ABSTRACT

OBJECTIVES This study sought to evaluate the effect of macitentan on hospitalization of patients with symptomatic pulmonary arterial hypertension (PAH).

BACKGROUND PAH is a progressive, life-threatening disease often requiring hospitalization.

METHODS In the multicenter, double-blind, randomized, event-driven, phase III SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve clinical outcome) trial, patients with symptomatic PAH were randomized (1:1:1) to receive placebo or 3 mg or 10 mg of macitentan. Effects of macitentan on the risk, rate, and number of hospital days for all-cause and PAH-related hospitalizations were compared with those for placebo. Risk and causes of hospitalizations unrelated to PAH were investigated.

RESULTS Of 742 randomized patients, 250 received placebo, 250 received 3 mg of macitentan, and 242 received 10 mg of macitentan; the overall median duration of treatment was 115 weeks. Risk of all-cause hospitalization was reduced by 18.9% (p = 0.1208) and 32.3% (p = 0.0051) in the macitentan 3-mg and 10-mg arm, respectively. Rates of all-cause hospitalizations and numbers of hospital days were reduced by 20.5% (p = 0.0378) and 30.6% (p = 0.0278), respectively, with 3 mg of macitentan and by 33.1% (p = 0.0005) and 31.0% (p = 0.0336), respectively, with 10 mg of macitentan. Risk of PAH-related hospitalizations were reduced by 42.7% (p = 0.0015) and 51.6% (p < 0.0001) in the macitentan 3-mg and 10-mg arms, respectively. Rate of PAH-related hospitalizations and numbers of hospital days were reduced by 44.5% (p = 0.0004) and 53.3% (p = 0.0001), respectively, with 3 mg of macitentan, and reduced by 49.8% (p < 0.0001) and 52.3% (p = 0.0003), respectively, with 10 mg of macitentan. Risk of non-PAH-related hospitalization was similar between treatment arms.

CONCLUSIONS Macitentan 10 mg significantly reduced the risk and rate of all-cause hospitalization, which was driven by reductions in the risk and rate of PAH-related hospitalization. (Study of Macitentan [ACT-064992] on Morbidity and Mortality in Patients With Symptomatic Pulmonary Arterial Hypertension; NCT00660179) (J Am Coll Cardiol HF 2015;3:1–8) © 2015 by the American College of Cardiology Foundation.
Pulmonary arterial hypertension (PAH) is a progressive, life-threatening disease that affects the pulmonary vasculature (1). The disease is characterized by sustained elevation of pulmonary vascular resistance ultimately resulting in right heart failure due to the inability of right ventricular contractility to adapt to the increasing afterload. Mortality rates in PAH are still high despite improvements in patient survival since the introduction of PAH-specific therapies (2-4).

The progressive nature of PAH means that morbidity events associated with the disease and the initiation of new PAH therapies can require hospitalization of patients (5). Hospitalization has a negative impact on patients’ quality of life and an adverse effect on the lives of their caregivers and represents a substantial health care burden (6). Data from the REVEAL (Registry to Evaluate Early And Long-term PAH Disease Management) registry showed that patients who were hospitalized for PAH were more likely to be rehospitalized and had worse survival at 3 years than those who were not hospitalized (7). Despite this considerable impact, information describing the effect of PAH-specific therapies on hospitalization is limited. Most randomized controlled trials in PAH have included PAH-related hospitalization as a component of secondary or exploratory “time to clinical worsening” endpoints and have captured only a relatively low number of hospitalizations due to low numbers of patients and short durations (12 to 24 weeks) (8-16). Therefore, it has not been possible to determine reliable annual rates of hospitalization from these studies.

Macitentan is a novel dual endothelin receptor antagonist with sustained receptor binding and enhanced tissue penetration (17,18). In the first event-driven, randomized controlled outcomes study in PAH, the SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve clinical outcome) trial, the risk of morbidity and mortality events (the primary endpoint) was significantly reduced by 30% with 3 mg of macitentan (p = 0.01) and by 45% with 10 mg of macitentan (p<0.001) compared to that with placebo (19). A composite secondary endpoint of “death due to PAH or hospitalization for PAH” was included in SERAPHIN, and the risk of such events was significantly reduced by 33% with 3 mg of macitentan (p = 0.01) and by 50% with 10 mg of macitentan (p < 0.001) compared with those with placebo (19).

Findings of the composite endpoint of death due to PAH or hospitalization for PAH suggest a marked effect on PAH-related hospitalizations. Therefore, we investigated the effect of macitentan on the risk, rate, and number of hospital days for all-cause and...
PAH-related hospitalizations. In addition, we examined the risk and causes of hospitalizations unrelated to PAH that occurred during the SERAPHIN trial.

METHODS

PATIENT POPULATION. Patients ≥12 years of age with World Health Organization (WHO) group 1 pulmonary hypertension diagnosed by right heart catheterization as idiopathic or heritable PAH, or diagnosed as PAH related to connective tissue disease, repaired simple congenital systemic-to-pulmonary shunts, human immunodeficiency virus infection, or drugs and toxins were included if they were in WHO functional classes (WHO FC) II to IV and had a 6-min walk distance ≥50 m. Previous diagnosis of PAH by right heart catheterization was required (mean pulmonary artery pressure of >25 mm Hg; pulmonary capillary wedge pressure of ≤15 mm Hg; pulmonary vascular resistance of ≥320 dyn·s·cm⁻⁵). Patients could be either treatment-naïve or receiving a stable dose of phosphodiesterase type 5 inhibitors, oral or inhaled prostanooids, calcium channel blockers, or L-arginine. Patients receiving endothelin receptor antagonists or intravenous or subcutaneous prostanooids were excluded.

Local institutional review boards or independent ethics committees approved the protocol, and written informed consent was obtained from all patients.

STUDY DESIGN. SERAPHIN was a multicenter, double-blind, randomized, placebo-controlled, event-driven, phase III trial (NCT00660179). The study design was described in detail previously (19). Briefly, patients were randomized (1:1:1) after screening to receive either placebo, 3 mg of macitentan, or 10 mg of macitentan once daily. Treatment was continued until patients experienced a primary endpoint event or until 285 confirmed events had occurred (end of study). Patients who had a nonfatal primary endpoint event and discontinued double-blind treatment were eligible to receive open-label macitentan at a dose of 10 mg, as were patients who were receiving the double-blind treatment until the end of the study.

OUTCOME MEASURES. The effects of macitentan on the time to first all-cause hospitalization and time to first PAH-related hospitalization up to the end of treatment were assessed by post-hoc analyses of all patients. The potential impact of sex, race, PAH therapy at baseline, PAH cause, and WHO FC at baseline was evaluated by exploratory subgroup analyses. The effect of macitentan on the total number of both all-cause and PAH-related hospitalizations...
per patient-year was also analyzed, as was the
total number of hospital days per patient-year. In
addition, the effect of macitentan on the time to first
non-PAH-related hospitalization was also assessed by
post-hoc analysis of all patients, and the causes of
these hospitalizations were examined. Whether PAH
was the cause of hospitalization was determined at
the discretion of the investigator.

STATISTICAL METHODS. All time-to-event endpoints
occurring in the intention-to-treat (all-randomized)
set were analyzed using the Kaplan-Meier method
and the log-rank test. Patients who stopped blinded
treatment without an event were censored at the time
of treatment discontinuation. Treatment effects were
expressed in terms of risk reductions and were pre-
sented using hazard ratios (HRs) and 95% con
fidence intervals (CIs) calculated from Cox regression models.
Exploratory subgroup analyses on the basis of pre-
specified baseline characteristics were performed
for time to all-cause hospitalization and time to
PAH-related hospitalization endpoints by means of
forest plots and interaction tests (20).

Rates of hospitalization and numbers of hos-
pital days (for both all-cause and PAH-related hospi-
talizations) up to end of treatment were assessed
descriptively in terms of patient-years of exposure in
each treatment arm and analyzed using generalized
linear regression models for count data. Pairwise
comparison versus placebo for each macitentan dose
was obtained using a Poisson regression model for the
rates of hospitalization and using a hurdle negative
binomial model for the number of hospital days (21).

RESULTS

PATIENTS AND TREATMENTS. In the SERAPHIN trial,
742 patients from 151 centers in 39 countries were ran-
domized to receive placebo (n = 250) or 3 mg (n = 250)
or 10 mg of macitentan (n = 242) and were included in
the intention-to-treat analyses. Patient demographics
and baseline characteristics were similar across the 3
treatment arms: patients were predominantly female
(76.5%), had a mean age of 45.6 ± 16.1 years, and had
predominantly idiopathic PAH (55%) or PAH associated
with connective tissue disease (30.5%), and the mean
time from PAH diagnosis was 2.7 ± 4.0 years (18). The
overall median duration of treatment was 115 weeks
(19). The safety profile of macitentan has been reported
previously: the most common adverse events in the
macitentan arms were nasopharyngitis, headache, ane-
mia, and bronchitis (19).

ALL-CAUSE HOSPITALIZATION. There were 117
(46.8%), 104 (41.6%), and 90 (37.2%) patients in the
placebo, macitentan 3-mg, and 10-mg arms, respec-
tively, who were hospitalized for any cause at least
once during double-blind treatment, and they expe-
r i e n c e dat o t a lo f1 7 1 ,1 5 9 ,a n d1 3 5a l l - c a u s eh o s p i t a l-
izations, respectively. Compared with that of placebo,
the risk of all-cause hospitalization with 3 mg of
macitentan was reduced by 18.9% (HR: 0.811; 95%
CI: 0.623 to 1.057; p = 0.1208) and with 10 mg
of macitentan by 32.3% (HR: 0.677; 95% CI: 0.514 to
0.891; p = 0.0051) (Figure 1).

Analysis does not suggest a signi
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cant treatment
effect of 3 mg of macitentan on the risk of all-cause
hospitalization in any of the subgroups of sex, race,
PAH therapy at baseline, PAH cause, and WHO FC at
baseline (Figure 2A). The magnitude of the risk
reduction observed in the macitentan 10-mg arm was
consistent across patient subgroups categorized
according to sex, race, or PAH cause (Figure 2B).
Patients not receiving PAH therapy at baseline and
patients categorized as WHO FC III/IV displayed a
more pronounced reduction in risk than those
receiving PAH therapy at baseline or those catego-
rized as WHO FC I/II, respectively.

Rates of all-cause hospitalization per 100 patient-
years were 41.5, 33.0, and 27.7 in the placebo, maci-
tentan 3-mg, and 10-mg arms, respectively. Compared
with placebo, the rate of all-cause hospitalization
was reduced by 20.5% with 3 mg of macitentan
and by 33.1% with 10 mg of macitentan (p = 0.0005). The treatment effect was similar when adjustment was made for WHO FC at baseline (data not shown).

The mean number of hospital days for all-cause hospitalizations were 4.1, 2.9, and 2.8 days in the placebo, macitentan 3-mg, and 10-mg arms, respectively. Compared with placebo, the mean number of hospital days was reduced by 30.6% with 3 mg of macitentan (p = 0.0278) and by 31% with 10 mg of macitentan (p = 0.0336). The treatment effect was similar when adjustment was made for WHO FC at baseline (data not shown).

**PAH-RELATED HOSPITALIZATION.** There were 80 (32.0%), 53 (21.2%), and 46 (19.0%) patients in the placebo, macitentan 3-mg, and 10-mg arms, respectively, who were hospitalized at least once for PAH during the double-blind treatment period, and they experienced a total of 91, 59, and 54 PAH-related hospitalizations, respectively. Compared with placebo, the risk of PAH-related hospitalization was reduced by 42.7% in patients treated with 3 mg of macitentan (HR: 0.573; 95% CI: 0.405 to 0.811; p = 0.0015) and by 51.6% in patients treated with 10 mg of macitentan (HR: 0.484; 95% CI: 0.337 to 0.697; p < 0.0001) (Figure 3). Among the total number of hospitalizations for PAH, 75.8% (69 of 91), 71.2% (42 of 59), and 64.8% (35 of 54) occurred in conjunction with primary morbidity or mortality endpoint events in the placebo, macitentan 3-mg, and 10-mg arms, respectively. Adverse events leading to PAH-related hospitalization (Online Table 1) were primarily worsening PAH and right ventricular failure.

The treatment effect of 3 mg of macitentan on PAH-related hospitalization was consistent across patient subgroups categorized according to sex, race, PAH therapy at baseline, PAH cause, and WHO FC at baseline (Figure 4A). The treatment effect of 10 mg of macitentan was consistent across the subgroups of sex, race, PAH cause, and WHO FC at baseline (Figure 4B). Patients not receiving PAH therapy at baseline displayed a more pronounced reduction in risk than those receiving PAH therapy at baseline.

Compared with placebo, the rate of PAH-related hospitalization was reduced by 44.5% in the macitentan 3-mg arm (p = 0.0004) and by 49.8% in the 10-mg arm (p < 0.0001) (Figure 5A). Treatment effects were similar when adjustment was made for WHO FC at baseline (Figure 6A). The mean number of annual hospital days for PAH-related hospitalizations was reduced by 53.3% in the 3-mg arm (p = 0.0001) and by 52.3% in the 10-mg arm (p = 0.0003) (Figure 5B). Treatment effects were similar when adjustment was made for WHO FC at baseline (Figure 6B).

**NON–PAH-RELATED HOSPITALIZATION.** There were 57 (22.8%), 67 (26.8%), and 57 (23.6%) patients in the placebo, 3-mg, and 10-mg macitentan arms who were hospitalized for non–PAH-related causes, and they experienced a total of 80, 100, and 81 hospitalizations, respectively. The risk of hospitalizations for causes unrelated to PAH were similar between patients treated with placebo and those treated with 3 mg of macitentan (HR: 1.08; 95% CI: 0.758 to 1.537; p = 0.6703) or 10 mg of macitentan (HR: 0.890; 95% CI: 0.616 to 1.285; p = 0.5347). The most common causes of non–PAH-related hospitalizations were infections of the lower respiratory tract (pneumonia, bronchitis) and, to a lesser extent, the upper respiratory tract.
These infections were more frequent in the placebo arm (4.8% [12 of 249 patients] vs. 8% [20 of 250 patients] vs. 2.1% [5 of 242 patients], respectively).

**DISCUSSION**

Results from the SERAPHIN trial reported here are the first to demonstrate the beneficial effects of a PAH-specific therapy on hospitalization in a large population of patients over a long period of time. Previously available clinical trial data for hospitalizations report PAH-related hospitalizations only and are limited due to the short durations of the studies and the small numbers of patients enrolled. In a meta-analysis of randomized controlled trials in PAH, only 8 of 23 trials (35%) included in the analysis collected information on hospitalizations (23). Since publication of the meta-analysis, several other randomized controlled trials have included PAH-related hospitalization as part of a time-to-clinical-worsening secondary endpoint (10,11,16), but, similar to the studies included in the meta-analysis (8–10,12–15,24), these trials were all of short duration (12 to 24 weeks) and enrolled only low-to-modest numbers of patients. This lack of information has previously limited the ability to reliably calculate annual rates of hospitalization.

In these post-hoc analyses, we observed that 10 mg of macitentan reduced the risk of both all-cause and PAH-related hospitalizations, with no increase in the risk of hospitalization for causes unrelated to PAH. The absence of an effect on hospitalizations unrelated to PAH combined with the consistent results from the all-cause and PAH-related hospitalization analyses implies that there were no tolerability issues with macitentan treatment. As expected for a PAH-specific therapy, the treatment effect of macitentan was driven by a reduction in the risk and rate of PAH-related hospitalizations. Macitentan reduced the risks of PAH-related hospitalization regardless of background PAH-specific therapy. The treatment effect was more pronounced in patients not receiving PAH-specific therapy at baseline. This could be expected as patients derived some benefit from the other PAH-specific therapies, thus making an incremental benefit difficult to demonstrate in those already receiving treatment. The reduction in the rate of PAH-related hospitalization with a dose of 3 mg was similar to that with 10 mg of macitentan. This result is in contrast to that of the study’s primary endpoint in that the 10-mg dose displayed a numerically superior effect, especially in patients receiving background therapy (19).

The reduced rates of all-cause and PAH-related hospitalizations observed in the macitentan treatment arms also resulted in decreases in the number of annual hospital days experienced by these patients.
This reduction in hospital days is linked directly to the ability of macitentan to reduce the rate of PAH-related hospitalization. With regard to PAH-related hospitalizations, the number of hospital days was approximately halved with macitentan compared with placebo. This demonstrates that, on a population level, treating PAH patients with macitentan results in substantially fewer hospital days for patients. Hospitalization for PAH is a sign of clinical deterioration and represents a burden to patients and caregivers. The reduction in the rate of hospitalizations and the number of hospital days observed with 10 mg of macitentan is substantial and represents a benefit relevant to patients, their caregivers, and the overall health care system.

**STUDY LIMITATIONS.** The analyses reported here have some potential limitations. The design of the SERAPHIN trial was such that patients experiencing a primary endpoint event discontinued double-blind treatment, which limited the trial’s ability to capture subsequent hospitalizations. However, patients included in the current analyses received double-blind treatment for a median duration of 115 weeks. This duration is more than 4 times longer than that of previous trials of PAH-specific agents. These data provide a comprehensive view of how macitentan affects hospitalizations over a prolonged period of time. A potential limitation for the PAH-related hospitalizations is that they were judged to be related or not related to PAH by the investigator. Nevertheless, a substantial proportion of PAH-related hospitalizations occurred in conjunction with primary endpoint events that were adjudicated by a clinical event committee and, therefore, provide reassurance that the judgment of the investigators was appropriate. In addition, the fact that the favorable treatment effect of macitentan is driven by the effect on PAH-related hospitalization validates the assessment of causality made by the investigator. Another point to consider is that there are variations in hospitalization practices from country to country. Although the results in the Online material outline differences between regions, the results should be interpreted with caution, as the analyses are exploratory, subject to small sample size and low numbers of events, and are not adjusted for multiple comparisons.

**CONCLUSIONS**

In conclusion, 10 mg of macitentan significantly reduced the risk and rate of hospitalization for any cause, in addition to the duration of hospital stay. These treatment effects were driven by reductions in the risk and rate of PAH-related hospitalization. Importantly, the reduction in PAH-related hospitalization was not offset by an increase in hospitalization for other causes. Overall, these findings provide further evidence of improved long-term outcomes in PAH patients treated with macitentan.

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**REFERENCES**


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APPENDIX For supplemental tables, please see the online version of this article.