

The tailor-made treatment in a particular case of pulmonary hypertension in thalassaemia intermedia: a case report

Federico B.M. Blasi ^{1,2}, Irene Rota³, Giovanna Graziadei⁴, and Marco Vicenzi ^{2,3*}

¹Department of Medicine and Surgery, Ospedale di Circolo, University of Insubria, Varese, Italy; ²Dyspnea Lab, Department Clinical Sciences and Community Health, University of Milan, Italy; ³Cardiovascular Disease Unit, Internal Medicine Department, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, via F. Sforza 35, 20122 Milan, Italy; and ⁴General Medicine Unit, Department of Medicine and Medical Specialities, Rare Diseases Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Italy

Received 21 November 2020; first decision 13 January 2021; accepted 22 April 2021

Background

Pulmonary hypertension (PH) is a haemodynamic condition, secondary to different causes. Thalassaemia may lead to PH of different origin and needs a comprehensive analysis to be correctly characterized and possibly treated.

Case summary

We present a case study of a patient with a non-transfusion-dependent thalassaemia and a previous diagnosis of group 5 PH. A complete diagnostic assessment led to a specific diagnosis of chronic thromboembolic PH. Thus, we were able to start a specific therapy with riociguat that provided an improvement in terms of haemodynamic, imaging, and functional status.

Discussion

A correct characterization and treatment of PH are essential in order to change the patient's prognosis. Chronic thromboembolic PH is a treatable cause of PH in thalassaemic patients and should be investigated.

Keywords

Pulmonary hypertension • Thalassaemia intermedia • Chronic thromboembolic pulmonary hypertension • Riociguat • Case report

Learning points

- Pulmonary hypertension (PH) needs a comprehensive analysis and a multidisciplinary discussion to be correctly characterized and to change the patient's prognosis.
- Chronic thromboembolic PH (CTEPH) should be investigated in thalassaemic patients as it is a treatable disease.
- We suggest the use of riociguat, a stimulator of soluble guanylate cyclase, as notable choice of therapy in patients with thalassaemia and pre-capillary PH, with findings of CTEPH.

Introduction

Thalassaemia may lead to pulmonary hypertension (PH) of different origin and needs a comprehensive analysis to be correctly characterized and potentially treated.

We present a case study of a patient with a non-transfusion-dependent thalassaemia (NTDT) and a previous diagnosis of group 5 PH under current classification.¹

This case proved how a complete diagnostic assessment can lead to a specific diagnosis and effective tailor-made treatment.

* Corresponding author. Tel: +39 (0)2 50320485, Email: marco.vicenzi@unimi.it

Handling Editor: Piotr Nikodem Rudziński

Peer-reviewers: Rafael Vidal-Perez and Dan Octavian Nistor

Compliance Editor: Brett Sydney Bernstein

Supplementary Material Editor: Fabienne Vervaat

© The Author(s) 2021. Published by Oxford University Press on behalf of the European Society of Cardiology.

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited. For commercial re-use, please contact journals.permissions@oup.com

Timeline

1991
Splenectomy
2010
First episode of deep vein thrombosis (DVT)
2012
Recurrence of DVT: started therapy with rivaroxaban 20 mg
November 2015
First right heart catheterization (RHC) and beginning of specific oral therapy with bosentan for pulmonary hypertension (PH)
June 2016
First evaluation in PH Clinic: perfusion lung scan and angioCT scan were performed before a second RHC, confirming pre-capillary PH identified as chronic thromboembolic PH.
We started riociguat and vitamin K Antagonist instead of rivaroxaban.
December 2017
Significant improvement at the reevaluation with echocardiography, cardiopulmonary exercise testing, and RHC
November 2019
Severe form of urinary tract infection complicated with sepsis and respiratory failure
February 2021
The patient is still alive and in stable condition

Case presentation

A woman born in 1975 with a diagnosis of PH was referred to our PH Clinic in June 2016 for a cardiovascular reevaluation.

She was known at Rare Diseases Center of our institution for an NTDT (genotype: compound heterozygosis β^0 Codon 39/ $\delta\beta$ sic, with average haemoglobin of 12 g/dL). She underwent splenectomy (in 1991) and had two events of deep vein thrombosis (2010 and 2012) treated with long-term therapy using rivaroxaban 20 mg.

A year before our contact, she underwent a right heart catheterization (RHC), which provided a diagnosis of PH (Table 1). It was considered as a group 5 PH and she was placed under specific treatment with bosentan 125 mg bid.

Once referred to our PH Clinic, the patient showed an impaired Functional Class (III NYHA FC) and elevated NT-proBNP (N-terminal pro-B type natriuretic peptide = 1085 pg/mL). Her physical examination showed no appreciable split second heart sound and no jugular distension, but a systolic murmur (2/VI) and signs of chronic venous insufficiency were noted.

We performed a morpho-functional assessment through echocardiography (Figure 1A and Table 2) and cardiopulmonary exercise testing. The patient presented typical findings of right ventricle (RV) overload in volume and pressure, as well as specific alterations in cardiopulmonary performance showing cardiogenic limitation, marked ventilatory inefficiency (VE/VCO₂ slope 62), early decline in oxygen pulse with reduced value at peak of exercise, and peripheral oxygen desaturation (SpO₂ 86%) (Table 3).

Table 1 Right heart catheterization

Haemodynamics	On DOAC (11/2015)	On ERA + DOAC (09/2016)	On ERA + sSGC + VKA (12/2017)
HR, b.p.m.	78	75	75
SAP systolic, mmHg	111	102	100
SAP diastolic, mmHg	79	68	60
PAP systolic, mmHg	90	94	70
PAP diastolic, mmHg	28	30	28
PAP mean, mmHg	45	51	42
RAP, mmHg	7	6	4
PAWP, mmHg	6	7	8
CO (thermodilution), L/min	3.8	5.4	6.5
CI (thermodilution), L/min/m ²	2.4	3.4	4.0
DPG, mmHg	22	23	20
TPG, mmHg	39	44	36
PVR, UW	10.3	8.3	5.2
SvO ₂ %	60	73	75

CI, cardiac index; CO, cardiac output; DOAC, direct oral anticoagulation (rivaroxaban); DPG, diastolic pressure gradient; ERA, endothelin receptor antagonist (bosentan); PAP, pulmonary arterial pressure; PCWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SAP, systemic arterial pressure; sSGC, stimulator of soluble guanylate cyclase (riociguat); SvO₂, venous oxygen saturation; TPG, trans pulmonary pressure; VKA, vitamin K antagonist.

Pulmonary function tests and diffusing capacity of the lungs for carbon monoxide were normal (respectively, FVC 126%, FEV1 111% and DLCO 80%, DLCO/VA 84%). Chest angioCT scan revealed irregular filling defects in the segmental arteries of the right inferior lobe, dilatation of bronchial arteries, and mosaic oligemia. Moreover, there were indirect signs of PH such as ectasia of the pulmonary arteries (common trunk: 37 mm; right pulmonary: 30 mm; left pulmonary: 27 mm), dilation of the RV and inversion of the septum IV curve. A perfusion scintigraphy (Q scan) confirmed multiple bilateral pulmonary perfusion defects (Figure 2A). Thus, we were able to re-define her PH aetiology as a form of chronic thromboembolic pulmonary hypertension (CTEPH).

In September 2016, we proceeded with RHC confirming the presence of pre-capillary PH without significant changes from baseline (Table 1).

Due to lack of evidence supporting the direct anticoagulant treatment in CTEPH, rivaroxaban was replaced by vitamin K Antagonist.¹ Then, we added riociguat to bosentan 125 mg bid as therapeutic strategy recommended by guidelines.^{1,2} After up-titrating period (2 months), the maximum dose of riociguat was well tolerated (2.5 mg TID).

At 6 months follow-up, she reported improvement in symptoms and in FC (NYHA II).

After 12 months (December 2017) of unchanged treatment, we documented a normalized NT-proBNP (168 pg/mL) and an impressive improvement in all instrumental parameters.

Echocardiogram showed a reverse remodelling of the right chambers, with a nearly restored shape of the interventricular septum and

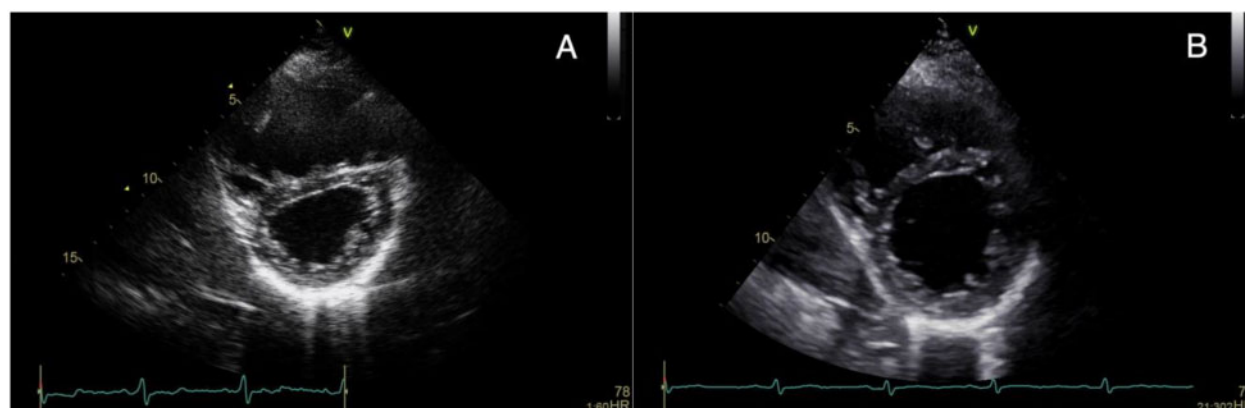


Figure 1 (A) Baseline echo; (B) on optimized therapy.

improved RV function (Table 2, Figure 1B, and Videos 1 and 2). Cardiopulmonary exercise testing reported improved ventilatory inefficiency (VE/VCO_2 slope 42.7), progressive increase of O_2 pulse with normal value at peak, and no desaturation (Table 3).

Right heart catheterization demonstrated a global improvement of haemodynamic with a 49.5% fall in pulmonary vascular resistance from baseline (Table 1).

In contrast with morphological, functional, and haemodynamic improvements, the Q scan remained substantially unmodified (Figure 2B), despite a second angioCT scan showed a partial resolution of the known proximal lesions (see Supplementary material online, Figure S1).

After surgical advice, the patient was definitively excluded from invasive treatment because of untreatable distal lesions.

To date (February 2021), the patient is still alive and in stable condition, even after a severe form of urinary tract infection complicated with sepsis and respiratory failure.

Discussion

This case demonstrates how a correct characterization of PH can change prognosis.

The form of PH linked to thalassaemia syndromes is thought to be the result of different pathogenic mechanisms, which include hypercoagulability, chronic haemolysis, and iron overload due to transfusion therapy.³ Moreover, as a consequence of splenectomy, in the peripheral blood, there is an increased presence of erythroblasts showing procoagulant molecules out of the cellular membrane.⁴

Splenectomy shares a significant correlation with the prevalence of PH in patients with thalassaemia intermedia.^{3–5} It is reasonable to assume that a percentage of pre-capillary PH could be secondary to multiple micro-embolic events and thus classified as CTEPH.

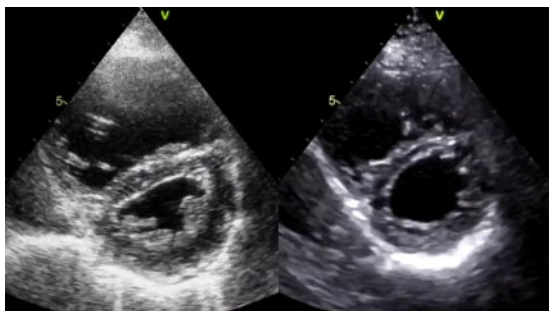
In our case, we believe that the specific drug-related pulmonary vasodilatation through riociguat led the whole clinical improvement. The recovery of RV function is a sign of greater pulmonary vascular compliance that is proved by a better cardiorespiratory and haemodynamic assessment.^{6,7}

Table 2 Echocardiographic data

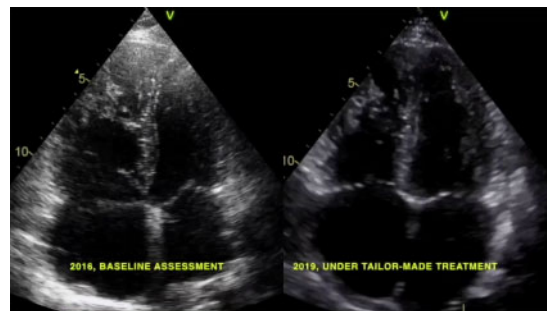
Parameter	On ERA + DOAC (06/2016)	On ERA + sSGC + VKA (12/2017)
RAA, cm ²	27.4	17
TDD RV, mm	54	36
TAPSE, mm	21	22
S' WAVE, cm/s	10	13
TRJET vel, cm/s	3.8	2.9
AV Gradient, mmHg	58	34
PAPS, mmHg	63–68	39
RVFAC, %	21	37
Eccentric index diastole	1.4	1.1
Eccentric index systole	1.7	1.5
Pericardial effusion	Absent	Absent
LVEF, %	60	60

AV gradient, atrio-ventricular gradient; DOAC, direct oral anticoagulation (rivaroxaban); ERA, endothelin receptor antagonist (bosentan); LVEF, left ventricle ejection fraction; PAPS, estimated systolic pulmonary arterial pressure; RAA, right atrial area; RVFAC, right ventricular fractional area change; S' wave, TDI-derived tricuspid lateral annular systolic velocity; sSGC, stimulator of soluble guanylate cyclase (riociguat); TAPSE, tricuspid annular plane systolic excursion; TDD RV, Right Ventricle's TeleDiastolic Diameter; TRjet vel, tricuspid regurgitation jet velocity; VKA, vitamin K antagonist.

To date, the use of pulmonary vasodilators in thalassaemia has remained limited to single centres' experience and no RCTs (randomized clinical trials) are available to support the routine use of such therapy.^{1,4} Two randomized placebo-controlled trials using riociguat, a stimulator of soluble guanylate cyclase (sGC), have been conducted in both PAH (pulmonary arterial hypertension) and CTEPH, but patients with PH related to haemoglobinopathies were not included in the trials.^{1,2} In thalassaemic disorders, erythrocyte dysfunction and by-products of chronic haemolysis contribute to impaired nitric oxide (NO) bioavailability as free haemoglobin inactivates NO and its vasodilatory properties within the pulmonary



Video 1 Short-axis parasternal view, baseline (left panel) and under tailor-made treatment sSGC (right panel).



Video 2 Four chambers apical view, baseline (left panel) and under tailor-made treatment (right panel).

Table 3 Cardiopulmonary exercise testing

	On ERA + DOAC (06/2016)	On ERA + sSGC + VKA (12/2017)
Cause of interruption	Dyspnoea and leg exhaustion	Dyspnoea and leg exhaustion
Maximum workload, Watt	60	75
Maximum HR, b.p.m. (predicted %)	155 (87)	164 (94)
RR	1.2	1.17
Peak VO_2/kg , mL/min/kg (predicted %)	16.8 (59)	19.5 (75)
Peak O_2 pulse, mL/min/b.p.m. (predicted %)	6.4 (71)	9.9 (104)
$\text{VE}/\text{VCO}_2@t$	51.7	45
VE/VCO_2 slope	62	42.7
$\text{PetCO}_2@t$, mmHg	23	25
At rest arterial oxygen saturation, %	93	95
Peak arterial oxygen saturation, %	86	91

DOAC, direct oral anticoagulation (rivaroxaban); ERA, endothelin receptor antagonist (bosentan); Peak VO_2 pulse, Oxygen consumption divided by heart rate at peak exercise; Peak VO_2/kg , Oxygen consumption at peak of exercise pro kilogram; $\text{PetCO}_2@t$, End Tidal Pressure of CO_2 at the threshold; RR, respiratory ratio; sSGC, stimulator of soluble guanylate cyclase (riociguat); VE/VCO_2 slope, minute ventilation and carbon dioxide production ratio's slope at the threshold; $\text{VE}/\text{VCO}_2@t$, minute ventilation and carbon dioxide production ratio at the threshold; VKA, vitamin K antagonist

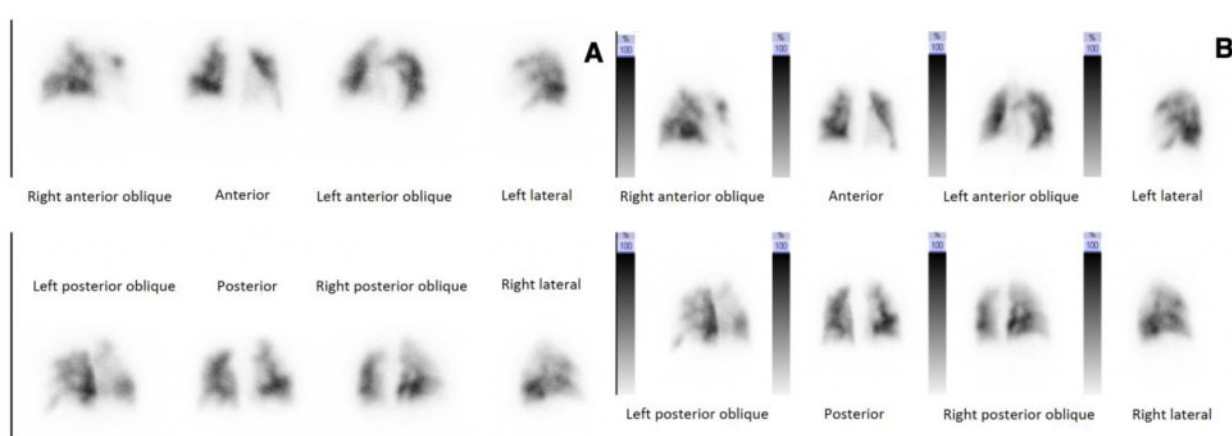


Figure 2 Q scan at baseline (A) and on optimized therapy (B).

circulation. Furthermore, NO synthesis is inhibited by release of arginase during haemolysis and subsequent depletion of the essential NO substrate L-arginine.⁴ Thus, riociguat seems acting on this target: it directly stimulates sGC regardless of NO availability and increases the sensitivity to NO, antagonizing vasoconstriction.² To date, we are not aware of other reports regarding the use of sGC stimulators in haemoglobinopathies. Despite this, patients with thalassaemia and pre-capillary PH with findings of CTEPH may benefit from treatment with riociguat if no surgical options are available.⁴

Conclusion

As recommended by ERS/ESC guidelines, PH patients in group 5 need a careful diagnosis and a tailored treatment. As thalassaemic patients have many risk factors for CTEPH, we cannot afford to miss a diagnosis that can lead to a specific and effective treatment. In our case, despite a still unresolved chronic thrombotic disease, we witnessed a great functional improvement and a reverse remodelling of the RV through medical therapy alone.

These changes are nothing but signs of a better prognosis: the aim of any treatment in chronic disease.

Lead author biography



Federico B.M. Blasi was born in 1992 in Italy. He completed his School of Medicine at University of Milan in 2017 with a thesis 'role of right heart catheterization in patients with respiratory disease and indication to lung transplant'. His professional training in pulmonary hypertension passed through University of Milan, ERS course in Lausanne, and the PH clinic of Polyclinic of Milan. At present, he is a Resident in Cardiovascular disease in Ospedale di Circolo, University of Insubria, Varese.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as [Supplementary data](#).

Consent: The authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidelines.

Conflict of interest: Marco Vicenzi reports consultancy fee paid from MSD Italy, Janssen-Cilag SpA and Neopharmed, outside the submitted work.

Funding: Fondazione IRCCS Ca' Granda *Cardiovascular* Department.

References

1. Galiè N, Humbert M, Vachiery J-L, Gibbs S, Lang I, Torbicki A 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 Respir J* 2015;**46**:903–975. 10.1183/13993003.01032-2015 26318161
2. Ghofrani H-A, D'Armini AM, Grimminger F, Hoeper MM, Jansa P, Kim NH et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med* 2013;**369**:319–329.
3. Derchi G, Galanello R, Bina P, Cappellini MD, Piga A, Lai M-E et al. Prevalence and risk factors for pulmonary arterial hypertension in a large group of β -thalassaemia patients using right heart catheterization: a Webthal study. *Circulation* 2014;**129**:338–345. 10.1161/CIRCULATIONAHA.113.002124 24081970
4. Taher AT, Cappellini MD, Bou-Fakhredin R, Coriu D, Musallam KM. Hypercoagulability and vascular disease in thalassemia. *Hematol Oncol Clin North Am* 2018;**32**:237–245.
5. Taher AT, Musallam KM, Karimi M, El-Beshlawy A, Belhoul K, Daar S et al. Overview on practices in thalassemia intermedia management aiming for lowering complication rates across a region of endemicity: the OPTIMAL CARE study. *Blood* 2010;**115**:1886–1892. 10.1182/blood-2009-09-243154 20032507
6. Caravita S, Faini A, Deboeck G, Bondue A, Naeije R, Parati G et al. Pulmonary hypertension and ventilation during exercise: role of the precapillary component. *J Heart Lung Transpl* 2017;**36**:754–762.
7. Tello K, Dalmer A, Vanderpool R, Ghofrani HA, Naeije R, Roller F et al. Impaired right ventricular lusitropy is associated with ventilatory inefficiency in pulmonary arterial hypertension. *Eur Respir J* 2019;**54**:1900342.