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Impact of Macitentan on the Health-Related Quality of Life in Pulmonary Arterial Hypertension in an Iranian Population

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Abstract

Background: Pulmonary arterial hypertension is a progressive disease of the lung vascular system which causes patients' functional limitations and reduces their Health-Related Quality of Life (HRQoL). This study was aimed at determining the effectiveness of Macitentan on the HRQoL of Iranian PAH patients by the emphasis 10 questionnaire.

Methods: 31 idiopathic class I pulmonary hypertension patients were enrolled in this cohort study. Patients completed the emphasis 10 questionnaire at baseline and 6 months after Macitentan consumption. The absolute changes in emphasis 10 scores were calculated. The effect of Macitentan on functional activity and paraclinical indexes was assessed.

Results: The mean quality of life scores before and after the Macitentan, were 25.83 (±11.80 SD) and 16.93 (±10.36 SD), respectively (p-value=0.001). Besides, administration of Macitentan increased the mean distance in the 6-minute walk test, from 227.00±(87.275 SD) to 263.67 (±115.855 SD) (p-value=0.044), led to a reduction in the mean hospitalization days from 2.23 (±4.049 SD) to 0.33 (±1.322 SD), (p-value=0.015) and reduction in times of hospitalization from 0.57(0.93) to 0.10(0.30), (p-value=0.017). Although it had a positive effect on mean PAP (81 to 68), O2 saturation at the beginning of 6MW (90 to 91%), final O2 Saturation in 6MW (81 to 85%), and pro-BNP (907 to 412), this effect was not statistically significant.

Conclusion: Treatment with Macitentan significantly improved patient functional activity and reduced the mean hospitalization days. Thus, due to the low side effects and high efficacy, it can be advised as the first line of treatment.

Keywords: Emphasis, Macitentan, Pulmonary hypertension, Quality of life

Introduction

Pulmonary Arterial Hypertension (PAH) is a progressive disease of the lung vascular system. A combination of dysfunctions in endothelium and small pulmonary arteries, and in situ thrombosis leads to narrowing of the blood vessels. This causes resistance to blood flow and an increase in pulmonary artery pressures (1–3); which leads to symptoms, including dyspnea and fatigue, and patients' functional limitations and reduces their Health-Related Quality of Life (HRQoL). The symptoms not only affect the physical aspects of patients' HRQoL but also social, economic, emotional, and psychological aspects (4–6). The goals for treating PAH are to improve patient symptoms, enhance functional capacity, slow the progression of the disease and prolong life; and the clinical response should be reassessed 3–6 months after the initial treatment based on different parameters, such as functional class, exercise capacity, biomarkers, echocardiography, and hemodynamic parameters (7,8). Macitentan, as a dual endothelin receptor antagonist, is one of the drugs that has been approved in PAH. SERAPHIN study evaluated the effect of Macitentan on morbidity and mortality in patients with PAH. The primary endpoint was health-related quality of life; and time to first morbidity/mortality event; changes in exercise capacity, World Health Organization (WHO) Functional Class (FC), and PAH-related death or hospitalization, were examined as secondary endpoints. It was the first study in the Iranian population to demonstrate that Macitentan reduces PAH-related hospitalizations and provides further evidence of the long-term clinical benefits (9).

The importance of improving the quality of life of chronic diseases such as PAH has increasingly been recognized in recent years. The most recent PAH guidelines recommended the psychological, social, emotional, and spiritual needs of patients to be addressed by the healthcare provider teams (10).

Various HRQoL instruments have been employed to measure the effects of PAH on patients' daily lives, and most of them are non-PAH-specific measures (11). More recently, other instruments, like emphasis-10 (12), and PAH-SYMPACT® (13), have also been developed to allow the adequate collection of patient-reported information on health status. This study aims to determine the effectiveness of Macitentan on the HRQoL of Iranian PAH patients by the emphasis 10 questionnaire.

Materials and Methods

Study design

This is a cohort study of consecutive patients with documented PAH followed at a tertiary care center in Iran. The patients were asked to complete the emphasis 10 questionnaire aimed at assessing their HRQoL before and after the consumption of Macitentan, and to complete a basic questionnaire on their demographic and clinical characteristics. Emphasis 10 questionnaire is freely available for clinical and academic use (12,14). Disease-specific clinical measures, including distance in 6MW (*m*), O2 Saturation in 6MW test (%) at the beginning of the study, final O_2 saturation in 6MW test (%), PAP in echocardiography (*mmHg*), pro-BNP, times of hospitalization, and duration of hospitalization (days), were retrieved during follow-up and from the hospital medical records. This study was approved by the Iran National Committee for Ethics in Biomedical Research (IR.SBMU.NRITLD.REC.1400.026) and followed the ethical guidelines outlined in the 1975 Helsinki Declaration. Informed consent was obtained for all the study participants before inclusion in the study.

Patient population

Patients were eligible to participate in the study if they were definite pulmonary hypertension patients, idiopathic class I based on the WHO classification of pulmonary hypertension, and despite standard treatment, were still symptomatic.

Data collection and instruments

The participants were asked to complete two questionnaires: (1) emphasis 10, (2) and a general demographic/clinical questionnaire, which evaluated age, gender, marriage status, employment status, time to diagnosis, time to treatment, time to starting Macitentan, and underlying diseases. Clinical and laboratory data were retrieved from a computerized database and patients' files.

Emphasis 10

Emphasis 10 was developed as a measure to assess the impact of Pulmonary Hypertension (PH) on HRQoL.

Table 1. Demographic data

Variables	N/% or Mean (SD) or Median [P25;P75]
Age	43(11.9)
Female Gender	27(87%)
Married	23(74%)
Employed	9(29%)
D1(months) (Symptom duration up to starting assessment)	13.4 (24.2) 2.5 [0;14]
D2(months) (Time from starting symptoms to final diagnosis)	17.7(24.5) 9 [1;24]
D3(months) (Time from definite diagnosis to starting treatment)	17.7(24.5) 9 [1;24]
D4(months) (Time from standard treatment to starting Macitentan)	85.2 (72.5) 55 [33;139]
D5(days) (Macitentan consumption duration)	103.1(69.6) 97 [41;147]
D6(months) (Total disease duration: from symptom to ending study)	111.6(67.8) 104 [49;152]
Comorbidities	17(54%)
Diabetic mellitus	3(9.7%)
Hypertension	2(6.5%)
Other heart diseases	6(19.4%)
GI disease	5(16.1%)
Hypothyroidism	5(16.1%)
Renal disease	2(6.5%)
Liver cirrhosis	1(3.2%)
Sarcoidosis	1(3.2%)
Others	5(16.1%)

Table 2. Complications of Macitentan

Complication	Frequency
Headache	7(23%)
Anemia	3(10%)
Gastro-intestinal problems	10(32%)
Peripheral edema	6(19%)
Weight loss	1(3%)
Dry skin	1(3%)
Flashing	1(3%)
Anorexia	1(3%)

It is a short and validated instrument that can be used in routine clinical practice and consists of 10 items formatted as a semantic six-point differential scale (12).

Statistical analysis

Statistical analysis was performed employing SPSS 21. Qualitative data were expressed as proportions and quantitative variables were expressed as means and SD or median and IQR for normal or non-normal distribution, respectively. ANOVA followed by POST HOC test (scheffe) was utilized after normal-distribution-confirmation regarding Kolmogorov–Smirnov test. Kruskal-walis test for the quantitative non-parametric variable and Chi-Square for categorical variables were applied. In all analysis confidence interval of 95% and significant level of 0.05 were considered.

Results

Study population characteristics

31 idiopathic class I pulmonary hypertension patients were included in this study; the patients' population was predominantly female (87%), and had a mean age of 43 (11.9) years. Table 1 contains the demographic and baseline clinical characteristics of the patients

Table 3. The effect of Macitentan on patient functional activity

Variables	Before Macitentan Mean±SD	3 months after Macitentan Mean±SD	p-value
Quality of life score(emphasis)	25.83(11.80)	16.93(10.36)	0.001*
Distance in 6MW (*m*)	227.00(87.27)	263.67(115.85)	0.044*
O2 Saturation at the beginning of 6MW (%)	90(4)	91(1)	0.50
Final O2 Saturation in 6MW (%)	81(7)	85(6)	0.40
PAP in echocardiography (*mmHg*)	81(19)	68 (45)	0.63
Pro-BNP	907(979)	412(214)	0.33
Times of hospitalization	0.57(0.93)	0.10(0.30)	0.017*
Duration of hospitalization(days)	2.23(4.05)	0.33(1.32)	0.015*

enrolled. The most frequent comorbidity was heart disease (19.4%), the mean symptom duration up to starting assessment was 2.5 (0; 14) months, time from starting symptoms to final diagnosis was 9 (1; 24] months, time from definite diagnosis to starting treatment was 9 (1; 24) months, time from standard treatment to starting Macitentan was 55 (33; 139) months, Macitentan consumption duration was 97 (41; 147) days, and total disease duration from symptom to ending study was 104 (49; 152) months. The patients had some transient side effects following the first dose of Macitentan, which were revealed with supportive measures, and no side effects led to the discontinuation of the drug. Gastrointestinal problems were the most prevalent side effects (32%) (Table 2). McNemar's analysis showed that with the start of Macitentan, the need for high doses of sildenafil, tadalafil, and ilomedin was reduced dramatically (p-value<0.001) (Figure 1).

Health-related quality of life assessed through emphasis 10

The emphasis-10 is a short questionnaire consisting of 10 questions for assessing HRQoL in pulmonary arterial hypertension which was shown in figure 2. The first question is feeling frustrated due to severe shortness of breath. The second question is interrupting conversations due to shortness of breath. The third question is the need to rest during the day. The fourth question is the feeling of constant exhaustion. Question five is the lack of energy. Question six is feeling severe breathless during climbing stairs. Question seven is lack of confidence in crowded or public places. Question eight is about controlling life. Question nine is about complete dependence. Question ten is about feeling overwhelmed. The first six questions were related to physical aspects and the severity of the disease and the next four questions were related to the patients' psychological aspects and personalities. The evaluation of the emphasis 10 questionnaire showed that this drug caused a significant improvement in the quality of life of these patients, the mean quality of life scores before and after the Macitentan, were 25.83 (±11.80 SD) and 16.93 (±10.36 SD), respectively. Macitentan made significant changes in all areas, but most of the changes were associated with the first, second, and sixth questions (p-value=0.001) (Figure 2).

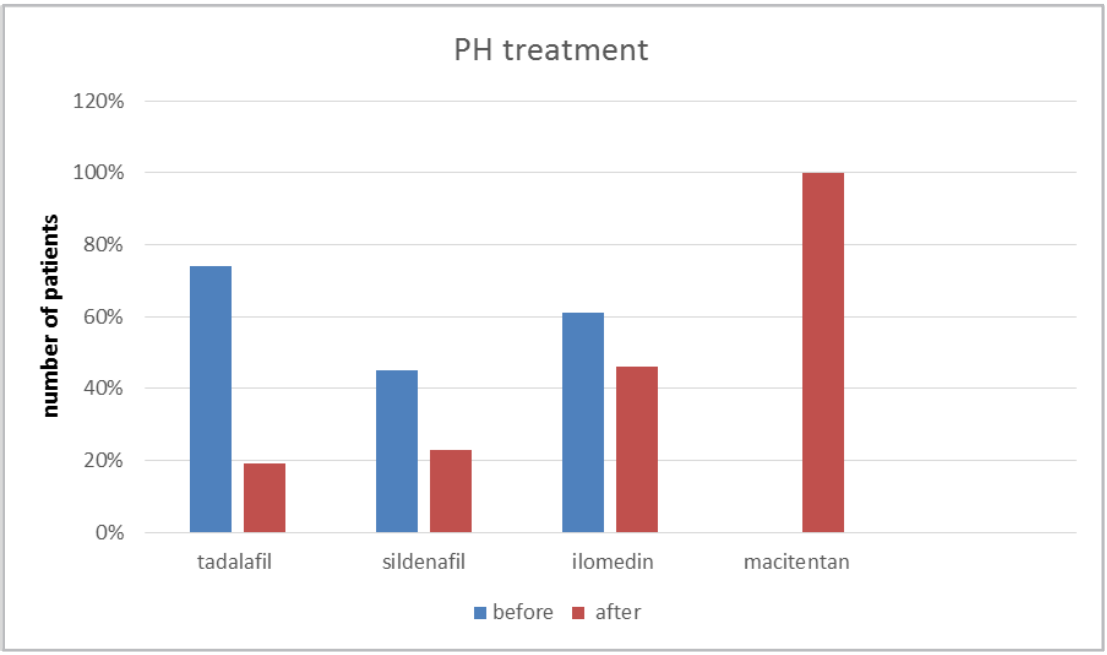

Figure 1. The effect of Macitentan on combination therapy.

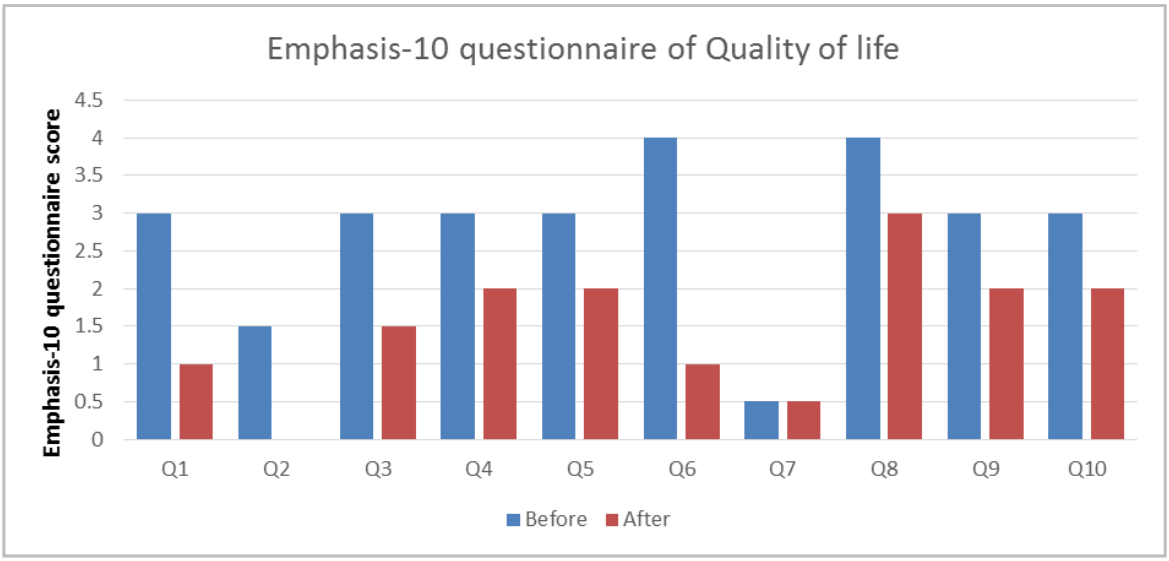

Figure 2. Improvement in HRQoL based on the emphasis -10 questionnaire.

Change in paraclinical findings

Table 3 contains the effect of Macitentan on quality-of-life score based on emphasis 10 questionnaire, patients' functional activity including distance in 6MW (m), first O2 saturation in 6MW (%), final O2 saturation in 6MW (%), PAP in echocardiography (*mmHg*), pro-BNP, times of hospitalization, and duration of hospitalization (days).

In addition to significant improvement in the quality of life, administration of Macitentan increased the mean distance in the 6-minute walk test, from 227.00± (87.275 SD) to 263.67 (±115.855 SD) (p-value=0.044), led to a reduction in the mean hospitalization days from 2.23 (±4.049 SD) to 0.33 (±1.322 SD), (p-value=0.015) and reduction in times of hospitalization from 0.57(0.93) to 0.10(0.30), (p-value=0.017). Although it had a positive effect on mean PAP (81 to 68) (p-value=0.63), O2 saturation at the beginning of 6MW (90 to 91%) (p-value=0.05),

final O2 saturation in 6MW (81 to 85%) (p-value=0.4), and pro-BNP (907 to 412) (p-value=0.33), this effect was not statistically significant.

Discussion

In this study, the evaluation of the emphasis 10 questionnaire showed that meanwhile, Macitentan caused a significant improvement in the patients' quality of life, the greatest effect of the drug was associated with physical aspects and the severity of the disease and not in the aspects related to the psychological and personality dimensions. Macitentan also improved patients' functional activity including mean distance in the 6-minute walk test, mean hospitalization days, and times of hospitalization significantly. Although it had positive effect on mean PAP during 6 months follow-up, O_2 saturation at the beginning of 6MW (%), final O_2 Saturation in 6MW (%), and pro-BNP, this effect was not statistically significant maybe due to small sample size of this study.

Improvement in HRQoL has been reported to different degrees, but comparisons between studies are challenging because of differences in trial design and variation in drugs and the instruments used to assess HRQoL (15). One systematic review study confirms that in several RCTs, the PAH-specific therapies improve HRQoL as an outcome measure; however, any firm conclusion about the clinical significance of these improvements is difficult (15).

SERAPHIN, using the SF-36 questionnaire, is the first study to demonstrate the benefit of Macitentan as PAH-targeted therapy, same as our study. It improved both the physical and mental component summary scores (4). Lower rates of hospitalization, as a significant treatment effect, were also observed in the Macitentan groups than in the placebo group (9).

In our study, there was also a remarkable correlation between the administration of macitenten and the rate of hospitalizations. Also, in Channick *et al* and SERAPHIN studies, Macitentan significantly reduced the risk and rate of all-cause hospitalization, which was driven by reductions in the risk and rate of PAH-related hospitalization (16).

Based on a meta-analysis of randomized controlled trials in pulmonary arterial hypertension, the 6MWD alone or in combination, was the primary endpoint in 17 studies (17); and investigational treatments significantly improved exercise capacity as assessed by the 6 MWD. In this study, administration of Macitentan increased the distance in the 6-minute walk test.

Joanna Pepke-Zaba *et al* study demonstrated that treatment with sildenafil in addition to significant improvements in exercise capacity also had significant benefits in HRQoL in patients with PAH (18). HRQoL was recorded by patients using the SF-36 and EQ-5D questionnaires at baseline and after 12 and 24 weeks of therapy. The baseline data confirm the considerable impairment experienced by patients with PAH. The analysis of our study showed that with the start of Macitentan, the need for high doses of sildenafil, tadalafil, and ilomedin was reduced dramatically.

Limitations

The most important limitation is that this study is a small single-center national study in comparison with other large trials. Also, although the gold standard to diagnose pulmonary arterial hypertension is right heart catheterization (RHC), there is no hemodynamic data based on this.

Conclusion

In conclusion, results from this study indicate significant improvements in HRQoL in Iranian PAH patients treated with Macitentan. Treatment with Macitentan significantly improved patients' functional activity and reduced the rate of hospitalizations and mean hospitalization days. Thus, due to the low side effects and high efficacy, it can be advised as the first line of treatment. Furthermore, it is encouraging that the importance of evaluating the impact of PAH therapies on patients' HRQoL is now well recognized. Therefore, according to the considerable efficacy of Macitentan on the quality of life of pulmonary hypertension patients, insurance organizations' support can help patients dramatically, especially in this COVID-19 pandemic situation that patients' compliance for on-time visits and follow-up may be decreased, and availability of these special efficient drugs can slow down the progression of

the disease. It remains difficult to draw any firm conclusion regarding the clinical significance of these impacts; so, further work is mandatory to explore new strategies.

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