Original Article

The clinical experience of macitentan in pulmonary hypertension in Indian cohort: 12-month follow-up

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ABSTRACT

Background: The effectiveness and safety of macitentan, an endothelin-receptor antagonist (ERA) in the treatment of pulmonary arterial hypertension (PAH), has been demonstrated in numerous randomized clinical trials including SERAPHIN, focused on the reduction of morbidity and mortality. **Objectives:** Our aim was to demonstrate the clinical and echocardiographic progression using macitentan in Indian patients with PAH. **Settings and Design:** It was a retrospective study of 20 patients with multiple etiologies of PAH who had begun macitentan in routine clinical practice from a single center. There were 55% of patients with existing PAH therapies. **Subjects and Methods:** The World Health Organization functional class (WHO-FC), 6-min walking distance, N-terminal prohormone of brain natriuretic peptide level (NT-pro-BNP), and echocardiographic data such as tricuspid annular plane systolic excursion (TAPSE), systolic pulmonary artery pressure (sPAP), and the occurrence of pericardial effusion were collected at baseline and 12-month follow-up. The statistical analysis was performed using SPSS software. **Results:** Of the 20 PAH patients, 70% were women. The majority were in WHO FC II (50%), while 35% were in FC III and 15% were in FC IV. The mean age was 43.4 years at the start of the therapy with macitentan. After 6 months of macitentan therapy, 85% showed substantial improvement in their FC, each increased its 6-min walking distance test ($P < 0.0001$), and there was a significant reduction in plasma levels of NT-pro BNP ($P < 0.0001$). There has also been an improvement in echocardiographic parameters such as TAPSE and sPAP ($P < 0.0001$). **Conclusions:** Our findings indicate that macitentan has been well tolerated and beneficial in Indian patients with PAH and further, future research is required to verify these results.

KEY WORDS: Echocardiography, endothelin-receptor antagonist, macitentan, N-terminal prohormone of brain natriuretic peptide, pulmonary arterial hypertension, pulmonary hypertension

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INTRODUCTION

Macitentan is an orally effective, unique, highly potent, tissue-specific endothelin-receptor antagonist (ERA) with improved endothelin-receptor occupancy compared to other ERAs.[1,2] It is essential for the long-term pharmacological management of pulmonary arterial hypertension (PAH) because of its better safety profile with less drug interaction as compared to other pharmacological therapies currently available for PAH.[3] Macitentan is the first PAH drug approved after a long-term, event-oriented clinical trial and as per the current ESC/ERS guidelines on PAH, it is indicated as a monotherapy or in a concurrent combination for PAH patients in WHO-FC II and III.[4-6] These guidelines established a new 1-year mortality risk assessment for PAH patients, categorizing patients as low, moderate, or high risk, taking into consideration clinical criteria, activity, and cardiac imaging. The validity of most of the criteria included was demonstrated at diagnosis in risk assessment, but their validity during follow-up of patients is unknown. However, other parameters such as age, sex, or etiology of PAH are not considered.[5] Our aim was to describe a single center's experience of the 12-month utilization of macitentan in patients with PAH in the clinical practice setting.

SUBJECTS AND METHODS

In this retrospective observational cohort study, we included all consecutive PAH patients in WHO-FC II–IV treated with macitentan under routine clinical practice in the Department of Cardiology, Yashoda Hospitals, Somajiguda, Hyderabad, India. This is a multidisciplinary unit coordinated by the cardiology, pulmonology, rheumatology, internal medicine, and other services, with a specialized outpatient department.

Determination of all patients' functional class was performed by two trained physicians. In case of a discrepancy, a third physician was consulted. Echocardiography was performed with Epiq ultrasound system (Philips) according to the guidelines. We followed the guideline protocol from the British Society of Echocardiography for the echocardiographic assessment of PAH.[7] If a reasonably good quality signal is able to measure peak tricuspid regurgitation velocity higher than 3.4 m/s, there is a strong chance that there may be PAH. Peak systolic pulmonary artery pressure (sPAP) more than 70 mm Hg was defined as severe pulmonary hypertension. Three consecutive cycles were averaged for each TAPSE.

Patients were followed from baseline till 12 months after macitentan initiation or to the last available information. Follow-up consisted of regular outpatient clinic visits alternating between a pulmonologist and cardiologist every 3 months. Outcomes of interest were the currently used secondary determinants of prognosis: history of syncope, World Health Organization functional class (WHO-FC) III or IV, 6-min walk distance (6MWD), N-terminal prohormone of brain natriuretic peptide (NT-pro-BNP), and tricuspid annular plane systolic excursion (TAPSE).

Follow-up assessments for this study were collected annually (from baseline) from the outpatient visit closest to 1-year follow-up dates. At baseline and after 12 months of treatment with macitentan, we reported relevant clinical, echocardiographic parameters, and medication safety. We classified the documented baseline and 12-month clinical variables in low-, medium-, and high-risk groups using the risk assessment table described in the 2015 ESC/ERS Guidelines. This classification serves as a pure benchmark given the uncertainty of PAH and the restricted applicability of the suggested cutoff values in real-world practice. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in *a priori* approval by the institution's human research committee. Informed consent was not required, as all investigations were performed for routine clinical care.

RESULTS

Twenty patients were treated with macitentan for 12 months between June 2019 and June 2020. The demographics, clinical characteristics, and administered treatments at baseline are shown in Table 1. Three patients with connective tissue-associated PAH presented with systemic scleroderma, systemic lupus erythematosus, and mixed connective tissue disorder. Three patients presented with ventricular septal defect, atrial septal defect, and patent ductus arteriosus, with persistent PAH (Eisenmenger's syndrome). Two patients presented with HIV infection-associated PAH and five patients were diagnosed with idiopathic PAH.

Before the initiation of therapy, 50% of patients were in WHO-FC II, 35% in class III, and 15% in class IV. About 40% of patients were treatment-naïve and macitentan was the first ERA. A sequential combination with macitentan plus phosphodiesterase-5 inhibitor (PDE5i) in 35% of those was already prescribed a PDE5i after not reaching therapeutic objectives. About 25% of patients had previous exposure to other ERAs such as ambrisentan (15%) and bosentan (10%). The switch over to macitentan was due

Table 1: Characteristics of patients at initiation of macitentan

Demographic characteristics	*n* (%)
Age (years), mean±SD	43.4
Female	11 (70)
Etiology of PAH	
Idiopathic	5 (25)
Connective tissue disorder	2 (10)
HIV	2 (10)
Congenital heart disease with Eisenmenger syndrome	3 (15)
Obstructive sleep apnea	4 (20)
Chronic pulmonary thromboembolism	3 (15)
Treatment at baseline	
Macitentan monotherapy	8 (40)
Macitentan + sildenafil/tadalafil	7 (35)
Switched over from other ERAs	5 (25)

SD: Standard deviation, PAH: Pulmonary arterial hypertension, ERA: Endothelin-receptor antagonist

to hepatotoxicity or no significant improvement with those ERAs.

Among 20 included patients, mean FC improved from 2.65 ± 0.75 to 1.45 ± 0.51 ($P < 0.0001$) [Figure 1]. The mean 6MWD improved from 331.65 ± 105.88 m to 436.65 ± 125.25 m ($P < 0.0001$). Furthermore, levels of plasma NT-pro-BNP were lowered from 549.74 pg/l interquartile range (IQR) 173.5–965.75) to 205.45 pg/l (IQR 38.36–207.17; $P < 0.0001$). Echocardiographic parameters such as sPAP reduced from 80.5 mm Hg (IQR 72.5–89.75) to 49.9 mm Hg (IQR 42.55–63; $P < 0.0001$), while there was improvement in TAPSE from 1.95 mm (IQR 1.525–2.275) to 2.1 mm (IQR 1.8–2.3; $P < 0.0001$). The improvement in the various parameters as described above is summarized in Table 2, whereas the pericardial effusion observed in 6 patients [30%] at baseline was not present after 12 month. After 12 months of treatment with macitentan, no cases resulted in hospitalization, or death.

Safety profile

Two patients suffered minor adverse effects such as nausea and nasal congestion and other cases had mild elevation of liver enzymes. All the cases normalized after symptomatic treatment. Furthermore, of worth noting is the good safety and tolerability observed.[8] In patients with multiple medications used for the medical management of the acquired immunodeficiency syndrome, the stability of the viral load and CD4 levels and the lack of drug–drug interactions between macitentan and the antiretrovirals used in patients with HIV-related PAH indicate a safety advantage. Neither macitentan nor its active metabolite has clinically significant inducer or inhibitory effects on cytochrome enzymes P450, and macitentan has a favorable hepatic safety profile relative to other ERAs.[9]

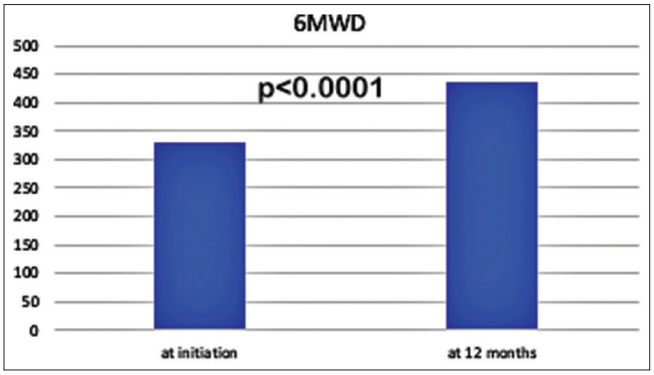

Figure 1: Comparison of World Health Organization functional class at baseline and 12-month follow-up

DISCUSSION

Current PAH therapy is not just long-term drug administration. Guidelines recommend close monitoring and individualized patient management. The aim of the treatment in PAH patients is to achieve a low-risk status associated with a 1-year mortality risk of <5%. However, this risk classification and therapeutic goals are not yet evident and need to be defined in subsequent studies.

After 12 months of macitentan treatment in patients with PAH in specific clinical conditions, preliminary findings from a single-center analysis showed a significant change in their clinical findings. This beneficial development was found in etiologies and clinical approaches, and regardless of previous therapies.[10-12] Progressively, clinical changes were also reported in the 5 patients who were previously treated with bosentan and ambrisentan and were associated with reasonable tolerability, consistent with recent publication reports, without elevation of liver enzymes.[10]

No cases lead to hospitalization due to worsening of PAH, or death after 12 months of therapy. Such findings correspond with the composite secondary endpoints of the SERAPHIN study (decrease in PAH related mortality or hospitalization), where the likelihood of these events decreased substantially by 50% ($P < 0.001$); however, the sample size and attributes vary and caution when contrasting them should be regarded.[13]

While patients were managed in a routine clinical care setting and had specific medical histories and demographic features, none of the assessed metrics were categorized under the high-risk group as specified in ESC/ERS recommendations for 2015 after 1 year of macitentan therapy. In addition, all parameters categorized as intermediate risk sustained or boosted their category of risk, and the low-risk features persisted under such classification.[6]

Study limitations

The reduced number of patients, single-center experience, and retrospective analysis, limiting its significance and potency. Furthermore, invasive catheterization was not performed progressed, and there is a lack of evidence that a regular catheterization in treated patients is associated

Table 2: Clinical and echocardiographic characteristics at the initiation and after 6 months of macitentan therapy

Variables	At initiation, median	IQR	At 12 months, median	IQR	*P*
6MWD (m)	336.5	280.70-382.60	447.5	378.03-495.27	<0.0001
NT-pro-BNP (pg/mL)	549.74	173.5-965.75	205.45	38.36-207.17	<0.0001
sPAP (mmHg)	80.5	72.5-89.75	49.9	42.55-63.0	<0.0001
TAPSE (mm)	1.95	1.525-2.275	2.1	1.8-2.3	<0.0001

IQR: Interquartile range, 6MWD: 6-min walking distance, NT-pro-BNP: N-terminal prohormone of brain natriuretic peptide, sPAP: Systolic pulmonary artery pressure, TAPSE: Tricuspid annular plane systolic excursion

with increased survival, especially if the other parameters are at low to intermediate risk levels. In our clinical practice, catheterization is not systematically performed unless we observed an unexplained clinical worsening, or a treatment decision can be expected from the results as baseline poor prognosis was not solely determined by hemodynamic criteria.

CONCLUSION

A significant improvement can be achieved in various clinical, echocardiographic parameters in a series of Indian patients with multiple PAH subclasses treated with macitentan for 12 months, with a significantly improved safety profile. These findings were found, regardless of the patient's previous pharmacological therapies. Such results need to be corroborated by further randomized controlled trials with longer follow-up periods. A significant improvement can be achieved in various clinical, echocardiographic parameters in a series of Indian patients with multiple PAH subclasses treated with macitentan for 12 months, with a significantly improved safety profile. These findings were found, regardless of the patient's previous pharmacological therapies. Such results need to be corroborated by further randomized controlled trials with longer follow-up periods.

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Conflicts of interest
There are no conflicts of interest.

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