IJC Heart & Vasculature 22 (2019) 163–168

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: http://www.journals.elsevier.com/ijc-heart-and-vasculature

Long-term clinical value and outcome of riociguat in chronic thromboembolic pulmonary hypertension

M.C.J. van Thor [a,b], L. ten Klooster [b], R.J. Snijder [b], M.C. Post [a], J.J. Mager [b,*]

[a] Dept of Cardiology, St. Antonius Hospital, Nieuwegein, the Netherlands
[b] Dept of Pulmonology, St. Antonius Hospital, Nieuwegein, the Netherlands

ARTICLE INFO

Article history:
Received 28 November 2018
Accepted 10 February 2019
Available online 28 February 2019

Keywords:
Chronic thromboembolic pulmonary hypertension
Riociguat
Clinical outcome
Survival
Clinical worsening

ABSTRACT

Background: To improve clinical outcome, patients with inoperable and residual chronic thromboembolic pulmonary hypertension (CTEPH) can be treated with riociguat. The aim of this study is to explore long-term outcomes and to compare our 'real world' data with previous research.
Methods: We included all consecutive patients with technical inoperable and residual CTEPH, in whom riociguat therapy was initiated from January 2014 onwards, with patients followed till January 2019. Survival, clinical worsening (CW), functional class (FC), N-terminal pro brain natriuretic peptide (NT-proBNP) and 6-minute walking distance (6MWD) were described yearly after riociguat initiation.
Results: Thirty-six patients (50% female, mean age 64.9 ± 12.1 years, 54% WHO FC III/IV and 6MWD 337 ± 138 m could be included, with a mean follow-up of 2.3 ± 1.2 years. Survival and CW-free survival three years after initiation of riociguat were 94% and 78%, respectively. The 6MWD per 10 m at baseline was a significant predictor (HR 0.90 [0.83–0.97], $p = 0.009$) for CW. At three years follow-up the WHO FC and 6MWD improved and NT-proBNP decreased compared to baseline.
Conclusion: Our study confirms that riociguat is an effective treatment in patients with technical inoperable and residual CTEPH at long-term follow-up. Although our results are consistent with previous studies, more 'real world' research is necessary to confirm long-term results.

1. Introduction

Chronic thromboembolic pulmonary hypertension (CTEPH) is a disease of progressive pulmonary artery remodelling with high morbidity and mortality [1–3]. Pulmonary endarterectomy (PEA) is the preferred treatment, as it has a good prognosis and outcome in operable patients [4,5]. Inoperable patients and patients with persistent pulmonary hypertension after PEA (residual PH) are treated with PH pharmacologic therapy to improve exercise capacity and hemodynamics, and to delay clinical worsening (CW) [5–7].

The soluble guanylate cyclase (sGC) stimulator riociguat is currently the only officially registered treatment for CTEPH. Short-term results from the Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial 1 (CHEST-1) [8] showed improvement of 6-minute walking distance (6MWD) and World Health Organization (WHO) functional class (FC), decreased pulmonary vascular resistance (PVR) and N-terminal pro brain natriuretic peptide (NT-proBNP) levels. The long-term extension study (CHEST-2) [9] showed that the use of riociguat is safe and efficacious up to one year after treatment initiation. However, long-term follow-up data and experiences from 'real world' data are both limited available.

In this article, we describe the long-term clinical outcome of technical inoperable and residual CTEPH patients on riociguat therapy. Furthermore we try to identify predictors for death and CW and we compare our 'real world' data with the previous (randomized, controlled) riociguat studies.

2. Methods

2.1. Study population

We retrospectively included all consecutive technical inoperable CTEPH and residual PH patients who started with riociguat treatment and were discussed in our multidisciplinary CTEPH team from January

Abbreviations: 6MWD, 6-minute walking distance; AE, adverse event; BPA, balloon pulmonary angioplasty; CO, cardiac output; CTEPH, chronic thromboembolic pulmonary hypertension; CHEST, Chronic Thromboembolic Pulmonary Hypertension Soluble Guanylate Cyclase-Stimulator Trial; CW, clinical worsening; e.g., exempli gratiā; ERA, endothelin receptor antagonist; FC, functional class; HR, hazards regression; i.e., id est; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro brain natriuretic peptide; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PEA, pulmonary endarterectomy; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; RAP, right atrial pressure; Residual PH, persistent pulmonary hypertension after PEA; SD, standard deviation; sGC, soluble guanylate cyclase; WHO, World Health Organization.

* Corresponding author at: St. Antonius Hospital Nieuwegein, Koekoekslaan 1, Postbus 2500, 3430 EM Nieuwegein, the Netherlands.
E-mail address: j.mager@antoniusziekenhuis.nl (J.J. Mager).

https://doi.org/10.1016/j.ijcha.2019.02.004

2014 onwards and were followed till January 2019. Our expert team consists of pulmonologists, cardiologists, radiologists, cardiothoracic surgeons and specialised nurse practitioners. The date of the final CTEPH multidisciplinary team meeting was used as date of diagnosis. We collected patient characteristics at time of diagnosis and additional test results performed within 3 months of diagnosis. Imaging tests (transthoracic echocardiography, ventilation/perfusion scans, chest computed tomography scan and pulmonary angiography), right heart catheterisation, blood tests and (cardiopulmonary) exercise testing were performed according to the current guideline to establish CTEPH diagnosis and to asses operability [10]. PH was defined as a mean pulmonary artery pressure (mPAP) of ≥ 25 mm Hg and a wedge pressure ≤ 15 mm Hg. The diagnosis of CTEPH was made when a considerable amount of pulmonary vessels showed evidence of chronic thromboembolisms in the presence of PH after a minimum of 3 months anticoagulation treatment, using two different imaging techniques. Patients were considered inoperable if they had peripheral (i.e. predominantly subsegmental or more distal) thromboembolic disease. Residual PH was defined as a persistent elevated (≥ 25 mm Hg) mPAP after PEA.

Both technical inoperable and residual CTEPH patients started with riociguat therapy. If the patient remained symptomatic or had severe hemodynamic impairment at baseline, pharmacologic therapy was extended to off-label pulmonary arterial hypertension (PAH) oral combination therapy. In case of disease progression under combination therapy, triple therapy using intravenous prostanoids was initiated.

All patients, including stable disease, were systematically evaluated for balloon pulmonary angioplasty (BPA) treatment to improve hemodynamics and consequently symptoms and outcomes. Patients were accepted for BPA treatment by the multidisciplinary CTEPH team, if they had accessible thromboembolic lesions and did not have severe contraindications for BPA.

2.2. Outcome, events and follow-up

Patients were annually followed from initiation of riociguat treatment till the last known date of riociguat use or until death, lost to follow-up or end of study. WHO FC, 6MWD, NT-proBNP and (adverse) events were collected at regular outpatients visits, which were scheduled every 3 months.

Time of death and time to clinical worsening (CW) were noted. Death was defined as all-cause mortality and CW was defined as a combination of death, or non-elective hospitalisation for CTEPH or disease progression. We defined disease progression as the initiation of intravenous prostanoids or a reduction in 6MWD by 15% compared to baseline combined with worsening WHO FC, except for patients already in functional class IV. Only the first event of CW was noted in patients with multiple events. Maximum riociguat dose and adverse events (AEs) during treatment were noted.

2.3. Statistical analyses

All statistical analyses were performed with SPSS (IBM SPSS statistics version 24). Distribution of continuous data was visually assessed and normally distributed data were presented as mean ± standard deviation (SD) and not normally distributed data as median (interquartile range (IQR)). Categorical data were presented as number and percentage. Change to baseline in WHO FC, NT-proBNP and 6MWD, was assessed with a paired *t*-test or Wilcoxon signed rank test. Differences

Table 1
Baseline patient characteristics and medication strategy for patients with or without CW.

	All patients ($n = 36$) (Mean ± SD)	No CW ($n = 29$) (Mean ± SD)	CW ($n = 7$) (Mean ± SD)	P-value
Demographic characteristics				
Age (years)	64.9 ± 12.1	65.1 ± 12.2	64.3 ± 12.8	0.879
Female gender, n (%)	18 (50.0)	13 (44.8)	5 (71.4)	0.402
Inoperable/residual CTEPH, n (%)	33 (91.7)/3 (7.3)	27 (93.1)/2 (6.9)	6 (85.7)/1 (14.3)	0.488
History taking				
Smokers (ever), n (%)	21 (58.3)	16 (55.2)	5 (71.4)	0.674
COPD, n (%)	11 (30.6)	9 (31)	2 (28.6)	1.000
Hypertension, n (%)	9 (25.0)	7 (24.1)	2 (28.6)	1.000
Diabetes, n (%)	4 (11.1)	3 (10.3)	1 (14.3)	1.000
Hyperlipidemia, n (%)	1 (2.8)	1 (3.4)	0	1.000
Thyroid dysfunction, n (%)	1 (2.8)	0	1 (14.3)	0.194
Hematologic disease, n (%)	14 (38.9)	11 (37.9)	3 (42.9)	1.000
Cardiac device, n (%)	1 (2.8)	0	1 (14.3)	0.189
Venous thrombosis, n (%)	6 (16.7)	5 (17.2)	1 (14.3)	1.000
Acute pulmonary embolism, n (%)	32 (88.9)	26 (89.7)	6 (85.7)	1.000
Clinical characteristics				
WHO FC I/II/III/IV (%)	0/46/51/3	0/46/50/4	0/43/57/0	1.000
NT-proBNP (pg/mL), median (IQR)	382 (186–2220)	364 (178–2188)	1345 (189–2418)	0.983
6MWD (m)	337 ± 138	363 ± 130	237 ± 128	0.027
Right-sided heart catheterization				
CO (L/min)	5.2 ± 1.6	5.2 ± 1.6	4.9 ± 1.7	0.693
RAP mean (mmHg)	7.9 ± 3.1	7.8 ± 3.3	8.0 ± 2.5	0.897
PAP mean (mmHg)	38.1 ± 9.3	38.6 ± 10.0	36.2 ± 5.4	0.391
PVR (WU)	6.1 ± 3.7	6.1 ± 4.0	5.9 ± 2.8	0.881
Treatment start follow-up				
VKA/NOAC/LMWH (%)	89/8/3	90/7/3	86/14/0	0.733
Riociguat, n (%)	17 (47.2)	13 (44.8)	4 (57.1)	0.684
Riociguat + ERA, n (%)	19 (52.8)	16 (55.2)	3 (42.9)	0.684
Treatment last follow-up				
Riociguat, n (%)	6 (16.7)	6 (20.7)	0	0.317
Riociguat + ERA, n (%)	26 (72.2)	20 (69.0)	6 (85.7)	0.645
Riociguat + ERA + prostanoid	1 (2.8)	0	1 (14.3)	0.194
Switch to PDE5 inhibitor	3 (8.3)	3 (10.3)	0	1.000
Concomitant BPA treatment	12 (33.3)	9 (31.0)	3 (42.9)	0.664

SD: standard deviation, CTEPH: chronic thromboembolic pulmonary hypertension, COPD: chronic obstructive pulmonary disease, WHO FC: World Health Organization functional class, NT-proBNP: N-terminal pro brain natriuretic peptide, 6MWD: 6-min walking distance, 6MWT: 6-min walking test, CO: cardiac output, RAP: right atrial pressure, PAP: pulmonary arterial pressure, PVR: pulmonary vascular resistance, ERA; endothelin receptor antagonist, PDE5 inhibitor: phosphodiesterase type 5 inhibitor; BPA: balloon pulmonary angioplasty. #Data do not add up to 100% due to rounding.

between riociguat patients with and without events were assessed with student *t*-tests, Mann-Whitney *U* test, Pearson Chi-Square and Fisher exact tests. Kaplan-Meier curves were used for assessment of survival and CW-free survival in the overall population and to assess (CW-free) survival with patients censored at start of BPA treatment. Cox proportional hazards regression analyses were used to identify predictors. All tests were 2-tailed and were considered statistically significant if the *p*-value was below 0.05. The time between diagnosis and the start of riociguat was corrected with a time-dependent covariate. The study was approved by the local ethical commission (number W17.132).

3. Results

3.1. Study population

We included 36 consecutive inoperable and residual CTEPH patients (50% female, mean age 64.9 ± 12.1 years) on riociguat therapy. Baseline characteristics are presented in Table 1.

The majority of patients had inoperable disease (92%), only 3 patients had residual CTEPH. Most patients had a history of thromboembolic event (89%) and at least one concomitant comorbidity (69%). There were no patients with a history of chronic osteomyelitis, ventriculoatrial shunt or inflammatory bowel disease. At the time of diagnosis patients were predominantly in WHO FC III/IV (54%). Patients had a mean pulmonary arterial pressure of 38.1 ± 9.3 mm Hg and a PVR of 6.1 ± 3.7 WU. At baseline 17 patients (47%) started combination therapy. At the end of the follow up period, however, 27 patients (75%) received combination or triple therapy. During follow-up twelve patients (33%) underwent concomitant balloon pulmonary angioplasty (BPA).

3.2. Safety and adverse events

We achieved the maximum riociguat dose (2.5 mg three times daily) in 30 (83%) patients, a dose of 2.0 mg three times daily in 3 (8%) patients and a dose of 1.5 mg three times daily in 3 (8%) patients. These last 3 patients got other PAH medication prescribed, as they received suboptimal riociguat dose and had adverse events. Mean riociguat treatment duration was 2.3 ± 1.2 years.

Twenty-four (67%) patients experienced at least one AE during treatment. Serious AEs of hypotension and severe dyspnoea occurred in respectively 6 (17%) and 1 (3%) of the patients, of which 2 (6%) discontinued riociguat treatment for these reasons. One patient discontinued treatment due to upper respiratory tract infection after riociguat initiation. Common AEs were dyspepsia (25%), headache (22%), diarrhoea (19%), upper respiratory tract symptoms (17%), dizziness (14%) and anaemia (11%). Individual patients could experience multiple (adverse) events. None of the patients experienced syncope, haemoptysis, acute renal or acute right ventricular failure (see supplemental table 1).

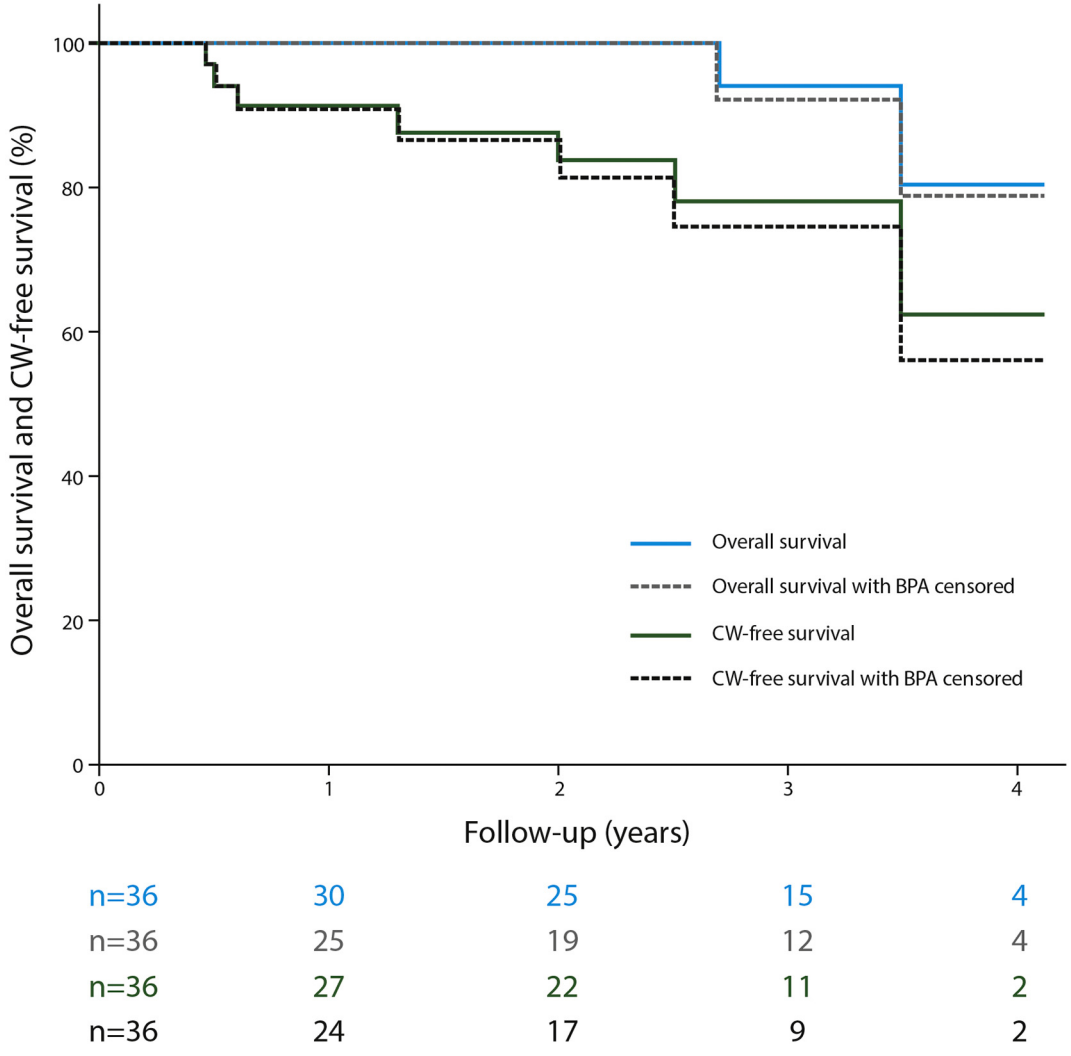

Fig. 1. Kaplan-Meier overall survival and CW-free survival curves and numbers at risk for riociguat patients after therapy initiation. Overall survival and CW-free survival with BPA patients censored are shown with dashed lines.

3.3. Survival and freedom from clinical worsening

In total 7 (19%) patients experienced CW during follow-up. Two (5%) patients died, both experienced CW prior to death. Five (14%) patients alive experienced CW, three (8%) of them needed intravenous prostanoids. The 3 patients with CW and BPA treatment had experienced CW before the start of BPA treatment.

Kaplan-Meier curves for overall survival and CW-free survival are shown in Fig. 1. Survival was 100%, 94%, and 80% at two, three and four years after riociguat initiation, respectively. One patient died in the third year and 1 in the fourth year after therapy initiation. If patients were censored at start of BPA treatment, survival at three and four years decreased to 92% and 79% respectively. Cox proportional hazards regression for survival showed no significant hazard ratios (HR) for baseline characteristics.

Most CW occurred in the first year, with a CW-free survival of 88%, 78% and 63% at two, three and four years after riociguat initiation. These numbers decreased to 87%, 75% and 56% respectively if patients were censored at the start of BPA treatment. A significant baseline predictor for CW was 6MWD per 10 m with HR 0.90 [0.83–0.97] (see supplemental table 2).

A comparison of baseline values between patients with or without CW showed a significant lower 6MWD in the CW group. Furthermore, all patients who experienced CW received combination therapy at the last follow-up compared to only 75% of the patients without CW.

3.4. Follow-up

Overall, WHO FC improved during the first year compared to baseline and stabilised afterwards in our study population. Most patients were in WHO FC I and II during follow-up. Results are shown in Fig. 2.

Median NT-proBNP decreased significantly in the overall population with −67 pg/mL (-1355-49) at one year ($p = 0.04$) and stabilised afterwards. A comparison between patients with and without CW showed no significant difference between changes to baseline in NT-proBNP (see supplemental fig. 1).

During follow-up the mean 6MWD significantly increased for the overall population with 55 ± 72 m at year 1 ($p = 0.0003$), with 60 ± 65 m at year 2 ($p = 0.0002$) and with 89 ± 61 m at year 3 ($p = 0.001$) compared to baseline (see supplemental fig. 2).

4. Discussion

In this article we report an effective and safe clinical outcome up to three years after the initiation of riociguat, in inoperable and residual CTEPH patients.

Previous (randomized) research showed safe and effective short-term results of riociguat treatment for CTEPH [6,11–13]. Riociguat stimulates and sensitizes sGC with a subsequent increase in cyclic guanosine monophosphate, leading to vasodilatation, altered pulmonary vascular tone and eventually to improved clinical functioning. Riociguat is currently the only registered CTEPH therapy for patients with inoperable or residual PH after PEA [10].

Although these controlled trials provide excellent evidence about treatment effectivity, generalizability may be low for patients seen in daily practice where treatment adherence and comorbidities differ [14]. Our 'real-world' data from our clinical care settings may add value to overcome this disadvantage, but should be used with care, as findings may be confounded [14].

We achieved the recommended riociguat dose in 83% of our patients, which is consistent with results reported in the CHEST studies [8,9,15] or a multicentre, non-randomized observational study by Halank et al. [16], including 41 inoperable CTEPH patients. We did not identify new safety issues nor any haemoptysis or pulmonary haemorrhage in our study population. In general, adverse events were limited in our cohort and were in line with results from the CHEST studies [15].

Patients in the CHEST-1 were excluded if they had received other PAH medications within 3 months before study entry [8]. In our cohort we also included patients with a longer CTEPH disease history or who were already on other PAH medication, as patients in daily practice often switch between therapies to achieve maximal treatment effect or due to adverse events. In addition, a recent study reported improved

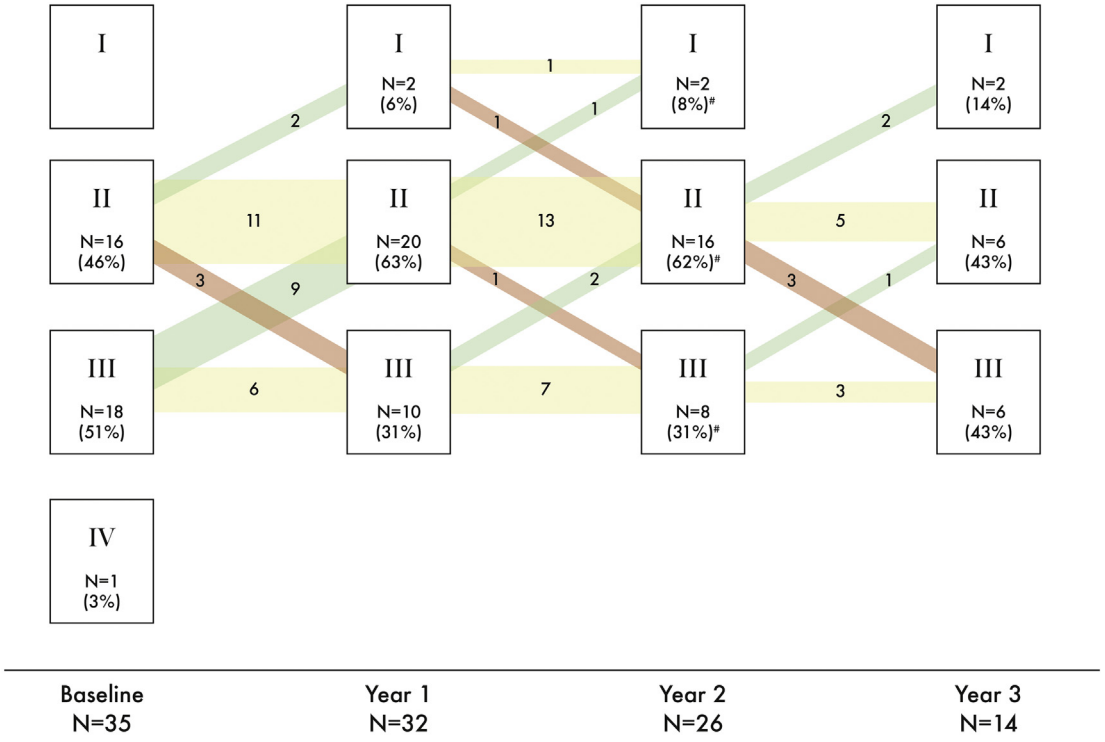

Fig. 2. WHO FC at baseline and follow-up. Number and percentage of patients at risk for each time point and change of patients between time points. Patients who got lost to follow-up or who died between time points were not noted at the next time point. #Data do not add up to 100% due to rounding.

WHO FC and pulmonary hemodynamics after a switch from sildenafil to riociguat [17], although another research showed that a switch may not be as effective as direct initiation of riociguat [18]. However, the patients in this transition group were older and had more severe CTEPH disease [18]. It is possible that patients in our cohort with a longer disease duration or who switched to riociguat had worse results compared to those in whom riociguat was immediate initiated, but this was not the focus of our current research.

The percentage of patients with combination therapy was low (7–10%) in the CHEST-1 [9,15] and was not separately specified for CTEPH patients by Halank et al. [16]. Research in PAH patients showed that combination therapy, e.g. with endothelin receptor antagonists, may delay CW and improve exercise capacity [19,20]. In our cohort we frequently treated patients with combination therapy, up to 75% at latest follow-up. Our hospital is a tertiary care centre for CTEPH, therefore we are able to start off-label PAH specific combination therapy in CTEPH patients. We initiate combination therapy if the patient remains symptomatic or has severe hemodynamic impairment at baseline, despite being clinically stable. The same applies for BPA treatment, as we try to improve hemodynamics and eventually outcome. However, as the guidelines recommend extension to combination therapy in symptomatic patients and BPA treatment in inoperable patients, we expect that our cohort is a good reflection of the current clinical (treatment) course in inoperable and residual CTEPH patients.

We found a survival of 100% during the first two years, with a decrease to 80% four years after initiation of riociguat. For CW-free survival this was 89% at two and 63% at four years respectively. Our values correspond with results reported in the CHEST [9,15] and were better than reported by Halank et al. [16]. However, definitions for CW differed between the studies; the CHEST combined PEA, hospitalisation due to PH, start of new PH treatment, decreased 6MWD, persistent worsening of WHO FC and death. Whereas Halank et al. combined PEA, the use of other PH medication and death in their observational study. In our study, we combined death, rescue intravenous prostanoid treatment, hospitalisation due to PH, or a decreased 6MWD combined with worsened WHO FC. As our definition of CW was stricter, our percentages of CW-free survival may be slightly different. However, there were no patients who underwent PEA after riociguat initiation in our cohort and the number of patients who had CW due to decreased 6MWD or WHO FC was low in the other studies. We decided to only note (rescue) prostanoid treatment as CW, as we extended treatment to combination therapy in accordance to the guideline [10]. Our patients were also systematically evaluated for BPA treatment to optimise treatment and disease control. As BPA improves outcome, it consequently may prevent or delay CW in our cohort and may result in a slightly overestimated treatment effect of riociguat [21]. However, censoring of BPA patients at their first BPA did not change outcomes significantly, probably because some of these patients had already experienced CW before the start of their BPA treatment.

An updated and uniform definition for (time to) CW in CTEPH is needed to improve the ability to compare (future) study results.

Fortunately, due to the low number of deaths, we were unable to identify predictors for survival. We did find that baseline 6MWD was a significant predictor for CW, what is consistent with previous publications of a worse prognosis and CW-free survival in CTEPH patients with low 6MWD [15,22–24]. However, as baseline 6MWD was already significant lower in patients with CW, less improvement and a shorter time to CW may be expected.

Overall, WHO FC improved and eventually stabilised in most of our patients. However, our results are less profound compared to the other studies [15,16]. A worse WHO FC at baseline and a longer disease duration in our cohort might explain this finding. The decrease in NT-proBNP one year after initiation of riociguat was consistent with results from the CHEST-2 [9]. The decrease in NT-proBNP persisted up to 3 years, although the decrease became less profound during follow-up.

Mean 6MWD increased with riociguat therapy during follow-up. As we also initiated riociguat treatment in patients with a 6MWD below 150 m, which were excluded in the CHEST-trial [9], a less profound increase in 6MWD may be expected. However, our overall results were comparable and during follow-up slightly better than results from the other studies [9,15,16].

4.1. Limitations

As our population was small, the mean follow-up time was limited and numbers of patients at risk differed at each time point, results should be interpret with caution. Nevertheless our results were largely consistent with previous studies. We performed a cohort study, what predisposes for bias and confounds result interpretation. Although we included all consecutive patients, patients who died prior to riociguat treatment are not included and this selection bias may result in an overestimated (CW-free) survival. Unfortunately we do not have data of quality-of-life measurements.

5. Conclusion

Long-term follow-up of riociguat therapy in our 'real world' CTEPH patients showed an effective long-term treatment effect, with a reasonable (CW-free) survival and significantly improved clinical parameters. The baseline 6MWD is a significant predictor for CW. Although WHO FC improvement was less profound, our results are largely consistent with other studies. More 'real world' research is necessary to establish more clinical long-term results.

Take home message

Riociguat is an effective treatment in technical inoperable and residual CTEPH up to three years after initiation.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Summary conflict of interest

M. van Thor reports grants from Actelion Pharmaceuticals, outside the submitted work. L ten Klooster has nothing to disclose. R. Snijder reports grants from Pfizer and Actelion Pharmaceuticals, outside the submitted work. M. Post reports grants and speaking fees from Actelion Pharmaceuticals and grants from GlaxoSmithKline, outside the submitted work. J.J. Mager reports grants from Actelion Pharmaceuticals, outside the submitted work.

Publication

All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. The authors declare that neither the work nor any part of its essential substance, tables or figures have been or will be published or submitted to another scientific journal or are being considered for publication elsewhere. There are no simultaneous submissions of similar or related manuscripts at the point of submission.

Acknowledgments

MvT and HM had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. MvT, LtK, RS, HM and MP contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript. All authors approve the final version to be submitted.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2019.02.004.

References

[1] G. Simonneau, A. Torbicki, P. Dorfmüller, N. Kim, The pathophysiology of chronic thromboembolic pulmonary hypertension, Eur. Respir. Rev. 26 (143) (2017 Mar 29).
[2] M. Riedel, V. Stanek, J. Widimsky, I. Prerovsky, Long-term follow-up of patients with pulmonary thromboembolism. Late prognosis and evolution of hemodynamic and respiratory data, Chest. 81 (2) (1982 Feb) 151–158.
[3] B.E. Scholzel, M.C. Post, H.W. Plokker, R.J. Snijder, Clinical worsening during long-term follow-up in inoperable chronic thromboembolic pulmonary hypertension, Lung 190 (2012) 161–167.
[4] D. Jenkins, M. Madani, E. Fadel, A.M. D'Armini, E. Mayer, Pulmonary endarterectomy in the management of chronic thromboembolic pulmonary hypertension, Eur. Respir. Rev. 26 (143) (2017 Mar 15).
[5] B.E. Schölzel, R.J. Snijder, J.J. Mager, et al., Chronic thromboembolic pulmonary hypertension, Neth. Hear. J. 22 (2014) 533–541.
[6] J. Pepke-Zaba, X. Jais, R. Channick, Medical therapy in chronic thromboembolic pulmonary hypertension, Ann. Am. Thorac. Soc. 13 (Suppl. 3) (2016 Jul) S248–S254.
[7] J. Pepke-Zaba, H.A. Ghofrani, M.M. Hoeper, Medical management of chronic thromboembolic pulmonary hypertension, Eur. Respir. Rev. 26 (143) (2017 Mar 29).
[8] H.A. Ghofrani, A.M. D'Armini, F. Grimminger, et al., CHEST-1 Study Group, Riociguat for the treatment of chronic thromboembolic pulmonary hypertension, N. Engl. J. Med. 369 (4) (2013 Jul 25) 319–329.
[9] G. Simonneau, A.M. D'Armini, H.A. Ghofrani, et al., Riociguat for the treatment of chronic thromboembolic pulmonary hypertension: a long-term extension study (CHEST-2), Eur. Respir. J. 45 (5) (2015 May) 1293–1302.
[10] N. Galiè, M. Humbert, J.L. Vachiery, et al., ESC Scientific Document Group, 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. 37 (1) (2016 Jan 1) 67–119.
[11] H.A. Ghofrani, M. Humbert, D. Langleben, R. Schermuly, J.P. Stasch, M.R. Wilkins, J.R. Klinger, Riociguat: mode of action and clinical development in pulmonary hypertension, Chest 151 (2) (2017 Feb) 468–480.
[12] T.Y. Lian, X. Jiang, Z.C. Jing, Riociguat: a soluble guanylate cyclase stimulator for the treatment of pulmonary hypertension, Drug Des. Devel. Ther. 11 (2017 Apr 13) 1195–1207.
[13] F. Grimminger, G. Weimann, R. Frey, et al., First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension, Eur. Respir. J. 33 (4) (2009 Apr) 785–792.
[14] R.E. Sherman, S.A. Anderson, G.J. Dal Pan, et al., Real-world evidence - what is it and what can it tell us? N. Engl. J. Med. 375 (2016) 2293–2297.
[15] G. Simonneau, A.M. D'Armini, H.A. Ghofrani, et al., Predictors of long-term outcomes in patients treated with riociguat for chronic thromboembolic pulmonary hypertension: data from the CHEST-2 open-label, randomised, long-term extension trial, Lancet Respir. Med. 4 (5) (2016 May) 372–380.
[16] M. Halank, M.M. Hoeper, H.A. Ghofrani, et al., Riociguat for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension: results from a phase II long-term extension study, Respir. Med. 128 (2017) 50–56.
[17] S. Darocha, M. Banaszkiewicz, A. Pietrasik, Sequential treatment with sildenafil and riociguat in patients with persistent or inoperable chronic thromboembolic pulmonary hypertension improves functional class and pulmonary hemodynamics, Int. J. Cardiol. 269 (2018) 283–288.
[18] K. Yamamoto, N. Tanabe, R. Suda, Riociguat for patients with chronic thromboembolic pulmonary hypertension: usefulness of transitioning from phosphodiesterase type 5 inhibitor, Respir. Investig. 55 (4) (2017 Jul) 270–275.
[19] A.C. Lajoie, S. Bonnet, S. Provencher, Combination therapy in pulmonary arterial hypertension: recent accomplishments and future challenges, Pulm Circ. 7 (2) (2017 Apr–Jun) 312–325.
[20] H.A. Ghofrani, N. Galiè, F. Grimminger, et al., PATENT-1 Study Group. Riociguat for the treatment of pulmonary arterial hypertension, N. Engl. J. Med. 369 (4) (2013 Jul 25) 330–340.
[21] I. Lang, B.C. Meyer, T. Ogo, et al., Balloon pulmonary angioplasty in chronic thromboembolic pulmonary hypertension, Eur. Respir. Rev. 26 (2017), 160119.
[22] R. Condliffe, D.G. Kiely, J.S. Gibbs, P.A. Corris, A.J. Peacock, D.P. Jenkins, K. Goldsmith, J.G. Coghlan, J. Pepke-Zaba, Prognostic and aetiological factors in chronic thromboembolic pulmonary hypertension, Eur. Respir. J. 33 (2) (2009 Feb) 332–338.
[23] J. Suntharalingam, K. Goldsmith, M. Toshner, N. Doughty, K.K. Sheares, R. Hughes, D. Jenkins, J. Pepke-Zaba, Role of NT-proBNP and 6MWD in chronic thromboembolic pulmonary hypertension, Respir. Med. 101 (11) (2007 Nov) 2254–2262.
[24] J.N. Gong, Z.G. Zhai, Y.H. Yang, Y. Liu, S. Gu, T.G. Kuang, W.M. Xie, R. Miao, C. Wang, Serum bilirubin and 6-min walk distance as prognostic predictors for inoperable chronic thromboembolic pulmonary hypertension: a prospective cohort study, Chin. Med. J. 128 (23) (2015 Dec 5) 3125–3131.