

Outcomes of selexipag for treatment of pulmonary arterial hypertension in an Asian population

Dear Editor,

Pulmonary arterial hypertension (PAH) is a progressive condition characterised by increased pulmonary arterial pressure and pulmonary vascular resistance, resulting in right ventricular dysfunction and eventually cardiac failure. In the early days, this was an often a fatal disease with significant morbidity. In recent years, there has been increasing awareness and therapeutic advancements in the field. The introduction of newer and combination therapies, coupled with a risk stratification approach have changed the practice of PAH, with significantly improved patient outcomes.¹ While there are multiple reports on the efficacy and tolerability of PAH treatment from PAH registries in Europe and the US,² data for Asians are lacking. Selexipag is an oral selective prostacyclin receptor agonist indicated for PAH treatment. Its efficacy was demonstrated in the GRIPHON trial, a phase 3 randomised controlled trial on 1,156 PAH patients, showing a 40% risk reduction in morbidity and mortality with selexipag.³ However, data on its real-world safety and efficacy in Asians is limited. As such, we sought to evaluate the clinical characteristics and real-world outcomes of PAH patients initiated on selexipag in Asia.

This was a retrospective study on consecutive PAH patients treated with selexipag in an Asian tertiary cardiac centre up to 2020. Baseline and follow-up data collected include demographics, clinical characteristics and investigation results. Clinical outcomes evaluated include hospitalisation for PAH-related complications and all-cause mortality. Using the COMPERA 2.0 four-strata risk score, patients were risk-stratified into low, intermediate-low, intermediate-high and high mortality risk.⁴ This is a validated model used to predict mortality in PAH, comprising 3 variables: World Health Organization functional class (WHO-FC), 6-minute walking distance (6MWD) and N-terminal pro-brain natriuretic peptide (NT-proBNP).¹

A total of 36 PAH patients were treated with selexipag. The baseline characteristics are presented in Table 1. At baseline, the mean age was 46 years old $\pm$ 15.3, and the majority were female (83.3%) and of Chinese ethnicity (52.8%). Most patients were WHO-FC II or III (33.3% and 47.2%, respectively),

with a NT-proBNP of 1335rg/mL (557–2918) and 6MWD duration of 327.5 ± 126.4 metres. Prior to initiation of selexipag, a majority of patients were receiving double therapy for PAH (80.6%), with 6 patients (16.7%) receiving monotherapy. At selexipag initiation, using the risk score, 3 patients were at low (8.3%), 11 patients at intermediate-low (30.6%), 12 patients at intermediate-high (33.3%) and 10 patients at high risk (27.8%) of mortality. The duration from PAH diagnosis to selexipag initiation was a median of 47 months (interquartile range [IQR] 49.1). Selexipag was initiated at 200mcg twice-daily dosage in all except one patient (who had started at 200 μ g once daily). The maximum tolerated dose ranged from 200 μ g twice daily to 1,400 μ g twice daily, with the majority tolerating up to 600 μ g twice daily (58.3%). See Supplementary Fig. S1. Side effects were reported in 23 patients (63.9%), of which headache (27.8%), diarrhoea (30.6%) or musculoskeletal symptoms (27.8%) were predominant. No serious side events were reported.

After a median follow-up of 25.9 ± 23.1 months, selexipag was stopped in 20 patients (55.6%), of which 7 were due to PAH progression requiring intravenous (IV) epoprostenol, and 13 patients due to selexipag-related side effects. The median duration of selexipag therapy in the overall cohort was 8.8 months (IQR 23.1). Of the patients who continued selexipag at last follow-up (n=13), 46.2% showed no change, 15.4% had an improvement, and 38.5% had an increased risk score. In the overall cohort, the majority (75%) had at least one hospitalisation for PAH-related complications and 15 patients (41.7%) demised. Of patients who demised, the majority were of intermediate-high (5 patients, 33%) or high (7 patients, 46.7%) risk status. Comparing connective tissue disorder (CTD)-associated versus non-CTD-associated PAH patients, there were no significant differences in selexipag discontinuation, change in risk scores, or death from any cause ($P>0.05$). To our knowledge, this is the first paper describing the clinical characteristics and outcomes of Southeast Asian PAH patients treated with selexipag. When compared with Western PAH studies,^{3,5} our patient demographics were similar, with predominantly middle-aged female patients of WHO-FC II or III. Majority of patients in our cohort

Table 1. Baseline characteristic of our study cohort.

Baseline characteristics	Overall (N=36)
Age, mean (SD), years	46 (15.3)
Male, no. (%)	6 (16.7)
WHO-FC, no. (%)	
I	2 (6.1)
II	12 (36.4)
III	17 (51.5)
IV	2 (6.1)
NT-proBNP, median (IQR), pg/mL	1335 (2361)
6MWD, mean (SD), m	327.5 (126.4)
Comorbidities, no. (%)	
Ischaemic heart disease	6 (16.7)
Atrial fibrillation	7 (19.4)
Asthma/COPD	4 (11.1)
Obstructive sleep apnoea	8 (22.2)
Chronic kidney disease	5 (13.9)
Connective tissue disorder	15 (41.7)
PAH subtypes, no. (%)	
Idiopathic	18 (50.0)
Congenital heart disease associated	3 (8.3)
Connective tissue disorder associated	15 (41.7)
Baseline transthoracic echocardiogram parameters at time of selexipag initiation	
LVEF, mean (SD), %	63.5 (8.8)
TAPSE, mean (SD), cm	1.7 (0.5)
RA area, mean (SD), cm ²	24.6 (12.1)
Estimated PASP, mean (SD), mmHg	73 (23.6)
Presence of pericardial effusion, no. (%)	8 (22.2)
Baseline haemodynamic data on right heart catheterisation	
Mean pulmonary artery pressure, mean (SD), mmHg	51.4 (9.8)
Mean RA pressure, mean (SD), mmHg	11 (6.0)
Cardiac output, mean (SD), L/min	3.61 (1.2)
PVR, median (IQR), WU	11.6 (8.5)
PAH specific medications, no. (%)	
No medication	1 (2.8)
Monotherapy	6 (16.7)
Double therapy	28 (77.8)

Table 1. Baseline characteristic of our study cohort. (Cont'd)

Baseline characteristics	Overall (N=36)
Triple therapy	1 (2.8)
COMPERA 2.0 risk scores, no. (%)	
Low	3 (8.3)
Intermediate-low	11 (30.6)
Intermediate-high	12 (33.3)
High	10 (27.8)
Duration from PAH diagnosis to selexipag initiation, median (IQR), months	47.0 (49.1)
Reported side effects from selexipag, no. (%)	
Headache	10 (27.8)
Diarrhoea	11 (30.6)
Nausea/vomiting	7 (19.4)
Musculoskeletal	10 (27.8)
Duration of selexipag therapy, median (IQR), months	8.8 (23.1)
Follow-up duration, median (IQR), months	25.9 (23.1)

6MWD: 6-minute walking distance; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; PAH: pulmonary arterial hypertension; PASP: pulmonary artery systolic pressure; PVR: pulmonary vascular resistance; RA: right atrium; SD: standard deviation; TAPSE: tricuspid annular plane systolic excursion; WHO-FC: World Health Organization functional class

could only tolerate low to medium doses of selexipag (up to 600µg twice daily). This is lower than those described in other studies. In the SPHERE registry on 500 patients in US, the median selexipag dose was 1,200µg twice a day.⁶ In the GRIPHON trial, the majority tolerated medium to high doses of selexipag (600µg and above). Nevertheless, the GRIPHON trial reported similar primary outcome rates regardless of selexipag dosing.³

When evaluating the safety profile of selexipag, the reported side effects from it in our cohort was lower than other study populations (63.9% versus 72.2% for SPHERE registry⁶ and 98.3% for GRIPHON study³). Tanabe et al. reported the tolerability of selexipag in 37 Japanese PAH patients over 192 weeks, while all patients reported at least one selexipag-related adverse event; only one patient had a serious event requiring selexipag discontinuation.⁷ As such, although side effects are frequently observed with selexipag treatment, the majority are mild.

In our study, less than 10% of the patients had low PAH risk, with more than 60% being intermediate-high or high risk. Seven patients required escalation to IV therapy, and mortality rate was 41.7% after 27 months follow up—this reflects a much higher risk group of PAH patients. In comparison, about half the patients in the GRIPHON trial were of low PAH risk, and patients with multiple comorbidities were excluded.³ In recent times, with greater focus on risk stratification, there is a shift towards earlier initiation of selexipag. The median duration from PAH diagnosis to selexipag initiation was 47 months but these included patients from early on where risk stratification may not have been routinely performed. Practically, the cost of selexipag therapy and tolerability remain significant barriers in the uptake of selexipag in the Asia. Due to costs, selexipag is often initiated as third-line combination therapy. Of note, selexipag should not be viewed as replacement for IV epoprostenol in high-risk patients who are suitable candidates for IV therapy, and early initiation of IV therapy in this high-risk cohort should be comprehensively considered where available.

Regarding limitations, this was a single centre study with a small sample population and may not reflect the varying practices across Asia. Nevertheless, this study is the first to report data on Southeast Asian PAH patients and may advise further practice in the region.

In conclusion, in this study on an Asian cohort with higher PAH risk, there was a significant subset of patients with disease progression or intolerance to selexipag. Of patients who continued selexipag at last follow-up, about 60% had a stable or improved risk strata. Further work on optimal patient selection and barriers to initiation are warranted.

Disclosure

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Germaine Loo ^{*1}_{MRCP}, Jonathan Yap ^{*1,2}_{MRCP},
Jin Shing Hon ¹, Aidila Ismail ¹, Wen Ruan ¹_{MRCP},
Andrea Low ³_{MRCP}, Soo Teik Lim ^{1,2}_{MRCP}, Ju Le Tan ^{1,2}_{MRCP}

¹Department of Cardiology, National Heart Centre Singapore, Singapore

²Duke-NUS Medical School, Singapore

³Department of Rheumatology and Immunology, Singapore General Hospital, Singapore

Correspondence: A/Prof Jonathan Yap, National Heart Centre Singapore, 5 Hospital Drive Singapore 169609.

Email: jonyap@yahoo.com

* Joint first authors