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Efficacy and tolerability of triple sequential combination therapies with selexipag in patients with pulmonary arterial hypertension: insights from a single-centre study

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Background and aims: In this single-centre study we aimed to evaluate the efficacy and tolerability of prostacyclin receptor agonist selexipag in patients with pulmonary arterial hypertension (PAH).

Methods: The study included 110 out of the 1071 patients enrolled in the Evaluation of Pulmonary Hypertension Risk factors Associated with Survival study (EUPHRATES) and treated with selexipag added on background dual PAH therapies. The ESC/ERS 2022, SPAHR, French Registry, COMPERA 2.0 and REVEAL lite 2 models were used for risk predictions.

Results: Age (mean+SD) was 43.4+16.5 years and 84.5 % of patients were female. The PAH was idiopatic, and was associated with congenital heart disease (CHD), connective tissue disease (CTD) and drug in 47.2 %, 46.4 %, 5.5 % and 1 %, respectively. Background dual therapies, functional class (FC) was II, III and IV in 20 %, 65 %, and 15 % of patients. Six-minute walk distance (6MWD) was 314 + 134 m and serum N-terminal-pro-brain natriuretic peptide (NT-proBNP) level was 882+1732 ng/l. Tricuspid annular planary excursion (TAPSE) and tissue velocity (St), right atrial area and pulmonary arterial diameter were 2.02+0.48 cm,12.4+2.8 cm/sec,21.4+7.2 cm2 and 3.54+0.77 cm, respectively. Invasively evaluated pulmonary arterial mean pressure was 60.2±19.9 mm Hg, and pulmonary vascular resistance was 12.3±10.8 Wood units. COMPERA 2.0 1st, 2nd, 3rd and 4th risk strata were noted in 15.5 %, 31.8 %, 2.7 % and 10 %, and French Registry strata 0,1,2 and 3 were documented in 70 %, 14.5 %, 11 %, and 4.5 %, respectively. The SPAHR and REVEAL Lite 2 scores were 1.9+0.5 and 5.9+2.6, respectively. Background combinations were as follows; macitentan+tadalafil in 46.6 %, macitentan+sildenafil in13.6 %, macitentan+ riociguat in 6.8 %, bosentan +tadalafil in 8.7 %, bosentan+sildenafil in 16.5 %, bosentan+riociguat in 1 %, ambrisentan +tadalafil in 1.9 %, and ambrisentan +sildenafil in 2.9 % of patients. Maximally tolerable selexipag doses (ug)were 1600 bid in 21%, 1400 bid in 5 %, 1200 bid in 11%, 1000 bid in 17%, 800 bid in 12%, 600 bid in 9%, 400 bid in 14%, and 200 bid in 11%.Median follow-up period was 527(278-831) days, and discontiuation rates of selexipag was 13.6 %. Headache, jaw-pain, diarrhoea, nausea, vomiting and flushing were main side effects. The changes in FC, 6MWD, Nt-pro-BNP and echocardiographic measures were not significant. French Registry score ($p<0.001$) and COMPERA 2.0 score ($p<0.001$) showed improvements, but SPAHR and REVEAL lite 2 did not. However, other PAH cohort compared with IPAH showed more pronounced improvements in REVEAL lite 2 and SPAHR scores. Clinical worsening and mortality rates were 23.6 % and 10.9 %, respectively. Survival for 1, 3 and 5 years were 95.8 %, 95.8 and 83.7 % in IPAH, and 92.6 %, 84.1 % and 78.8 % in other PAH patients.

Conclusion: Our results seem to be consistent with efficacy and tolerability of selexipag-included combinations in patients with PAH.