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Early Diagnosis Key to Improving Long-term Outcomes in Patients with Pulmonary Arterial Hypertension

Amsterdam - The benefits of treating pulmonary arterial hypertension (PAH) at an early stage of the disease have been clearly demonstrated and are supported by current treatment guidelines. PAH patients in NYHA/WHO functional class (FC) II have a markedly improved prognosis compared with those in FC III/IV. However, diagnosis of PAH is typically delayed as registry data show that the majority of PAH patients are diagnosed in FC III or IV. New data from the EARLY open-label extension trial demonstrated that treatment in patients with FC II PAH can delay disease progression over the longer term. The impact of a screening program on earlier identification and survival rates has also been shown. However, new data from registries of PAH patients, including those with congenital heart disease, continue to reveal the need to improve rates of early detection, management and long-term survival.

Chief Medical Editor: Dr. Léna Coïc, Montréal, Quebec

Over the past 2 decades, progress in treating pulmonary arterial hypertension (PAH) has been "fantastic" for a rare disease, stated Prof. Gérald Simonneau, Université Paris-Sud XI, Kremlin-Bicêtre, and Centre National de Référence de l'Hypertension Artérielle Pulmonaire, Hôpital Antoine Béclère, Clamart, France. "Today we have improved the outcome of the disease with 7 drugs available and by being able to use oral drugs we have simplified the therapeutic approach," he told delegates here at the ERS.

Although current medical therapies improve quality of life, exercise capacity, hemodynamics and survival, there is no cure for PAH and response to therapies is not uniform. "We need to do better," Prof. Simonneau urged, noting that recent data from the French PAH Registry showed a 3-year survival of 58.2% (Humbert et al. *Circulation* 2010;122:156-63), highlighting that diagnosis of PAH is typically delayed. According to data from the French PAH Registry, 24% of patients were diagnosed in NYHA/WHO functional class (FC) II, but the majority (75%) were diagnosed in FC III or IV (Humbert et al. *Am J Respir Crit Care Med* 2006;173:1023-30).

EARLY Treatment and Long-term Outcomes

The long-term benefit of early treatment of PAH was reported in new data from the EARLY (Efficacy and Safety of Oral Bosentan in Pulmonary Arterial Hypertension Class II) open-label extension study, presented by Dr. Olivier Sitbon, Hôpital Antoine Béclère. It is the only randomized clinical trial to assess targeted medical therapy in a patient population who were all FC II PAH at baseline. In the main study, 185 patients, most with idiopathic PAH, were randomly assigned to receive treatment with the endothelin antagonist bosentan or placebo for 6 months (Galiè et al. *Lancet* 2008;371:2093-100). Dr. Sitbon noted that patients in EARLY had true FC II disease, with similar exercise capacity and hemodynamics to FC II patients in the French PAH Registry. At baseline, mean 6-minute walk distance (6MWD) was 430 m and mean pulmonary vascular resistance (PVR) was very elevated at 800 dyn/s/cm^{-5}. The main results showed significant improvement with bosentan vs. placebo in both primary end points, with a 22.6% reduction in PVR (P<0.0001) and an increase in mean 6MWD of 19.1 m (P=0.0758). Active treatment was associated with a lower incidence of patients worsening from FC II to class III/IV (3% vs. 13% (RR 0.26; P=0.0285). "The most impressive result was probably the effect of bosentan on time to clinical worsening," Dr. Sitbon noted, with a 77% RR reduction in PAH progression compared with placebo (P=0.0114).

From the EARLY double-blind phase, 157 patients enrolled in the open-label extension phase. Patients on bosentan continued on treatment and those on placebo transitioned to the endothelin antagonist. During either phase of the study, a total of 173 patients (96.0% in FC II at baseline) received active treatment (median exposure 41.7 months). Those patients have now been followed for up to 5 years. Survival estimate at 3 years was 89.9%. At 30 months, 68.2% of patients had maintained their FC and 20.2% had improved, while 11.6% had worsened. No significant change was seen in baseline 6MWD (mean change at 30 months +7.6 m).

Dr. Sitbon told delegates that based on a good level of evidence, current European guidelines recommend treatment of patients in FC II with ambrisentan, bosentan, sildenafil or tadalafil (Galiè et al. *Eur Respir J* 2009;34:1219-63). "For orally administered drugs it is more logical to start with monotherapy in those patients. But as in all patients, it is very important to monitor efficacy of treatment and to reassess after 3 to 6 months with clinical assessment, 6MWD, exercise capacity and also hemodynamic evaluation," he stated.

Continued

PAH and Congenital Heart Disease

PAH is a major complication of congenital heart disease (CHD), usually the result of a systemic to pulmonary shunt due to moderate-to-large defects leading to an increase in PVR. Although epidemiological data on PAH associated with CHD are scarce, new findings from the French PAH Registry suggest PAH is diagnosed in approximately 60% of known CHD cases. However, although the majority of these patients had PAH FC III, most were not receiving any PAH-specific therapy.

Dr. Xavier Jais, Université Paris-Sud XI, presented data from patients enrolled in the second prospective PAH registry conducted by the France PAH Network at 26 centres between November 2006 and December 2009. PAH was diagnosed by right heart catheterization and defined by the presence of a mean pulmonary arterial pressure (mPAP) ≥25 mm Hg with a pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg. Targeted therapies were administered at the discretion of treating clinicians.

Out of a total of 2585 patients, 255 (9.8%) were identified with PAH-CHD. Mean age was 36.8 years and 60% were female. CHD diagnosis was isolated pre-tricuspid shunts (95 patients), isolated post-tricuspid shunts (134), combined pre-and post-tricuspid shunts (11) and complex CHD (15). Atrial septal defect was the main CHD diagnosed concomitantly or after PAH. Mean PCWP in these patients was 8.3 mm Hg, mPAP 59 mm Hg and 6MWD 370 m.

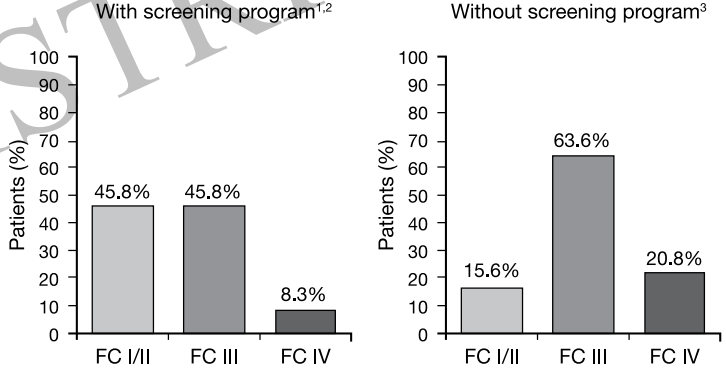
Approximately 66% of patients were receiving PAH-specific treatment, with approximately 60% on monotherapy and 64% taking bosentan. Improvement in FC was seen in patients under treatment, with 59% in FC I-II at last follow-up compared with 39% at inclusion, Dr. Jais reported. He added that PAH-CHD patients with pre-tricuspid shunts appeared to respond to PAH-specific therapy more rapidly than patients with post-tricuspid shunts and they remained stable over a long period. Mortality during follow-up was low: 20 patients died, 4 from sudden death, 8 from PAH progression and 8 from other causes. Seven patients needed a heart-lung transplantation.

The 34% of patients not receiving any PAH-specific treatment included 43% of the 140 patients with FC III disease. "We do not know the reason for this, although we have some hypotheses," Dr. Jais told delegates. "The majority of these patients had a long history of dyspnea and they were stable for a long time, so doctors may have decided not to treat them because they were stable."

Screening for Early Disease

Dr. Sitbon presented data showing how screening populations at high risk of developing PAH, such as those with systemic sclerosis (SSc), can identify patients earlier than routine practice (Figure 1). His group studied 2 cohorts of incident SSc-PAH patients from the same management era (2002-2003). A routine practice cohort included 16 consecutive symptomatic adult SSc patients diagnosed with PAH by right heart catheterization (RHC) at the time of recruitment into the French PAH Registry. A detected cohort comprised 16 consecutive SSc patients who entered a systematic PAH detection program and were subsequently found to have PAH on RHC.

Figure 1. **Earlier Detection of PAH in SSC Patients Through Screening Program**



Adapted from: 1. Hachulla et al. *Arthritis Rheum* 2005;52:3792-800. 2. Hachulla et al. *Arthritis Rheum* 2009;60:1831-9. 3. Hachulla et al. *Arthritis Rheum* 2010;42:940-4.

At the time of PAH diagnosis, detected patients had less advanced pulmonary vascular disease compared with routine practice patients, as evidenced by lower FC, mPAP and PVR and higher cardiac output (Humbert et al. *Arthritis Rheum* Epub July 18, 2011). Of detected patients, 50% had FC I/II PAH compared with only 12.5% of routine practice patients. Although detected patients were less likely to receive diuretics and warfarin, there was no difference in treatment with PAH-specific therapies. Survival rates at 1, 3, 5 and 8 years were 75%, 31%, 25% and 17%, respectively, in routine practice patients compared with 100%, 81%, 73% and 64% in detected patients (P=0.0037). "These exciting results may extend to other subpopulations, leading to earlier identification of PAH and to improved outcomes," Dr. Sitbon concluded. □

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