Heart, Lung and Circulation (2017) xx, 1–4
1443-9506/04/$36.00
http://dx.doi.org/10.1016/j.hlc.2016.12.011

BRIEF COMMUNICATION

Early Experience of Macitentan for Pulmonary Arterial Hypertension in Adult Congenital Heart Disease

S. Herbert, BSc [a], W. Gin-Sing, RGN [b], L. Howard, MBBS, DPhil, FRCP [b], R.M.R. Tulloh, BMBCh, MA, DM, MRCP, FRCPCh [a*]

[a]Department of Congenital Heart Disease, Bristol Heart Institute, Bristol, UK
[b]Pulmonary Hypertension, Hammersmith Hospital, London, UK

Received 29 September 2016; received in revised form 15 December 2016; accepted 22 December 2016; online published-ahead-of-print xxx

Background Endothelin receptor antagonists (ERA) have been recognised as effective therapy for pulmonary arterial hypertension in congenital heart disease (CHD-PH), and Eisenmenger syndrome (ES) since the Breathe 5 study. A new dual receptor antagonist – Macitentan – is currently undergoing trials to determine its efficacy in simple ES. To date there is little information on this therapy in CHD and we report our first experience, some with more complex diseases.

Methods Data was collected prospectively from September 2014. Patients with CHD-PH were started on or converted to macitentan if they required therapy with phosphodiesterase 5 inhibitor (PDE5i) or if there was insufficient response or a reaction to bosentan, especially those with trisomy 21. Patients were seen approximately three months after starting therapy to assess echocardiography, six minute walk test, clinical response and tolerability. All patients underwent monthly liver tests initially, but this was reduced to three-monthly in Q4 2015.

Results Fifteen patients with CHD-PH (eight male, seven female) were started on macitentan, median (range) age 38 (23–61) years, and eight patients with Down's syndrome. Eight patients had complex CHD with one having unoperated double inlet left ventricle with ventriculo-arterial discordance, one had double outlet right ventricle and six with complete atrio-ventricular septal defect. Six patients were ERA naïve and nine patients changed from bosentan to macitentan in order to achieve improved drug-drug interaction. Median length of time of treatment with macitentan is 289 (0–694) days to date. One discontinued due to rash and feeling unwell; one was unable to comply with medication due to learning difficulties and one died soon after commencing rescue therapy. This last patient was functional class IV with oxygen saturation of 67% at rest, with right heart failure and was unable to perform a walk test before commencing therapy. All patients who remained on therapy had significant increase in six minute walk test from median 286 (120–426) to 360 m (150–450)($p < 0.05$), most notably in those treatment naïve. Functional class median remained at 3 but the range was reduced (1–3). Resting oxygen saturations improved from median 83 range (77–95%) at rest to 91 (77–96%) and at end walk from 78 (48–90%) to 79 (62–96%). Tricuspid regurgitant peak Doppler derived pressure drop did not change (as expected) at 4.6 (4.3–5.5)m/s. There were no episodes of liver dysfunction.

*Corresponding author at: Professor of Congenital Cardiology, Department of Congenital Heart Disease, King David Building, University Hospitals Bristol NHS Foundation Trust, Bristol BS2 8BJ., Email: Robert.Tulloh@Bristol.ac.uk

Please cite this article in press as: Herbert S, et al. Early Experience of Macitentan for Pulmonary Arterial Hypertension in Adult Congenital Heart Disease. Heart, Lung and Circulation (2017), http://dx.doi.org/10.1016/j.hlc.2016.12.011

Conclusions The introduction of this new therapy has been simple and mostly well tolerated in our sick group of patients. With the usual reservations concerning the open-label nature of our observations, macitentan has good signals regarding oxygen saturations and encouraging signals relating to efficacy.

Keywords Pulmonary hypertension • Eisenmenger Syndrome • Trisomy 21 • Endothelin Receptor Antagonists • Macitentan

Introduction

Pulmonary arterial hypertension (PAH) is a life limiting, chronic disease severely compromising both respiratory and cardiac function. Defined as a mean pulmonary arterial pressure greater than 25 mmHg on right heart catheterisation in the absence of left atrial hypertension and congenital heart disease, it contributes one third of cases in adults (ACHD-PH) [1,2].

ACHD-PH usually follows from congenital left to right shunt causing increased pulmonary blood flow and eventual increased pulmonary vascular resistance (PVR), Eisenmenger Syndrome (ES) and hypoxaemia [3,4,6]. Therapy usually progresses from phosphodiesterase Va inhibitor (PDE5i) such as sildenafil, then endothelin receptor antagonists (ERA) most recently macitentan and lastly epoprostenol which is expensive and not generally used in ES due to the risk of paradoxical embolus with a central venous line [7].

High endothelin levels are seen in ES and blockade of receptors results in vasodilation and lowering of the PVR [8–11]. In order to reduce drug-drug interaction macitentan was licensed for ACHD-PH in both WHO functional class II and III with corrected simple CHD [12,13]. It has a high affinity for endothelin receptors and sustained receptor binding which is non-competitive and has more effective receptor antagonism than other agents [14]. Pre-clinical and *in vitro* data has demonstrated favourable results regarding tolerability and safety, little impact on bile salts and has been shown to have the greater tissue targeting potential in comparison to bosentan [15–17]. The SERAPHIN study demonstrated a 55% reduction of a morbidity or mortality event by the use of macitentan when compared to placebo [18]. Those who switched from bosentan to macitentan in ACHD-PH have shown a potential improvement in WHO functional class ($p = 0.11$), significant reduction in NT-pro-BNP ($p = 0.031$), but no difference in six minute walk distance (6mwd) at three-months follow-up [19]. A current trial (Maestro) is looking to collect data on exercise capacity in ERA naïve patients with ACHD-PH [20].

Macitentan has been used in our patients since September 2014 in both ERA naïve ACHD-PH patients and those previously on bosentan. We describe here the first information available on the early effects of macitentan in naïve and complex ACHD-PH.

Methods

Demographic and clinical data was collected prospectively from patients prescribed macitentan for ACHD-PH from the South-West of England and Wales from September 2014. Patients were started for safety as a day-case or converted if they required therapy with PDE5i or wished to reduce the frequency of blood tests and were seen three months later for assessment. Liver blood tests were reduced to three-monthly in Q4 2015. Data is expressed as median (range).

Results

Fifteen patients (eight male, seven female) since September 2014 have been started on macitentan for ACHD-PH. These patients had been on therapy for a median of 289 days (range = 0–694). The median age was 38 years (range = 23–61), eight patients had trisomy 21, and the most common cardiac abnormality was AVSD (n = 7). Six patients had simple Eisenmenger Syndrome or were postoperative and seven had more complex disease (Table 1). Six patients were naïve to ERA, two of those were on concomitant PDE5i and four on no therapy. In those previously exposed to ERA, all had been exposed to bosentan and nine were switched to macitentan to improve drug-drug interactions with PDE5i (Table 1).

On therapy 6MWD increased from 286 m (120–426) to 360 m (150–450)($p < 0.05$), WHO functional class was unchanged at 3, oxygen saturations at rest increased from 83% (77–95) to 91% (77–96) (p = ns) and after walk test from 78% (48–90) to 79% (63–96) (p = ns), blood pressure was 105/74 mmHg (89–128/55–98) before and 108/69 mmHg after (96–145/58–86), and Borg Dyspnoea index reduced from 4 (1–7) to 3 (0–5). Echocardiography showed no change in long axis function (TAPSE) from 1.7 cm (0.8–2) to 1.8 cm (1.8–2.9) (p = ns), but right ventricle S wave velocity increased from 11 cm/s (7–12) to 13 cm/s (10–18) ($p < 0.05$).

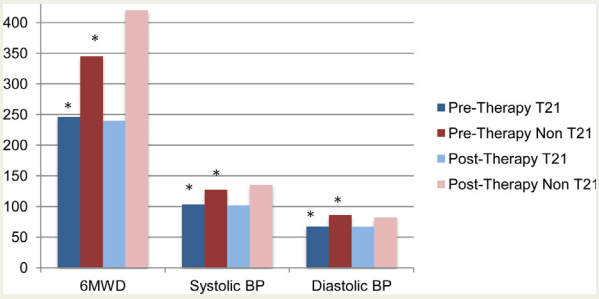

Figure 1 Graph demonstrating the comparison of people with T21 and people without before and after therapy. * Indicates p-value <0.05.

Please cite this article in press as: Herbert S, et al. Early Experience of Macitentan for Pulmonary Arterial Hypertension in Adult Congenital Heart Disease. Heart, Lung and Circulation (2017), http://dx.doi.org/10.1016/j.hlc.2016.12.011