supplementary figure).

3.1. Baseline demographics and clinical characteristics

The mean age of the 16 patients randomised was 47.3(±9.8) years and 11(68%) were women. Of the twelve patients that completed the study: 8 (68%) had a large unrepaired ventricular septal defect (VSD),

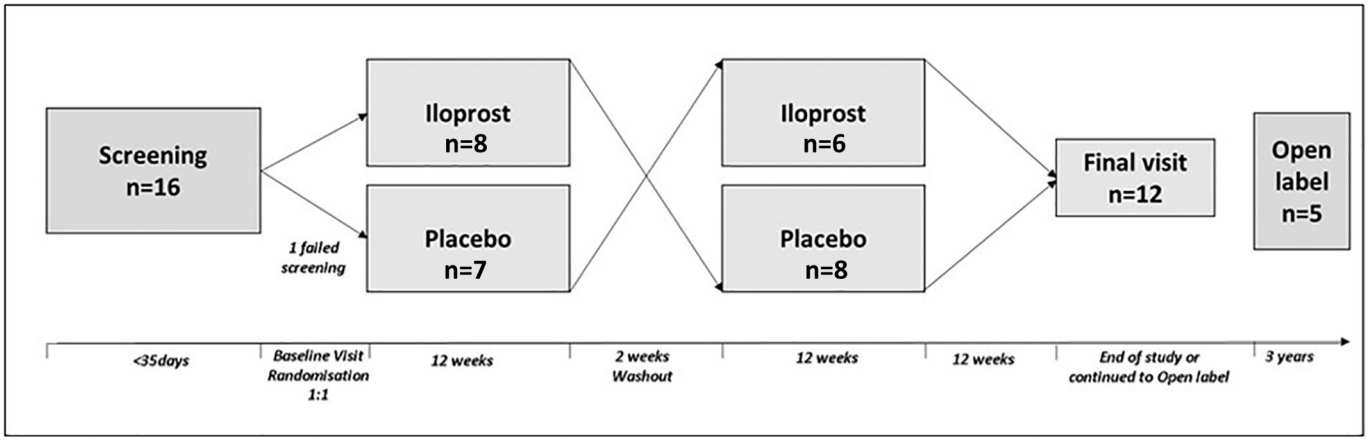

Fig. 1. Schematic diagram illustrating the trial design.

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2 (16%) had unrepaired truncus arteriosus, 1 (8%) had pulmonary atresia associated with a VSD and major aortopulmonary collaterals (segmental PH) and 1 (8%) had unrepaired complete atrioventricular septal defect (AVSD).

At baseline, all patients had significant functional impairment (n = 16, 100% in WHO functional class III) with resting oxygen saturations of 84[81–87] % and a 6MWD of 290[260–300] meters. Fourteen patients were on dual combination PAH therapy with a PDE-5i and an ERA for a median duration of 29[25–53] months. Two patients had previously been intolerant to PDE-5i and were on an ERA only (Table 1).

3.1.1. Compliance

Investigational drug compliance during both treatment arms was assessed as outlined in the methodology. The mean compliance rate was 94.1 [92.5–98.5] % in the placebo treated group and 95.3 [93.5–99.2] % in the iloprost treated group.

3.1.2. Primary endpoint analysis

All 12 patients who completed the main study could perform a 6-minute walk test at baseline and after 12 weeks of therapy, as per protocol. At baseline, 6MWD was 330[296–356]m in the iloprost and 318 [293–367]m in the placebo group. At the end of treatment, 6MWD was 330[315–360]m after iloprost and 325[300–364]m after placebo. There was no statistical difference in the change in 6MWD between active and placebo treatment: 0[−4–9]m after iloprost versus 10[−15–51]m after placebo, $p = 0.58$ (Fig. 2).

3.1.3. Secondary endpoint analyses

Secondary endpoints are summarized in Table 2. In total 3 (25%) patients in the placebo group improved functionally, moving from WHO-FC class III to II, compared to 5 (40%) in the iloprost group ($p = 0.34$ between groups). No patient deteriorated in terms of WHO-FC during the study. There was also no significant change in BNP plasma concentration between treatments: −22[−137–28]ng/L after iloprost versus +18[−4–64]ng/L after placebo, $p = 0.11$. No difference was observed between treatments in the change in quality of life as determined by the emPHasis-10 questionnaire: iloprost, +1[−1–3] points versus placebo +1 [−4–3.5], $p = 0.91$.

There was no significant difference in the tricuspid annular plane excursion (TAPSE), a measure of RV function, $p = 0.19$. There were no significant changes in the RV effective systolic to diastolic duration, right and left atrial areas between the treatment groups. Further echocardiographic parameters measured are listed in Table 2.

Table 1
Data is presented as mean ± SD or median[IQR]. Demographic and clinical information of patients at baseline. Abbreviations: WHO-FC; World Health Organisation Functional class, 6MWD; 6-minute walk distance, FEV; forced expiratory volume, FVC; forced vital capacity.

Baseline characteristics	n = 16
Age, years	47.3 ± 9.8
Female (%)	11 (68%)
WHO FC III/IV	16/0
Clinical characteristics	
6MWD, m	290 [260–300]
Oxygen Saturation, %	84[81–87]
FEV1/FVC	72[40]
EmPHasis-10 score	38.0 ± 21.1
Dual combination therapy, months	29[25–53]
Anatomical classification	
Pre-tricuspid	1(6%)
Post-tricuspid	10 (63%)
Complex	5(31%)

3.2. Safety and tolerability

Overall, 15 patients received at least one dose of the study medication and were included in the safety analyses. Important medical events were described as either serious adverse events (SAEs) or serious adverse reactions (SARs) during the trial. There were a total of 8 SAEs or SARs during the study period, of which 5 were SAEs and 3 were SARs. Only 1 of these events occured in a patient recieving iloprost, 4 events occured in patient recieving placebo and 3 events when not on any investigational treatment, either during washout or after completing therapy but before the final visit. A total of 5 SAEs occured in 4 (26%, n = 15) patients, of these only 1 event took place in a patient recieving the active drug, iloprost. The type of events that occured were as follows: 2 had significant diarrhoea neccessitating hospitalisation (1 on placebo, 1 during washout); 1 had a syncopal event after completing treatment but before the final visit; 1 patient had 2 arrhythmia episodes neccessitating hospitalisation (1 on iloprost, 1 on placebo). A total of 3 SARs occured in 3 (20%, n = 15) patients. All SARs occured in patients receiving placebo or during the washout stage. Of these, 2 reactions presented as bronchospasm and 1 was haematuria (summary in appendix supplementary table). Three (20%, n = 15) patients were withdrawn from the study due significant events whilst receiving placebo, two SARs and one SAE. Both SARs were related to bronchospasm. The SAE, necessitating study withdrawal, was related to severe diarrhea. One patient had a significant drop in platelet count with subsequent hematuria, during the washout period, with no significant clinical sequelae and completed the trial. No patient died during the study period.

A safety measure endpoint was a drop of >5% in resting oxygen saturation during the treatments. There was no significant difference in the change in resting oxygen saturations between treatments during the main study: −1.8 [−4–1.25] during iloprost versus +1.5[−3–2.25] % placebo, $p = 0.16$, Fig. 2. Four (25%) patients on iloprost and 1(8%) patient on placebo had a drop >5% in their oxygen saturations during the study, but this difference did not reach statistical significance ($p = 0.12$).

3.2.1. Open-Label continuation of the study

Five (42%) patients who completed the randomised study agreed to be enrolled to the open-label extension study. Of these, three were on iloprost and continued treatment. Two were on placebo at the time of commencing the open-label treatment. One patient, who had been on iloprost immediately prior to commencing the open-label treatment, discontinued treatment prematurely during the open-label period, withdrawing consent. The remaining four patients tolerated the treatment well. One patient had 3 SAEs, all related to atrial tachyarrhythmias and underwent ablation during the open-label phase. At 12 weeks of open-label treatment, there was a median increase in 6MWD of 10 [−32−30] m. Patients did not experience any improvement in their WHO-FC or emPHasis-10 scores.. There was also no clinically significant change in oxygen saturation (+ 5 [9] %), biochemical or echocardiographic parameters.

4. Discussion

In our cross-over placebo-controlled randomised study, patients with ES did not experience a significant improvement in exercise capacity at 12 weeks with the addition of nebulised iloprost on a background of maximally tolerated oral PAH therapy. Moreover, no significant difference was seen in resting oxygen saturations, BNP, quality of life, functional class or major echocardiographic parameters. Whilst no significant safety concerns arose with the use of nebulised iloprost, the role of this PAH therapy in the treatment of ES remains uncertain.

Although single and combination PAH therapy is well established in idiopathic PAH, treatment algorithms are less well developed for patients with ES; particularly on the effect of combination therapy and parenteral medication, such as inhaled or intravenous prostanoids. [9]

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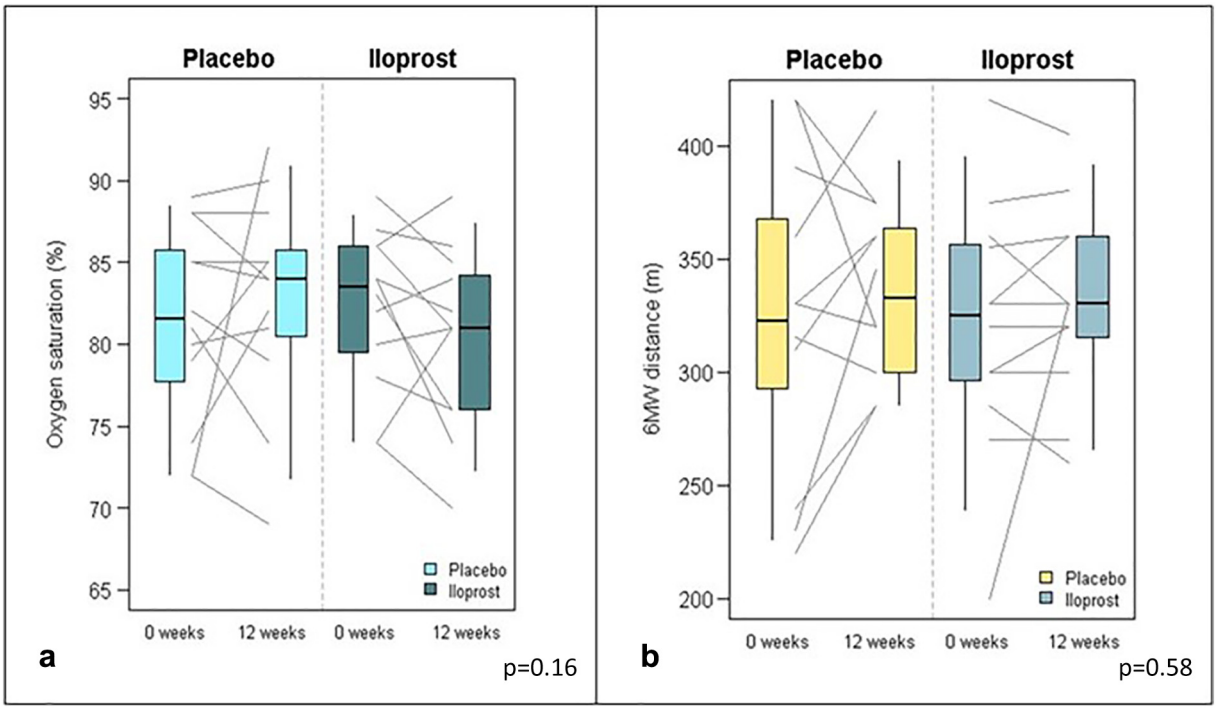

Fig. 2. a) Change in arterial oxygen saturations at 0 and 12 weeks after placebo and iloprost treatment. There was no difference in arterial oxygen saturations between the iloprost- and placeob-treated groups, $p = 0.16$. b) Impact of placebo and iloprost on 6MWD during the study. There was no significant improvement in 6MWD after 12 weeks of iloprost inhalation $p = 0.58$.

[10] Despite the lack of evidence, most expert centres provide ES patients with combination therapy when a single agent becomes insufficient (usually combining ERAs with PDE-5is) [11], especially as there is mounting evidence that PAH therapy is safe and improves morbidity and mortality in this cohort. [7,10,12–16] In other forms of PAH (e.g., idiopathic or CTD-related PAH), failure of oral combination therapy is usually an impetus to start prostanoid therapy. [9] There is very little evidence to support prostanoid therapy in CHD-PAH [10], yet in a recent study of 340 ES patients, 7.6% (n = 25) were on triple therapy, including prostanoids, despite the lack of evidence [14] Thus, there is pressing need to further understand the safety and efficacy of prostanoids in ES, which was the rationale for our study. Although intravenous epoprostenol is thought to be more efficacious than nebulised iloprost, the risk of infection or embolic phenomena related to indwelling catheters in patients with right to left shunts has limited its use in this cohort, underscoring the need for alternative therapies for patients failing oral therapies. [17]

Table 2
Data is presented as median[IQR]. Change in pre-specified outcomes at 12 weeks of treatment. Abbreviations: 6MWD; 6-minute walk distance, WHO-FC; World Health Organisation Functional class, BNP; B-type natriuretic peptide, TAPSE; tricuspid annular planar systolic excursion, RA; right atrium, LA; left atrium, RV S: D ratio; right ventricular systolic to diastolic ratio.

Primary Endpoint	Iloprost	Placebo	*p*Value
Δ 6MWD, m	0[−4–9]	10[−15–51]	0.58
Secondary Endpoints			
Δ Resting oxygen saturation, %	-2[−4–1]	0[−3–2]	0.16
Δ WHO-FC (II/III)	5/7	3/9	0.34
Δ BNP, ng/ml	−22[−137–28]	18[−4–64]	0.11
Δ emPHasis-10 score	1[−1–3]	1[−4–3.5]	0.92
Echocardiographic parameters			
Δ TAPSE, cm	−0.5[−2.0–1.3]	1.0[0.0–2.0]	0.19
Δ RA area, cm^2	0.0 [−2.0–1.8]	0.0[−0.8–2.0]	0.79
Δ LA area, cm^2	0.0[−1.0–1.1]	0.0[−1.0–1.3]	0.86
Δ Medial E/e'	−4.0 [−5.6–0.3]	−0.5[−1.6–2.6]	0.04
Δ Lateral E/e'	−1.2[−2.7–0.5]	0.0. [−1.3–1.1]	0.81
Δ RV S: D ratio	0.1[0.05–0.3]	0.1[0.05–0.2]	0.06

Whilst this was a cross-over randomised trial, powered for 12 patients, the sample size is still quite low for definitive conclusions to be drawn on the efficacy of inhaled iloprost in what is clearly a very heterogeneous population. It has been suggested that patients with more complex lesions are less likely to respond to PAH therapies compared to patients with simple lesions [18]. Furthermore, we have included one patient with segmental PAH, for simplification we have classified them as ES, where PAH therapy is not routine. Clearly, the small sample size and study design do not allow for meaningful subgroup analyses.

The commonest cause of death in this cohort is congestive heart failure, commonly related to right ventricular dysfunction. Echocardiographic parameters reflecting RV function and cardiac physiology have been shown to predict mortality in patients with ES, but were not influenced by treatment with iloprost. [19] More advanced echo imaging techniques, such as speckle-tracking and strain analysis may provide additional information on biventricular function in the setting of PH, allowing a more "global" assessment of RV function, unlike for example TAPSE, which only evaluates longitudinal function [20]. In our study, the only echocardiographic parameter that improved with iloprost reflected LV diastolic function (medial E/e') and, in this setting, the interaction between ventricles. In isolation, this parameter is of limited clinical importance however, but may be hypothesis generating for further studies.

Nebulised iloprost was well-tolerated and safe in this population. Drug compliance rates of >80% were achieved in patients who completed the study. Reported difficulties that could affect compliance included the frequency of nebulisations, prolonged delivery times and time needed to maintain the I-Neb® device. As a result, few patients opted to continue open-label treatment. A new delivery system, the Breelib™ nebuliser, has been developed to reduce inhalation times. [21] In a randomised study comparing Breelib™ to the I-Neb® nebuliser, the former reduced inhalation times from 10.9 to 2.6 min, had good tolerability and improved iloprost aerosol therapy convenience, thus, in theory improving patient uptake of the therapy. [21] SAEs were not more common after iloprost treatment and there was no significant drop on resting oxygen saturations.

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Recruitment of patients to this study was slow, despite the large number of patients with ES followed at our centre. Up to a third of our adult patients have Down syndrome and thus were not considered in the study due to concerns about consent, ability to use the delivery system and reliably test our primary endpoint, namely 6MWD. [22] Furthermore, many adult patients with ES seemingly remain stable and have not yet reached maximal oral PAH therapy. Further multicentre randomised control trials are needed but should be carefully designed and powered to account for the heterogeneity of this population, using endpoints that are clinically meaningful, but also important to patients, e.g. quality of life. Moreover, efforts should be made to allow inclusion of patients with Down syndrome, if appropriate.

5. Conclusion

This pilot randomised, double-blind, placebo controlled, cross-over study provides preliminary evidence that the addition of nebulised iloprost to maximum oral PAH therapy did not improve exercise capacity, functional class, BNP or echocardiographic parameters in ES. Moreover, there were no safety concerns with the use of nebulised iloprost in our population. Considering the limitations of small sample size and population heterogeneity, further multi-centre trials, utilising contemporary advanced delivery systems of inhaled prostanoids in CHD-PAH are warranted.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.07.004.

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References

[1] G.P. Diller, M.A. Gatzoulis, Pulmonary vascular disease in adults with congenital heart disease, Circulation 115 (Feb 27 2007) 1039–1050.
[2] K. Dimopoulos, R. Inuzuka, S. Goletto, G. Giannakoulas, L. Swan, S.J. Wort, et al., Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension, Circulation 121 (Jan 5 2010) 20–25.
[3] E.L. Tay, M. Papaphylactou, G.P. Diller, R. Alonso-Gonzalez, R. Inuzuka, G. Giannakoulas, et al., Quality of life and functional capacity can be improved in patients with Eisenmenger syndrome with oral sildenafil therapy, Int. J. Cardiol. 149 (Jun 16 2011) 372–376.
[4] N. Galie, M. Beghetti, M.A. Gatzoulis, J. Granton, R.M. Berger, A. Lauer, et al., Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study, Circulation 114 (Jul 4 2006) 48–54.
[5] T.P. Singh, M. Rohit, A. Grover, S. Malhotra, R. Vijayvergiya, A randomized, placebo-controlled, double-blind, crossover study to evaluate the efficacy of oral sildenafil therapy in severe pulmonary artery hypertension, Am. Heart J. 151 (Apr 2006) 851 e1–5.
[6] K. Iversen, A.S. Jensen, T.V. Jensen, N.G. Vejlstrup, L. Sondergaard, Combination therapy with bosentan and sildenafil in Eisenmenger syndrome: a randomized, placebo-controlled, double-blinded trial, Eur. Heart J. 31 (May 2010) 1124–1131.
[7] S. Mukhopadhyay, S. Nathani, J. Yusuf, D. Shrimal, S. Tyagi, Clinical efficacy of phosphodiesterase-5 inhibitor tadalafil in Eisenmenger syndrome–a randomized, placebo-controlled, double-blind crossover study, Congenit. Heart Dis. 6 (Sep-Oct 2011) 424–431.
[8] M.A. Gatzoulis, M. Landzberg, M. Beghetti, R.M. Berger, M. Efficace, S. Gesang, et al., Evaluation of Macitentan in patients with Eisenmenger syndrome, Circulation 139 (Jan 2 2019) 51–63.
[9] N. Galie, M. Humbert, J. L. Vachiery, S. Gibbs, I. Lang, A. Torbicki, *et al.*, "2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT)," *Eur Heart J*, vol. 37, pp. 67–119, Jan 1 2016.
[10] K. A. Nashat H, Price LC, Harries C, Alonso-Gonzalez R, Gatzoulis MA, Wort SJ, Dimopoulos K, "Eisenmenger syndrome: current perspectives" Res. Rep. Clin. Cardiol. vol. 8 pp. 1–12, 2017.
[11] G.P. Diller, M.A. Korten, U.M. Bauer, O. Miera, O. Tutarel, H. Kaemmerer, et al., Current therapy and outcome of Eisenmenger syndrome: data of the German National Register for congenital heart defects, Eur. Heart J. 37 (May 7 2016) 1449–1455.
[12] C.S. Hjortshoj, A.S. Jensen, L. Sondergaard, Advanced therapy in Eisenmenger syndrome: A systematic review, *Cardiol Rev*, vol. 25, pp. 126–132, May/Jun, 2017.
[13] M.K. Chon, K.I. Cho, K.S. Cha, J.S. Seo, D.S. Kim, Effects of long-term iloprost treatment on right ventricular function in patients with Eisenmenger syndrome, J. Cardiol. 69 (May 2017) 741–746.
[14] S. Hascoet, E. Fournier, X. Jais, L. Le Gloan, C. Dauphin, A. Houeijeh, et al., Outcome of adults with Eisenmenger syndrome treated with drugs specific to pulmonary arterial hypertension: a French multicentre study, Arch. Cardiovasc. Dis. 110 (May 2017) 303–316.
[15] S. Hascoet, A.E. Baruteau, M. Humbert, G. Simonneau, X. Jais, J. Petit, et al., Long-term outcomes of pulmonary arterial hypertension under specific drug therapy in Eisenmenger syndrome, J. Heart Lung Transplant. 36 (Apr 2017) 386–398.
[16] M.A. Gatzoulis, M. Beghetti, N. Galie, J. Granton, R.M. Berger, A. Lauer, et al., Longer-term bosentan therapy improves functional capacity in Eisenmenger syndrome: results of the BREATHE-5 open-label extension study, Int. J. Cardiol. 127 (Jun 23 2008) 27–32.
[17] A.K. Doran, D.D. Ivy, R.J. Barst, N. Hill, S. Murali, R.L. Benza, et al., Guidelines for the prevention of central venous catheter-related blood stream infections with prostanoid therapy for pulmonary arterial hypertension, Int. J. Clin. Pract. Suppl. (Jul 2008) 5–9.
[18] K. Dimopoulos, G. P. Diller, A. R. Opotowsky, M. D'Alto, H. Gu, G. Giannakoulas, *et al.*, "Definition and Management of Segmental Pulmonary Hypertension," J. Am. Heart Assoc., vol. 7, Jul 4 2018.
[19] P. Moceri, K. Dimopoulos, E. Liodakis, I. Germanakis, A. Kempny, G.P. Diller, et al., Echocardiographic predictors of outcome in Eisenmenger syndrome, Circulation 126 (Sep 18 2012) 1461–1468.
[20] P. Moceri, X. Iriart, P. Bouvier, D. Baudouy, P. Gibelin, R. Saady, et al., Speckle-tracking imaging in patients with Eisenmenger syndrome, Arch. Cardiovasc. Dis. 109 (Feb 2016) 104–112.
[21] T. Gessler, H.A. Ghofrani, M. Held, H. Klose, H. Leuchte, H. Olschewski, et al., The safety and pharmacokinetics of rapid iloprost aerosol delivery via the BREELIB nebulizer in pulmonary arterial hypertension, Pulm Circ. 7 (Apr-Jun 2017) 505–513.
[22] J.C. Vis, H. Thoonsen, M.G. Duffels, R.A. de Bruin-Bon, S.A. Huisman, A.P. van Dijk, et al., Six-minute walk test in patients with down syndrome: validity and reproducibility, Arch. Phys. Med. Rehabil. 90 (Aug 2009) 1423–1427.

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