ELSEVIER

The Journal of Heart and Lung Transplantation

http://www.jhltonline.org

Impact of lung morphology on clinical outcomes with riociguat in patients with pulmonary hypertension and idiopathic interstitial pneumonia: A post hoc subgroup analysis of the RISE-IIP study

Steven D. Nathan, MD,[a] Vincent Cottin, MD,[b,c] Juergen Behr, MD,[d] Marius M. Hoeper, MD,[e] Fernando J. Martinez, MD,[f] Tamera J. Corte, MD,[g] Anne M. Keogh, MD,[g,h] Hanno Leuchte, MD,[i] Nesrin Mogulkoc, MD,[j] Silvia Ulrich, MD,[k] Wim A. Wuyts, MD,[l] Zhen Yao, MD,[m,#] Julia Ley-Zaporozhan, MD,[n] Ullrich G. Müller-Lisse, MD,[n] Frank-Detlef Scholle, PhD,[o] Günther Brüggenwerth, MD,[o] Dennis Busse, Dipl Stat,[p,#] Sylvia Nikkho, MD,[o] and Athol U. Wells, MD[q]

From the [a]Advanced Lung Disease and Transplant Program, Inova Heart and Vascular Institute, Falls Church, Virginia; [b]National Reference Centre for Rare Pulmonary Diseases, Department of Respiratory Medicine, Louis Pradel Hospital, Lyon, France; [c]Hospices Civils de Lyon, Université Claude Bernard Lyon 1, Lyon, France; [d]Department of Internal Medicine V, Ludwig Maximilian University of Munich, Comprehensive Pneumology Center, Helmholtz Zentrum, Munich, Germany; [e]Clinic for Respiratory Medicine, Hannover Medical School, Hannover, Germany; [f]Department of Medicine, Weill Cornell Medical College, New York-Presbyterian Hospital/Weill Cornell Medical Center, New York, New York; [g]Royal Prince Alfred Hospital and University of Sydney, Sydney, Australia; [h]St Vincent's Hospital, Sydney, Australia; [i]Department of Internal Medicine II, Neuwittelsbach Academic Hospital, Ludwig Maximilian University, Munich, Germany; [j]Department of Pulmonology, Ege University Hospital, Izmir, Turkey; [k]Clinic of Pulmonology, University Hospital Zürich, Zürich, Switzerland; [l]Unit for Interstitial Lung Diseases, University Hospitals of Leuven, Leuven, Belgium; [m]Bayer Healthcare Company Ltd., Beijing, China; [n]Department of Radiology, University of Munich, Munich, Germany; [o]Bayer AG, Berlin, Germany; [p]Chrestos Concept GmbH & Co. KG, Essen, Germany; and the [q]Interstitial Lung Disease Unit, Royal Brompton Hospital, London, United Kingdom.

KEYWORDS:
combined pulmonary fibrosis and emphysema;
high-resolution computed tomography;
riociguat;

BACKGROUND: Riociguat in Patients with Symptomatic Pulmonary Hypertension associated with Idiopathic Interstitial Pneumonias (RISE-IIP), a randomized, controlled, phase 2b trial of riociguat for pulmonary hypertension associated with idiopathic interstitial pneumonia, was terminated early due to increased mortality in riociguat-treated patients. Baseline characteristics of enrolled patients demonstrated a low diffusing capacity of the lung for carbon monoxide (DL_{CO}) with preserved lung volumes at baseline, suggesting the presence of combined pulmonary fibrosis and emphysema (CPFE) in some

[#]Z. Yao is currently an employee of BeiGene, Beijing, China; D. Busse is now an independent statistician in Dortmund, Germany

Reprint requests: Steven D. Nathan, MD, Advanced Lung Disease and Transplant Program, Inova Heart and Vascular Institute, Inova Fairfax Hospital, 3300 Gallows Rd, Falls Church, VA 22042. Telephone: 703-776-3610. Fax: 703-776-3515.

E-mail address: Steven.Nathan@inova.org

https://doi.org/10.1016/j.healun.2021.02.006

pulmonary hypertension associated with idiopathic interstitial pneumonia; Clinical trials registration. NCT02138825

patients. This post hoc analysis of RISE-IIP was undertaken to explore lung morphology, assessed by high-resolution computed tomography, and associated clinical outcomes.

METHODS: Available baseline/pre-baseline high-resolution computed tomography scans were reviewed centrally by 2 radiologists. The extent of emphysema and fibrosis was retrospectively scored and combined to provide the total CPFE score.

RESULTS: Data were available for 65/147 patients (44%), including 15/27 fatal cases (56%). Of these, 41/65 patients (63%) had CPFE. Mortality was higher in patients with CPFE (12/41; 29%) than those without (3/24; 13%). Fourteen patients with CPFE had emphysema > fibrosis (4 died). No relationship was observed between CPFE score, survival status, and treatment assignment. A low DL_{CO}, short 6-min walking distance, and high forced vital capacity:DL_{CO} ratio at baseline also appeared to be risk factors for mortality.

CONCLUSIONS: High parenchymal lung disease burden and the presence of more emphysema than fibrosis might have predisposed patients with pulmonary hypertension associated with idiopathic interstitial pneumonia to poor outcomes in RISE-IIP. Future studies of therapy for group 3 pulmonary hypertension should include centrally adjudicated imaging for morphologic phenotyping and disease burden evaluation during screening.

J Heart Lung Transplant 2021;40:494−503

The idiopathic interstitial pneumonias (IIPs) comprise a heterogeneous group of fibrotic lung disorders, of which idiopathic pulmonary fibrosis (IPF) is the most common.[1] Pulmonary hypertension (PH) is a common, serious complication of IIPs; mortality is significantly higher when IIP is complicated by PH (PH-IIP) compared with IIP alone.[2,3] How best, in whom, and indeed whether to treat PH in patients with PH-IIP remains uncertain. Ambrisentan is contraindicated in PH-IIP, with no evidence of benefit for other endothelin receptor antagonists.[4] Data on sildenafil are conflicting, and there are too little data on prostanoid therapy for any recommendation to be made.

Riociguat is a soluble guanylate cyclase stimulator approved for the treatment of patients with pulmonary arterial hypertension and patients with inoperable or persistent/recurrent chronic thromboembolic PH.[5-8] Soluble guanylate cyclase stimulators have antifibrotic and antiproliferative effects in preclinical models,[9-13] and riociguat showed promising preliminary results in a phase 2a proof-of-concept study in patients with PH associated with interstitial lung disease (ILD).[14] However, the use of riociguat in patients with PH-IIP was immediately contraindicated following the results of the Riociguat in Patients with Symptomatic Pulmonary Hypertension associated with Idiopathic Interstitial Pneumonias (RISE-IIP) study.[15]

RISE-IIP (riociguat in patients with symptomatic pulmonary hypertension associated with Idiopathic Interstitial Pneumonias; NCT02138825) was a 26-week, multicenter, double-blind, randomized, placebo-controlled, phase 2b trial, including an open-label extension, to evaluate the efficacy and safety of riociguat in symptomatic PH-IIP. RISE-IIP was terminated early on the recommendation of the independent Data Monitoring Committee due to increased serious adverse events and mortality in riociguat-treated patients. In addition, there was no evidence that riociguat improved the primary endpoint of 6-min walking distance (6MWD).

To better understand potential reasons for the unfavorable risk:benefit ratio observed with riociguat in PH-IIP, a data review was conducted at the request of the European Medicines Agency. There were no identifiable differences between the treatment groups in pulmonary function testing, hemodynamics, or arterial blood gas measurement to explain the outcome, nor in oxygen saturation measured via pulse oximetry during the 6MWD tests.[15] In some cases, a low baseline diffusing capacity of the lung for carbon monoxide (DL_{CO}) was observed with relatively well-preserved lung volumes. It was hypothesized that these patients might have had combined pulmonary fibrosis and emphysema (CPFE) which may have affected the study outcomes. Therefore, we explored the relationship between lung morphology, assessed by high-resolution computed tomography (HRCT), and clinical outcomes in this post hoc subset analysis of RISE-IIP.

Patients and methods

RISE-IIP study design and patients

The methodology for RISE-IIP has recently been described in detail.[15] Although patients with CPFE were eligible for the trial, a key exclusion criterion was HRCT evidence of a greater extent of emphysema than fibrotic changes, as assessed by the treating centers. Central adjudication of HRCT scans was not required, as patients could have any of the IIP subgroups; therefore, it was unnecessary to scrutinize these for diagnostic purposes.

Assessment of lung fibrosis and pulmonary emphysema extent by HRCT

For this post hoc central review, participating centers provided baseline or prebaseline (any other time since their diagnosis of PH-IIP) HRCT scans. HRCT data were independently analyzed by 2 radiologists from the University of Munich with experience in reading HRCT scans. The radiologists sat side-by-side and

evaluated all cases together; the readers discussed the HRCT images and together decided the final scoring and provided free-text comments. Any initial discordance between radiologists was resolved through single case discussions. Scans were viewed using a dedicated image visualization system at the General Clinical Imaging Services facilities at Bayer AG, Berlin. Figure S1 online shows examples of HRCT scans for patients with and without CPFE. Data entry was supervised by a monitor and assistance with the electronic case report form was provided. Where possible, axial and coronal HRCT views were read. Images used for consensus evaluation were anonymized and remained blinded, that is, the readers had no access to patient clinical information, treatment assignment, or mortality outcome.

The extents of pulmonary emphysema and fibrosis in each scan were evaluated using previously defined criteria.[16] The right and left lungs were divided into 3 portions: upper (apex to aortic arch), middle (aortic arch to inferior pulmonary vein), and lower (inferior pulmonary vein to the diaphragm) portions. Reticular shadowing and honeycombing, with or without ground-glass opacities, were considered signs of pulmonary fibrosis. Distinct centrilobular, panlobular, or paraseptal emphysema were considered when at least 80% of the emphysema that was present fell into one of these categories; otherwise, a mixed type of emphysema was assumed. The estimated amount of lung affected by fibrosis or emphysema in each portion was scored as 0 (no fibrosis or emphysema), 1 (mild, <25%), 2 (moderate, 25%-50%), 3 (marked, >50%-75%), or 4 (severe, >75%). The scores for each portion in both lungs (i.e., a total of 6 portions) were combined to obtain a total fibrosis score and a total emphysema score (maximum score of 24 for each). Scoring was limited to the extent of fibrosis and emphysema only; however, the radiologists could comment on additional findings at their discretion and were also asked to identify signs of pulmonary veno-occlusive disease (PVOD) or acute lung infection or exacerbation.

Statistical analysis

The impact of CPFE (defined as the presence of any emphysema, i.e., a total emphysema score > 0, plus the presence of any pulmonary fibrosis, i.e., a total fibrosis score > 0) at baseline on survival status was explored. Further analysis of the impact on the survival status of a greater extent of emphysema than pulmonary fibrosis at baseline was also performed. Finally, the potential impact of baseline characteristics (pulmonary function variables, hemodynamic variables, and 6MWD) on survival status was assessed in subgroups defined by (1) the presence of CPFE vs non-CPFE; (2) the extent of emphysema (emphysema score > fibrosis score); and (3) the extent of parenchymal disease burden (HRCT total score $\geq$ 20 vs < 20, based on the median HRCT total score of 20). Further information is included in the online supplement.

Results

Out of 147 patients with PH-IIP, 65 (44%; riociguat, $n = 35$; placebo $n = 30$) had available HRCT scans and were included in these retrospective post hoc analyses. Baseline characteristics in the HRCT subgroup were similar between treatment groups and consistent with the overall RISE-IIP population (Table 1). Also, baseline characteristics were similar when comparing patients with and without HRCT data at baseline, except for a higher proportion of females in the treatment group and higher pulmonary vascular resistance (PVR) in the placebo group of the subgroup without HRCT data vs the HRCT subgroup (Table 1).

Out of 27 deaths in RISE-IIP, 15 (56%) occurred in the 65 patients with baseline HRCT data (Figure 1): based on the start date of the adverse event that led to death, 8 patients died during the main study (riociguat $n = 6$, placebo $n = 2$), 3 during the LTE (former riociguat $n = 1$, former placebo $n = 2$), and 4 during safety follow-up (former riociguat $n = 1$, former placebo $n = 3$).

Fibrosis scores were similar in the overall riociguat and placebo groups (mean $\pm$ standard deviation [SD], 13.2 $\pm$ 4.7 and 13.9 $\pm$ 5.3, respectively), as were mean emphysema scores (6.7 $\pm$ 7.5 and 6.3 $\pm$ 6.5, respectively). Of the fatal cases, the emphysema score was 11.0 $\pm$ 11.4 ($n = 8$) in the riociguat group and 4.9 $\pm$ 5.9 ($n = 7$) in the placebo group (p value not significant), with large interindividual variations in scores in both groups. Emphysema scores in non-fatal cases were similar (5.4 $\pm$ 5.5 and 6.7 $\pm$ 6.8, respectively).

Of 65 patients, 41 (riociguat $n = 22$, placebo $n = 19$; 63%) had evidence of CPFE (Figure 2). Among the fatal cases, 80% (12/15; riociguat $n = 6$, placebo $n = 6$) had CPFE vs 58% of the non-fatal cases (29/50; riociguat $n = 16$, placebo $n = 13$) (Figures 3 and S1). The burden of CPFE was particularly high (HRCT total score > 30) in 6/41 patients (15%), 4 of whom died. Across all phases of the study, 12/41 patients (29%; riociguat $n = 6$, placebo $n = 4$, former placebo $n = 2$) with CPFE died, compared with 3/24 patients (13%; riociguat $n = 2$, placebo $n = 1$) with no evidence of emphysema (Figure 3). In the main phase alone, 5 patients with CPFE died (riociguat $n = 4$, placebo $n = 1$) and 3 patients with no evidence of emphysema died (riociguat $n = 2$, placebo $n = 1$).

Among patients with CPFE, 14 had an emphysema score greater than fibrosis score at baseline (Figures 4 and S1), an exclusion criterion for RISE-IIP. The mean emphysema score in these patients was 15.9 $\pm$ 5.4, while the mean fibrosis score was 9.1 $\pm$ 2.1. Among these 14 patients, 4 died during the study (Figures 4 and S1). Notably, 3/4 fatal cases with a high burden of parenchymal disease (total score > 30) also had an emphysema score greater than the fibrosis score.

No signs of PVOD were observed in any HRCT scan, nor the post-mortem lung histology evaluation of 1 patient. Acute lung infection or acute exacerbation signs were detected in HRCT scans of 2 patients, both of whom had a non-fatal outcome.

Although not analyzed statistically, patients with HRCT who died ($n = 15$) appeared to have a numerically lower DL_{CO}% (28% vs 32%), shorter 6MWD (292 m vs 334 m), and higher forced vital capacity (FVC)%: DL_{CO}% ratio (3.3 vs 2.5) at baseline than those who were alive at the end of RISE-IIP ($n = 50$); the same was observed in patients with CPFE (Table 2). Findings were consistent with the overall RISE-IIP population ($n = 147$; DL_{CO}% 27% vs 32% for those who were alive vs dead, respectively; 6MWD 288 m vs 322 m).[15] In fatal vs non-fatal cases, DL_{CO}% was 19% vs 32%, 6MWD was 242 m vs 334 m, and FVC%: DL_{CO}% ratios were 5.6 vs 2.9 in patients with emphysema scores higher than fibrosis scores, and 23% vs 29%, 269 m

Table 1 Comparison of Baseline Characteristics at Study Start in the HRCT Subgroup and the Overall RISE-IIP Study Population

	Overall RISE-IIP population ($n = 147$)		RISE-IIP HRCT subgroup ($n = 65$)		RISE-IIP no HRCT subgroup ($n = 82$)	
	Riociguat up to 2.5 mg tid ($n = 73$)	Placebo ($n = 74$)	Riociguat up to 2.5 mg tid ($n = 35$)	Placebo ($n = 30$)	Riociguat up to 2.5 mg tid ($n = 38$)	Placebo ($n = 44$)
Female, *n* (%)	23 (32)	29 (39)	9 (26)	10 (33)	14 (37)	19 (43)
Age, years	68 (8)	69 (8)	68 (7)	68 (10)	68 (9)	69 (7)
Body mass index, kg/m^2	29.8 (5.1)	28.5 (5.9)	28.7 (4.7)	27.4 (4.8)	30.7 (5.4)	29.2 (6.6)
Classification of IIP, *n* (%)						
IPF	54 (74)	49 (66)	26 (74)	19 (63)	28 (74)	30 (68)
Idiopathic NSIP	9 (12)	14 (19)	4 (11)	6 (20)	5 (13)	8 (18)
Respiratory bronchiolitis-ILD	1 (1)	0 (0)	1 (3)	0 (0)	0 (0)	0 (0)
Cryptogenic organizing pneumonia	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (2)
Acute interstitial pneumonia	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (2)
Idiopathic LIP	0 (0)	2 (3)	0 (0)	1 (3)	0 (0)	1 (2)
Unclassifiable IIPs	9 (12)	7 (9)	4 (11)	4 (13)	5 (13)	3 (7)
WHO FC II/III/IV, %	22/68/10	30/61/9	20/71/9	33/57/10	24/66/11	27/64/9
6MWD[a], m	307.0 (80.0)	324.0 (66.0)	313.8 (83.1)	336.7 (72.7)	313.6 (77.0)	326.0 (60.7)
Hemodynamics						
RAP, mm Hg	6.7 (4.0) $n = 71$	6.7 (4.5) $n = 73$	6.2 (4.4) $n = 34$	7.2 (3.8)	7.1 (3.6) $n = 37$	6.4 (4.9) $n = 43$
mPAP, mm Hg	33.2 (8.2)	33.5 (9.4)	33.5 (9.1)	31.9 (8.2)	32.9 (7.3)	34.5 (10.1)
Diastolic PAP, mm Hg	22.0 (6.8)	22.6 (7.5)	22.6 (7.4)	21.6 (7.1)	21.5 (6.1)	23.3 (7.8)
Systolic PAP, mm Hg	55.6 (13.4)	55.2 (14.8)	55.4 (14.8)	52.6 (12.5)	55.7 (12.1)	56.9 (16.2)
PVR, dyn.s.cm^{-5}	390.7 (204.5) $n = 72$	417.9 (256.9) $n = 72$	409.2 (258.2) $n = 34$	355.3 (187.0) $n = 29$	374.2 (142.0)	460.2 (289.4) $n = 43$
Cardiac index, L/min/m^2	2.6 (0.7) $n = 72$	2.6 (0.7) $n = 69$	2.7 (0.7) $n = 34$	2.8 (0.7) $n = 29$	2.5 (0.6)	2.5 (0.7) $n = 40$
PAWP, mm Hg	10.6 (3.2)	10.6 (3.0) $n = 73$	10.4 (3.0)	10.7 (2.9)	10.9 (3.5)	10.6 (3.1) $n = 43$
Pulmonary function tests						
FVC, %	76.2 (19.1)	74.3 (15.7)	74.7 (17.1)	73.0 (17.0)	77.6 (21.0)	75.2 (14.9)
FEV_1, %	75.5 (19.1)	75.1 (16.4)	74.7 (17.8)	76.2 (16.8)	76.2 (20.4)	74.4 (16.3)
FEV_1:FVC	0.8 (0.1)	0.8 (0.1)	0.8 (0.1)	0.9 (0.1)	0.8 (0.1)	0.8 (0.1)
TLC, %	66.1 (14.6) $n = 71$	66.3 (12.0)	65.7 (13.5) $n = 34$	64.6 (12.1)	66.4 (15.7) $n = 37$	67.4 (11.8)
DL_{CO}, %	32.0 (11.8) $n = 69$	30.5 (10.9) $n = 71$	31.7 (11.9) $n = 33$	30.5 (11.4) $n = 29$	32.3 (12.0) $n = 36$	30.5 (10.7) $n = 42$

Abbreviations: 6MWD, 6-min walking distance; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LIP, lymphoid interstitial pneumonia; mPAP, mean pulmonary artery pressure; NSIP, non-specific interstitial pneumonia; PAP, pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; tid, 3 times daily; TLC, total lung capacity; WHO FC, World Health Organization functional class.

Data are mean ± standard deviation unless otherwise stated.

[a]Mean of the maximum values from 3 6MWD measurements taken at baseline.

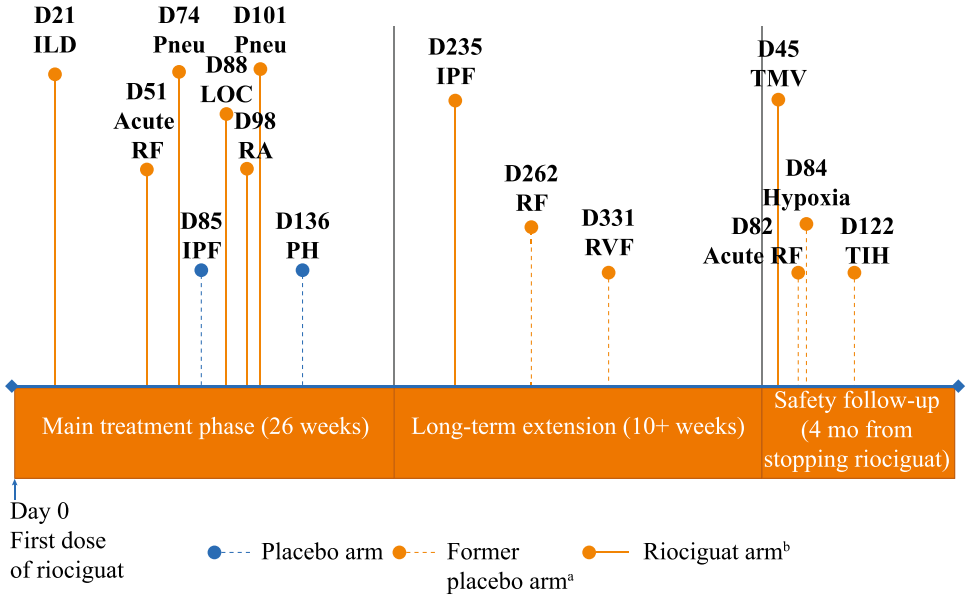

Figure 1 Timeline of deaths in patients in RISE-IIP with available HRCT data relative to the start day according to treatment group and duration of riociguat treatment. D, day; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LOC, loss of consciousness; Pneu, pneumonia; PH, pulmonary hypertension; RA, respiratory arrest; RF, respiratory failure; RVF, right ventricular failure; TIH, traumatic intracranial hemorrhage; TMV, thrombosis mesenteric vessel. [a]Patients who initiated riociguat at the start of the long-term extension. [b]Patients who received riociguat in both the main treatment phase and the long-term extension.

vs 322 m, and 4.2 vs 2.8, respectively, in patients with a high degree of parenchymal disease burden (total score ≥ 20). Three-dimensional plot analysis of fibrosis and emphysema scores by FVC% predicted and mean pulmonary arterial pressure (mPAP) suggested that fibrosis scores were numerically higher in patients with low FVC, whereas FVCs were numerically higher in patients with high emphysema scores (Figure S2).

No relationship was observed between CPFE score, survival status, and treatment assignment. Odds ratios (95% CIs) for the differences in fatal outcome incidences between patients with and without CPFE were 0.56 (0.03-9.87) for placebo, 1.22 (0.19-7.82) for riociguat, and 0.98 (0.21-4.60) overall.

Post hoc analyses suggested that total HRCT lung scores correlated positively with PVR and FVC% and negatively with DL_{CO}% (Table 3). Baseline emphysema score correlated positively with FVC%, FEV_1% (forced expiratory volume in 1 second, % predicted), mPAP, and PVR, and negatively with DL_{CO}% and cardiac index,

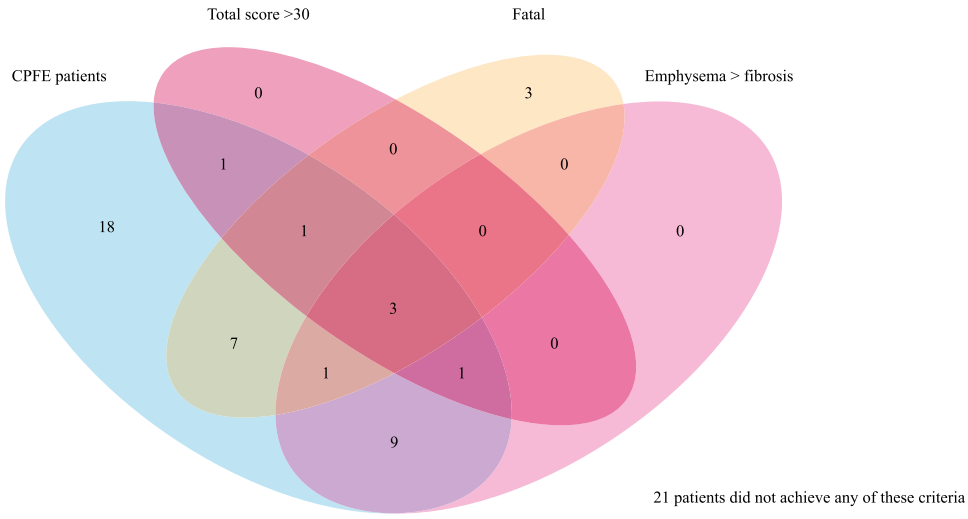

Figure 2 Venn diagram of patients in RISE-IIP with available HRCT data showing proportions of patients with CPFE, high parenchymal disease burden (total score > 30), emphysema score > fibrosis score, and patients who died. Areas of overlap include patients who fit

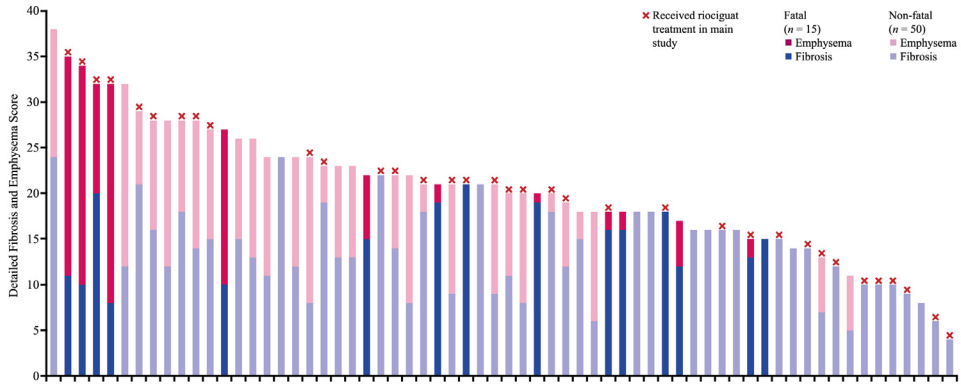

Figure 3 Plot of emphysema and fibrosis scores according to survival status in patients in RISE-IIP with available baseline HRCT data ($n = 65$). HRCT, high-resolution computed tomography. One patient was assessed as having a total score of 0 due to the absence of established idiopathic interstitial pneumonia pattern and evidence of cystic lung disease.

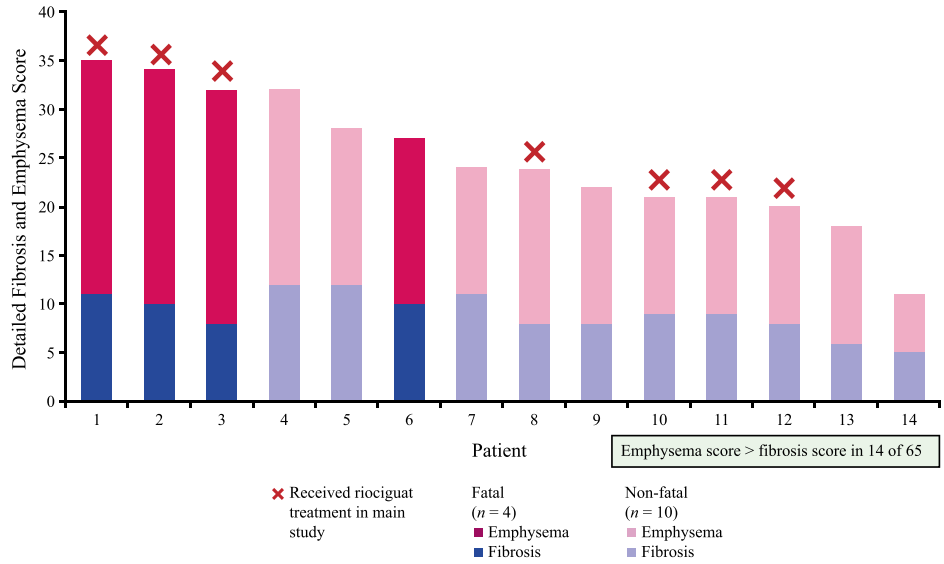

Figure 4 Plot of emphysema and fibrosis scores according to survival status in patients in RISE-IIP with available HRCT data and emphysema score > fibrosis score ($n = 14$).

while the baseline fibrosis score correlated negatively with FVC% and DL_{CO}% (Table 3). 6MWD correlated negatively with emphysema score, total HRCT lung score, mPAP, and PVR, and positively with cardiac index, but did not correlate with pulmonary function parameters (Table 4).

Discussion

RISE-IIP showed an unfavorable risk:benefit profile in patients with PH-IIP receiving riociguat, with increased serious adverse events in riociguat-treated patients (27/73; 37%) vs placebo (17/74; 23%).[15] There were 11 deaths in the main study (riociguat, $n = 8$; placebo, $n = 3$) and 9 in the extension (riociguat, $n = 1$; former placebo [after riociguat initiation], $n = 8$). There was no improvement in 6MWD or clinical worsening with riociguat vs placebo, consistent with previous studies of pulmonary arterial hypertension targeted agents.[17–21] It is important to understand the reasons for the increased mortality in riociguat-treated patients and to apply any lessons to future trial designs. Thus, we conducted a post hoc analysis of the RISE-IIP study in patients with available HRCT data to investigate the relationship between lung morphology and the presence of CPFE, and clinical outcomes.

Whether patients with CPFE might have affected the RISE-IIP outcomes was a consideration as some patients had low baseline DL_{CO} with relatively well-preserved lung volumes. This is a characteristic physiologic CPFE manifestation resulting from the counter-balancing effects of lower lung volumes due to fibrosis and increased lung volumes due to emphysema.[22] The extent of parenchymal lung disease is typically weighed against the severity of the associated PH when identifying patients with PH-IIP who might respond to pulmonary vasodilator therapy. On evaluation, patients in RISE-IIP appeared to have an

Table 2 Baseline Pulmonary Function Parameters, Hemodynamics, and 6MWD According to Survival Status in Patients With CPFE vs Non-CPFE

	CPFE		Non-CPFE	
	Fatal ($n = 12$)	Non-fatal ($n = 29$)	Fatal ($n = 3$)	Non-fatal ($n = 21$)
Female, *n* (%)	3 (25.0)	8 (27.6)	1 (33.3)	7 (33.3)
Age, years	69.6 (4.1)	69.8 (8.7)	71.0 (2.6)	65.3 (9.4)
6MWD[a], m	283.8 (84.5)	327.1 (78.3)	324.0 (77.0)	344.0 (73.0)
RAP, mm Hg	7.7 (2.8)	6.4 (4.3)	9.7 (11.6)	6.2 (2.8)
mPAP, mm Hg	34.9 (10.5)	34.1 (9.2)	35.6 (11.7)	29.3 (5.2)
PVR, dyn.s.cm^{-5}	515.1 (348.6)	410.5 (222.3)	356.2 (158.2)	279.0 (86.9)
Cardiac index, L/min/m^2	2.5 (0.8)	2.6 (0.6)	3.1 (1.0)	3.1 (0.7)
PAWP, mm Hg	9.7 (3.1)	10.8 (2.9)	11.7 (3.1)	10.4 (3.0)
FVC, %	77.4 (25.3)	76.2 (14.0)	80.9 (7.2)	67.9 (15.1)
FEV_1, %	75.3 (21.5)	77.1 (15.7)	86.1 (11.0)	71.6 (17.4)
TLC, %	63.1 (17.5)	68.9 (11.7)	60.7 (4.9)	61.7 (11.4)
DL_{CO}, %	27.0 (10.6)	32.2 (11.8)	29.8 (10.7)	32.0 (12.1)
FVC%:DL_{CO}%	3.5 (1.9)	2.6 (1.0)	2.9 (0.9)	2.3 (0.7)
Supplemental oxygen, %	66.7	69.0	66.7	52.4

Abbreviations: 6MWD, 6-min walking distance; CPFE, combined pulmonary fibrosis and emphysema; DL_{CO}, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; TLC, total lung capacity.

Data are mean ± standard deviation unless otherwise stated.

[a]Mean of the maximum values from 3 6MWD measurements taken at baseline.

Table 3 Correlation of Lung Scores With Baseline Pulmonary Function Parameters and Hemodynamics

Variable 1	Variable 2	*n*	Pearson's correlation coefficient	Lower 95% CI	Upper 95% CI	*p*-value
Emphysema score	Pulmonary function					
	FVC%	65	0.487	0.272	0.651	<0.001
	FEV_1%	65	0.301	0.060	0.506	0.014
	DL_{CO}%	62	−0.251	−0.469	0.001	0.049
	Hemodynamics					
	mPAP	65	0.351	0.115	0.546	0.004
	RAP	64	0.035	− 0.213	0.278	0.784
	Cardiac index	63	− 0.268	− 0.482	− 0.019	0.033
	PVR	63	0.472	0.250	0.642	<0.001
Fibrosis score	Pulmonary function					
	FVC%	65	−0.248	−0.462	−0.002	0.046
	FEV_1%	65	−0.160	−0.387	0.089	0.205
	DL_{CO}%	62	−0.293	−0.504	−0.044	0.020
	Hemodynamics					
	mPAP	65	−0.135	−0.366	0.114	0.286
	RAP	64	−0.011	−0.256	0.236	0.933
	Cardiac index	63	0.179	−0.073	0.408	0.160
	PVR	63	−0.146	−0.379	0.107	0.255
Total score	Pulmonary function					
	FVC%	65	0.288	0.045	0.495	0.020
	FEV_1%	65	0.174	−0.074	0.400	0.166
	DL_{CO}%	62	−0.418	−0.602	−0.184	<0.001
	Hemodynamics					
	mPAP	65	0.237	−0.010	0.453	0.058
	RAP	64	0.025	−0.222	0.269	0.843
	Cardiac index	63	−0.132	−0.367	0.121	0.305
	PVR	63	0.344	0.103	0.544	0.005

Abbreviations: CI, confidence interval; DL_{CO}%, diffusing capacity of the lung for carbon monoxide, % predicted; FEV_1%, forced expiratory volume in 1 second, % predicted; FVC%, forced vital capacity, % predicted; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

Table 4 Correlation of Baseline 6MWD With Lung Scores, Pulmonary Function Parameters, and Hemodynamics

Variable 1	Variable 2	*n*	Pearson's correlation coefficient	Lower 95% CI	Upper 95% CI	*p*-value
6MWD[a]	HRCT score					
	Emphysema score	65	−0.245	−0.460	0.000	0.049
	Fibrosis score	65	−0.093	−0.329	0.155	0.463
	Total score	65	−0.288	−0.496	−0.046	0.019
	Pulmonary function					
	FVC%	65	0.068	−0.180	0.306	0.594
	FEV_1%	65	0.081	−0.167	0.318	0.525
	DL_{CO}%	62	0.185	−0.070	0.414	0.151
	Hemodynamics					
	mPAP	65	−0.365	−0.557	−0.130	0.003
	RAP	64	−0.217	−0.438	0.032	0.084
	Cardiac index	63	0.296	0.050	0.505	0.018
	PVR	63	−0.478	−0.647	−0.258	<0.001

Abbreviations: 6MWD, 6-minute walking distance; CI, confidence interval; DL_{CO}%, diffusing capacity of the lung for carbon monoxide, % predicted; FEV_1%, forced expiratory volume in 1 second, % predicted; FVC%, forced vital capacity, % predicted; HRCT, high-resolution computed tomography; mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

[a]Mean of the maximum values from 3 6MWD measurements taken at baseline.

appropriate phenotype, based on their baseline mild restrictive physiology and accompanying moderate-to-severe PH.[15] However, over-representation of patients with CPFE might have led to underestimation of the global burden of parenchymal lung disease based on physiology alone. This post hoc exploratory analysis suggested that, in patients with HRCT data, those who died were more likely to have CPFE. Furthermore, patients at particularly high risk of death were those with a greater extent of emphysema than fibrosis, an exclusion criterion for the study. No statistical difference in the emphysema score was seen between the placebo and riociguat-treated arms, but we would note that the analysis was not powered to detect a difference. The contraindication of riociguat in patients with PH-IIP means the qualitative differences observed cannot be studied beyond the analysis presented here. Other factors predisposing to death appeared to be an overall high burden of parenchymal disease (total score ≥ 30), lower baseline DL_{CO}% and 6MWD values, and high baseline FVC%:DL_{CO}% ratio.

Using our methodology, CPFE was evident in 63% of patients with available HRCT scans and in 80% of patients who died, suggesting this might have contributed to poor survival. Indeed, 29% of patients with CPFE died compared with 12.5% without evidence of emphysema. This is consistent with other studies, in which patients with PH associated with CPFE tended to have poor survival. One study (n = 110) reported median survival of 25 vs 34 months in patients with CPFE vs IPF without emphysema, attributing poor survival to the development of severe PH.[17] Another study reported a 5-year survival rate of 25% in patients with CPFE with PH at diagnosis compared with 75% in those without PH.[23] A retrospective multicenter study reported a dismal prognosis (1-year survival, 60%) in 40 patients with CPFE and right heart catheterization-confirmed precapillary PH.[24] Furthermore, the present HRCT analysis suggested that extent of emphysema was a risk factor for mortality in patients with IIP. One surprising finding was that 14 patients (≥10% of the RISE-IIP population) should have been excluded due to the greater extent of emphysema than fibrosis. This exclusion criterion was recommended by the Steering Committee to ensure that patients with a predominance of fibrosis were recruited. In this analysis, 4/14 patients (29%) with emphysema greater than fibrosis died, likely contributing to the poor survival outcome in RISE-IIP. The pathophysiologic mechanism for CPFE and a greater extent of emphysema than fibrosis as potential high-risk factors for mortality is unclear. As both emphysema and fibrosis affect the vasculature and are likely to result in pulmonary vasculature "drop-out," there may be an inflection point of a reduced pulmonary vascular bed where pulmonary vasodilator therapy could be deleterious.[22] Patients with CPFE in RISE-IIP appeared to be generally sicker than those without emphysema, with worse baseline hemodynamic and exercise parameters. Such patients can have a poor prognosis despite preserved lung volumes. It should, however, be noted that the observation of preserved lung volumes with low diffusion capacity could be attributable to conditions other than CPFE. Mild to moderate lung fibrosis and significant pulmonary vascular disease has been defined as a distinct phenotype in some patients.[15]

Another potential reason for the poor outcomes in RISE-IIP is the presence of PVOD-like lesions. It is well established that PVOD is a contraindication to PH therapy. However, the HRCT scans in this analysis showed no evidence of PVOD, making it unlikely that PVOD contributed to poor survival. However, HRCT scans cannot conclusively confirm or exclude PVOD, particularly in patients with ILD. Autopsies were unavailable for most patients who died during RISE-IIP, and only 3 patients had a lung biopsy before the study. PVOD, therefore, cannot be definitively excluded.

A strength of this HRCT analysis is the use of a formal scoring system for both emphysema and fibrosis, enabling quantification of global disease burden. Advantages of the Sato scoring system are that it encompasses the main forms of pulmonary morphology including both fibrosis and emphysema, is relatively simple, and has been used by other researchers.[25] Several other scoring systems are available, with a greater number of scoring subdivisions, for example, 5% categorization and/or ability to detect other abnormal lung pathologies beyond emphysema and fibrosis alone. However, the use of a simple scoring system may provide higher reproducibility, which may be preferable in multicenter clinical trials.

There are several limitations to this study that must be taken into consideration. First, this was a post hoc exploratory analysis of subgroups from a prematurely terminated trial with small numbers of patients, thus firm conclusions cannot be drawn. Second, only 44% of patients had baseline HRCT data for review. Central collection and adjudication of HRCT scans were not included in the protocol, as these were required only for IIP diagnosis, which was left to the discretion of the study site investigators. Distinguishing among different IIPs was considered unnecessary, and the broad inclusion criteria were regarded as an advantage. Further scan analysis was thought unnecessary at the time as the importance of disease burden extent and the relative extent of fibrosis vs emphysema only became apparent subsequently. This post hoc analysis was, therefore, conducted after study termination, with subsequent requests to the local participating centers for all obtainable HRCT scans. Nevertheless, this subgroup of patients with HRCT appeared to be representative of the overall study population based on a comparison of their characteristics to patients without HRCTs. In addition, the majority of patients who succumbed during the study had HRCTs available for review (56%), further suggesting that this analysis was representative of the overall study. Another caveat is that patients with an emphysema score > 0 were considered to have CPFE; therefore, it is likely that the CPFE subgroup included patients with low levels of emphysema. This analysis used the criteria of Sato and colleagues[16] to evaluate the extent of pulmonary emphysema and fibrosis in each patient and our findings demonstrate the wide variability in both fibrosis and emphysema scores in the RISE-IIP population. Individual patient data provide insight into how differing score cutoffs would affect whether or not patients would be defined as having CPFE. Indeed, there is currently no established definition for CPFE with the suggestion of defining CPFE as the presence of 15% emphysema across the whole lung.[26]

In conclusion, despite the limitations noted above, the presence of CPFE appears to be a risk factor for mortality in patients with PH-IIP. This mortality risk may be further heightened by a high burden of parenchymal lung disease, and more so perhaps if the extent of emphysema is greater than that of the fibrosis. Absence of a relationship between CPFE score, survival status, and treatment assignment suggests that the findings were not specific to riociguat-treated patients. Therefore, while the use of riociguat in patients with PH-IIP was immediately contraindicated following the availability of the RISE-IIP results, our findings should be considered when planning future studies of other agents in PH-IIP. In addition, central adjudication of HRCT scans at study enrollment can provide a morphologic evaluation of disease burden and ensure enrollment of suitable patients.

Disclosure statement

The authors have reported to the *Journal of Heart and Lung Transplantation* the following: S. D. Nathan reports consultation fees and Inova Fairfax Hospital receiving research funding for work pertaining to the RISE-IIP study from Bayer AG. V. Cottin reports grants from Actelion, Boehringer Ingelheim, GSK, Pfizer, and Roche, and personal fees from Bayer AG, Biogen Idec, Boehringer Ingelheim, Gilead, GSK, Intermune, Merck Sharp & Dohme, Novartis, Pfizer, Roche, and Sanofi. J. Behr reports receiving personal fees from Actelion, Bayer AG, Biogen, BMS, Boehringer Ingelheim, Galapagos, and Roche for consulting and lectures. M. M. Hoeper reports consultancy fees from Actelion, Bayer AG, and Pfizer, and personal fees from Actelion, Bayer AG, Pfizer, and Merck Sharp & Dohme. F. J. Martinez reports grants from National Institutes of Health and National Heart, Lung and Blood Institute, and support from Academic CME, Amgen, Annenberg, AstraZeneca, ATS, Axon, Axon Communication, Biogen, Bioscale, Boehringer Ingelheim, California Society for Allergy and Immunology, Carden Jennings, Centocor, CME Incite, CSA Medical, Falco, Forest, Genentech, Genzyme, GSK, Gilead, Inova Health System, Haymarket Communications, Ikaria, Informa, Integritas, InThought, Ikaria/Bellerophon, Janssen, Johnson & Johnson, Kadmon, MedScape, Merck, Miller Medical, National Association for Continuing Education, Novartis, Nycomed/Takeda, Paradigm, Pearl, Peer Voice, Pfizer, Promedior, Roche, Spectrum Health System, St John's Hospital, St Mary's Hospital, Sunovion, Theravance, University of Texas Southwestern, Unity Biotechnology, UpToDate, Western Society of Allergy and Immunology, Vertex, and Veracyte. T. J. Corte reports grants and personal fees from Boehringer Ingelheim and Roche, grants from Bayer AG, Gilead, and Intermune, and personal fees from AstraZeneca. A. M. Keogh reports grants and personal fees from Bayer AG. H. Leuchte reports personal fees from Actelion, Bayer AG, GSK, Merck Sharp & Dohme, and Pfizer, and nonfinancial support from Bayer AG. N. Mogulkoc reports receiving personal fees from Boehringer Ingelheim, Roche, Actelion, Bayer AG, and Nobel for consulting and lectures. S. Ulrich reports personal fees from Actelion and Bayer AG, and grants from Swiss National Science Foundation, United Therapeutics, and Zurich Lung League. W. A. Wuyts reports grants from Boehringer Ingelheim, FWO Flanders, Roche, and National Institutes of Health. Z. Yao was an employee of Bayer AG during the conduct of the RISE-IIP study. J. Ley-Zaporozhan reports consultation fees from Bayer AG and Boehringer Ingelheim. U. G. Müller-Lisse reports no conflicts of interest. F-D. Scholle, G. Brüggenwerth, and S. Nikkho were employees of Bayer AG during the conduct of the RISE-IIP study.

D. Busse was an employee of Chrestos Concept GmbH & Co. during the development of this manuscript. A. U. Wells reports personal fees from Bayer AG, Roche, and Boehringer Ingelheim.

The authors thank the RISE-IIP study investigators and patients. Medical writing services provided by Robyn Bradbury, PhD, of Adelphi Communications Ltd. (Macclesfield, United Kingdom) were funded by Bayer AG (Berlin, Germany) in accordance with Good Publications Practice 3 guidelines.

The RISE-IIP study was funded by Bayer AG, Berlin, Germany, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. D.B. performed statistical analyses, funded by Bayer AG, Berlin, Germany.

Author contributions

S.D.N., V.C., J.B., M.M.H., F.J.M., T.J.C., A.M.K., H.L., N.M., S.U., W.A.W., Z.Y., J.L-Z., U.G.M-L., F-D.S., G.B., D.B., S.N., and A.U.W. (all authors) contributed to the conception and design of the study, the collection and interpretation of the data and the drafting and revising of the manuscript, and approved the final version for publications. D.B. performed statistical analyses.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2021.02.006.

References

1. Travis WD, Costabel U, Hansell DM, et al. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013;188:733-48.
2. Lettieri CJ, Nathan SD, Barnett SD, Ahmad S, Shorr AF. Prevalence and outcomes of pulmonary arterial hypertension in advanced idiopathic pulmonary fibrosis. Chest 2006;129:746-52.
3. Seeger W, Adir Y, Barbera JA, et al. Pulmonary hypertension in chronic lung diseases. J Am Coll Cardiol 2013;62:D109-16.
4. Nathan SD, Barbera JA, Gaine SP, et al. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J 2019;53. pii:1801914.
5. Bayer AG. Adempas (Riociguat Tablets): EU Summary of Product Characteristics. 2019. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002737/WC500165034.pdf.
6. Bayer AG. Adempas, US Prescribing Information. 2019. Available at: http://labeling.bayerhealthcare.com/html/products/pi/Adempas_PI.pdf.
7. Ghofrani HA, D'Armini AM, Grimminger F, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. N Engl J Med 2013;369:319-29.
8. Ghofrani HA, Galiè N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013;369:330-40.
9. Beyer C, Reich N, Schindler SC, et al. Stimulation of soluble guanylate cyclase reduces experimental dermal fibrosis. Ann Rheum Dis 2012;71:1019-26.
10. Beyer C, Zenzmaier C, Palumbo-Zerr K, et al. Stimulation of the soluble guanylate cyclase (sGC) inhibits fibrosis by blocking non-canonical TGFβ signalling. Ann Rheum Dis 2015;74:1408-16.
11. Dees C, Beyer C, Distler A, et al. Stimulators of soluble guanylate cyclase (sGC) inhibit experimental skin fibrosis of different aetiologies. Ann Rheum Dis 2015;74:1621-5.
12. Stasch JP, Evgenov OV. Soluble guanylate cyclase stimulators in pulmonary hypertension. Handb Exp Pharmacol 2013;218:279-313.
13. Weissmann N, Lobo B, Pichl A, et al. Stimulation of soluble guanylate cyclase prevents cigarette smoke-induced pulmonary hypertension and emphysema. Am J Respir Crit Care Med 2014;189:1359-73.
14. Hoeper MM, Halank M, Wilkens H, et al. Riociguat for interstitial lung disease and pulmonary hypertension: a pilot trial. Eur Respir J 2013;41:853-60.
15. Nathan SD, Behr J, Collard HR, et al. Riociguat for idiopathic interstitial pneumonia-associated pulmonary hypertension (RISE-IIP): a randomised, placebo-controlled phase 2b study. Lancet Respir Med 2019;7:780-90.
16. Sato S, Tanino Y, Misa K, et al. Identification of clinical phenotypes in idiopathic interstitial pneumonia with pulmonary emphysema. Intern Med 2016;55:1529-35.
17. Mejia M, Carrillo G, Rojas-Serrano J, et al. Idiopathic pulmonary fibrosis and emphysema: decreased survival associated with severe pulmonary arterial hypertension. Chest 2009;136:10-5.
18. King TE Jr., Brown KK, Raghu G, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2011;184(1):92-9.
19. Kolb M, Raghu G, Wells AU, et al. Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis. N Engl J Med 2018;379:1722-31.
20. Raghu G, Behr J, Brown KK, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med 2013;158:641-9.
21. Raghu G, Million-Rousseau R, Morganti A, Perchenet L, Behr J. Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. Eur Respir J 2013;42:1622-32.
22. Cottin V. The impact of emphysema in pulmonary fibrosis. Eur Respir Rev 2013;22:153-7.
23. Cottin V, Nunes H, Brillet PY, et al. Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 2005;26:586-93.
24. Cottin V, Le PJ, Prevot G, et al. Pulmonary hypertension in patients with combined pulmonary fibrosis and emphysema syndrome. Eur Respir J 2010;35:105-11.
25. Rogliani P, Mura M, Mattia P, et al. HRCT and histopathological evaluation of fibrosis and tissue destruction in IPF associated with pulmonary emphysema. Respir Med 2008;102:1753-61.
26. Cottin V, Hansell DM, Sverzellati N, et al. Effect of emphysema extent on serial lung function in patients with idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2017;196:1162-71.