Idiopathic Pulmonary Arterial Hypertension in Asians

A Long-term Study on Clinical Outcomes

To the Editor:

Pulmonary vasodilators have improved the outcomes of patients with idiopathic pulmonary arterial hypertension (IPAH) but they remain inaccessible in most developing Asian countries without medical subsidies. This letter describes the first Asian IPAH long-term follow-up study to our knowledge.

Data were prospectively collected from 2001 to 2013 from a single IPAH center. Observed survival was described using Kaplan-Meier analysis and was compared with that predicted by National Institutes of Health[1] and Pulmonary Hypertension Connection (PHC) registry[1] equations using χ^2 analysis. All patients demonstrating a vasodilatory response received calcium channel blockers or were initiated on low-dose vasodilators with gradual escalation where indicated during subsequent 3-monthly reviews.

The mean age of the 55 patients with IPAH was 50.0 ± 20.9 years (80% women). Mean baseline right atrial pressure, pulmonary arterial pressure, and cardiac index were 12.5 ± 5.4 mm Hg, 55.9 ± 14.0 mm Hg, and 2.14 ± 0.73 L/min/m^2, respectively. Median N-terminal pro-B-type natriuretic peptide levels and mean 6-min walk distance (6MWD) were 1,363 (interquartile range, 704-3,001) pg/mL and 354.6 ± 100.1 m, respectively. Fifteen patients (27.3%) demonstrated World Health Organization functional class III/IV (Table 1). Forty patients (72.7%) received monotherapy and 13 (23.6%) received combination therapy; two (3.5%) declined treatment (Table 2). Forty patients (73%) received lower-than-recommended doses (Fig 1). Mean follow-up was 4.83 (95% CI, 4.0-5.7) years, and 21.8% died at the end of follow-up, with 41.7% being cardiac-related deaths. Kaplan-Meier-observed survival rates were 96.0%, 86.4%,

TABLE 1] Comparison of Baseline Demographics of Patients With IPAH in the NUHCS Pulmonary Hypertension Registry With Other PAH Registries

Subjects	NIH[2] (n = 187)	PHC Registry[1] (n = 282)	Chinese Registry[3] (n = 173)	NUHCS (n = 55)
Age, y	36.0 ± 15.0	46.0 ± 14.0	33.4 ± 15.3	50.0 ± 20.9
Sex, female	214 (76)	118 (63)	121 (70)	44 (80)
Right atrial pressure, mm Hg	9 ± 6	11 ± 6	12 ± 6	13 ± 5
Pulmonary atrial pressure, mm Hg	60 ± 18	55 ± 12	63 ± 18	56 ± 14
Cardiac index, L/min/m^2	2.3 ± 0.9	2.0 ± 0.6	3 ± 1	2.1 ± 0.7
Pulmonary capillary wedge pressure, mm Hg	9 ± 4	10 ± 4	13 ± 5	11 ± 4
Peripheral vascular resistance, Wood units	NA	13.9 ± 6.7	17.1 ± 9.9	15.1 ± 9.9
Body surface area, m^2	NA	NA	1.5 ± 0.3	1.63 (1.49, 1.77)[a]
BMI, kg/m^2	…	…	…	23.5 (20.5, 28.2)[a]
WHO FC I/II	NA	NA	83 (48)[b]	40 (72.7)
WHO FC III/IV	133 (71)[1, c]	449(80)[1, c]	90 (52)[c]	15 (27.3)
6-min walk distance, m	NA	NA	394.0 ± 114.2	354.6 ± 100.1
NT-proBNP, pg/mL	NA	NA	1,025 ± 859	1,363 (704, 3,001)[a]

Data are presented as mean ± SD or No. (%). NIH, PHC, and Chinese Registry data are listed for comparison and are not included in any data analysis. IPAH = idiopathic pulmonary arterial hypertension; NA = not available; NIH = National Institutes of Health; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NUHCS = National University Heart Centre of Singapore; PAH = pulmonary arterial hypertension; PHC = Pulmonary Hypertension Connection; WHO FC = World Health Organization functional class.

[a]Data represent the 95% CI.

[b]Data represent No. patients (%) in WHO FC I/II.

[c]Data represent No. patients (%) in WHO FC III/IV.

TABLE 2] Vasodilator Regimens for NUH Patient Cohort

Therapy and Doses	Total (N = 55)
None[a]	2
Monotherapy (n = 40 [72.7%])	
Sildenafil	
25 mg, mane	1
25 mg, bid	3
25 mg, tid	10
50 mg, bid	2
50 mg, tid	2
Bosentan	
31.25 mg, bid	1
125 mg, bid	2
Tadalafil	
10 mg, eod	5
10 mg, mane	4
20 mg, mane	2
40 mg, mane	1
Inhaled iloprost	
20 μg, tid	1
1 vial, 4-5×/d	1
Riociguat	
1.5 mg, tid	2
2.5 mg, tid	2
Missing	1
Dual therapy (n = 12 [23.6%])	
Sildenafil and bosentan	
50 mg, tid; 62.5 mg, bid	2
50 mg, tid; 31.25 mg, bid	1
50 mg, tid; 125 mg, bid	1
50 mg, q6h; 62.5 mg, bid	1
50 mg, q6h; 125 mg, bid	1
75 mg, tid; 31.25 mg, mane	1
Tadalafil and bosentan	
20 mg, mane; 62.5 mg, bid	1
Inhaled iloprost and sildenafil	
20 μg, bid; 50 mg, tid	1
20 μg, tid; 25 mg, bid	1
Inhaled iloprost and tadalafil	
20 μg, tid; 20 mg, mane	1
Tadalafil and macicentan	
20 mg, mane; 10 mg, mane	1
Triple therapy (n = 1 [0.02%])	
Iloprost, bosentan, sildenafil	
20 μg, mane; 125 mg, mane; 50 mg, tid	1

eod = every other day; mane = morning; NUH = National University Hospital.
[a]Declined active treatment.

79.0%, 64.8%, and 64.8% at 1, 3, 5, 7, and 9 years, respectively, and were significantly higher than mean National Institutes of Health-predicted and PHC-predicted survival (Fig 2). Of the 13 deaths, eight received monotherapy, three dual therapy, and one triple therapy.

Although most patients presented with World Health Organization functional class I/II, they exhibited hemodynamics comparable to functional class III white populations, including higher median N-terminal pro-B-type natriuretic peptide levels and shorter 6MWD compared with the Chinese population, despite receiving phosphodiesterase-5 inhibitor (PDE5I) (Table 1). This is consistent with poor prognostic and survival outcomes in patients with baseline 6MWD < 325 m in the Sildenafil Use in Pulmonary Arterial Hypertension (SUPER)-2[4] study. Thus, these patients had more advanced disease despite milder presentations.

Initiating PAH therapy at lower doses is viable. Asians have smaller BMI/body surface areas relative to whites and possess a different drug metabolism with variable drug responses. Thus, they may benefit from dose adjustments according to body surface area/weight. Genetic polymorphisms[5] of cytochrome P450 enzymes, common in Asians, can generate large ethnic variability in PDE5I[6] and endothelin receptor antagonist[6] metabolism and lower intrinsic clearances to achieve target therapeutic levels with lower doses.

Our study outcomes are compatible with published cohorts despite our low-dose PAH therapy. This presents a safe, cost-effective strategy for Asians and provides the impetus for funding agencies in developing countries to support this life-saving cause.

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