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Initial experience in children with the use of macitentan in pulmonary arterial hypertension after side effects with other endothelin receptor antagonists

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ABSTRACT

Among the different lines of treatment of pulmonary arterial hypertension are endothelin receptor antagonists. Macitentan is an orally active, potent and dual endothelin receptor antagonist. We want to report our initial experience with the use of macitentan in two pediatric patients.

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive and chronic disease characterized by an abnormal vascular proliferation and remodeling that increases pulmonary arterial pressure and vascular resistance. PAH is defined as a mean pulmonary arterial pressure ≥ 25 mm Hg, a pulmonary arterial wegde pressure ≤ 15 mm Hg and a pulmonary vascular resistance > 3 UW·m^2 assessed by right heart catheterization [1].

Endothelin receptor antagonists (bosentan, ambrisentan, macitentan) [1] are one of the three different lines of treatment for PAH available nowadays, as well as prostanoids and phosphodiesterase type 5 inhibitors. Protanoids stimulate the cAMP pathway to increase pulmonary vasodilation. Phosphodiesterase type 5 inhibitors increase smooth muscle cell cGMP levels and promote pulmonary vascular dilation and remodeling.

Endothelin-1 is involved in an aberrantly activated process of mitogenesis, angiogenesis, fibrosis and inflammation that occurs in pulmonary vessels in patients with PAH [2]. Macitentan is an orally active, potent and dual endothelin receptor antagonist which inhibits endothelin-1 from binding to endothelin$_A$ and endothelin$_B$ receptors [2]. It has a slow receptor dissociation kinetic compared to other endothelin receptor antagonists that contribute to a sustained receptor binding [3] and to a greater affinity with lipophilic membranes. This enables an enhanced tissue penetration without interfering to bile acid secretion and therefore reducing the risk of hepatoxicity [5].

At present, safety and effectiveness data of macitentan in children has not been well established.

In this paper, we want to report our initial experience with the use of macitentan in two pediatric patients with severe pulmonary hypertension who developed an increase in liver enzymes while being on other endothelin receptor antagonist and were treated with macitentan without side effects.

1.1. Case reports

CASE 1: 6-year-old child with severe PAH in the context of an atrial septal defect and a persistent patent ductus arteriosus. Initially seen at 2 years of age due to cyanosis and found to have a medium sized patent ductus arteriosus with right to left shunt and a 4.7 mm *ostium secundum* atrial septal defect with bidirectional shunt. In view of these echocardiographic findings of PAH an extended diagnostic work up was performed including an exhaustive clinical history, physical examination, chest X-ray, 12 lead ECG and detailed echocardiogram as well as a pulmonary function assessment and a 6-min walk test [4]. Left heart and valvar disease were excluded as a possible underlying lung disease. In addition, cardiac catheterization showed severe pulmonary arterial hypertension with a mean pulmonary arterial pressure of 70 mm Hg in the presence of a pulmonary wedge pressure of 5 mm Hg and a pulmonary vascular resistance of 22.5 UW·m^2 (mean aortic pressure was 67 mm Hg and the arterial oxygen saturation 77%). After the cath, the patient was started on sildenafil and bosentan (doses of 1 mg/kg three times daily and 2 mg/kg two times daily respectively). However, after a year of treatment, the patient developed significant elevation of her

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liver function with an aspartate aminotransferase and alanine aminotransferase 3 times the upper limit of the normal range. This obliged to switch treatment with bosentan to ambrisentan at a dose of 5 mg/per day once liver enzyme levels normalized. However, transaminases rose up again in the follow up (aspartate aminotransferase 100 UI/l, alanine amino-transferase 114 UI/l) and ambrisentan was discontinued. At this stage, treatment with macitentan was associated at a dose of 5 mg/per day (patient's weight 23 kg), with good tolerance and without side effects after 7 months on the treatment (normal liver function on repeated blood tests).

CASE 2: 15-month-old premature infant with a low weight for gestational age (1150 g, 34 weeks of gestational age), diagnosed after birth with a severe valvular aortic stenosis and a borderline left ventricle. An initial balloon aortic valvuloplasty was performed at 3 days after birth with no complications. However, as the baby could not be weaned from prostaglandin E_1 infusion a hybrid Norwood procedure (balloon atrioseptostomy, bilateral banding and ductal stenting) was performed at the age of 1 month. 6 months later a Norwood-Sano procedure was completed. The postoperative period was complicated with severe refractory hypoxemia which was initially treated for 7 days with extracorporeal membrane oxygenation (ECMO). Afterwards inhaled nitric oxide and sildenafil were added to improve oxygenation. However, as the baby continued with mild hypoxemia 3 months after the surgery a cardiac catheterization was performed. The angiography and hemodynamics demonstrated a stenosis in the Sano conduit which was stented on the same procedure. In addition, the hemodynamics showed evidence of pulmonary hypertension with a mean pulmonary arterial pressure of 31 mm Hg, a pulmonary arterial wedge pressure of 10 mm Hg and a pulmonary vascular resistance of 4 UW·m^2. For this reason, treatment with bosentan was added to sildenafil at a dose of 2 mg/kg which had to be discontinued later on because of a transaminases elevation (aspartate aminotransferase 110 UI/l, alanine aminotransferase 192 UI/l). Once transaminases came down again to a normal range, the patient was started on macitentan (weight 7.7 kg) at an initial dose of 2,5 mg/per day. Dose was shortly increased to 3,3 mg/per day with excellent tolerance. After 6 months of treatment, the patient has not had any side effects from the medication and his second palliative step (Glenn procedure) has already been performed, with no major complications. He was discharged home on no oxygen. A repeated cardiac catheterization after his Glenn completion showed no signs of pulmonary hypertension (mean pulmonary arterial pressure of 15 mm Hg, pulmonary arterial wedge pressure of 11 mm Hg and pulmonary vascular resistance of 1.6 UW·m^2) and therefore treatment with macitentan has been discontinued.

In the Study of Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN), 10 mg of macitentan significantly reduced by 45% the risk of having a morbidity or mortality event compared to placebo [5].

Relating to frequent adverse events, as could be the elevation in liver enzyme levels and peripheral edema, the incidence between the macitentan group and the placebo group is simialr [4]. Macitentan is slowly absorbed and eliminated, allowing a single dose per day.

In addition to the other endothelin receptor antagonists, macitentan is a promising drug in pulmonary arterial hypertension treatment also in the pediatric population, because of its convenient dosage, oral administration and decrease in side effects related to hepatotoxicity, although multicentric studies are necessary to determine safety, effectiveness and posology in children.

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Conflicts of interest

None.

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