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Short communication

Identifying potential parameters associated with response to switching from a PDE5i to riociguat in RESPITE

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ABSTRACT

Background: RESPITE evaluated patients with pulmonary arterial hypertension and an inadequate response to phosphodiesterase type 5 inhibitors (PDE5i) who switched to riociguat. This post hoc analysis assessed response to this switch in parameters associated with clinical improvement.
Methods: RESPITE was a 24-week, uncontrolled pilot study (n = 61). Differences in functional, hemodynamic, and cardiac function parameters, REVEAL risk score (RRS), and biomarkers were compared between responders (free from clinical worsening, World Health Organization functional class I/II, and ≥30 m improvement in 6-min walking distance at Week 24) and non-responders.
Results: Of 51 patients (84%) completing RESPITE, 16 (31%) met the responder endpoint. At baseline, there were significant differences between responders and non-responders in *N*-terminal prohormone of brain natriuretic peptide (NT-proBNP), growth/differentiation factor 15 (GDF-15), and RRS, whereas there were no differences in hemodynamics or cardiac function. At Week 24, responders had significant improvements in pulmonary arterial compliance, pulmonary vascular resistance, and mean pulmonary arterial pressure, while non-responders showed no significant change. Cardiac efficiency and stroke volume index significantly improved irrespective of responder status.
Conclusions: NT-proBNP, GDF-15, and RRS were identified as potential predictors of response in patients switching from PDE5i to riociguat. Further prospective controlled studies are needed to confirm the association of these parameters with response.

1. Introduction

In patients with an inadequate response to phosphodiesterase 5 inhibitors (PDE5i), there is a rationale for switching to the soluble guanylate cyclase stimulator riociguat [1,2]. In the RESPITE study,

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patients with pulmonary arterial hypertension (PAH) in World Health Organization functional class (WHO FC) III switching from PDE5i to riociguat had significant improvements from baseline in exercise capacity, functional class, and *N*-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels [2]. Overall, 31% met a predefined composite endpoint of clinical response. The objective of the present analysis was to assess differences between responders and non-responders in functional, hemodynamic, and cardiac function parameters, and REVEAL risk score (RRS) [3] in order to identify parameters that may indicate a patient's likelihood of response to a switch to riociguat.

2. Methods

2.1. Patient, study design, and procedures

RESPITE (ClinicalTrials.gov: NCT02007629) was a 24-week, prospective, open-label, uncontrolled study in patients with PAH. Eligibility criteria are shown in the Supplement. All patients underwent a PDE5i washout of 1–3 days before starting riociguat (adjusted to a maximum of 2.5 mg three times daily). Full details of RESPITE have been published previously [2].

Informed consent was obtained from each patient. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Outcome measures

Prespecified exploratory endpoints in the study included change from baseline to Week 24 in 6-min walking distance (6MWD), WHO FC, and hemodynamic parameters measured by right heart catheterization (RHC). Patients classified as responders at Week 24 were free from clinical worsening (see Supplement for definition), improved to WHO FC I/II, and had an improvement in 6MWD of ≥30 m [2].

Pulmonary arterial compliance (PAC) and cardiac function parameters were calculated post hoc using RHC data (see Supplement for details). The relationship between response and stroke volume index (SVI) and right atrial pressure (RAP) was assessed using thresholds shown to be independently associated with long-term outcomes (SVI ≥ 31 mL/beat/m^2 and RAP < 10 mmHg) [4]. Biomarkers assessed in RESPITE included NT-proBNP, growth/differentiation factor 15 (GDF-15), suppression of tumorigenicity 2 (ST-2), and asymmetric dimethylarginine (ADMA). The updated REVEAL risk score 2.0 (RRS) [5] was used to assess patient risk of mortality.

Details of the statistical analysis are shown in the Supplement.

3. Results

Of 61 patients enrolled in RESPITE [2], 51 (84%) completed 24 weeks of treatment and were included in the Week 24 analyses. Sixteen patients (31%) met the combined responder endpoint. Baseline characteristics for the RESPITE population have been published previously [2].

3.1. Hemodynamics and cardiac function

At baseline there were no significant differences between responders and non-responders in any of the assessed hemodynamic parameters or cardiac function markers (Supplementary Fig. S1 and S2; Table 1). From baseline to Week 24, responders experienced significant improvements in PAC ($p = .016$, Supplementary Fig. S1), pulmonary vascular resistance (PVR) ($p = .006$, Supplementary Fig. S2), and mean pulmonary artery pressure (mPAP) ($p = .037$, Supplementary Fig. S2), while non-responders showed no significant change. In addition, significant improvements were seen in cardiac efficiency (stroke volume/mPAP; responders $p = .011$, non-responders $p = .013$), stroke volume (cardiac output/heart rate (HR); responders $p = .040$, non-responders $p = .044$), and SVI (cardiac index/HR; responders $p = .048$, non-responders $p = .042$) from baseline to Week 24, regardless of responder status (Table 1).

Assessment of predetermined thresholds of SVI (≥31 mL/beat/m^2) and RAP (<10 mm Hg) found that, at baseline, 44% of responders and 32% of non-responders had favorable SVI and RAP levels, while 6% of responders and 26% of non-responders had unfavorable SVI and RAP (Supplementary Fig. S3A). At Week 24, 69% of responders and 48% of non-responders had achieved favorable SVI and RAP, while 13% of responders and 23% of non-responders had not (Supplementary Fig. S3B).

3.2. Biomarkers

NT-proBNP and GDF-15 at baseline were significantly lower in responders than non-responders ($p = .017$ and $p = .012$, respectively) (Fig. 1A, B; Supplementary Table S1 shows overall population). Although non-responders showed a greater numerical change from baseline in NT-proBNP (−392 vs. −249 pg/mL in responders), the relative reduction was greater in responders (37%; $p = .025$) than non-responders (14%; $p = .207$; Fig. 1A). There was no significant change in GDF-15 from baseline to Week 24 in responders or non-responders (Supplementary Table S1; Fig. 1B). There was no significant difference in ADMA at baseline between responders and non-responders, and no significant change from baseline to Week 24 (Supplementary Fig. S4; Supplementary Table S1). ST-2 at baseline was numerically higher in non-responders than responders, with no significant change from baseline to Week 24 (Fig. 1C). In the overall RESPITE population, there was a positive correlation between ST-2 at baseline and REVEAL risk score at baseline ($r = 0.71$; $p < .0001$) and at Week 24 ($r = 0.61$; $p < .0001$).

3.3. Exercise capacity and REVEAL risk score

Responders had a higher baseline 6MWD than non-responders (not significant), and a significant improvement from baseline to Week 24 ($p < .0001$) (Supplementary Fig. S5). Mean RRS was lower at Week 0, and improved to a greater extent at Week 24, in responders than in non-responders, although improvements in both groups were significant ($p < .0001$ and $p = .006$, respectively) (Fig. 1D).

4. Discussion

In this analysis, NT-proBNP, GDF-15, and RRS at baseline were identified as potential predictors of response. In addition, significant differences in change from baseline to Week 24 were seen between responders and non-responders for several hemodynamic and cardiac function parameters.

The rationale for the responder endpoint was to identify patients with clinical improvement. The 6MWD threshold of 30 m is close to the reported clinically minimal important difference in 6MWD of 26–33 m [6,7]; WHO FC at baseline and follow-up can predict survival in patients with PAH [8,9]; and clinical worsening events have been shown to predict further clinical worsening and mortality [10].

Although there were small numerical differences in hemodynamic and functional parameters between responders and non-responders at baseline, non-responders had no significant change in hemodynamic parameters whereas responders experienced significant improvements in PVR, PAC, and mPAP.

This analysis suggests a potential value of biomarker data at baseline to predict response to treatment. GDF-15 and ST-2 are biomarkers of cardiac remodeling and NT-proBNP is a marker of right heart dysfunction; all three are known to correlate with disease severity in PAH [11–13]. Additionally, a recent study in patients with PAH found that higher NT-proBNP and ST-2 were associated with higher pulmonary pressures and PVR, lower 6MWD, and an increased risk of death [14]. At baseline in RESPITE, GDF-15, ST-2, and NT-proBNP showed differences between the subgroups (although ST-2 was not significant),

Table 1
Differences between parameters of cardiac function at baseline and Week 24 between responders and non-responders.

Parameter Mean (SD)	Baseline			Change from baseline to Week 24			
	Responders[a]	Non-responders	p-value[d]	Responders[a]	p-value[e]	Non-responders	p-value[e]
Cardiac efficiency (L/beat/mmHg)	1.30 (0.44)	1.17 (0.40)[b]	0.291	0.42 (0.58)	0.011	0.17 (0.37)[f]	0.013
Stroke volume (mL/beat)	64.36 (11.66)	57.65 (15.24)[b]	0.124	6.35 (11.30)	0.040	4.73 (12.75)[f]	0.044
SVI (mL/beat/m^2)	34.39 (6.01)	32.04 (7.26)[b]	0.264	3.18 (5.91)	0.048	2.92 (7.64)[g]	0.042
RV work (L/min*mmHg)	3.29 (0.90)	3.19 (1.04)[c]	0.740	0.13 (0.71)	0.465	0.17 (0.84)[h]	0.265
RV work index (L/min/m^2/mmHg)	1.74 (0.42)	1.78 (0.58)[c]	0.780	0.06 (0.36)	0.513	0.13 (0.45)[f]	0.105
Pulmonary artery elastance (mmHg/mL/beat)	1.46 (0.53)	1.62 (0.55)[b]	0.309	−0.19 (0.43)	0.094	−0.11 (0.59)[f]	0.315
RV power (mmHg[L/min])	0.51 (0.14)	0.49 (0.16)[c]	0.740	0.02 (0.11)	0.465	0.03 (0.13)[h]	0.265

RV, right ventricle; SVI, stroke volume index.
[a] n = 16.
[b] n = 36.
[c] n = 38.
[d] Difference between responders and non-responders at baseline.
[e] Change from baseline to Week 24.
[f] n = 32.
[g] n = 31.
[h] n = 33.

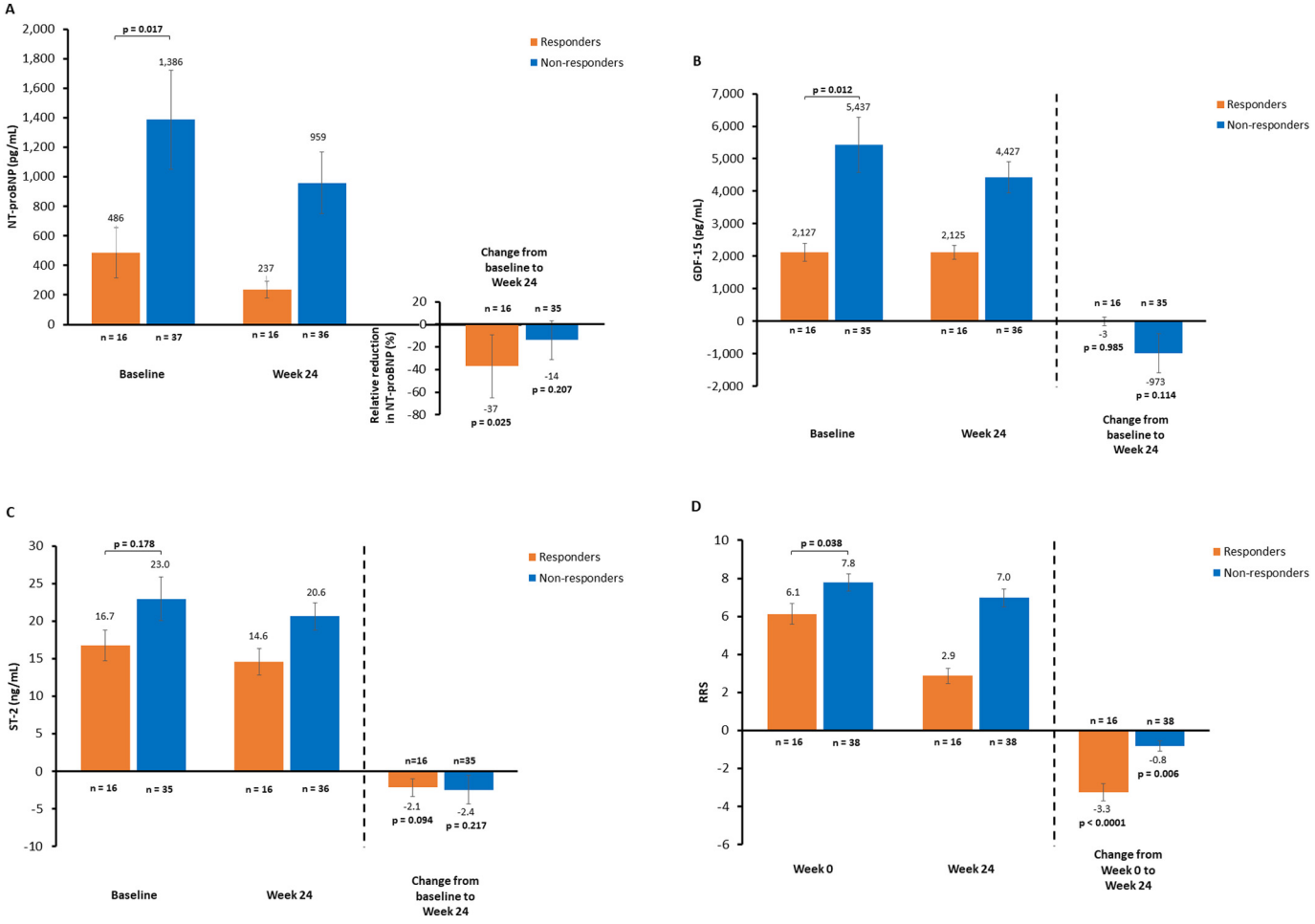

Fig. 1. Mean differences in baseline and Week 24 values between responders and non-responders for A, NT-proBNP; B, GDF-15; C, ST-2; and D, RRS. Baseline was defined as the last documented value while still receiving PDE5i. Week 0 was the last documented value before receiving riociguat (after washout). Error bars are SEM. GDF-15, growth/differentiation factor 15; NT-proBNP, *N*-terminal prohormone of brain natriuretic peptide; RRS, REVEAL risk score; SEM, standard error of the mean; ST-2, suppression of tumorigenicity 2.

whereas there was no difference in ADMA levels. Unlike NT-proBNP, there was no significant change in GDF-15, ST-2, or ADMA in either responders or non-responders at Week 24, suggesting that GDF-15 and ST-2 may be useful biomarkers at baseline to predict response, but not for assessment of post-switch response to riociguat, while ADMA did not differentiate responders from non-responders at any timepoint.

Responders had significantly lower RRS than non-responders at Week 0, and significant improvement in RRS from Week 0 to Week 24. Non-responders also had a significant, although more modest,

improvement in RRS (−0.8 points vs. −3.3 points in responders). The RRS is reflective of right ventricular (RV) function [3], and it is logical that patients with greater improvements in hemodynamic and cardiac function would have a lower RRS. Previous data indicate that a 1-point reduction in RRS is associated with significantly better survival and clinical worsening-free survival in patients with PAH [15].

The hemodynamic interplay between RV morphology and function and PVR is well established [16,17]. While the greater reduction in PVR observed in responders from baseline to Week 24 may explain the improvement in parameters of RV function compared with non-responders, the improvements in hemodynamics and lower RRS at Week 24 in responders lead us to speculate that a responder may be characterized by disease in which the RV and pulmonary vasculature are not yet significantly uncoupled. The lower ST-2 levels (reflective of right heart fibrosis [18,19]) at Week 24 and RAP/SVI assessments (markers of congestion and RV function [20–22]) in responders may also suggest that the RV is not yet terminally adversely remodeled. The results of the present study highlight the importance of evaluating RV function and risk assessment following therapeutic manipulation, a conclusion also reached by Badagliacca and colleagues in an analysis of the hemodynamic burden in pulmonary hypertension, the importance of echocardiographic evaluation of the RV, the impact of current treatments on hemodynamic parameters, and the identification of patients who are more likely to benefit from an aggressive therapeutic approach [23].

As RESPITE was an open-label, single-arm study, further prospective studies are required to confirm the association between these parameters and response to switching to riociguat. The ongoing Phase IV randomized, controlled Riociguat rEplacing PDE5i Therapy evaluated Against Continued PDE5i thErapy (REPLACE) study (ClinicalTrials.gov: NCT02891850) will further assess the strategy of switching to riociguat in patients with PAH and an insufficient response to PDE5i.

Strengths of this study include the wide range of biomarkers monitored, hemodynamic data collected at baseline and Week 24, and the use of RRS as a secondary endpoint in the study, meaning that consistent data are available for these analyses. Limitations include that only 84% of patients completed the study as well as the post hoc nature of the assessment and the arbitrary definition of clinical response. A further limitation is the small patient cohort, with only 16 of 51 patients who completed the study being classed as responders. However, results from RESPITE showed that non-responders still experienced benefits from riociguat after switching from PDE5i [2].

5. Conclusion

Several parameters, including NT-proBNP, GDF-15, and RRS may be useful to assess whether patients are likely to improve their risk status if switched from PDE5i to riociguat. After switching to riociguat, improvement in hemodynamic parameters (particularly PAC) as well as 6MWD, NT-proBNP, and RRS were indicators of treatment response. Further prospective controlled studies are needed to assess these parameters and their association with response.

Declaration of Competing Interest

RLB reports grants from Bellerophon, Bayer AG, Actelion, and EIGER. PAC reports grants and personal fees (University Research Fund) from Bayer AG, and personal fees from Actelion and GSK. JRK reports his institution received grant support for clinical trials in pulmonary hypertension from Actelion, Bayer AG, Lung Biotechnology, and United Therapeutics. DL reports honoraria, consultation fees, research support, and/or travel expenses from Actelion, Arena, Bayer AG, Northern Therapeutic, PhaseBio, and United Therapeutics. RN reports Advisory Board member fees from Actelion, Bayer AG, and Lung Biotechnology Corporation, personal fees from Actelion and GSK, and grants from Reata. GS reports grants, personal fees, and non-financial support from Actelion, Bayer AG, GSK, and Merck. HAG reports grants and personal fees from Actelion, Bayer AG, Ergonex, and Pfizer, and personal fees from Gilead, GSK, Merck, and Novartis. PJ reports being an investigator for Actelion and Bayer AG, and personal fees from AOP. SR reports grants and personal fees from Actelion, Bayer AG, Gilead, GSK, Novartis, Pfizer, United Therapeutics, Arena, Ferrer, Merck Sharp& Dohme, and Abbott, and research support from Actelion, Bayer AG, Novartis, Pfizer, and United Therapeutics. LS has nothing to disclose. TT reports personal fees (Advisory Board/CME) from Actelion and Gilead. AR reports honoraria from Bayer AG, research support from United Therapeutics, and consulting fees from St Jude. CM is an employee of Bayer AG. DB was an employee of Chrestos Concept GmBH & Co during writing of the manuscript. MMH reports consultancy fees from Actelion, Bayer AG, and Pfizer, and personal fees from Actelion, Bayer AG, Pfizer, and MSD.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2020.05.044.

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