



revista portuguesa de
PNEUMOLOGIA
portuguese journal of pulmonology
www.revportpneumol.org



CASE SERIES

Macitentan in daily clinical practice: A single centre, 1-year experience

S. Cadenas-Menéndez^{a,*}, P. Álvarez-Vega^a, J. Martín-Moreiras^b,
M. Barreiro-Pérez^b, M.Á. Gómez-Sánchez^c, P.L. Sánchez-Fernández^b

^a Pulmonology Service, Pulmonary Hypertension Unit, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain

^b Cardiology Service, Pulmonary Hypertension Unit, Complejo Asistencial Universitario de Salamanca, Salamanca, Spain

^c Cardiology Service, Hospital General Nuestra Señora del Prado, CIBER de Enfermedades Respiratorias (CIBERES), Talavera de la Reina, Spain

Received 14 July 2017; accepted 2 October 2017

KEYWORDS

Pulmonary arterial hypertension;
Macitentan;
Endothelin-receptor antagonist;
Clinical practice;
Phosphodiesterase 5 inhibitors;
Prostaglandins

Abstract The effectiveness and safety of macitentan, a dual endothelin-receptor antagonist (ERA) approved for the treatment of pulmonary arterial hypertension (PAH), were shown in an extensive clinical trial oriented towards morbidity and mortality events. Our aim was to describe a single centre's experience of the utilization of macitentan in patients with PAH in clinical practice settings. Thirteen patients with different aetiologies and previous PAH treatments were studied. After 12 months of macitentan treatment, 11 patients improved their functional class (FC), all patients improved their 6-minute walk distance (6MWD) test, and 10 patients lowered their NT-proBNP plasma levels. Additionally, cardiac imaging parameters were also improved. No cases resulted in hospitalization, septostomy, transplant or death.

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Introduction

Macitentan is an ERA showing enhanced tissue penetration, higher pKa,¹ increased ET-receptor occupancy² and

superior oral efficacy in animal models compared to other ERAs.¹ It also shows minimal risk of relevant drug-drug interactions and low risk of hepatotoxicity when administered for PAH.³⁻⁵ Macitentan is the first drug for PAH approved after a long-term, event-oriented clinical trial, showing a decrease in morbidity and mortality.⁴ Macitentan is recommended as monotherapy or in sequential combination for PAH patients in WHO-FC II and III in the latest European ESC/ERS guidelines for pulmonary hypertension (PH).⁶ These

* Corresponding author.

E-mail address: sercam.2007@gmail.com (S. Cadenas-Menéndez).

<https://doi.org/10.1016/j.rppnen.2017.10.001>

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guidelines established a new assessment of 1-year mortality risk in PAH patients, classifying patients as low, intermediate or high risk, taking into account clinical parameters, exercise, cardiac imaging and haemodynamics.⁶ However, other parameters such as age, sex or PH aetiology are not considered. The validity of most comprised parameters has been demonstrated in risk assessment at diagnosis but their validity during patients' follow-up is uncertain. Our aim was to describe a single centre's experience of the 1-year utilization of macitentan in patients with PAH in the clinical practice setting.

Methods

Retrospective series of PAH patients in WHO-FC II or III treated with macitentan under routine clinical practice in the Pulmonary Hypertension Unit of the Complejo Asistencial Universitario de Salamanca (Spain). This is a multidisciplinary unit coordinated by the pulmonology and cardiology Services, with 4 specialized outpatient visits each week, including 1 congenital visit; and over 100 patients attended.

We recorded available clinical, cardiac imaging and haemodynamic variables at baseline and after 12 months of treatment with macitentan, and drug safety. We categorized the registered clinical variables at baseline and 12-months in low-, medium- and high-risk categories using the risk assessment table published in the 2015 ESC/ERS guidelines.⁶ This classification serves as a mere reference given the complexity of PAH and the limited applicability of proposed cut-off values at a case-by-case level in real-world practice. This study was approved by the Hospital Ethics Committee. All participants provided written informed consent.

Results

Thirteen patients, (6 *naïve*), were treated with macitentan for 12 months between September/2014 and October/2016. The demographic and clinical characteristics, and administered treatments at baseline and after 12 months are shown in Table 1. Six patients were treatment-naïve and 4 started sequential combination with macitentan plus sildenafil after not reaching therapeutic objectives with sildenafil alone. Additionally, three patients who received triple-combination therapy, including systemic prostaglandins ($N=2$) and inhaled iloprost ($N=1$), started macitentan due to hepatotoxicity of other ERAs. These patients were included in this analysis as they remained on stable doses of prostaglandins and diuretics during the treatment period. Patients with connective tissue associated PAH presented limited form of systemic scleroderma (Patients 5, 6 and 13) or systemic lupus erythematosus (SLE) (Patients 7, 8 and 12). Patient 9 presented ventricular septal defect and Patient 10 atrial septal defect, with persistent PAH after defect correction. One patient (Patient 4) presented HIV infection associated PAH and four patients (Patients 1, 2, 3, and 11) were diagnosed with idiopathic PAH.

Among 13 included patients, 11 improved their FC, 13 their 6MWD (average: 55 m), and 10 lowered their NT-proBNP plasma levels (average: -31%). Regarding cardiac imaging, 11 patients reduced their right atrial area, whereas the

pericardial effusion observed in three patients at baseline was not present after 12 months (Table 1). Haemodynamic parameters were not available in all patients at 12 months given their favourable disease progression.

After 12 months of treatment with macitentan no cases resulted in hospitalization, septostomy, transplant or death. Two patients required additional therapies for PAH: After an initial clinical improvement, Patient 2 required a rapid step-up to triple therapy at month 6 due to clinical worsening (imaging/haemodynamic confirmation), achieving positive outcome. Patient 4 added a phosphodiesterase-5 inhibitor after failing to meet therapeutic objectives (imaging parameters, month 5).

Safety profile

Two patients reported cephalaea. Patient 8 had 10 g/dL of baseline haemoglobin and developed anaemia during the study due to: SLE, hypersplenism and a potential effect of the drug. There were no treatment discontinuations or hospitalizations caused by PAH worsening. In patient 4 (HIV-associated PAH), viral load and antiretroviral (tenofovir, darunavir, ritonavir, raltegravir) and CD4 levels were closely monitored without detecting interactions with the baseline treatment. There were no oedema or transaminase elevation events.

Discussion

Our results from a single-centre study showed a noticeable improvement in clinical observations after 12 months of macitentan treatment in patients with PAH in clinical practice settings. This favourable evolution was observed across aetiologies and therapeutic strategies, and irrespective of previous treatments. Increasingly, the clinical improvements were also observed in the 3 patients previously treated with bosentan, and were associated with a good tolerability, aligned with recently published reports,⁷⁻⁹ without transaminase elevation events.

After 12 months of treatment, no cases resulted in hospitalization due to PAH, septostomy, transplant or death. These results are consistent with the composite secondary endpoint (reduction death due to PAH or hospitalization for PAH) of the SERAPHIN trial, in which the risk of such events was significantly reduced by 50% ($p < 0.001$),⁴ although comparisons have to be made with caution given the disparity of the population size and characteristics.

Current treatment for PAH is not a mere long-term administration of drugs. Guidelines recommend a close monitoring and an individualized management of patients.⁶ The treatment goal in patients with PAH is achieving a low risk status, associated to a 1-year mortality risk <5%.⁶ However, this risk classification and the therapeutic objectives are not yet manifest and have to be defined in subsequent studies.¹⁰ They are also increasingly ambitious, not always realistic for certain patients, which bolsters the relevance of our results. Although patients were treated on a clinical practice basis and had different disease histories and baseline characteristics, after 1 year of macitentan treatment none of the measured parameters were classified under the high risk category as defined per 2015 ESC/ERS guidelines. Furthermore,

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