EUROPEAN RESPIRATORY journal
OFFICIAL SCIENTIFIC JOURNAL OF THE ERS

The effects of parenteral prostacycline therapy as add-on treatment to oral compounds in Eisenmenger syndrome

Journal:	*European Respiratory Journal*
Manuscript ID	ERJ-01401-2019.R1
Manuscript Type:	Research Letter
Date Submitted by the Author:	n/a
Complete List of Authors:	D'Alto, Michele; Monaldi Hospital, Cardiology Constantine, Andrew; Royal Brompton Hospital, Adult Congenital Heart Centre and National Centre for Pulmonary Hypertension; Balint, Olga; Gottsegen Hungarian Institute of Cardiology Romeo, Emanuele; Monaldi Hospital, Cardiology Argiento, Paola; Monaldi Hospital, Cardiology Ablonczy, Laszlo; Gottsegen Hungarian Institute of Cardiology Skoro-Sajer, Nika; Medical University of Vienna, Department of Internal Medicine II Giannakoulas, George; Aristotle University of Thessaloniki, First Cardiology Department, AHEPA University Hospital Dimopoulos, Konstantinos; Royal Brompton Hospital,
Key Words:	pulmonary arterial hypertension, prostanoids, cardiovascular disease
Abstract:	

The effects of parenteral prostacycline therapy as add-on treatment to oral compounds in Eisenmenger syndrome

Authors:

Michele D'Alto[1], Andrew Constantine[2], Olga Hajnalka Balint[3], Emanuele Romeo[1], Paola Argiento[1], Laszlo Ablonczy[3], Nika Skoro-Sajer[4], George Giannakoulas[5], Konstantinos Dimopoulos[2].

Author affiliations:

[1]Department of Cardiology, University "L. Vanvitelli" - Monaldi Hospital, Naples, Italy

[2] Adult Congenital Heart Centre and National Centre for Pulmonary Hypertension, Royal Brompton Hospital, London, United Kingdom

[3]György Gottsegen Hungarian Institute of Cardiology, Budapest, Hungary

[4]Department of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Austria

[5]Department of Cardiology, AHEPA University Hospital, Aristotle University of Thessaloniki, Greece

Address for correspondence:

Dr Kostas Dimopoulos, Adult Congenital Heart Centre, Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, SW3 6NP London, UK.

Tel +44 2073528121 ext 2771, Fax +44 207351 8629, E-mail: k.dimopoulos02@gmail.com

Manuscript word count: 1301

Key words:

Congenital heart disease - Eisenmenger syndrome – Pulmonary arterial hypertension – Prostanoids – Triple combination therapy.

Key questions:

What is already known about this subject?

Pulmonary arterial hypertension (PAH) therapy has revolutionised the therapy of patients with Eisenmenger syndrome.

Combination of 2 or more treatments can maximise the efficacy of PAH therapy, yet there is little evidence for triple combination therapy with parenteral prostanoids Eisenmenger syndrome.

What does this study add?

This study assessed the effect of the addition of subcutaneous treprostinil and intravenous epoprostenol, as part of a regimen of triple combination therapy, in a contemporary European cohort of patients with Eisenmenger syndrome.

The study provides evidence that treatment with prostanoids in this group of patients is safe and is associated with significant improvements in exercise capacity, natriuretic peptide levels and haemodynamic parameters over a median follow-up period of over 2 years.

How might this impact on clinical practice?

Eisenmenger patients on dual oral PAH therapy may benefit from consideration for timely escalation to prostanoid treatment.

Moreover, by assessing the response to therapy of these Eisenmenger patients against the criteria set by the European Society of Cardiology PAH risk score, we highlight the urgent need for a risk assessment tool specific to this unique group of patients to aid goal-directed therapy.

Research letter

Pulmonary arterial hypertension (PAH) develops in 5-10% of patients with congenital heart disease (CHD),[1] and PAH associated with congenital heart disease (PAH-CHD) accounts for a significant proportion of PAH cases (34-42%).[2] Eisenmenger syndrome (ES) is at the extreme end of the spectrum of PAH-CHD, with an untreated 10-year mortality rate of 30-40%.[3] Despite a decreasing incidence in developed countries,[4] ES is likely to remain a common complication of CHD in low- to middle-income countries.[5] The emergence of PAH therapies has significantly altered the management of ES, with evidence of an improvement in clinical status, exercise tolerance and haemodynamics.[6,7] Oral combination therapy and intravenous epoprostenol, both well-established in the treatment of idiopathic PAH, have been used successfully in ES to further improve outcomes.[8,9] Studies evaluating the safety and efficacy of "triple combination therapy" in ES, however, remain scarce, being limited to small patient cohorts or lacking information on invasive haemodynamics.[10–12] Furthermore, concerns regarding the safety of long-term intravenous therapy and indwelling central venous catheters in patients with pulmonary-to-systemic shunts may have contributed to the slow uptake of prostanoid therapy in this cohort. Nonetheless, there is an early signal of benefit of combination therapy with prostanoids in Eisenmenger syndrome requiring further investigation. We sought to evaluate the use of add-on parenteral prostanoids after failure of dual oral combination therapy in a contemporary cohort of ES patients.

This retrospective, longitudinal, cohort study recruited patients with ES under active follow-up in 3 European tertiary centres between January 2012 and October 2018. All patients were on baseline therapy with both a phosphodiesterase-5 inhibitor and an endothelin receptor antagonist. Patients were considered for prostanoid therapy following an inadequate clinical or haemodynamic response to combination therapy or disease progression after a period of

stability. Other forms of PAH-CHD were excluded. For each patient, clinical and haemodynamic variables were collected prior to initiation of prostanoid therapy and at the last available follow-up. Survival status was assessed to April 2019.

A total of 28 patients were included (average age 38±14years, 21% male). The majority of patients had a post-tricuspid shunt (68%). The most common defect was a ventricular septal defect in 13 (46%) patients, followed by an atrial septal defect in 29% (63% secundum, 25% primum, 13% sinus venosus). Average resting saturations were 82±6%, with the vast majority (96%) exhibiting resting saturations <90% on air. The majority of patients (89%) were in NYHA functional class 3(78%) or 4(21%). Average 6-minute walk test (6MWT) distance was low (233±140m), and 39% walked <200m. Serum NT-proBNP concentration was also significantly raised with a median concentration of 3087[234-7428]pg/mL (normal<125pg/mL). Baseline haemodynamics confirmed severe precapillary pulmonary hypertension: PVR 20.7±9.6Wood Units (WU), 86% with PVR>10WU, and Qp/Qs 1.0±0.1 (bidirectional shunting). Systemic cardiac output (Qs) was reduced (3.2±0.9L/min), with 57% having a systemic cardiac index (Qsi) <2.0L/min/m^2.

The vast majority of patients (26, 92.9%) received subcutaneous treprostinil and the remainder intravenous epoprostenol. The median doses of treprostinil and epoprostenol at the end of uptitration were 40[22-65]ng/kg/min and 33[32-34]ng/kg/min, respectively. At a median follow-up of 27[2-65]months (repeat cardiac catheterisation in 57 %), there was no drop in saturations (82±6 versus 82±4%) or resting blood pressure, but a significant increase in 6MWT distance (mean 272±109 versus 365±113m, p=0.0003, Figure 1A). WHO functional class improved in 64%, remained unchanged in 8(29%), and deteriorated in 2(7%) patients (p=0.002). A reduction in NT-proBNP levels was observed (median 3087[234-7428] versus 1126[123-5882]pg/mL, p<0.0001, Figure 1B). Using the cut-offs proposed by the ESC/ERS guideline risk assessment tool for PAH patients,[13] the following variables

improved: WHO functional class in 64%, 6MWT distance in 25%, and NT-proBNP level in 32%. Patients who moved into a lower risk category in at least 2 parameters were more likely to have a post-tricuspid defect (p=0.04) and a lower 6MWT distance (216±75.2 versus 312±115m, p=0.03). Treatment resulted in 18% patients moving into the low-risk category with respect to at least 2 parameters, whereas none improved to the low-risk group with respect to these 3 parameters.

On follow-up cardiac catheterisation, significant reductions in mean pulmonary artery pressure (72±17 versus 68±12mmHg, p=0.005) and PVR (21±10 versus 17±7WU, p=0.008, Figure 1C) were accompanied by an improvement in cardiac index (2.0±0.5 versus 2.3±0.3L/min/m^2, p=0.005, Figure 1D) and a reduction in right atrial pressure compared to baseline (11±5 versus 8±2mmHg, p=0.01). Finally, there was a small increase in the fraction of pulmonary-to-systemic shunting (Qp/Qs 1±0.1 versus 1.1±0.1, p=0.03). Survival following prostanoid initiation was 92% and 80% at 1 and 2 years, respectively. During follow-up, 6(21%) patients died, 3(11%) patients were listed for and 1(4%) underwent lung transplantation. No patients discontinued treatment during the study period.

In this study, parenteral prostanoid therapy was safe with no instances of discontinuation of therapy. Third-line therapy in this ES cohort was associated with an improvement in exercise capacity, natriuretic peptide levels and haemodynamics. Early escalation to combination PAH therapy is fundamental to the modern management of idiopathic (IPAH) and connective tissue-related PAH (CTD-PAH). While PAH-CHD is as common as IPAH and CTD-PAH, there is still limited evidence on the efficacy of combination therapy. It is likely that prostanoids are introduced late in many ES patients, even though assessing functional limitation through symptoms can be difficult in this cohort. Our study strongly supports the value of escalation of PAH therapies in ES, moving patients towards a lower-risk profile.

The ESC/ERS PH guidelines provide a risk assessment tool for IPAH using published prognostic variables, which may apply to other forms of PAH; the goal of PAH therapy is to move patients towards the low-risk group and improve their survival. In our study, the addition of parenteral treatment was associated with a significant improvement in clinical parameters, suggesting that ES patients on oral combination therapy can be further optimised. This was especially true for patients with post-tricuspid shunts and those with a lower 6MWT distance, supporting escalation in those who have not responded sufficiently to combination therapy. Despite significant improvement in multiple variables, few patients improved to a low-risk status with respect to all 3 parameters from the ESC/ERS guideline risk assessment tool assessed in our study. A minority of patients achieving a low-risk profile is in line with other studies evaluating add-on prostanoid therapy in other cohorts, consisting mostly of patients with IPAH.[14,15] However, ES patients differ significantly from other types of PAH in terms of pathophysiology and prognosis,[16] and a risk score accounting for the unique features of ES is urgently needed. Eisenmenger patients who are candidates for third-line PAH therapy remain at significant risk of death and should be considered for heart-lung or lung transplantation with repair of the cardiac defect. Early referral for assessment is key in maximising suitability for transplantation, before the development of multiorgan failure. In our cohort, only one patient underwent lung transplantation with CHD repair. Given the decline in heart-lung transplantation, in conjunction with the continued expansion of the CHD population,[17] achieving stability on PAH therapies, via timely step-wise escalation, is essential.[7]

The limitations of this study include its retrospective design, limited numbers of patients with a rare condition, the availability of repeat cardiac catheterisation in only a subset of patients reflecting differing clinical practices between centres, and the lack of a comparison group. The time from initiation of therapy to follow-up was not predefined and varied between

patients. The low event rate during follow-up meant that we were unable to perform any meaningful survival analysis in this population.

In conclusion, this study has demonstrated that the addition of a parenteral prostanoid in ES patients on dual oral combination therapy is safe with no patients needing to interrupt therapy due to side effects at 2 years of follow-up, resulting in a significant improvement in clinical and haemodynamic variables. Further trials are needed to define the optimal strategy for treatment escalation in ES patients, and the role of alternative modes of delivery (e.g. implantable pumps).

Competing interests

Professor D'Alto has been a consultant to and received grants and personal fees from Actelion, Pfizer, GlaxoSmithKline, Dompè, and Bayer/MSD. Dr Constantine has received an unrestricted educational grant from Actelion UK. Dr Balint has been a consultant to and received personal fees from Actelion, Lilly, AOP Orphan and Bayer/MSD. Dr Romeo received grants and personal fees from GlaxoSmithKline, Dompè and MSD. Dr Argiento received grants and personal fees from GlaxoSmithKline, Dompè and MSD. Dr Skoro-Sajer has received grants and personal fees from AOPOrphan Pharmaceuticals, Actelion, Bayer, GlaxoSmithKline, Pfizer and United Therapeutics. Dr Giannakoulas has received grants and/or personal fees from Actelion, Pfizer, GlaxoSmithKline, Bayer, MSD, Pfizer, Lilly and United Therapeutics. Dr Dimopoulos has received nonfinancial support from Actelion Pharmaceuticals; and has been a consultant to and received grants and personal fees from Actelion UK, Pfizer, GlaxoSmithKline, and Bayer/MSD.

Acknowledgements

None.

Funding

None.

References

1 van Riel ACMJ, Schuuring MJ, van Hessen ID, *et al.* Contemporary prevalence of pulmonary arterial hypertension in adult congenital heart disease following the updated clinical classification. *Int J Cardiol* 2014;**174**:299–305. doi:10.1016/j.ijcard.2014.04.072

2 van der Velde ET, Vander VET, Vriend JWJ, *et al.* CONCOR, an initiative towards a national registry and DNA-bank of patients with congenital heart disease in the Netherlands: rationale, design, and first results. *Eur J Epidemiol* 2005;**20**:549–57.

3 Diller G-P, Kempny A, Inuzuka R, *et al.* Survival prospects of treatment naïve patients with Eisenmenger: a systematic review of the literature and report of own experience. *Heart* 2014;**100**:1366–72. doi:10.1136/heartjnl-2014-305690

4 Hjortshøj CS, Jensen AS, Sørensen K, *et al.* Epidemiological changes in Eisenmenger syndrome in the Nordic region in 1977-2012. *Heart* 2017;**103**:1353–8. doi:10.1136/heartjnl-2016-310979

5 Kempny A, Dimopoulos K, Gatzoulis MA. Declining incidence and prevalence of Eisenmenger syndrome in the developed world: a triumph of modern medicine. *Heart* 2017;**103**:1313–4. doi:10.1136/heartjnl-2017-311396

6 Galiè N, Beghetti M, Gatzoulis MA, *et al.* Bosentan Therapy in Patients With Eisenmenger Syndrome: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Study. *Circulation* 2006;**114**:48–54. doi:10.1161/circulationaha.106.630715

7 Dimopoulos K, Inuzuka R, Goletto S, *et al.* Improved survival among patients with Eisenmenger syndrome receiving advanced therapy for pulmonary arterial hypertension. *Circulation* 2010;**121**:20–5. doi:10.1161/circulationaha.109.883876

8 Rosenzweig EB, Kerstein D, Barst RJ. Long-term prostacyclin for pulmonary hypertension with associated congenital heart defects. *Circulation* 1999;**99**:1858–65.

9 D'Alto M, Romeo E, Argiento P, *et al.* Bosentan–sildenafil association in patients with congenital heart disease-related pulmonary arterial hypertension and Eisenmenger physiology. *International Journal of Cardiology* 2012;**155**:378–82. doi:10.1016/j.ijcard.2010.10.051

10 Thomas IC, Glassner-Kolmin C, Gomberg-Maitland M. Long-term effects of continuous prostacyclin therapy in adults with pulmonary hypertension associated with congenital heart disease. *Int J Cardiol* 2013;**168**:4117–21. doi:10.1016/j.ijcard.2013.07.072

11 Hascoet S, Fournier E, Jaïs X, *et al.* Outcome of adults with Eisenmenger syndrome treated with drugs specific to pulmonary arterial hypertension: A French multicentre study. *Archives of Cardiovascular Diseases* 2017;**110**:303–16. doi:10.1016/j.acvd.2017.01.006

12 Skoro-Sajer N, Gerges C, Balint OH, *et al.* Subcutaneous treprostinil in congenital heart disease-related pulmonary arterial hypertension. *Heart* 2018;**104**:1195–9. doi:10.1136/heartjnl-2017-312143

13 Galiè N, Humbert M, Vachiery J-L, *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). *European Respiratory Journal* 2015;**46**:903–75. doi:10.1183/13993003.01032-2015

14 Bartolome SD, Sood N, Shah TG, *et al.* Mortality in Patients With Pulmonary Arterial Hypertension Treated With Continuous Prostanoids. *Chest* 2018;**154**:532–40. doi:10.1016/j.chest.2018.03.050

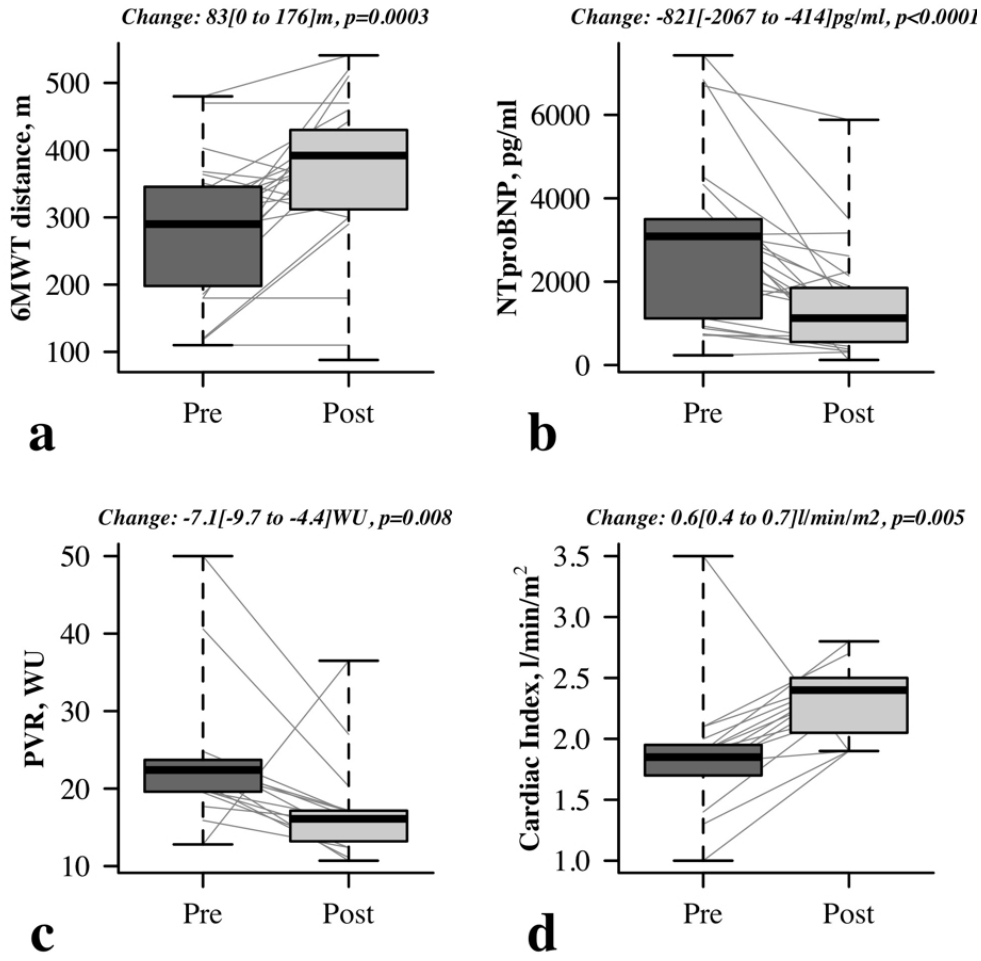
15 Olsson KM, Richter MJ, Kamp JC, *et al.* Intravenous treprostinil as an add-on therapy in patients with pulmonary arterial hypertension. *J Heart Lung Transplant* 2019;**38**:748–56. doi:10.1016/j.healun.2019.05.002

16 Dimopoulos K, Wort SJ, Gatzoulis MA. Pulmonary hypertension related to congenital heart disease: a call for action. *European Heart Journal* 2014;**35**:691–700. doi:10.1093/eurheartj/eht437

17 Dimopoulos K, Muthiah K, Alonso-Gonzalez R, *et al.* Heart or heart-lung transplantation for patients with congenital heart disease in England. *Heart* 2019;**105**:596–602. doi:10.1136/heartjnl-2018-313984

Figure 1 legend

Effect of prostanoid therapy on (a) 6-minute walk test (6MWT) distance, (b) N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level, (c) pulmonary vascular resistance (PVR) and (d) cardiac index. The bold horizontal line represents median values, the box 25th and 75th percentiles, and the vertical dotted line range. The change with therapy in each patient is shown as light grey connecting lines.



Effect of prostanoid therapy on (a) 6-minute walk test (6MWT) distance, (b) N-terminal prohormone of brain natriuretic peptide (NT-proBNP) level, (c) pulmonary vascular resistance (PVR) and (d) cardiac index. The bold horizontal line represents median values, the box 25th and 75th percentiles, and the vertical dotted line range. The change with therapy in each patient is shown as light grey connecting lines.

159x159mm (150 x 150 DPI)