Original Article

Changes in Exercise Capacity and Cardiac Performance in a Series of Patients with Eisenmenger's Syndrome Transitioned from Selective to Dual Endothelin Receptor Antagonist

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Background: **Differences in clinical effects between selective and dual endothelin (ET) receptor antagonists (ERA) in patients with pulmonary arterial hypertension (PAH) are currently unknown. We aimed to assess prospectively how transition from selective (sitaxsentan) to dual (bosentan) ERA affected exercise capacity and cardiocirculatory performance in patients with Eisenmenger's syndrome.**

Methods: **A series of seven stable patients with Eisenmenger's syndrome aged 40.0 (30.0–56.0) years old treated with sitaxsentan were assessed before and three months after transition to bosentan. Six minute walk test and magnetic resonance to assess LV and RV mass, volume and ejection fraction, and pulmonary flow, and laboratory tests were performed.**

Results: **We observed an increase in LV mass [96.5 (66.0–116.0) vs. 123.0 (93.0–146.0) g; $p = 0.03$], LV ejection fraction [55.0 (44.0–63.0) vs. 65.0 (58.0–70.0)%; $p = 0.02$)], and pulmonary flow [64 (53.0–71.0) vs. 69.0 (55.0–84.0) ml/beat; $p = 0.046$]. This was accompanied by an increase of oxygen saturation, elongation of 6MWD [435.0 (378.0–482.3) vs. 474 (405.0–534.7); $p = 0.02$], decrease of NTproBNP level and increase of ET-1 level.**

Conclusions: **Three month follow-up of stable patients with Eisenmenger's syndrome transitioned from sitaxsentan to bosentan revealed improvement of exercise capacity despite significant elevation of ET-1 level. Concurrent increase of LV ejection fraction and pulmonary flow might have contributed to these favourable effects.**

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Keywords. Pulmonary hypertension; Endothelin; Magnetic resonance imaging; Exercise capacity; 6 Minute walk test; Bosentan; Sitaxsentan; Eisenmenger's syndrome

Background

Endothelin-1 (ET-1) expression is increased in pulmonary arterial hypertension (PAH) and correlates with disease severity [1–3]. ET-1 is secreted primarily by endothelial cells of pulmonary vessels in which it promotes vasoconstriction and proliferation of the smooth muscle cells and fibroblasts through endothelin receptor A (ETA receptor) and B (ETB receptor) [4]. Small amounts of ET-1 are released to the arterial lumen where it binds to endothelial ETB receptor to induce endothelial cells proliferation and arterial vasodilatation through release of nitric oxide and prostacyclin [5–7]. ET-1 is also expressed in the heart where it exerts its inotropic and hypertrophic effect through ETA receptor [8]. ET-1 clearance is mediated by ETB receptors, primarily in the pulmonary circulation [8].

Selective ETA receptor antagonists such as sitaxsentan and dual ETA and ETB receptor antagonists such as bosentan have been used with success in the treatment of PAH [9,10]. Although there is no doubt about the significance of the ETA receptor blockade in the treatment of PAH, there remains a debate whether additional ETB receptor antagonism is of harm or benefit. Theoretically maintenance of ETB receptor activity with use of the selective ETA receptor antagonists may be of value considering its vasodilatory

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effect as well as its role in ET-1 clearance. However the clinical relevance of the differences in pharmacodynamics between selective and dual ET receptor antagonists have been unknown.

Currently only bosentan and ambrisentan are ET receptor antagonists recommended for use in PAH [11]. Sitaxsentan, due to cases of fatal liver injury was withdrawn in December 2010 and it was recommended to replace it with another ET receptor antagonist [11].

In this prospective case series study of seven patients with PAH due to congenital heart disease (CHD-PAH) with Eisenmenger's syndrome we aimed to assess the effects of transition from selective to dual ET receptor antagonist (sitaxsentan to bosentan) on exercise capacity, right (RV) and left (LV) ventricular structure and function, and pulmonary haemodynamics.

Methods and Materials

Subjects

We enrolled in this study patients with Eisenmenger's syndrome that were under care of our centre and who had been transitioned from sitaxsentan to bosentan due to premature termination of STRIDE-3 trial at 9th December 2010. One patient with Down syndrome was excluded due to poor cooperation. Diagnosis of pulmonary hypertension had been confirmed in right heart catheterisation (RHC) in every patient before starting the treatment with sitaxsentan and other aetiologies of pulmonary hypertension were excluded at that time. At the same time patients were disqualified from CHD correction due to high pulmonary artery pressure and resistance as recommended by the European Society of Cardiology [12].

Study Protocol

All patients were admitted to a cardiology ward in January and February 2011 (visit 1) to change PAH specific therapy from sitaxsentan to bosentan. Before transition, patients had been taking sitaxsentan orally at standard dose of 100 mg once daily. Next day after last dose of sitaxsentan patients were given bosentan orally at a dose of 62.5 mg twice daily for four weeks and thereafter 125 mg twice daily as currently recommended. Clinical examination, laboratory tests, echocardiography, 6 minute walk test (6 MWT) and cardiovascular magnetic resonance (CMR) were performed during hospital stays twice: at visit 1 just before transition to bosentan and after three months of bosentan therapy (visit 2). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional ethics committee. Informed consent was obtained from each patient before starting the study.

Laboratory Tests

Laboratory tests including heamoglobin, haematocrit, alanine (ALT) and aspartate aminotransferase (AST), N-terminal proB natriuretic peptide (NTproBNP) and ET-1 were performed in all the subjects at visit 1 and 2. Serum ET-1 levels were assayed with a commercially available ELISA Kit (Human Endothelin-1, Quantikine R&D Systems, MN, USA) according to the manufacturer's instructions. This sandwich enzyme-linked immunoassay permits ET-1 measurements with a detection limit of 0.39 pg/ml.

Exercise Capacity

The modified New York Heart Association (NYHA) functional class and 6 MWT were used to assess exercise capacity. Six-MWT was performed by one trained technician according to the guidelines [13]. During the test we assessed the distance (6MWD) as well as heart rate and oxygen saturation (SaO_2) before and at the end of exercise. We also retrospectively assessed 6MWD performed three to six months before visit 1 during routine ambulatory visit.

CMR

Breath-hold, ECG-gated CMR imaging was performed using cardiac phased array coil on 1.5 T whole-body scanner (Magnetom Sonata Maestro Class, Siemens, Erlangen, Germany) in LV and RV short-axis and axial views. After scout imaging, cine imaging (steady-state free precision gradient echo technique; slice thickness 8 mm, no gap, matrix 256×192, in-plane resolution $1.3\,\text{mm} \times 1.3\,\text{mm}$) was acquired in LV and RV short-axis and axial views [14,15]. Afterwards free-breathing, retrospectively gated, velocity encoding imaging sensitised for the flow in the through-plane direction was performed perpendicularly to the main pulmonary artery and to the ascending aorta 1 cm above the aortic and pulmonary valve, respectively. Typically the maximum encoding velocity (V_{ENC}) was $\leq$2.5 m/s, but was increased if the peak velocity could be predicted to be higher based on the patient's cine images. If velocity aliasing occurred, flow images were reacquired with correct V_{ENC} [16]. Cine and velocity encoding images were assessed off-line (MASS Medis, Leiden, The Netherlands) by an independent, experienced observer blinded to other data. Endocardial and epicardial LV and RV borders were outlined on short-axis cine images as previously described [14,15]. If the basal slice contained both ventricular and atrial myocardium, contours were drawn up to their junction and joined by straight line through the blood pool. In the basal slice, if pulmonary valve was visible, only the portion of volume surrounded by trabeculated myocardium below the pulmonary valve level was included. For RV inflow portion blood volume was excluded from right ventricle volume if the surrounding wall was thin and not trabeculated, as it was considered to be in right atrium. LV and RV end-diastolic volume (EDV), end-systolic volume, myocardial mass and ejection fraction (EF) were computed. Based on velocity encoding images the through-plane blood flow per cardiac cycle was calculated separately for the main pulmonary artery and the aorta ascending after careful contouring of vessel wall throughout the cardiac cycle.

Statistics

Statistical analysis was performed with StatSoft, Inc. (2010). STATISTICA (data analysis software system),