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Change of right heart size and function by long-term therapy with riociguat in patients with pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension☆

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ABSTRACT

Background: Riociguat is a soluble guanylate cyclase stimulator approved for pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH). The objective of this study was to evaluate the change of right heart size and function assessed by echocardiography during long-term treatment with riociguat.

Methods: We assessed patients who started riociguat treatment (1.0–2.5 mg tid) within the trials PATENT, PATENTplus, EAS and CHEST and continued for 3–12 months. Echocardiography, 6-minute walking distance (6MWD) and further clinical parameters were analyzed at baseline, after 3, 6 and 12 months. Right heart catheterization was performed at baseline and after 3 months. For missing data we performed the last and baseline observation carried forward (LOCF, BOCF) method as sensitivity analyses.

Results: Thirty-nine patients (21 PAH, 18 CTEPH, mean pulmonary arterial pressure 43 ± 2 mm Hg, PVR 600 ± 43 dyn∗s∗cm^{-5}, 56.4% treatment-naïve) were included. Mean right ventricular (RV) area significantly decreased after 3 (−2.1 ± 3.9 cm^2, equals −7.4 ± 15.3%, p = 0.002), 6 (−4.2 ± 3.2 cm^2, equals −16.1 ± 11.5%, p < 0.001) and 12 months (−5.9 ± 4.6 cm^2, equals −22.1 ± 14.2%, p < 0.001) compared to baseline. Right atrial area significantly decreased after 12 months (−3.5 ± 4.1 cm^2, equals −16.8 ± 19.2%, p < 0.001) and TAPSE significantly improved after 6 (+2 ± 4.7, equals 12 ± 25.8%, p = 0.025) and 12 months (+3.6 ± 5.4, equals 21.0 ± 29.6%, p = 0.002). Furthermore, RV wall thickness and 6MWD significantly improved after 3, 6 and 12 months (p < 0.05). Invasive hemodynamics significantly improved after 3 months. Both LOCF and BOCF showed similar significance and lower effect sizes.

Conclusion: Long-term treatment with riociguat significantly reduced right heart size and improved RV function in PAH and CTEPH. Further prospective studies are needed to confirm these results.

1. Introduction

Pulmonary arterial hypertension (PAH) and chronic thromboembolic pulmonary hypertension (CTEPH) are both rare diseases which are usually diagnosed in late stages with functional class (FC) III or IV [1] and lead to severe right heart failure with premature death [2,3]. Most patients show a severely enlarged right heart with increased right ventricular (RV) and right atrial (RA) areas (>16 cm^2) and impaired cardiac output (CO) at diagnosis. Riociguat is the first drug that has been

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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approved for the treatment of both PAH and CTEPH [4,5]. In the 12-week PATENT-1 study (Pulmonary Arterial Hypertension Soluble Guanylate Cyclase-Stimulator Trial), riociguat significantly improved the primary endpoint 6-minute walking distance (6MWD) in patients with PAH and several secondary endpoints, including pulmonary vascular resistance (PVR), N-terminal prohormone brain natriuretic peptide (NT-proBNP), WHO-FC, time to clinical worsening and Borg dyspnea score [4]. Patients completing PATENT-1 were eligible to enter the PATENT-2 open-label extension study, which assessed the long-term safety and efficacy of riociguat in patients with PAH [4]. In the CHEST-1 study (Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial), riociguat significantly improved 6MWD and a range of secondary endpoints, including PVR, NT-proBNP, and WHO-FC in patients with inoperable CTEPH or persistent/recurrent pulmonary hypertension (PH) after pulmonary endarterectomy [5]. In the EAS (Early Access Study) and PatentPlus [6] studies, riociguat has also been used but without a placebo controlled arm.

Despite the great clinical relevance of the results provided by riociguat studies [4,5], there is still a lack of data about the effects of this drug on right heart size and performance (pump function), although these parameters are independent prognostic markers [7]. These parameters are of importance taking into account that right heart function is the key determinant of outcomes in PAH and CTEPH patients [7,8]. RA area has been shown to be one of the most important independent prognostic factors in PAH patients [9–11]. The area of the right atrium is easy to measure non-invasively by echocardiography and reflects RV pump function [12–14]. RV size is also a useful parameter of utmost clinical importance since it reflects pressure and volume load of the pulmonary circulation and is strongly associated with prognosis of PH-patients [10,13]. Interestingly, in both PATENT-1 [4] and CHEST-1 [5] studies, a remarkable improvement in CO was recorded in patients receiving riociguat. However, in these studies cardiac pump function was only an exploratory parameter. Therefore, in this study we aimed to analyze, if the treatment with riociguat affects right heart size and function after 3, 6 and 12 months.

2. Methods

2.1. Study population and design

For analysis we used the echocardiographic and clinical data obtained in the multicenter, parallel-group, placebo-controlled clinical studies PATENT 1 and CHEST 1 and the corresponding long-term extension trials and included the patients of the PATENTplus and EAS-trails. We assessed all patients who received riociguat within these trails in the PH-center of Heidelberg according to the following inclusion criteria: 1) enrollment in the riociguat trials (PATENT, PATENTplus, EAS and CHEST); 2) PAH (for patients enrolled in PATENT, PATENTplus) or CTEPH (for patients enrolled in CHEST and EAS) diagnosed according to current guidelines [15]; 3) at least 12 weeks of riociguat administration and 4) since echocardiography was not mandatory in these trials a further inclusion criterion for this analysis was that patients had received at least 2 echocardiographic assessments with one at baseline and a second after 3, 6 or 12 months.

Except minor changes in diuretics and anticoagulation dosages, concomitant medication remained stable throughout the observation period. An intra-individual comparison of patients who received riociguat verum therapy either in the core and/or extension studies measured at baseline, 3, 6 and 12 months by echocardiography was performed. “Baseline” was considered as the time when patients started riociguat therapy.

The primary end-point of the study was the change of RA and RV areas from baseline to 12 months of riociguat therapy. Secondary endpoints were changes of RA and RV areas from baseline to 3 and 6 months, and changes after 3, 6 and 12 months in Tricuspid Annular Plane Systolic Excursion (TAPSE), S′ wave of RV free wall pulsed tissue Doppler imaging (TDI), inferior vena cava (IVC) diameter and IVC collapse, eccentricity index, S′ wave of RV free wall pulsed TDI, 6MWD, and NT-proBNP serum levels. Further secondary end-point was the change of hemodynamic parameters assessed by right heart catheterization (RHC) at baseline and after 3 months. All patients gave written informed consent to the riociguat trials, which were approved by the Ethics Committee at the Medical Faculty of the University of Heidelberg.

2.2. Clinical assessment

Clinical parameters at each time-point included WHO-FC, 6MWD and Borg dyspnea score. 6MWD was carried out under standardized conditions [16]. At the end of the 6-minute walking test, the Borg dyspnea scale (with 6 representing no exertion and 20 maximal exertion) was assessed [17]. Furthermore, safety and tolerability were assessed by monitoring of adverse reactions. Change of PH-specific treatment was recorded throughout the study. Routine laboratory parameters as hemoglobin and creatinine have been obtained at baseline, 3, 6, and 12 months.

2.3. Echocardiographic assessment

Two-dimensional and color-flow guided continuous-wave-Doppler-echocardiographic recordings were routinely obtained at rest by experienced cardiac sonographers (EG and CN) using 2.5 MHz Duplex probes and conventional equipment (Vivid 7, GE Healthcare, Milwaukee, Wisconsin) every three months in our center. In accordance with the American Society of Echocardiography (ASE) guidelines [18], RA area and RV area were measured at the end of ventricular diastole (largest volume), tracing following the endocardium from the lateral aspect of the tricuspid annulus to the septal aspect, excluding the area of the annulus and the leaflets (with regard to RA area) and excluding the area of the annulus and trabecular structures (with regard to RV area). S wave of the RV free wall was measured using TDI. TAPSE was calculated using M-mode from the lateral tricuspid annulus.

2.4. Hemodynamics

RHC was performed at baseline and after 3 months in the PATENT, CHEST and PATENTplus core studies. The examination was performed in a supine position using the transjugular approach with an 8F introducer set (MXI100, MEDEX, Smiths Group PLC, UK). RHC was done by triple-lumen 7F-Swan–Ganz thermodilution catheters (Edwards Lifesciences, Irvine, CA, USA). CO was measured at least in triplicate by thermodilution with a variation of less than 10% between the measured values. The zero reference point for pressure recordings was set at the level of the right atrium in the midaxillary line (phlebostatic axis). All examinations and measurements were performed by the same experienced team.

2.5. Statistical analysis

The analysis was performed by two statisticians (NE and CF). Data are given as mean ± standard deviation for each time point. We also present the mean of individual changes as absolute values and as percentage. The comparisons of baseline and 3, 6 and 12 months for echocardiographic parameters, 6MWD, Borg dyspnea index, RHC parameters, biochemical assay blood pressure and heart rate were conducted by paired t-tests, and the McNemar test for WHO-FC. All tests were two-sided and a p-value of 0.05 was considered statistically significant. Efficacy parameters were available for statistical analysis at baseline and after 3 months in all patients. We performed a nonparametric sensitivity analysis by using the Wilcoxon rank-sum test. To deal with missing data, two imputation methods: the last observation carried forward (LOCF) and the baseline observation carried forward (BOCF) methods were performed. This means, that in case of a missing value, the value from the previous

observation (for LOCF) or from the baseline value (for BOCF) of a subject is imputed.

3. Results

3.1. Study population

Thirty-nine patients were enrolled in the selected riociguat studies at the PH center in Heidelberg. Baseline characteristics of the patients are shown in Table 1. More than half of the patients were treatment naïve (56.4%) and most of the patients (87%) have been up titrated to the maximum riociguat dosage of 2.5 mg, three times a day. Five patients were also treated with PDE5 inhibitors, which were allowed in the PATENTplus trial only. All 39 patients completed 3 months of riociguat therapy, 6- and 12-month follow-up was completed by 32 and 27 patients, respectively (see Fig. 1).

Two patients withdrew therapy with riociguat before the 12 month follow-up: after 4 months of treatment one patient experienced diarrhea reversible after riociguat withdrawal, one patient who also received treatment with an endothelin receptor antagonist, which is associated with liver toxicity [19], showed a sudden rise of hepatic transaminases. In this patient, both treatments were withdrawn and switched to other PAH-drugs for safety reasons.

Another five patients did not complete 6 months and additional four patients (in total 9) did not complete 12 months of riociguat treatment at the end of the analysis. Moreover, one patient was lost to follow-up after 6 months of therapy. After three months, one patient received additional PH-targeted medication with inhaled Iloprost and Bosentan. This patient had been on placebo during the PATENT-1 study.

3.2. Change of the right heart size

After 3 months of therapy, mean RV area significantly reduced by 2.1 ± 3.9 cm^2 ($p = 0.002$, equals −7.4 ± 25.3%) and continued to decrease after 6 months by 4.2 ± 3.2 cm^2 ($p < 0.001$, equals −16.1 ± 11.5%) as well as after 12 months by 5.9 ± 4.6 cm^2 ($p < 0.001$, equals −22.1 ± 14.2%), respectively. Similarly, RA area continuously decreased during the study course by 1.1 ± 4.0 cm^2 ($p = 0.11$, equals −4.4 ± 19.4%), 1.5 ± 4.2 cm^2 ($p = 0.06$, equals −6.8 ± 22.6%) and 3.5 ± 4.1 cm^2 ($p < 0.001$, equals −16.8 ± 19.2%) after 3, 6 and 12 months compared to baseline, respectively. Individual RA areas at baseline and after 12 months are given in Fig. 2.

Riociguat administration was also associated with a significant reduction of RV free wall thickness by 1.1 ± 2.8 mm ($p < 0.05$, equals −6.5 ± 20.4%), 1.4 ± 3.3 mm ($p < 0.01$, equals 9.8 ± 27.3%) and 1.9 ± 3.5 mm ($p < 0.01$, equals 3.8 ± 26.8%) after 3, 6 and 12 months respectively. Both the LOCF and BOCF showed identical significance and lower effect sizes (see Figs. 3 and 4).

Table 1
Baseline characteristics of the study population.

Patients	39
Female sex (%)	23 (58.7%)
Age years	55.72 ± 15.11
BSA (m^2)	1.95 ± 0.32
WHO functional class n (%)	
II	11 (28.2%)
III	28 (71.8%)
Cause of PH (%)	
IPAH	10 (25.6%)
Connective tissue diseases—APAH	10 (25.6%)
Portal hypertension—APAH	1 (2.6%)
Inoperable—CTEPH	5 (12.5%)
Persistent/recurrent—CTEPH	13 (33.3%)
PH-targeted medication (%)	
ERA	12 (30.8%)
PDE_5-inhibitor	2 (5.1%)
ERA + PDE_5-inhibitor	3 (7.7%)
Treatment naïve	22 (56.4%)
Riociguat final dose (mg TID)	2.3 ± 0.5
Baseline 6MWD	378.24 ± 100.3
Right heart catheterization	
Mean pulmonary artery pressure (mm Hg)	43.18 ± 13.29
PVR ($dyn*s*cm^{-5}$)	600.08 ± 267.95
RA pressure (mm Hg)	8.11 ± 5.7
PAWP (mm Hg)	9.42 ± 3.41
Cardiac output ($L*min^{-1}$)	4.8 ± 1.0
Cardiac index ($L*min^{-1}*m^{-2}$)	2.59 ± 0.47

Data are presented as n, n (%) or mean ± SD. WHO: World Health Organization; BSA: body surface area; PH: pulmonary hypertension; IPAH: idiopathic pulmonary arterial hypertension; APAH: associated pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension; ERA: endothelin receptor antagonists; PDE_5: phosphodiesterase-5; TID: three times a day; 6MWD: six-minute walking distance; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure.

3.3. Change of the right heart function

Improvement during the study was also seen in further parameters reflecting right heart function. Compared to baseline values, TAPSE significantly improved after 6 (+2 ± 4.7 mm, $p = 0.025$, equals 12.1 ± 25.8%) and 12 months (3.6 ± 5.4 mm, $p = 0.002$, equals 21.0 ± 29.6%; Fig. 5). The significant improvement of the right heart function was also reflected in the velocity of the annular movement, measured by TDI S wave. Tricuspid annular velocity showed a significant improvement after 12 months with an increase of 1.7 ± 2.9 mm/s ($p = 0.006$, equals 19 ± 32%) while the improvement after 3 and 6 months was not statistically significant ($p = 0.062$, $p = 0.089$, Table 2). Accordingly with the reduction of RV size we observed a significant improvement of RV remodeling assessed by LV eccentricity index after 6 months (−0.3 ± 0.5, $p = 0.003$, equals −1.9 ± 17.3%) and 12 months (−0.1 ± 0.2, $p = 0.03$, equals −6.7 ± 16.0%). PA and IVC diameters did not significantly change during the study course. Nonparametric sensitivity analysis showed similar significant changes. Both LOCF and BOCF confirmed the significant results observed in the complete case analysis (see Fig. 4).

RHC was performed at baseline and after 3 months in the PATENT-1 and CHEST-1 trials (Table 2). Thus, only hemodynamic data of patients who received verum therapy in the core studies were analyzed. Riociguat administration was associated with a significant reduction in systolic (sPAP) and mean pulmonary arterial pressure (mPAP) by 6.2 ± 12.5 mm Hg and 6.9 ± 11.9 mm Hg, respectively ($p = 0.03$ each). No changes in diastolic pulmonary arterial pressure (dPAP) were recorded. A remarkable improvement of CO (+1.7 ± 1.0 L/min, $p < 0.001$) and cardiac index (+0.9 ± 0.5 L/min/m^2, $p < 0.001$) was recorded. Accordingly, PVR substantially improved after 3 months (−207 ± 151 $dyn*s*cm^{-5}$ compared to baseline, $p < 0.001$). RA pressure (indicating central venous pressures) and pulmonary arterial wedge pressure (PAWP) did not change after 3 months.

3.4. Change of further clinical parameters

Physical exercise capacity, measured by 6MWD, showed a significant improvement after 3 and 6 months (3 months +27 ± 60 m, $p = 0.008$, 6 months +51 ± 71 m compared to baseline, $p = 0.001$) and a further albeit not statistically significant improvement after 12 months (+33 ± 90 m, $p = 0.083$, equals 11.2 ± 33.6%). The smaller improvement after 12 months was mainly caused by one patient who decreased in her walking distance by almost 180 m (~50%), which was due to acute pain by her knee- and hip-arthrosis. Leaving this patient out of the analysis, the walking distance after 12 months improved significantly ($p = 0.01$). Borg dyspnea index, blood gas exchange (measured as oxygen saturation at rest and at the end of 6 minute walking test) and WHO-FC, did not significantly change during the study course.

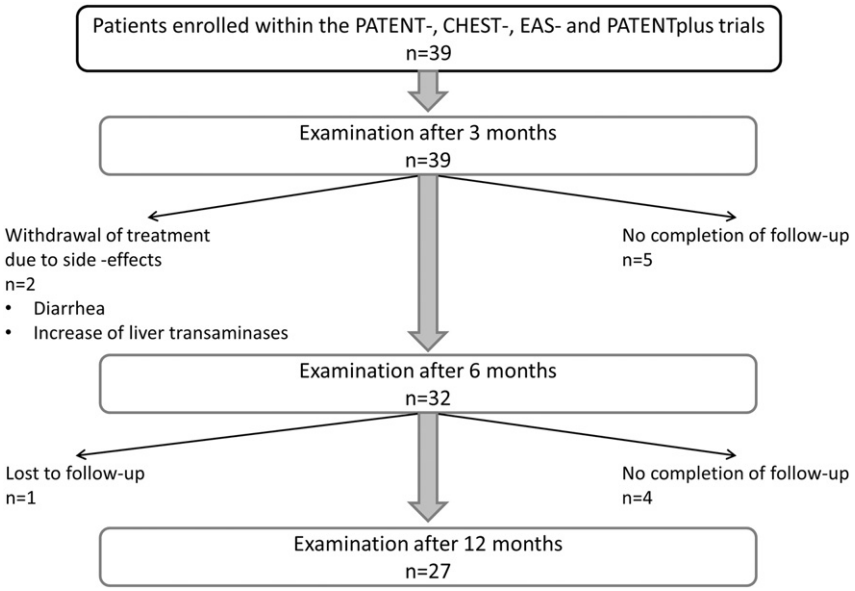

Fig. 1. Flow-chart of study population. Number of patients included in the analysis, exclusions and loss to follow-up are given for each time point.

3.5. Renal function, hemoglobin and NT-proBNP serum values

An unexpected improvement in renal function (although always within the normal ranges) was recorded after 6 months (15% decrease in serum creatinine values after 6 months $p < 0.05$) with stabilization after 12 months ($p < 0.001$ vs baseline). Even though we observed a remarkable reduction in serum NT-proBNP levels, the statistical significance was not reached. No changes were recorded with regard to hemoglobin concentration.

3.6. Outcomes and tolerability

In one patient, PH-specific treatment was escalated after 4 months. Two further patients received an endothelin receptor antagonist after 3 and 6 months respectively. As these two patients did not complete further follow-up assessments, data after initiation of further PH-treatment was not included in the analysis.

As reported above, 2 patients experienced side effects within the first 3 months of the study, which led to withdrawal of riociguat. In one patient who experienced diarrhea, the side effect stopped after withdrawal of riociguat, suggesting probable relation to drug administration.

In a second patient, a sudden rise of transaminase was recorded (3 times the upper limit of normal). In this patient, riociguat was withdrawn for safety reasons. However, the patient was already taking Ambrisentan, which is infrequently associated with liver toxicity [19]. No deaths, unplanned hospital admissions, lung transplantations and sudden worsening of functional status were recorded during the study course. All RHCs have been performed without complications.

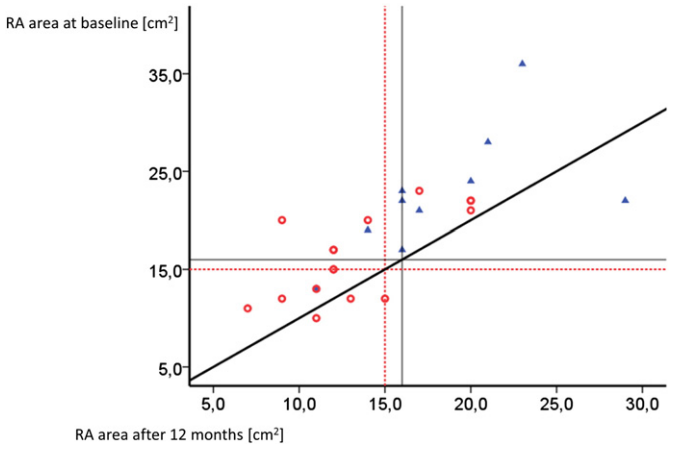

Fig. 2. Individual RA area at baseline and after 1 year. RA areas for each patient are given for baseline and 12 months, circles for females and triangles for males. The corresponding cut-off values with 15 cm^2 for females (dashed) and 16 cm^2 for males (straight) are given as horizontal and vertical lines. The diagonal represents no change between time points.

4. Discussion

This is the first study demonstrating that riociguat administration significantly improved or even normalized mean RA and RV areas after 12 months of treatment in patients with severe PAH and CTEPH who had markedly enlarged mean right heart size at baseline. Riociguat treatment also improved RV pump function and reduced hypertrophy after 3 months measured by RCH and echocardiography. The improvement of right heart size and function was associated with an improvement of exercise capacity, WHO-FC and renal function. Hemodynamic changes measured by RHC showed a significant increase of cardiac index with significant decrease of PVR.

4.1. Effect of riociguat on right heart size and function

The observed changes of clinical parameters are in-line with the previous results of riociguat trials. According to previously published studies [4,5] riociguat administration was associated with an improvement of hemodynamics assessed by RHC. Specifically a decrease in sPAP, mPAP and PVR and a remarkable improvement of CO and cardiac index were recorded [4,5]. Both PATENT and CHEST reported a significant improvement in 6MWD (primary end-point of the study) and hemodynamics (secondary end-point) associated with riociguat administration. However, in the last years 6MWD [20,21] and hemodynamics [22] as surrogate end-points of clinical events have been questioned. A growing body of evidences suggests that RV failure is a key prognostic determinant in both clinical conditions PAH and CTEPH [23,24]. Echocardiography is a valuable tool for assessing right heart size and function and in turn to assess prognosis of PAH and CTEPH patients [7]. Both TAPSE [25] as well as RV and RA areas [10] are strongly associated with prognosis in PAH patients. Furthermore, RA area at baseline seems to be one of the most robust echocardiographic

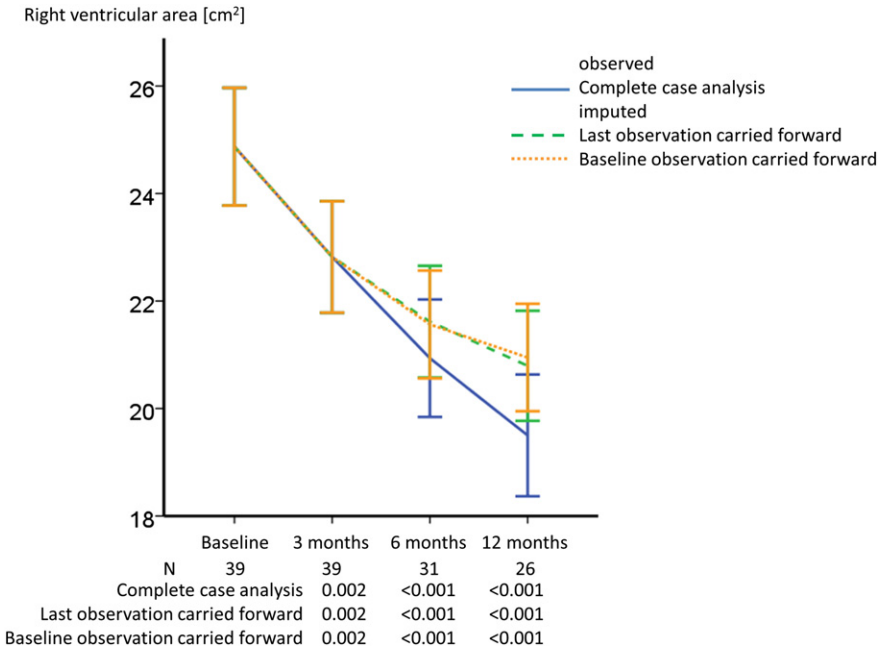

Fig. 3. Mean RV area during the course of the study. For each time point mean RV area ± standard error of the mean is given. p-Values are given compared to baseline for all analyses. The complete case analysis is given as straight line, the last observation carried forward as dashed line and baseline observation carried forward as dotted line. Mean RV area significantly decreased at all time-points compared to baseline. Results of the two imputation methods showed the same significances with smaller effect sizes.

determinants of outcome [9,10]. An improved RA and RV area might reflect an improved RV contractile reserve and may be of high clinical relevance. Altogether, 22 of 26 patients who performed their 12 months assessment showed an improvement of RA area. Using the proposed cut-off for a normal RA area of 15 cm^2 in female and 16 cm^2 in males [14] seven patients who presented with baseline values above these cut-offs showed values within the normal ranges after one year of riociguat treatment. For the RV area, the cut-off value suggested by recent echocardiographic guidelines [18] is 25 cm^2 for male and female. Regarding this cut-off, eight patients who presented with baseline values above 25 cm^2 showed values below this cut-off after 12 months.

However, the role of these echocardiographic parameters as a follow-up marker to guide therapy needs to be further assessed [26]. This is due to two main reasons. First, the lack of standardized echocardiographic methods of assessing right heart size and function of the RV together with technical difficulties in obtaining reproducible right-sided

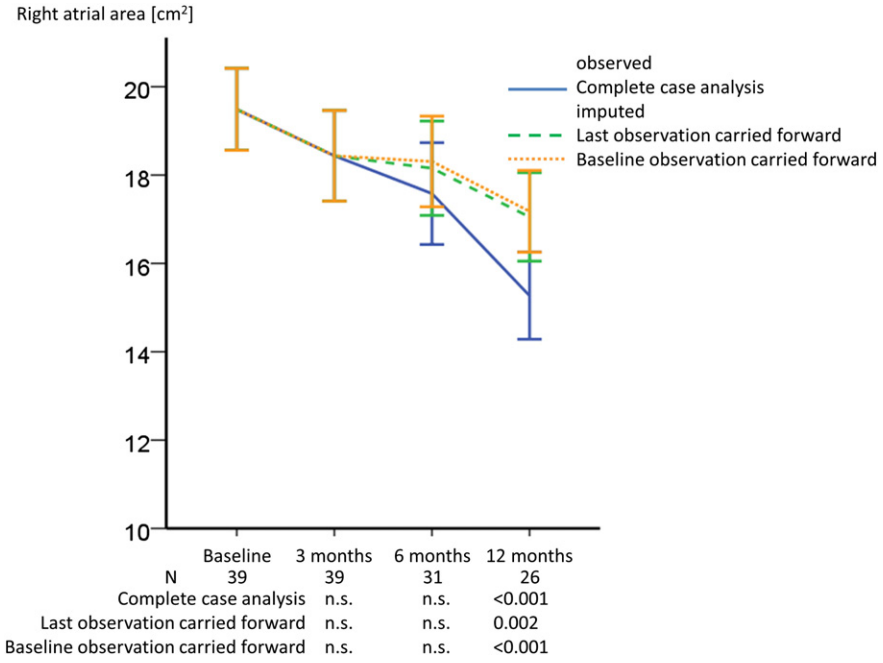

Fig. 4. Mean RA area during the course of the study. For each time point mean RV area ± standard error of the mean is given. p-Values are given compared to baseline for all analyses. The complete case analysis is given as straight line, the last observation carried forward as dashed line and baseline observation carried forward as dotted line. Mean RA area significantly decreased after 12 months compared to baseline. Results of the two imputation methods showed the same significances with smaller effect sizes.

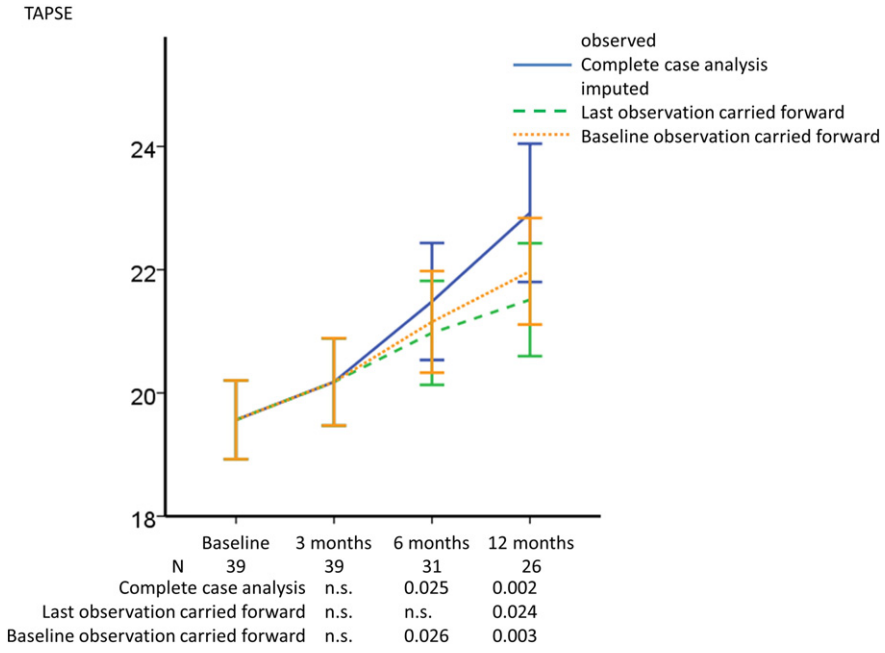

Fig. 5. Mean TAPSE during the course of the study. For each time point mean RV area ± standard error of the mean is given. p-Values are given compared to baseline for all analyses. The complete case analysis is given as straight line, the last observation carried forward as dashed line and baseline observation carried forward as dotted line. Mean TAPSE significantly decreased after 6 and 12 months compared to baseline.

chamber measurements [26]. Second, there are only few reports analyzing the effect of a PAH-targeted drug on right heart size and function.

In a recent trial [27] the acute hemodynamic effect of a single dose of riociguat was tested in patients affected by left heart failure with preserved ejection fraction (HFpEF). In this study 2 mg of riociguat reduced RV area by −5.6 cm^2. The cardioprotective effect due to riociguat administration might lead to a future use of this treatment in heart failure patients [6]. However this finding should be confirmed by future research. One patient received additional medication 4 months after baseline, which might have influenced the results. However, results were similar when leaving this patient out of the analysis.

4.2. Molecular and cellular effects of riociguat on the right ventricle

The sGC/NO pathway plays a pivotal role in PAH and represents one of the main therapeutic targets of PAH specific drugs [28]. The direct

Table 2
Echocardiographic assessment, 6MWD, WHO class, right heart catheterization at baseline and after 3, 6 and 12 months of riociguat administration.

	Baseline	3 months	6 months	12 months
Echocardiographic parameters, n	39	39	32	27
RA area, cm^2	19.49 ± 5,79	18.44 ± 6.41	17.58 ± 6.42	15.27 ± 5.02***
RV area, cm^2	24.87 ± 6.84	22.82 ± 6.47**	20.94 ± 6.08***	19.50 ± 5.78***
TAPSE, mm	19.56 ± 3.99	20.18 ± 4.42	21.48 ± 5.28*	22.92 ± 5.72**
S′ wave lateral wall TDI, mm	10.90 ± 2.68	11.64 ± 3.00	12.00 ± 3.41	12.96 ± 3.35**
RV free wall thickness, mm	9.50 ± 3.87	8,34 ± 2.78*	8.28 ± 3.39**	8.12 ± 2.95**
IVC diameter, mm	17.12 ± 4.70	17.59 ± 5.57	16.83 ± 4.48	15.62 ± 3.85
PA diameter, mm	24.24 ± 3.32	24.80 ± 3.06	22.19 ± 6.28	23.38 ± 2.86
LV eccentricity index	1.21 ± 0.25	1.20 ± 0.28	0.95 ± 0.58**	1.09 ± 0.17*
6MWD, m	378.24 ± 100.30	407.31 ± 110.51**	440.60 ± 104.95***	408.54 ± 130.02**
Borg dyspnea index	4.41 ± 1.83	4.28 ± 1.82	3.97 ± 1.92	4.04 ± 1.68
Oxygen saturation at rest	98.18 ± 2.42	95.68 ± 2.01	95.51 ± 2.46	95.61 ± 2.46
Oxygen saturation during exercise	89.64 ± 5.80	90.23 ± 5.10	90.92 ± 4.39	90.96 ± 5.13
WHO functional class	2.72 ± 0.46	2.74 ± 0.44	2.75 ± 44	2.69 ± 0.47
Right heart catheterization, n	39	22		
sPAP, mm Hg	75.13 ± 22.11	68.14 ± 18.36*	–	–
mPAP, mm Hg	43.18 ± 13.29	36.27 ± 12.54**	–	–
dPAP, mm Hg	26.90 ± 10.21	23.73 ± 9.96	–	–
PVR, $dyn*s*cm^{-5}$	600.08 ± 267.95	370.64 ± 187.86***	–	–
RA pressure, mm Hg	8.11 ± 5.70	7.45 ± 5.06	–	–
PAWP, mm Hg	9.42 ± 3.41	10.18 ± 3.13	–	–
Cardiac output, $L*min^{-1}$	4.80 ± 1.0	6.69 ± 1.49***	–	–
Cardiac index, $L*min^{-1}*m^{-2}$	2.59 ± 0.47	3.57 ± 0.52***	–	–
Creatinine, mg/dl	0.97 ± 0.32	0.95 ± 0.35	0.82 ± 0.36*	0.82 ± 0.27**
Hemoglobin, mg/dl	14.10 ± 1.90	13.90 ± 2.16	14.00 ± 2.32	13.81 ± 2.04
NT-proBNP, pg/dl	1722.26 ± 2891.30	1486.10 ± 2748.52	1240 ± 2885.92	497.58 ± 720.75

Data are presented as n, n (%) or mean ± SD. RA: right atrium, RV: right ventricle; TAPSE: Tricuspid Annular Plane Systolic Excursion; TDI: tissue Doppler-imaging; IVC: inferior vena cava, 6MWD: 6-minute walking distance; SvO_2%: partial venous oxygen saturation; SaO_2%: partial arterial oxygen saturation; WHO: World Health Organization; PAP: pulmonary arterial Pressure; PVR: pulmonary vascular resistance; PAWP: pulmonary arterial wedge pressure.*: $p < 0.05$; **: $p < 0.01$; ***: $p < 0.001$. All p-values are based on two-tailed student's t-test compared to baseline.

pharmacological stimulation of sGC by riociguat demonstrated to reverse right heart dilatation and hypertrophy and to improve systolic function in several preclinical studies that have employed different animal models of PH [29–31]. Of note, riociguat demonstrated to exert a cardio-protective action of higher extent compared to sildenafil, as demonstrated by Lang et al. who have tested both drugs in rat PAH model exposed to vascular endothelial growth factor receptor antagonist SU5416 and hypoxia [29].

Riociguat might exert cardio-protective effects through different mechanisms. A reduction of collagen content was found in the aforementioned study performed by Lang et al. [29]. In a study of Geschka S. et al. [32] riociguat was administrated to Dahl salt-sensitive rats maintained on a high salt diet for 14 weeks. Histological examination of the heart revealed that riociguat carried a remarkable positive effect on fibrotic tissue remodeling and degeneration. Furthermore, the authors recorded that riociguat was able to reduce the mRNA expression in the myocardium of pro-fibrotic biomarkers such as osteopontin, tissue inhibitor of matrix metalloproteinase-1 and plasminogen activator inhibitor-1. In the same study riociguat was also able to reduce myocardial inflammation, cardiomyocyte diameter and increase RV contractility [32].

However, the specific mechanism of action of riociguat on right heart size and function remains to be investigated.

4.3. Limitations

This study presents some limitations. For our analysis of long-term effects we did not have a placebo control group. However, in our study cohort most patients showed an improvement in RA (26% went into normal ranges after 1 year [14]) and RV areas (30.7% went into normal ranges after 1 year [18]). Another limitation is that our cohort is only a small part of the entire study population enrolled in riociguat trials [4,5]. Our sample almost mirrored the baseline characteristics of these studies, except for the lack of WHO class IV patients, which in turn represent only a small amount of the study population. At database closure some patients did not yet attend their routine visits in our center and could therefore not be included into the analysis of original data. All patients were contacted via phone and showed no clinical worsening or worsening of symptoms. The sample size did also not allow a subanalysis regarding PH specific therapy. Future research should also focus on whether treatment-naïve patients on riociguat monotherapy show a larger improvement than patients who already receive PH targeted therapy.

5. Conclusion

Long-term treatment with riociguat significantly reduced and even normalized right heart size and improved RV function in PAH and CTEPH. Riociguat treatment also improved RV pump function and reduced hypertrophy after 3 months measured by RHC and echocardiography. The improvement of right heart size and function was associated with an improvement of exercise capacity, WHO-FC and renal function. Further prospective studies are needed to confirm these results.

Conflict of interest

AMM nothing to declare, BE nothing to declare, NE received lecture fees by Actelion, Pfizer and Bayer Healthcare, CF nothing to declare, CAE nothing to declare, CN nothing to declare, EB nothing to declare, AC nothing to declare, MH received lecture fees, honoraria for advisory boards and reimbursement of travel expenses from Actelion, Bayer, GSK, Novartis, OMT and Pfizer, HG received speaker fees, honoraria for advisory boards, research grants and reimbursement of travel expenses from AstraZeneca, Actelion, Bayer, Pfizer, GSK, OMT, United Therapeutics, Novartis, Lilly, and Janssen-Cilag, KMO received lecture fees from Actelion, GSK, Pfizer and Lilly, TJL member of advisory boards from Actelion, Bayer and GSK, received lecture fees from Actelion, AOP orphan, GSK, Novartis and Pfizer, reimbursement of travel expenses and congress registration from Actelion, AOP orphan, Bayer, GSK and Pfizer, EG member of national and international advisory boards from Bayer HealthCare, Novartis, Actelion, Pfizer and GlaxoSmithKline and received speaker honoraria and reimbursement of travel expenses from Bayer HealthCare, Novartis, Actelion, Pfizer, United Therapeutics, Gilead and GlaxoSmithKline.

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