Abstract: **5022**

Clinical phenotypes and outcomes of heritable and sporadic pulmonary veno-occlusive disease

Authors:
B. Girerd[1], D. Montani[1], X. Jais[1], M. Levy[2], L. Savale[1], P. Dorfmuller[1], E. Lau[1], J. Le Pavec[3], F. Parent[1], D. Bonnet[2], F. Soubrier[4], E. Fadel[3], O. Sitbon[1], G. Simonneau[1], M. Humbert[1], [1]Hôpital Bicêtre, Service de pneumologie - Le Kremlin Bicêtre - France, [2]Hospital Necker, Reference Centre for Complex Congenital Heart Diseases - Paris - France, [3]Surgical Centre Marie Lannelongue, Service de Chirurgie Thoracique, Vasculaire et Transplantation Cardiopulmonaire - Le Plessis Robinson - France, [4]AP-HP - Hospital Pitie-Salpetriere - Paris - France,

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Background: Bi-allelic mutations of EIF2AK4 gene cause heritable pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis (PVOD/PCH). We aimed to assess the effect of EIF2AK4 mutations on the clinical phenotypes and outcomes of PVOD/PCH.

Methods: We reviewed the clinical data and outcomes from all patients referred in our center with either confirmed or highly probable PVOD/PCH. We sequenced the coding sequence and intronic junctions of the EIF2AK4 gene, and compared clinical characteristics and outcomes between EIF2AK4 mutation carriers and non-carriers. Medical therapies approved for pulmonary arterial hypertension (PAH) (prostacyclin derivatives, ERA and PDE5-i) were given to patients according to the clinical judgment and discretion of treating physicians. The primary outcome was the event-free survival (death or transplantation). Secondary outcomes included response to therapies for PAH. A satisfactory clinical response to specific therapy for pulmonary arterial hypertension was defined by achieving NYHA functional class I or II, a 6-min walk distance of more than 440 m, and a cardiac index greater than 2·5 L/min per m^2 at the first reassessment after initiation of specific therapy for PAH.

Results: We identified 94 patients with sporadic or heritable PVOD/PCH (confirmed or highly probable). 27 (29%) of these patients had bi-allelic EIF2AK4 mutations. PVOD/PCH due to EIF2AK4 mutations occurred from birth to age 50 years, and these patients were younger at presentation than non-carriers (median 26·0 years [range 0–50.3] vs 60·0 years [6.7–81.4] years; $p<0·0001$). At diagnosis, both mutations carriers and non-carriers had similarly severe precapillary pulmonary hypertension and functional impairment. 22 (81%) of mutations carriers and 63 (94%) of non-carriers received therapy approved for pulmonary arterial hypertension. Drug-induced pulmonary oedema occurred in five (23%) of treated EIF2AK4 mutations carriers and 13 (21%) of treated non-carriers. Follow-up assessment after initiation of treatment showed that only three (4%) patients with PVOD/PCH reached the predefined criteria for satisfactory clinical response. The probabilities of event-free survival (death or transplantation) at 1 and 3 years were 63% and 32% in EIF2AK4 mutations carriers, and 75% and 34% in non-carriers. No significant differences occurred in event-free survival between the 2 groups ($p=0.38$).

Conclusion: Heritable PVOD/PCH due to bi-allelic EIF2AK4 mutations is characterised by a younger age at diagnosis but these patients display similar disease severity compared with mutation non-carriers. Response to therapy approved for pulmonary arterial hypertension in PVOD/PCH is rare. PVOD/PCH is a devastating condition and lung transplantation should be considered for eligible patients.