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Lessons from the trials

Macitentan in pulmonary arterial hypertension: The SERAPHIN trial

Karim Said*

Aswan Heart Centre, Aswan, Egypt
*Email: kareemsaid@gmail.com

ABSTRACT

Major limitations of pulmonary arterial hypertension (PAH) drug trials include the small number of enrolled patients, short term follow up (12-16 weeks), and lack of morbidity and mortality primary endpoints. The recently published SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome) trial represents an important landmark in the history of clinical trials in PAH being the largest and longest clinical study conducted thus far in PAH patients with morbidity and mortality events as primary endpoint. SERAPHIN trial investigated whether long-term treatment with the new endothelin receptor antagonist macitentan would reduce the risk of mortality and morbidity in PAH patients.

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BACKGROUND

Current clinical research in pulmonary arterial hypertension (PAH) focuses on the development of more potent and less toxic drugs that target pathophysiologic pathways known to be important in PAH with special emphasis on endothelin, nitric oxide and prostacyclin pathways.

Endothelin is one of the most potent vasoconstrictor ever identified with additional proliferative and profibrotic activities. Endothelin exerts its effects by binding to 2 distinct receptor isoforms in the pulmonary vascular smooth muscle cells, endothelin-A and -B receptors.

Until recently, only two endothelin receptor antagonists (ERAs) have been approved for the treatment of PAH: bosentan (an oral active dual endothelin-A and -B receptor antagonist) and ambrisentan (a selective for the endothelin-A receptor blocker). A third agent, sitaxsentan, was withdrawn from the market in December 2010 after cases of potentially drug-induced fatal hepatotoxicity had been reported

ERAs are associated with important adverse events including elevation of hepatic transaminases and peripheral edema. Approximately 3% of patients will need to discontinue bosentan due to these adverse effects on hepatic function.[1] Another limitation of available ERAs is drug-drug interaction. Of interest are the interactions of bosentan with sildenafil, a frequently used combination therapy, where sildenafil plasma levels are reduced by about 50% while bosentan concentrations rise by approximately 50%.[2–3]

Recently, the US Food and Drug Administration has approved a new ERA macitentan to treat PAH in adults. Support for approval of macitentan comes from the recently published SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary arterial Hypertension to Improve cliNical outcome) trial.[4]

MACITENTAN

Macitentan is a dual ERA that was developed by modifying the structure of bosentan to increase efficacy and safety. Macitentan is characterized by slow receptor dissociation kinetics and enhanced tissue penetration.[5,6] The receptor occupancy half-life of mecitentan is 15-times greater than bosentan[6] allowing for a once-a-day dosing regimen, as ambrisentan, whereas bosentan is dosed twice daily. In contrast to other ERAs, macitentan has a low propensity for drug–drug interactions.[7–8]

SERAPHIN TRIAL

The SERAPHIN study is double-blind, randomized, placebo-controlled study that was designed to evaluate the efficacy and safety of long term treatment with macitentan. The study involved 742 patients with PAH in 151 centers in 39 countries all over the world. Patients were randomized 1:1:1 to placebo ($n = 250$), macitentan 3 mg ($n = 250$) or macitentan 10 mg ($n = 242$) once daily. The mean duration of study treatment was: 85.3 weeks, 99.5 weeks, and 103.9 weeks for the placebo, the 3-mg dose, and the 10-mg dose, respectively.

The study recruited patients with PAH (confirmed by right-heart catheterization) of almost any etiology with WHO functional class II–IV. Patients were allowed to receive PAH background therapy throughout the study; hence 64% of all patients were receiving concomitant treatment with oral phosphodiesterase type 5 inhibitors (61.4%) or oral or inhaled prostanoids (5.4%).

The primary end point was the time from the initiation of treatment to the first occurrence of a composite end point of death, atrial septostomy, lung transplantation, initiation of treatment with IV or SC prostanoids, or worsening of PAH. Worsening of PAH was defined by the occurrence of all three of the following: a decrease in the 6-minute walk distance (6MWD) of at least 15%; worsening of symptoms; and the need for additional treatment for PAH. Secondary efficacy endpoints were: change from baseline to month 6 in 6MWD, change from baseline to month 6 in WHO functional class and time to either death due to PAH or hospitalization due to PAH.

The results showed that over the study period macitentan 10 mg reduced the risk of primary end point by 45% ($p < 0.0001$) compared with those who received placebo. This corresponds to an absolute risk reduction of 16% and a number-needed-to-treat of 6 patients. For macitentan 3 mg, risk of primary endpoint was reduced by 30% ($p = 0.0108$) relative to placebo. Risk reduction was driven primarily by reductions in PAH worsening. Worth mentioning, the benefit in the primary end point was the same with PAH-drug-therapy-naive patients as with patients treated with combination therapy.

Compared to placebo group, the composite risk of PAH-related death or hospitalization was significantly reduced by 34% for the 3 mg macitentan dose and 50% for the 10 mg dose. When death

was considered alone, there was a trend toward reduction in the rate of death due to PAH ($p = 0.07$) with the 10-mg dose of macitentan as compared with placebo.

Relative to the placebo group, the 6MWD at 6 month had increased by 16.8 m ($p = 0.01$) in the group that received 3 mg macitentan and by 22 m ($p = 0.008$) in the group that received 10 mg macitentan. The WHO functional class improved from baseline to month 6 in 13% of the patients in the placebo group, as compared with 20% of those in the group that received 3 mg of macitentan ($p = 0.04$) and 22% of those in the group that received 10 mg of macitentan ($p = 0.006$)

Macitentan was generally well tolerated with similar rates of patients discontinuing treatment due to adverse events across all groups. Rates of elevated hepatic transaminases or peripheral edema were similar across the three study groups. In particular, 4.5% of patients in the placebo group experienced elevations of hepatic transaminases aminotransferases (>3 times the upper limit of normal) compared with 3.6% of patients in the 3 mg macitentan group and 3.4% in the 10 mg macitentan group. Importantly, a hemoglobin level <8 gm/dl was encountered more frequently among patients receiving 10 mg or 3 mg macitentan (4.3% and 1.7% respectively) compared to placebo group (0.4%).

WHAT HAVE WE LEARNED?

SERAPHIN trial may represent an important landmark in the history of clinical trials in PAH for several reasons. First, it is the largest randomized, controlled study in PAH patients; second, it is the first randomized PAH trial to include morbidity and mortality events as primary endpoint; third, it is the first randomized PAH study with a predefined long-term treatment follow up (median duration of more than 2 years).

In pivotal studies of PAH, clinical endpoints had been secondary or exploratory endpoints without adjudication and with very low event rates. The traditional primary endpoint in these studies has been the 6MWD and, accordingly, nearly all available treatments for PAH have been approved based on change in 6MWD. However the prognostic relevance of 6MWD to long-term outcomes is questionable. In a recent meta-analysis of 3,112 patients from 22 clinical trials, changes in 6MWD were not predictable of the favorable effects of pharmacological treatments on clinical events including all-cause death, hospitalization for PAH, transplant, initiation of rescue therapy, and composite outcome.[9] In addition, improvement in 6MWD may not be noticed in patients who are already on effective background therapy or in patients with less severe symptomatic disease who have high baseline walk distances but, nevertheless, may have substantial pathology (ceiling effect).[10] Accordingly, current guidelines suggest that the primary end point in phase 3 trials of new treatments for PAH should be morbidity and mortality.[11,12,13] In accordance with this, SERAPHIN used a robust definition of morbidity and mortality as a primary end-point to capture clinically relevant events which reflect the true progression of PAH. The success of SERAPHIN study demonstrates that such trials are feasible in the field of PAH.

One of the important limitations of phase 2 and 3 PAH trials, as is the case with orphan diseases in general, is the small sample size. The large number of patients ($n = 742$) enrolled in SERAPHIN trial was possible only with the contribution of 151 centers in 39 countries all over the world. This highlights the importance of multicentre international design for future PAH studies.

Besides recruiting large number of patients, PAH trials should be long enough in duration to enable enough events to occur to allow adequate statistical powering of the study. However, currently available PAH-targeted therapies have been approved for the treatment of PAH on the basis of short-term trials (12 to 16 weeks). Importantly, patients in the SERAPHIN trial were followed with an average duration of 2 years; this is important to assess the effect of therapy on a chronic progressive disease such that of PAH.

In the SERAPHIN trial, about two thirds of patients were on background therapy (mostly phosphodiesterase type 5 inhibitor). This high rate of combination therapy is important for several reasons:

(1) With the progressive nature of PAH disease, many patients will need the introduction of additional treatments. Accordingly, permitting combination therapy in the majority of patients in SERAPHIN trial reflects everyday practice in treating real PAH patients and increases the validity of the trial. The use of background therapy in the placebo group eliminates ethical concerns regarding depriving these patients from an effective therapy. With the long term follow up the SERAPHIN trial, it would have been difficult to maintain the randomized patients on a single PAH-targeted therapy because of disease progression. The positive results of the study practically eliminate the concern that the inclusion of patients on a background effective therapy may reduce the ability to demonstrate a statistically

significant difference between the placebo and the active treatment groups. Given the low likelihood of drug-drug interaction (specifically with sildenafil and warfarin), macitentan may be the appropriate ERA drug to be used in combination therapy.

Although there was a trend for a macitentan-related reduction in death, this was not statistically significant. The SERAPHIN study was not powered to detect difference in mortality outcome. In addition, since PAH is a progressive disease and clinical deterioration is likely to precede death, it was unlikely that death was recorded as the first event.[4]

In the SERAPHIN study, "worsening of PAH" was more likely to be the driver of the primary endpoint. However, this endpoint was very precisely defined, and an expert adjudication committee confirmed each event in a blinded fashion, emphasizing the robustness and clinical relevance of this endpoint

In the SERAPHIN trial, the 6MWD had increased by a mean of 22 m among patients on 10 mg macitentan, relative to placebo. This change in 6MWD parallels those reported in other trials. In a pooled analysis of 10 randomized placebo-controlled trials previously submitted to the FDA, active PAH treatment was associated with associated with change of 6MWT at 12 week of 22.4 m (95% CI: 17.4–27.5 m) relative to placebo.[9] Nevertheless, the change in 6MWD is less than 41.8 meters, a value that was previously reported to correspond to a statistically significant reduction in clinical events.[14] This again challenges the use of 6MWD as a surrogate endpoint in PAH trials.

Macitentan was well tolerated in the SERAPHIN trial and, remarkably, rates of adverse events commonly associated with the ERA drug class (elevated liver aminotransferases and peripheral edema) were similar in the placebo and macitentan groups. Compared with placebo, a higher proportion of macitentan-treated patients had headache and respiratory adverse events, particularly those affecting the upper respiratory tract, mainly nasopharyngitis. These adverse events are known with ERAs and thought to be the results of vasodilatation.

In terms of liver test abnormalities, macitentan appears to have a better safety profile compared with bosentan and similar to amrisentan. Results of European post-marketing surveillance of bosentan in pulmonary hypertension showed elevated transaminases in 8% of patients with a discontinuation rate of 3% in bosentan-naive patients.[1] Accordingly, liver function test should be performed monthly in patients receiving bosentan or ambresntan.[15] It has been reported that bosentan inhibits the bile salt export pump, which may lead to cholestatic liver injury due to the intracellular accumulation of bile salts.[16] Macitentan has no significant inhibitory effects on hepatic bile salt transport and, therefore, has the potential for a favorable liver safety profile.[17]

Reduction in blood hemoglobin < 8 g/dl was observed in 4.3% of patients receiving 10 mg of macitentan compared to only 0.4% of patients in the placebo group. Due to an as yet incompletely identified mechanism, potentially related to vasodilatation and decreased vascular permeability with subsequent fluid shift producing haemodilution, all ERAs are associated with a modest dose-dependent and partially transient reduction in haemoglobin levels. The significance of this hemoglobin reduction noticed with macitentan can only be firmly established postmarketing.

REFERENCES

[1] Humbert M, Segal ES, Kiely DG, Carlsen J, Schwierin B, Hoeper MM. Results of European post-marketing surveillance of bosentan in pulmonary hypertension. *Eur Respir J*. 2007;30:338–344.
[2] Paul GA, Gibbs JS, Boobis AR, Abbas A, Wilkins MR. Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br J Clin Pharmacol*. 2005;60:107–112.
[3] Burgess G, Hoogkamer H, Collings L, Dingemanse J. Mutual pharmacokinetic interactions between steady-state bosentan and sildenafil. *Eur J Clin Pharmacol*. 2008;64:43–50.
[4] Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani HA, Jansa P, Jing ZC, Le Brun FO, Mehta S, Mittelholzer CM, Perchenet L, Sastry BK, Sitbon O, Souza R, Torbicki A, Zeng X, Rubin LJ, Simonneau G, SERAPHIN Investigators. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *New Engl J Med*. 2013;369:809–818.
[5] Iglarz M, Binkert C, Morrison K, Fischli W, Gatfield J, Treiber A, Weller T, Bolli MH, Boss C, Buchmann S, Capeleto B, Hess P, Qiu C, Clozel M. Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist. *J Pharmacol Exp Ther*. 2008;327:736–745.
[6] Gatfield J, Mueller Grandjean C, Sasse T, Clozel M, Nayler O. Slow receptor dissociation kinetics differentiate macitentan from other endothelin receptor antagonists in pulmonary arterial smooth muscle cells. *PLoS One*. 2012;7:e47662.
[7] Bruderer S, Hopfgartner G, Seiberling M, Wank J, Sidharta PN, Treiber A, Dingemanse J. Absorption, distribution, metabolism, and excretion of macitentan, a dual endothelin receptor antagonist, in humans. *Xenobiotica*. 2012;42:901–910.
[8] Bruderer S, Aänismaa P, Homery MC, Häusler S, Landskroner K, Sidharta PN, Treiber A, Dingemanse J. Effect of cyclosporine A and rifampin on the pharmacokinetics of macitentan, a tissue-targeting dual endothelin receptor antagonist. *AAPS J*. 2012;14:68–78.

[9] Savarese G, Paolillo S, Costanzo P, D'Amore C, Cecere M, Losco T, Musella F, Gargiulo P, Marciano C, Perrone-Filardi P. Do changes of 6-minute walk distance predict clinical events in patients with pulmonary arterial hypertension? A meta-analysis of 22 randomized trials. *J Am Coll Cardiol.* 2012;60:1192–1201.
[10] Frost AE, Langleben D, Oudiz R, Hill N, Horn E, McLaughlin V, Robbins IM, Shapiro S, Tapson VF, Zwicke D, DeMarco T, Schilz R, Rubenfire M, Barst RJ. The 6-min walk test (6MW) as an efficacy endpoint in pulmonary arterial hypertension clinical trials: demonstration of a ceiling effect. *Vascul Pharmacol.* 2005;43:36–39.
[11] Snow JL, Kawut SM. Surrogate end points in pulmonary arterial hypertension: assessing the response to therapy. *Clin Chest Med.* 2007;28:75–89.
[12] McLaughlin VV, Badesch DB, Delcroix M, Fleming TR, Gaine SP, Galiè N, Gibbs JS, Kim NH, Oudiz RJ, Peacock A, Provencher S, Sitbon O, Tapson VF, Seeger W. Endpoints and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol.* 2009;54(Suppl 1):S97–S107.
[13] Gomberg-Maitland M, Bull TM, Saggar R, Barst RJ, Elgazayerly A, Fleming TR, Grimminger F, Rainisio M, Stewart DJ, Stockbridge N, Ventura C, Ghofrani AH, Rubin LJ. New trial designs and potential therapies for pulmonary artery hypertension. *J Am Coll Cardiol.* 2013;62:D82–D91.
[14] Gabler NB, French B, Strom BL, Palevsky HI, Taichman DB, Kawut SM, Halpern SD. Validation of 6-minute walk distance as a surrogate end point in pulmonary arterial hypertension trials. *Circulation.* 2012;126:349–356.
[15] Galiè N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G, ESC Committee for Practice Guidelines (CPG). Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2009;30:2493–2537.
[16] Fattinger K, Funk C, Pantze M, Weber C, Reichen J, Stieger B, Meier PJ. The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: a potential mechanism for hepatic adverse reactions. *Clin Pharmcol Ther.* 2001;69:223–231.
[17] Bolli MH, Boss C, Binkert C, Buchmann S, Bur D, Hess P, Iglarz M, Meyer S, Rein J, Rey M, Treiber A, Clozel M, Fischli W, Weller T. The discovery of N-[5-(4-Bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N′-propyl-sulfamide (macitentan), an orally active, potent dual endothelin receptor antagonist. *J Med Chem.* 2012;55:7849–7861.