EE295

INDIRECT TREATMENT COMPARISON AND COST-MINIMIZATION ANALYSIS OF RIOCIGUAT VERSUS SELEXIPAG IN PATIENTS WITH PULMONARY ARTERIAL HYPERTENSION

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Background

Pulmonary arterial hypertension (PAH) is a rare disease clinically defined by increased pulmonary vascular resistance and a mean pulmonary arterial pressure above 25 mm Hg at rest (or 30 mm Hg during exercise); the disease affects mainly young and middle-aged women [1,2].

Currently available therapies for PAH patients use three different pathways: endothelin receptor antagonists (ERA), prostacyclin receptor agonists and analogs (selexipag, epoprostenol, treprostinil, iloprost), and nitric oxide (NO)–soluble guanylate cyclase (sGC)–cyclic guanosine monophosphate (cGMP) [3]. The latter category includes the phosphodiesterase-5 inhibitors (PDE5i), sildenafil and tadalafil, and the sGC stimulator riociguat [4].

The open-label, randomized controlled trial, REPLACE, demonstrated that riociguat was effective when switching from PDE5i treatment in PAH patients. The odds ratio for the primary outcome compared to maintenance therapy with PDE5i was estimated to be 2.78 (95% CI 1.53–5.06; p=0.001) (a composite endpoint of clinical improvement in the absence of clinical worsening of others) [5]. Nevertheless, head-to-head comparisons of riociguat with alternative therapies currently reimbursed in the Czech Republic are missing since no relevant trials have been initiated.

Objectives

The objective of this study was to assess the comparative efficacy between riociguat and selexipag in patients with pulmonary arterial hypertension (PAH), which has never been described in literature. Our aim was to prepare indirect treatment comparison (ITC) to evaluate the cost-effectiveness of riociguat in Czechia.

Methods

A systematic literature review, to complement an exhaustive literature review previously published by Fu et al. [6] with a data-lock-point of December 2020, identified two relevant trials with comparable endpoints to inform an ITC. Two outcomes were measured similarly in both studies: (1) worsening of WHO functional class and (2) 6MWD test. Worsening of WHO functional class was reported in a secondary analysis after 26 weeks by Sitbon et al. [7] (GRIPHON trial) and after 24 weeks of treatment by Hoeper et al. [5] (REPLACE trial). The difference in the measurement (24 vs. 26 weeks) is negligible in the context of a PAH diagnosis and is best illustrated by the low ratio of events over time [5,7]. 6MWD was evaluated in a secondary analysis after 26 weeks by Sitbon et al. [11] and after 24 weeks of treatment by Hoeper et al. [5]. For the indirect comparison, the full analysis data set was used.

We conducted a Bucher ITC via a common comparator (placebo + background therapy) to assess the relative and absolute efficacy between riociguat (add-on to ERA) and selexipag (add-on to ERA and PDE5i). The outcomes of Bucher ITC are presented using odds ratios (OR) to describe relative effects (i.e., the odds of not improving in WHO functional class III, FC) and walking distances to describe absolute effects (i.e., changes in 6-minute walking distances 6MWD). Confidence intervals were calculated based on the assumption of additive variance.

Given the comparable efficacy of riociguat and selexipag, a cost-minimization analysis (CMA) was conducted. This study used the healthcare payer's perspective (public health insurance funds) since the payer reimbursed all the drugs. The cost per defined daily dose (DDD) of riociguat (brand name Adempas, flat pricing, DDD of three tablets) was 79.18 EUR, and for selexipag (brand name Uptravi, flat pricing, DDD of two tablets) was 121.94 EUR. The cost of selexipag was based on a list of reimbursed medicines published by the national HTA agency, the State Institute for Drug Control (SUKL). The cost of riociguat was calculated based on the lowest referenced prices in Europe as of May 2021 since this is the standard requirement for price regulation of newly reimbursed drugs or indications in the Czech Republic. Since the cost analysis was conducted with a perspective time horizon of one year, we applied no cost discounting. No other cost was assumed since none of the therapies required any further costs related to drug administration, application, or monitoring.

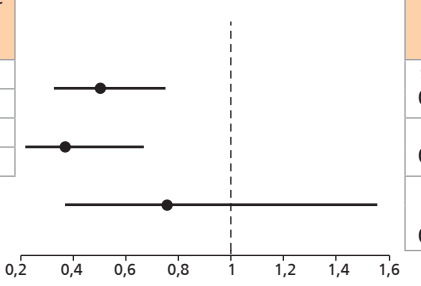
Table 1. Characteristics of enrolled patients reported in the REPLACE [5] and GRIPHON [7] trials

Characteristic	REPLACE		GRIPHON	
	Riociguat (n=111)	PDE 5i (n=113)	Selexipag (n=574)	Placebo (n=582)
Age (years)				
Mean (SD)	49.4 (16.16)	49.1 (15.69)	48.2 (15.19)	47.9 (15.55)
Median	48.0	51.0	-	-
Min, Max	19, 75	18, 75	-	-
Age (categorized)				
< 65 years	81 (73.0%)	91 (80.5%)	475 (82.8%)	474 (81.4%)
≥ 65 years	30 (27.0%)	22 (19.5%)	99 (17.2%)	108 (18.6%)
Sex				
Male	29 (26.1%)	19 (16.8%)	-	-
Female	82 (73.9%)	94 (83.2%)	457 (79.6%)	466 (80.1%)
Race				
White	86 (77.5%)	88 (77.9%)	-	-
Black or African American	4 (3.6%)	5 (4.4%)	-	-
Asian	17 (15.3%)	19 (16.8%)	-	-
American Indian or Alaska Native	1 (0.9%)	0	-	-
Native Hawaiian or Other Pacific Islander	0	0	-	-
Not Reported	3 (2.7%)	1 (0.9%)	-	-
Ethnicity				
Hispanic or Latino	32 (28.8%)	31 (27.4%)	-	-
Not Hispanic or Latino	75 (67.6%)	79 (69.9%)	-	-
Not Reported	4 (3.6%)	3 (2.7%)	-	-
Geographic region				
Asia	-	-	115 (20.0%)	113 (19.4%)
Eastern Europe	-	-	149 (26.0%)	155 (26.6%)
Latin America	-	-	54 (9.4%)	56 (9.6%)
North America	-	-	95 (16.6%)	98 (16.8%)
Western Europe and Australia	-	-	161 (28.0%)	160 (27.5%)
Dana point classification of PH				
Idiopathic PAH (IPAH)	69 (62.2%)	73 (64.6%)	312 (54.4%)	337 (57.9%)
Heritable PAH (HPAH)	4 (3.6%)	4 (3.5%)	13 (2.3%)	13 (2.2%)
Drug and toxin induced	1 (0.9%)	4 (3.5%)	17 (3.0%)	10 (1.7%)
Connective Tissue Disease	24 (21.6%)	19 (16.8%)	167 (29.1%)	167 (28.7%)
Portal Hypertension	7 (6.3%)	6 (5.3%)	-	-
Congenital Heart Diseases	6 (5.4%)	7 (6.2%)	-	-
Associated with HIV infection	-	-	5 (0.9%)	5 (0.9%)
Associated with corrected-congenital shunts	-	-	60 (10.5%)	50 (8.6%)
PAH classes at baseline				
IPAH/HPAH/PAH	74 (66.7%)	81 (71.7%)	-	-
PAH CHD, PAH PoPH	13 (11.7%)	13 (11.5%)	-	-
PAH CTD	24 (21.6%)	19 (16.8%)	-	-
Time from confirmatory RHC to randomization (years)				
Mean (SD)	4.436 (6.1540)	4.650 (6.3704)	2.3 (3.49)	2.5 (3.75)
Median	2.516	2.197	-	-
Min, Max	0.04, 39.00	0.04, 37.30	-	-
Combination therapy and monotherapy				
ERAs and PDE 5i	79 (71.2%)	81 (71.7%)	179 (31.2%)	197 (33.8%)
PDE 5i Monotherapy	32 (28.8%)	32 (28.3%)	189 (32.9%)	185 (31.8%)
ERAs	-	-	94 (16.4%)	76 (13.1%)
None	-	-	112 (19.5%)	124 (21.3%)
6 minute walking distance				
< 320 m	17 (15.3%)	22 (19.5%)	-	-
≥ 320 m	94 (84.7%)	91 (80.5%)	-	-
meters: mean (SD)	-	-	358.5 (76.31)	348.0 (83.23)
WHO functional class				
I	0 (0.0%)	0 (0.0%)	4 (0.7%)	5 (0.9%)
II	0 (0.0%)	0 (0.0%)	274 (47.7%)	255 (43.8%)
III	111 (100.0%)	113 (100.0%)	293 (51.0%)	314 (54.0%)
IV	0 (0.0%)	0 (0.0%)	3 (0.5%)	8 (1.4%)
cMRI				
Performed	11 (9.9%)	16 (14.2%)	-	-
Not Performed	100 (90.1%)	97 (85.8%)	-	-

Abbreviations: cMRI = cardiac magnetic resonance imaging; ERA = endothelin receptor antagonist; HIV = human immunodeficiency virus; HPAH = heritable PAH; IPAH = idiopathic PAH; PAH = pulmonary arterial hypertension; PAH CHD = PAH associated with congenital heart disease; PH = pulmonary hypertension; PAH PoPH = PAH portopulmonary PAH; PAH CTD = PAH associated with connective tissue disease; PDE 5i = phosphodiesterase 5 inhibitors; RHC = right heart catheterization; SD = standard deviation; WHO = World Health Organization

Table 2. Indirect Comparison for Relative Effects in WHO FC Improvement Odds

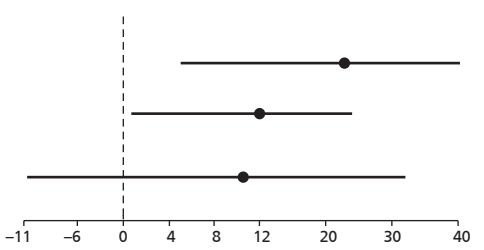
Trial subgroup	Treatment arm	Total number of patients with baseline WHO FC III	Number of patients who did not improve plus patients with worsened WHO FC
GRIPHON	Comparator	314	273
	Selexipag	293	225
REPLACE	Comparator	113	87
	Riociguat	111	62



Odds ratio (confidence interval)
Selexipag vs. comaprator 0.497 (0.325–0.761)
Riociguat vs. comparator 0.378 (0.213–0.673)
Indirect relative estimate riociguat vs. selexipag 0.761 (0.372–1.558)

Table 3. Indirect Comparison for Absolute Effects in 6MWD

Trial	
REPLACE (full analysis population)	Riociguat vs. comparator
GRIPHON (full analysis population)	Selexipag vs. comparator
Indirect absolute effect estimate riociguat vs. selexipag (meters)	Riociguat vs. selexipag



Average change in 6MWD; meters (confidence interval)
22.56 (5.03–40.10)
12 (1.00–24.00)
10.56 (–10.69–31.81)

Results

The GRIPHON clinical trial [7] included PAH patients who were not receiving treatment for pulmonary arterial hypertension and those receiving an ERA and/or a PDE5i. The trial compared the efficacy and safety of selexipag with a placebo. The primary end-point was a composite of death from any cause or a complication related to pulmonary arterial hypertension through the end of the treatment period [7]. The REPLACE clinical trial [5] included PAH WHO functional class (WHO FC) III patients receiving treatment with a PDE5i (with or without an ERA) for at least six weeks before randomization. The study explored the efficacy of riociguat compared to PDE5i maintenance therapy. The primary endpoint was clinical improvement by week 24, defined as the absence of clinical worsening and prespecified improvements in at least two of three variables (i.e., 6MWD, WHO FC, and N-terminal prohormone of brain natriuretic peptide (NTproBNP)) [5].

Patients enrolled in the GRIPHON and REPLACE studies were generally comparable, except for the proportion of WHO functional class and frequency of ERAs+PDE5i pretreatment (**Table 1**).

A Bucher ITC provided evidence for the comparable relative efficacy of riociguat defined as the odds of unimproved functional class III 0.761 (95% CI 0.372 to 1.558; p = 0.455) compared to selexipag, **Table 2**, and a comparable absolute efficacy defined as a difference in the 6-minute walking distance of 10.560 meters (95% CI -10.692 to 31.812; p = 0.330), **Table 3**.

The CMA identified riociguat as the cost-saving therapy. In the base-case scenario, the annual treatment cost associated with riociguat was estimated to be 28,922 EUR. The annual treatment cost of selexipag was substantially higher, i.e., 44,538 EUR, leading to the incremental annual savings of 15,617 EUR (35%) per patient compared to riociguat. Cost of background therapy is not included, because it is insignificant, and also conservative assumption since PDE5i therapy is only continued with selexipag treatment and not with riociguat treatment. The results are presented in greater detail in **Table 4**. We did not perform any sensitivity analysis; the cost minimization model was informed with the direct cost of evaluated drugs that were not subject to considerable uncertainty.

Table 4. Cost Minimization Analysis

Cost minimization analysis	Selexipag	Riociguat	Background therapy PDE5i	Background therapy ERA
Cost per day	121.94 €	79.18 €	6.02 €	20.71 €
Annual costs	44 538.23 €	28 921.60 €	2 198.27 €	7 565.49 €
Annual savings per patient riociguat vs. selexipag		**-15 616.64** €		
Costs of background therapy (ERA+PDE5i vs. ERA only)	9 763.76 €	7 565.49 €		
Additional savings due to a reduction in background therapy		-2 198.27 €		

Note: Costs per day were calculated from the reimbursed price per package/number of daily doses per package. Flat pricing was used, meaning that the price per tablet was the same regardless of tablet strength. Background costs of selexipag treatment consist of ERA+ PDE5i treatment. Background costs of riociguat consist of ERA only, because PDE5i are discontinued and replaced by riociguat. Abbreviations: ERA = endothelin receptor antagonist; PDE5i = phosphodiesterase-5 inhibitors

Discussion

Due to the absence of any other ITC of riociguat and selexipag in PAH patients who failed on PDE5i+ERA combination therapy, we could not assess the external validity of our results. Nevertheless, a comparable efficacy for selexipag and riociguat was demonstrated in a published mixed network meta-analysis (NMAs), including patients with various NYHA classes and previous treatment [8,9].

Both selexipag and riociguat are centrally registered in the European union by EMA. Although riociguat is reimbursed in some European countries, no cost-effectiveness results have been published to date. Riociguat (Adempas) in combination with ERA has permanent reimbursement approval in the Czech Republic from SUKL as of October 2021 in the following indication: *"patients with pulmonary arterial hypertension (PAH) with inadequate response to the combination of phosphodiesterase-5 inhibitors (PDE5i) plus an endothelin receptor antagonist (ERA)"* [10]. The approval was granted based on the cost-minimization analysis informed by the Bucher ITC presented in this paper.

Conclusions

Switching to riociguat represents the cost-saving therapy for PAH patients who were inadequately compensated with the PDE5i+ERA therapy. Consequently, riociguat has been introduced to the list of reimbursed medicines in Czechia from October 2021. Based on two global trials, we prepared the first indirect treatment comparison followed with CMA of these therapies that may improve future decision-making for PAH indications.

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