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Clinical Efficiency of Macitentan in Patients with Pulmonary Hypertension. Real World in Argentina

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Abstract

Background: Pulmonary Arterial Hypertension (PAH) is a chronic and progressive disease characterized by an increase in the pulmonary pressure and pulmonary vascular resistance that leads to high morbidity and mortality. Macitentan is an endothelin receptor antagonist (ERA), that has shown benefit in terms of morbidity and mortality (as a composite endpoint) in a randomized controlled trial (SERAPHIN), but information regarding the use of this drug in the daily clinical practice is limited in our region.

Objective: To describe clinical outcomes in patients with a diagnosis of Pulmonary Hypertension (PH) treated with Macitentan in Argentina.

Methods: Retrospective, observational study including adult patients with a diagnosis of PH, confirmed by right heart catheterization, who were treated with Macitentan in Argentina between March 2015 and April 2019. All the information was obtained from a designed database. Patients receiving Macitentan for at least 9 months were included and the clinical outcome was defined as improvement in the functional class (FC) from advanced (III/IV) to non-advanced (I/II) and in the 6-minute walk test (6MWT).

Results: 126 patients with a median age of 46 years, with a predominance of female gender (74%) and PH group 1 (97%) were included. Before starting Macitentan, 78.9% of patients had advanced FC and the average number of meters walked in the 6MWT was 311 (SD 121 m). At six and twelve months, the percentage of patients in advanced FC was significantly reduced and the 6MWT distance increased to 360 and 361 meters respectively, both results with statistically significant benefit ($p<0.001$).

Conclusions: In our cohort of patients, treatment with Macitentan was associated with a significant clinical benefit, with improvement both in FC and in the 6MWT distance at 6 and 12 months. This information is consistent with the results of the SERAPHIN study, and it is the first contribution on the use of this drug in a real-world scenario in our region.

Keywords: Pulmonary hypertension; Macitentan; Clinical efficiency; Argentina

Introduction

Pulmonary arterial hypertension (PAH) is characterized by an increase in pulmonary pressure and pulmonary vascular resistance that leads to right ventricular dysfunction, heart failure and death [1]. The current diagnosis of PAH is made by the presence of precapillary PH at right heart catheterization (mean pulmonary arterial pressure >20 mmHg at rest, wedge pressure <15 mmHg and high pulmonary vascular resistance >3 Wood units) in the absence of other causes of precapillary PH, such as lung disease or chronic thromboembolic pulmonary hypertension (CTEPH). PAH is a rare disease [2] (with a prevalence of less than 1/2000 cases in Europe or fewer than 200,000 cases in the United States) but it is being increasingly recognized as a severe and progressive condition. Recent large multicenter trials have provided low estimates of PAH prevalence and incidence (15 and 2.4 cases/million adult habitants/year in France, and 10.6 and 2 cases/million habitants in the United States) [3,4].

Multiple pathophysiological mechanisms are involved in the genesis of PAH, many of which have been used as therapeutic targets. Among these mechanisms, the endothelin pathway plays an important role through vasoconstrictive and mitogenic effects. This is why the Endothelin Receptor Antagonists (ERA), together with the phosphodiesterase 5 inhibitors (PDE5-I) and Prostanoids have been tested and approved for the treatment of this disease [5]. A meta-analysis showed that therapy with these three drug groups improved mortality, as compared to controls [6].

Increased levels of endothelin-1 (ET-1) have been observed in the plasma and pulmonary vascular endothelium of patients with PH, and increased plasma levels were also observed in experimental animal models of PAH. ET-1 is the main isoform observed in the cardiovascular system, and it is one of the largest potent vasoconstrictors. The activity of ET-1 is mediated through two distinct receptors: ETA and ETB [7,8].

The dual ERA Bosentan was approved as the first oral therapy for PAH, based on two randomized controlled trials (RCTs) showing improvements in exercise capacity [9], hemodynamic parameters and time to clinical worsening [10,11]. In 2013, the FDA approved the promising drug Macitentan which is another ERA with unique characteristics [12].

Macitentan is a dual ERA that inhibits both type A and B endothelin receptors, located in the smooth muscle cells of pulmonary vessels. This drug has a compact conformation facilitating deep penetration into the receptor and allowing precise occupation of a hydrophobic pocket in the ETA receptor. ET-1 acts as a tissue (paracrine or autocrine) factor, therefore an ERA that can easily penetrate tissue is more potent to increase ET-1 receptor blockade [13].

In experimental models, Macitentan exhibits higher antagonistic potency than Bosentan and Ambrisentan in pulmonary smooth muscle cells. Compared to Ambrisentan and Bosentan, it has a longer duration of action, reflected by the longer half-life, as well as other pharmacodynamic benefits attributed to its active metabolite, ACT-132577.

The effects of Macitentan have been extensively investigated in

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different phase I studies in more than 300 subjects, a phase II study (in patients with idiopathic pulmonary fibrosis) with 26 patients and the pivotal phase III study with an ERA in PAH to improve clinical effects in morbidity and mortality (as a composite endpoint) [14,15]. Macitentan was approved in 2013 by the United States Food and Drug Administration and European Medicines Agency for the treatment of PAH to delay disease progression and to reduce hospitalizations and for the long-term treatment of adults in FC II–III, as monotherapy or in combination therapy.

In spite of all this published information about the effects of this drug, there is a scarcity of reports concerning real-world scenarios. At present, there are different ongoing trials evaluating the use of this drug in daily clinical practice based on real world information. This publication describes the clinical efficacy and safety of Macitentan treatment in our patients with PH.

Methods

A multicenter prospective study including patients with a confirmed diagnosis of PH (group 1 and 4) by right cardiac catheterization, treated with Macitentan for at least 9 months and followed for at least 12 months was conducted. Patients treated with this drug between March 2015 and April 2019 in Argentina was included.

In addition to survival data, information was collected from all patient records regarding demographic variables (i.e age, gender), clinical diagnosis (i.e type of PAH), and time to diagnosis. Both WHO FC and the 6MWT distance in meters were recorded as functional outcomes.

All the information in this study was obtained from a consecutive and prospective registry provided with data on clinical, functional, hemodynamic and echocardiographic variables; both in baseline conditions and in the standard follow up at 6th and 12th months.

The patients treated for at least 9 months with Macitentan (10 mg once daily) were included in the study. The primary endpoint of clinical efficacy was defined as an improvement from advanced FC (III-IV) to non-advanced FC (II-I) or an increase in the distance walked in the 6MWT greater than 15% as compared to baseline. Drug safety variables were evaluated as a secondary objective and defined by the occurrence of adverse events associated with the drug, such as anemia and/or liver toxicity (AST/ALT elevation >5).

Entry to the study was established by the start of treatment and the follow-up was performed at 6 and 12 months, with analysis of clinical efficacy parameters and adverse events.

Categorical variables were presented as percentage with their respective confidence intervals (95%CI) and continuous variables as mean and standard deviation (SD) or median and interquartile range (IQR), according to distribution.

Normality was analyzed by D'Agostino-Pearson test. Student´s t-test was used for quantitative variables, chi2 for categorical variables and McNemar for paired variables. The $p<0.05$ was defined as significant and STATA 14 software was used for the analysis.

Results

One hundred twenty six patients with PH treated with Macitentan for at least 9 months were assessed. Baseline, 6 and 12 months follow up assessments of FC and 6MWT distance were performed.

The mean age of the population was 46 years (SD 20), with a predominance of female gender (74%), group 1 (97%) (The rest of the patients were in group 4). The predominant etiologies within group 1 were: idiopathic 69% and scleroderma 22%. Baseline treatment included sildenafil/tadalafil 81%, prostanoids 13%, bosentan/ambrisentan 53% (discontinued before the start of Macitentan) and 19% without any treatment. The characteristics of the population are summarized in Table 1.

Variables	**N=126**
Age (years)	45.87 (SD 20.25)
Female gender	73.80%
PH group I	97%
Idiopathic	68%
Scleroderma	22%
Congenital	4%
Familial	2%
Toxins	1%
HIV	1%
Porto-pulmonary	1%
PH group IV	3%
Doses 10 mg/day	97.90%
FC	
I	3.60%
II	26.40%
III	60.60%
IV	9.40%
6MWT (meters)	311 (DS 110)
Sildenafil/Tadalafil	81%
Bosentan/Ambrisentan	53%
Prostanoids	13%
No treatment	20%

Table 1: Baseline characteristics of the study population

In baseline conditions the FC presented the following distribution: FC I 3.6%, FC II 26.4%, FC III 60.6%, and FC IV 9.4% (advanced FC 70%). The average distance walked in the 6MWT was 311 meters (SD 121 m).

At 6 months of follow-up the FC was distributed as follows: FC I 13.0%, FC II 56.8%, FC III 23.2% and FC IV 7% (30.2% was in advanced FC). Therefore, FC improved significantly ($p<0.001$). At 12 months the FC distribution was: I 13%, II 52%, III 25.8% and IV 9.2% (35% was in advanced FC) with a significant improvement with respect to the baseline ($p<0.001$) (Figure 1).

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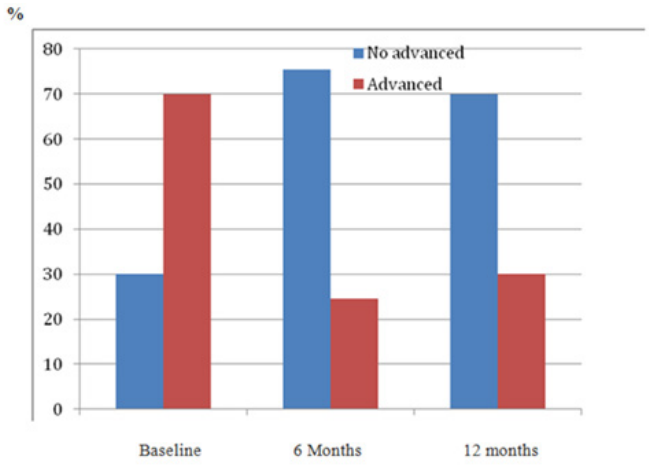

Figure 1: Advanced CF response.

A significant increase in the 6MWT distance compared to the initial value, with an average of 360 m at 6 months (SD 121 m) (p<0.001) was observed. This benefit in 6MWT was sustained at 12 months, with 361 meters walked (p<0.001 from baseline), which represents a 50-m improvement between the initial evaluation and the follow-up (additional 16%) (Table 2). In regards to other clinic data that was reported, 21 patients (16.6%) had at least one hospital admission, with an annual mortality of 6% (Figure 2).

Baseline (%)	6 months (%)	12 months (%)	p value
I 3.6	18	15	<0.01
II 26.4	57.8	55	<0.01
III 60.6	24.1	24.8	<0.01
IV 9.4	2	5.2	<0.01

Table 2: Functional class results-Variation of the baseline FC, at 6 and 12 months of treatment.

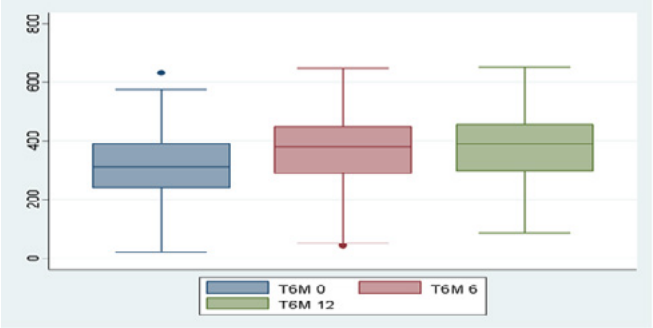

Figure 2: Variation in the baseline 6MWT distance, and at 6 and 12 months of treatment.

Clinical benefit was observed regardless of the initial treatment and even in the 20% who were not receiving any medication. Finally only 4 patients had to discontinue treatment due to different adverse effects (2 due to liver toxicity and 2 due to severe anemia), which represents 3.1%. Overall, 97% of patients continued on Macitentan throughout the study (Table 3) (Figure 3).

Baseline	6 months	12 months	*p value*
311 (DS 121)	360 (DS 110.0)	361 (DS 113)	0.001

Table 3: Variation in the baseline 6MWT distance, and at 6 and 12 months of treatment.

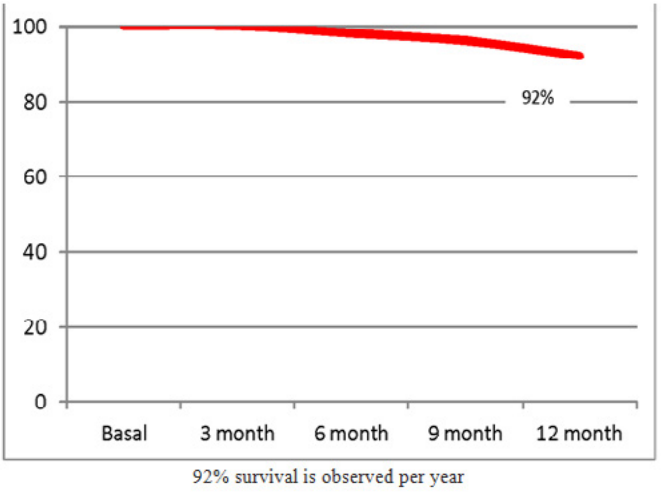

Figure 3: Kaplan-Meier survival curve.

Discussion

The SERAPHIN trial, a randomized, double-blind, multicenter study evaluated the efficacy and safety of two doses of Macitentan (3 mg and 10 mg once daily) by using a composite primary endpoint of time to first morbidity and (all-cause) mortality event in 742 patients with symptomatic PAH. Eligible patients were 12 years of age or older with a confirmed PAH diagnosis (idiopathic or heritable, PAH associated with connective tissue disease, repaired congenital systemic to pulmonary shunts, HIV infection, drug use or toxin exposure). This is the first large-scale study showing a benefit in terms of morbi-mortality in PAH.

Head-to-head comparisons of Macitentan and other drugs approved for PAH treatment are not available, so it is difficult to choose the appropriate agent. All of the ERAs have shown clear clinical benefit in double blind, randomized, placebo-controlled trials but as the trials have different designs, it is difficult to compare one ERA with another. Comparative studies would be needed to prove the incremental value of Macitentan in the treatment of PAH.

Our trial included patients with idiopathic PAH (68%) and scleroderma (22%) predominantly, and 80% of the study population was receiving a specific drug. In the SERAPHIN trial the FC at 6 months was improved in a higher percentage of patients receiving 10 mg of Macitentan (p=0.006), and the treatment effect on the 6MWT with a 10 mg dose versus placebo was 22.0 m (97.5% confidence interval (CI), 3.2-40.8; p=0.008). In our study, the 6MWT showed a significant increase (p=0.001) in the distance walked from 311 meters to 361 meters, a greater improvement than the 50 meter (16%), observed in the randomized study. This impact must be analyzed in

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the context of an observational study and the presence of confounding factors.

In our cohort of 126 patients with PH (97% PAH), in a real world setting, we confirmed the positive clinical results of treatment with Macitentan. Clinical improvements were evident after 6 months of initiation of treatment regarding FC and the 6MWT. It is important to note that these benefits were sustained over time and long term follow up at 12 months.

This information is vital for clinicians to observe the response to drugs in the real world and also provides data on effectiveness in a sample that is not as restrictive as in a randomized clinical trial.

Macitentan has been the first drug demonstrating a long-term effect on the outcomes in PAH in addition to improvements in FC and exercise capacity. Several publications (from basic science to RCTs) have illustrated and supported the evidence on the efficacy and safety of this drug. In our trial the mortality rate was of 6% per year, data consistent with intermediate risk patients with PAH.

This study represents the first report on the clinical impact of Macitentan in South America which makes the study even more robust when considering the small number of patients from this region in the SERAPHIN study. Moreover, although our population is similar to that of the SERAPHIN study in terms of baseline characteristics, patients with more advanced FC were included in our experience, which confirms the benefits in more advanced stages of the disease.

The analysis of FC and 6MWT distance is an accessible method to assess both response to treatment and prognosis which are widely used as clinical variables in the follow-up. However, we also recognize the value of other clinical, echocardiographic or hemodynamic tools to predict risk in PH. These variables should also be used to stratify patients and were not reported in our study.

This study has certain limitations. First, this registry lacks certain prognostic data such as neurohormonal or hemodynamic variables. This may be because it is a national registry in the context of a heterogeneous health system, which also makes data collection difficult in the follow-up. Also, a remarkable loss of information at 6 and 12 months was seen. In addition, as an open cohort, the beneficial impact of Macitentan may be attributed to another pharmacological intervention in the follow-up.

Based on these results we are reporting not only our experience in the daily clinical practice but also findings that are consistent with the improvement of the FC and the 6MWT distance observed in the SERAPHIN trial.

Therefore, further similar studies should be conducted in the real world, perhaps with larger samples and considering clinical events such as hospitalizations or mortality during follow-up.

Conclusion

In this study, treatment with Macitentan was associated with a significant clinical benefit, assessed by the improvement in functional class and in the 6MWT distance, at 6 and 12 months. This data is consistent with the results of the SERAPHIN trial and represents the first contribution to the knowledge of the effect of this drug in the real world setting in our region.

Declarations

- Ethics approval and consent to participate: The protocol was approved by the independent central ethics committee and all patients provided written informed consent before participation.
- Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.
- Conflicts of Interest: All authors have no conflicts of interest to declare.
- Funding: without financing
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Declarations

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