Treatment of pulmonary arterial hypertension with the dual endothelin receptor antagonist macitentan: clinical evidence and experience

Ther Adv Respir Dis
2019, Vol. 13: 1–13
DOI: 10.1177/1753466618823440

Catharina Belge and Marion Delcroix

Abstract: Macitentan (10 mg once daily orally), a dual endothelin receptor antagonist (ERA) developed by modifying the structure of bosentan to increase the efficacity and safety, is approved for the treatment of pulmonary arterial hypertension (PAH). The pivotal SERAPHIN trial, (a landmark trial in the history of PAH trials because of the large number of included patients, the long-term follow up and the first trial with morbidity/mortality as the primary endpoint) showed a reduction of the risk of a morbidity or mortality event by 45% over the treatment time compared with placebo. The positive effect on the primary endpoint was observed whether or not the patient was already on PAH therapy. There has been no direct comparison between macitentan and other ERAs, which were approved based on improved exercise capacity, but preclinical and clinical data suggest better pharmacological and safety profiles. Further analyses of the SERAPHIN trial investigated the predictive value of different indices and events on long-term outcome and mortality. The efficacy in children, the long-term effects and safety of macitentan and its place in combination therapy compared with other ERAs are still under investigation. This review presents the preclinical evidence of superiority of macitentan compared with other ERAs, and the available clinical trial data. The place of macitentan in the therapeutic algorithm for PAH treatment, post-marketing experience and future perspectives are discussed.

Keywords: endothelin receptor antagonist, macitentan, pulmonary arterial hypertension

Received: 13 July 2018; revised manuscript accepted: 14 December 2018.

Introduction

Pulmonary arterial hypertension (PAH) is a fatal and progressive condition characterized by the presence of precapillary pulmonary hypertension at right heart catheterization (mean pulmonary arterial pressure ⩾25 mmHg at rest and wedge pressure ⩽15 mmHg) and high pulmonary vascular resistance (>3 Wood units) in the absence of other causes of precapillary pulmonary hypertension, like lung disease or chronic thromboembolic pulmonary hypertension.[1] PAH is the first group of the pulmonary hypertension classification[1] (Table 1). In the idiopathic form, no etiology is found. In the heritable form there is a context of familial history or a genetic mutation. Other forms are associated with drugs and toxins, connective tissue diseases, liver disease, human immunodeficiency virus (HIV), congnital heart disease or schistosomiasis.

PAH is a rare disease, defined by a prevalence lower than 1/2000 in Europe or fewer than 200,000 people at any given time in the United States (US) but is being increasingly recognized. Recent large multicenter registries have provided low estimates of PAH prevalence of 15 cases/million inhabitants and incidence of 2.4 cases/million adult inhabitants/year in France, and 10.6 and 2 respectively in the US.[2,3]

Correspondence to:
Catharina Belge
Department of respiratory diseases, University Hospitals Leuven, Herestraat 49, B3000 Leuven, Leuven, Belgium
catharina.belge@uzleuven.be

Marion Delcroix
Universitaire Ziekenhuizen Leuven, Leuven, Belgium

Table 1. Clinical classification of pulmonary hypertension.[1]

Group 1. Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2 mutation
1.2.2 Other mutations
1.3 Drug and toxin induced
1.4 Associated with
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart diseases
1.4.5 Schistosomiasis
Group 1′. Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis
Group 1″. Persistent pulmonary hypertension of the newborn
Group 2. Pulmonary hypertension due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstructions and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis
Group 3. Pulmonary hypertension due to lung diseases or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
Group 4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma

Table 1. (Continued)

Group 1. Pulmonary arterial hypertension
4.2.2 Other intravascular tumors
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries stenoses
4.2.5 Parasites (hydatidosis)
Group 5. Pulmonary hypertension with unclear or multifactorial mechanisms

PAH, pulmonary arterial hypertension.

Remodeling of the pulmonary vasculature is responsible for an increase in pulmonary vascular resistance leading to progressive right heart failure and ultimately death. It is partially explained by an imbalance between three main pathways, the prostacyclin, the nitric oxide and the endothelin pathways.[4] Current treatments aim to re-establish the balance between the vasoactive and vasodilatory capacities in the lung vasculature.

Endothelin and the pulmonary circulation

Increased levels of endothelin (ET)-1 have been observed in the plasma and pulmonary vascular endothelium of patients with pulmonary hypertension and increased plasma levels were also observed in experimental animal models of PAH.[5–7] ET-1 is the principal isoform in the cardiovascular system,[8] and it is one of the most potent vasoconstrictors. The activity of ET-1 is mediated through two distinct receptors: ET_A and ET_B.[9,10] In physiological conditions vasoconstriction is essentially mediated by ET_A receptors which predominate on vascular smooth muscle cells (SMCs). ET_B receptors are mainly expressed on the vascular endothelium and mediate vasodilation. This is the reason why theoretically it was thought that selective ET_A inhibition may be more efficient. However, in pathological conditions like PAH, ET_B receptors are upregulated on SMCs and downregulated on endothelial cells,[11–13] suggesting that dual endothelin receptor antagonism (ERA) may be better than ET_A-selective inhibition.[14] There is however no clinical evidence of improved efficacy of one or the other type of ERA.

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,[15,16] hemodynamic parameters[15] and time to clinical worsening.[16] However, the treatment was associated with an increased, dose-dependent, incidence of elevated liver transaminases, and an increase in plasma bile salts and alkaline phosphatases[17] attributed to inhibition of the bile salt export pump by bosentan and its metabolites.[18] Peripheral edema was also observed with bosentan.[16] An extensive drug discovery program was then started to maximize the inhibition of the ET receptors and minimize the risk of elevated liver enzymes and fluid retention.[19]

Macitentan pharmacology

Macitentan is the result of this optimization program. It is a dual ERA with enhanced tissue penetration (related to greater lipophilicity) and receptor binding properties, and superior efficacy in animal models.[19–21] The structure of macitentan is derived from the structure of bosentan. Increased receptor affinity and increased lipophilicity was obtained by replacing the sulfonamide moiety present in bosentan with a sulfamide moiety. Macitentan has a compact conformation facilitating deep penetration into the receptor and allowing precise occupation of a hydrophobic pocket in the ET_A receptor. ET1 acts as a tissular (paracrine or autocrine) factor, therefore an ERA that can easily penetrate tissue is more potent to increase ET receptor blockade. Optimization of the ability to target the tissue has been achieved by optimization of physiochemical properties of the molecule. This was achieved by increasing the pKa value (6.2 for macitentan compared with 5.1 for bosentan and 3.5 for ambrisentan) and by increasing the distribution coefficient leading to increased affinity for the tissue (800:1, lipid phase: aqueous phase for macitentan compared

with 20:1 for bosentan whereas 1:20.5 for ambrisentan which has more affinity for the aqueous milieu than for lipids). Macitentan also binds longer to the receptor (receptor occupancy half-time ≈1020 s for macitentan, ≈70 s for bosentan and ≈40 s for ambrisentan) resulting in a better blockade of ET signaling and making it possible to have a once daily dosing.[14,19,20,22]

Macitentan does not inhibit bile salt transport.[23] Macitentan also shows a favorable drug–drug interaction profile.[24] Concomitant use of rifampicin, which reduces macitentan exposure, should be avoided.[25]

Macitentan: clinical evidence

The effects of macitentan have been extensively investigated in 15 phase I studies in more than 300 subjects,[14] a phase II study (in patients with idiopathic pulmonary fibrosis)[26] and the pivotal phase III study with an ERA in PAH to improve clinical outcome (SERAPHIN trial[27]). Specific efficacy aspects have been detailed in many more publications (effect on hospitalizations,[28] on prevalent and incident patients,[29] on hemodynamic parameters,[30] on health-related quality of life,[31] and on the relationships between the 6 minute walking distance (6MWD) and long-term outcomes,[32] between morbidity and mortality,[33] and between pharmacokinetics and hemodynamic efficacy[34]). New studies have also been dedicated to different pulmonary hypertension (PH) groups (inoperable chronic thromboembolic pulmonary hypertension[35] and pulmonary hypertension due to left ventricular dysfunction[36]), to exploratory end-points (Table 2), and to real-life experience (Table 2).

The SERAPHIN trial evaluated the efficacy and safety of two doses of macitentan (3 and 10 mg once a day) by using a composite primary endpoint of time to first morbidity and (all-cause) mortality event in 742 patients with symptomatic PAH in a randomized, double-blind, multicenter, placebo-controlled, event-driven trial. After randomization, 250 patients received placebo, 250 received macitentan 3 mg and 242 received macitentan 10 mg.

Eligible patients were aged ⩾12 years with confirmed PAH diagnosis (idiopathic or heritable PAH, PAH associated with connective tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection, drug use or toxin exposure). Patients were required to have a 6MWD ⩾ 50 m and a World Health Organization (WHO) functional class (FC) II, III or IV. Patients naïve to PAH treatment or those receiving a phosphodiesterase type 5 inhibitor (PDE5i), oral or inhaled prostanoids, calcium channel blockers or L-arginine at stable doses for at least 3 months could be included. Patients treated with intravenous or subcutaneous prostanoids or ERAs were excluded.

Morbidity and mortality

Macitentan 3 and 10 mg daily was effective in delaying the disease progression, reducing the risk of a morbidity or mortality event by 45% (10 mg) and by 30% (3 mg) over the treatment time as compared with placebo.[27]

Macitentan treatment also significantly reduced the composite secondary endpoint of death due to PAH or hospitalization for PAH by 50% (10 mg *versus* placebo, $p < 0.001$). The risk of hospitalization for PAH in the group treated with 10 mg of macitentan was reduced by 51.6% compared with the placebo group ($p < 0.0001$), the rate of hospitalization for PAH by 49.8% ($p < 0.0001$), and the number of hospital days by 52.3% ($p = 0.0003$).[28]

The incidence of all-cause death and death due to PAH did not differ significantly between the macitentan and placebo group. However, as PAH is a progressive disease, clinical deterioration is likely to precede death which is rarely the first recorded event.[27]

To overcome the hurdle of evaluating survival benefits in rare diseases the use of real-world observational data has been proposed to complement RCT data. To this end, a prediction model based on the US REVEAL registry data has been used to further explore the effect of macitentan on mortality. This analysis suggested that, over 3 years, the risk of mortality with macitentan 10 mg was 31% lower than that predicted from the model ($p = 0.033$).[37]

It is noteworthy that the patients enrolled in the SERAPHIN trial were younger than currently observed in the western countries; the mean age of PAH patients at diagnosis averaging 50 ±14 and 65 ±15 years in recent registries (French, COMPERA and US REVEAL registries).[38] The

Table 2. Clinical trials with macitentan in pulmonary arterial hypertension.

Trial	Number of patients target population instrument	Time frame	Design	Primary endpoint	Status	Conclusion
SERAPHIN NCT00660179	742 IPAH, PAH-CTD, PAH-CHD closed defect morbi-mortality	36 months	Interventional randomized double-blind placebo-controlled parallel assignement phase III	Time to first confirmed morbidity or mortality event up to end of treatment	completed	primary endpoint reached
MAESTRO NCT01743001	266 PAH-CHD 6-minute walk test	16 weeks	Interventional randomized double-blind placebo-controlled parallel assignement phase III	Change from baseline to week 16 in exercise capacity as measured by 6-minute walk distance	completed	primary enpoint not met
MAESTRO-OL NCT01739400	220 PAH-CHD Safety	3 years	Interventional open label single arm phase III	Treatment-emergent serious adverse events up to 30 days after study drug discontinuation Treatment-emergent marked lab abnormalities Proportion of patients with treatment-emergent ALT or AST abnormality	completed	NA
OPTIMA NCT02968901	60 (estimated) PAH right heart cath	16 weeks	Interventional open label single arm phase IV	Change from baseline to Week 16 in % of patients with clinically meaningful improvement of PVR (decrease of 30% from baseline to Week 16) combination therapy with tadalafil	recruiting	NA
OPUS NCT02126943	5000 PAH safety	1 year	Interventional open label single arm phase IV	To estimate incidence rates for specified outcomes Liver test, hepatic and any other adverse events Discontinuation, hospitalization and death	recruiting	NA
ORCHESTRA NCT02081690	160 PAH* PRO	16 weeks	Interventional open label single arm phase III	To evaluate the psychometric characteristics of reliability and construct validity of the French, Italian and Spanish versions of the PAH-SYMPACT™	completed	NA

(Continued)

Table 2. (Continued)

Trial	Number of patients target population instrument	Time frame	Design	Primary endpoint	Status	Conclusion
ORCHESTRA extension NCT02112487	160 (estimated) PAH* safety	6 months	Interventional open label single arm phase III	To assess the long-term safety of macitentan in patients with pulmonary arterial hypertension	active not recruiting	NA
PORTICO NCT02382016	84 (estimated) POPH RHC	12 weeks	Interventional randomized double-blind placebo-controlled parallel assignement phase IV	Relative change from baseline to week 12 in PVR	active not recruiting	primary endpoint reached (unpublished)
REPAIR NCT02310672	100 (estimated) PAH# MRI	52 weeks	Interventional open label single arm phase IV	Change in RV stroke volume and ratio of week 26 to baseline PVR	recruiting	NA
RUBATO NCT03153137	134 (estimated) Fontan-palliated CPET	16 weeks	Interventional randomized double-blind placebo-controlled parallel assignement phase III	Change in peak VO_2 (oxygen uptake)	recruiting	NA
SERAPHIN-OL NCT00667823	550 PAH	55 months	Interventional open label single arm phase IV	Number of patients with treatment-emergent adverse events and serious adverse events	active not recruiting	NA
TOMORROW NCT02932410	300 (estimated) pediatric PAH disease progression	6 years	Interventional open label parallel assignement phase IV	Time to the first disease progression event in children	recruiting	NA

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CHD, congenital heart disease; CPET, cardiopulmonary testing; CTD, connective tissue disease; HIV, human immunodeficiency virus; (I)PAH, (idiopathic) pulmonary arterial hypertension; lab, laboratory; NA, not applicable; NCT, National Clinical Trials identifier; POPH, portopulmonary hypertension; PRO, patient-related outcome; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricle.
PAH*: IPAH, heritable PAH, drug or toxin-induced PAH, PAH associated with CTD or with CHD with simple systemic-to-pulmonary shunt at least 1 year after surgical repair or with HIV.
PAH#: IPAH, heritable PAH, drug or toxin-induced PAH, PAH associated with CHD [only simple (atrial septal defect, ventricular septal defect, patent ductus arteriosus) congenital systemic-to-pulmonary shunts at least 2 year post-surgical repair].

geographical distribution of the included patients was heterogeneous. While in the placebo arm patients were mainly European or Asian, in the macitentan arms patients came mainly from Eastern Europe or Asia. Patients from North America were underrepresented in all arms. Therefore, the real-world effects of macitentan on morbi-mortality may be different from a clinical trial.

The strengths of the SERAPHIN trial are the large number of included patients and the prolonged observation time of the trial. It is also the first study in PAH powered for a robust clinical endpoint (morbidity and mortality) instead of a change in 6MWD.

Functional class and exercise capacity

The WHO FC at 6 months improved in a higher percentage of patients receiving 10 mg of macitentan ($p = 0.006$), and the treatment effect on the 6MWD with 10 mg dose *versus* placebo was 22.0 m [97.5% confidence interval (CI), 3.2–40.8; $p = 0.008$].

Interestingly, a *post hoc* analysis of the SERAPHIN trial showed that patients with higher absolute values of the 6MWD at baseline or at month 6 had better prognosis but that the magnitude of change in 6MWD was not associated with long-term clinical outcomes.[33] This confirms that establishing absolute thresholds of 6MWD as treatment goals in daily clinical practice make sense.[39] Similarly a meta-analysis of 22 short-term RCTs in PAH (including 3112 patients), showed that improvements in the 6MWD did not reflect the benefit in clinical outcomes, such as death, hospitalization for PAH and initiation of PAH rescue therapy.[40]

Furthermore, the MAESTRO study conducted in patients with PAH associated with Eisenmenger syndrome, did not reach its primary endpoint of change in 6MWD from baseline to week 16 of treatment,[41] while macitentan reduced the exploratory endpoint N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in the global cohort and improved pulmonary vascular resistance index and exercise capacity in the hemodynamic substudy. The results of this RCT are difficult to interpret as there was an unexpected improvement in the placebo arm, which had not been observed in a previous study conducted with bosentan,[42] and significantly contribute to the failure to achieve the primary endpoint in the MAESTRO trial. Of note, this study, as opposed to the bosentan study in Eisenmenger patients, included a significant proportion of patients with Down's syndrome and patients with complex cardiac defects. The long-term open-label trial in Eisenmenger patients (MAESTRO-OL; ClinicalTrials.gov identifier: NCT01739400) is also completed but results are not yet available (Table 2).

Hemodynamics

A subset of 187 patients in the SERAPHIN trial (68 randomized to placebo, 62 to macitentan 3 mg and 57 to macitentan 10 mg) underwent right heart catheterization at baseline and after 6 months ($n = 147$) of treatment.[27,30] Cardiopulmonary hemodynamic parameters and NT-proBNP were assessed. The baseline characteristics of the patients in the hemodynamic substudy were similar to the total SERAPHIN population and balanced between the different treatment groups. Both doses of macitentan significantly reduced pulmonary vascular resistance (PVR) and increased cardiac index, as compared with the placebo group.[27] Absolute levels of cardiac index, right atrial pressure (RAP), and NT-proBNP at baseline and after 6 months of treatment, but not their changes, were associated with morbidity or mortality events. Lower risk for morbidity or mortality was observed in patients with cardiac index > 2.5 l/min/m^2, RAP < 8 mmHg, or NT-proBNP < 750 fmol/ml after 6 months of treatment [hazard ratio (HR) 0.49, 95% CI 0.28–0.86; HR 0.72, 95% CI 0.42–1.22 and HR 0.22, 95% CI 0.15–0.33, respectively].[30,31] Reaching threshold values of cardiac index, RAP and NT-proBNP should thus lower the risk of morbidity or mortality in PAH patients. Interestingly the findings of the SERAPHIN trial confirm the original findings of the National Institutes of Health registry where baseline cardiac index and RAP were the most predictive hemodynamic parameters of survival. Moreover, the SERAPHIN trial also shows the predictive value of these variables at the 6-month follow up, offering indirect validation of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) risk stratification at baseline and during follow up. The fact that changes in some hemodynamic parameters are not associated with a better outcome can be partly explained by patient baseline condition (a

low-risk patient with small improvement after treatment may have a better outcome).

The mechanism of action by which macitentan influences hemodynamic parameters will be studied in the ongoing REPAIR (right ventricular remodeling in pulmonary arterial hypertension) trial evaluating the effects of macitentan on right ventricle remodeling in PAH assessed by cardiac magnetic resonance imaging (ClinicalTrials.gov Identifier: NCT02310672) (Table 2).

Quality of life

Macitentan (10 mg) improved seven to eight domains of the short form health survey (SF-36) questionnaire assessing health-related quality of life (HRQoL)[31] and reduced significantly the risk of a three-point or greater deterioration in physical component summary score (HR 0.60; 95% CI, 0.47–0.76; $p < 0.0001$) and mental component summary score (HR 0.76; 95% CI, 0.61–0.95; $p = 0.0173$) until end of treatment. Patients with a HRQoL at baseline greater than the median baseline value had improved long-term outcomes. Potential limitation of these analyses is that the SF-36 questionnaire is a generic measure tool of HRQoL and is not created to specifically assess quality of life in PAH patients. Also, the long-term effect is difficult to evaluate due to missing data: at 6 months HRQoL was not available for 134 (18.9%) of patients and imputation for missing data was used. At 12 months 30% of data were missing making it impossible to analyze.

Of note, a disease-specific patient-reported outcome (PRO) instrument, the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPACT®) questionnaire, has been recently finalized and validated using data from the SYMPHONY trial which included 278 US patients with PAH treated with macitentan.[43]

Tolerability and safety

Macitentan was generally well tolerated in the SERAPHIN study. Similar rates of adverse events were reported in the three study arms: 96% in patients treated with macitentan 3 mg daily, 94.6% in patients treated with macitentan 10 mg daily and 96.4% in patients from the placebo group. Serious adverse events were similarly reported in the three groups: 52% with macitentan 3 mg daily, 45% with macitentan 10 mg daily and 55% with placebo.[27]

There was no difference in incidence of edema, a well-known adverse event of ERAs, between the placebo and the macitentan arms (18.1% *versus* 18.2%).[27] Treatment with ERAs, especially with bosentan, has been associated with increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) due to inhibition of the bile salt transport.[17] In the SERAPHIN trial, 3.4% of patients with macitentan compared with 4.5% of patients in the placebo group developed ALT or AST levels >3 times the upper limit of normal (ULN) and bilirubin levels >2 times the ULN.[27] Severe anemia (hemoglobin ⩽ 8 g/dl) was observed more frequently in the macitentan group (10 mg) compared with the placebo group (4.3% *versus* 0.4%).

Anemia, nasopharyngitis, bronchitis and headache were reported more frequently (delta>3%) in the group treated with macitentan 10 mg compared with the placebo group.[27] Of note, the SERAPHIN trial was underpowered for the identification of rare severe side effects.

Although the trough plasma concentration of macitentan and its active metabolite was about two-fold higher in PAH patients from the SERAPHIN trial than in healthy people, this did not translate to a significant difference in exposure expressed as maximum plasma concentration (Cmax) or area under the plasma concentration–time curve (AUC) over a dosing interval.[44]

Dosage and (contra) indications

Macitentan (10 mg once daily orally) was approved in 2013 by the United States Food and Drug Administration (US FDA) and European Medicines Agency for the treatment of PAH to delay disease progression and to reduce hospitalizations (US, https://opsumit.com/opsumit-prescribing-information.pdf) and for the long-term treatment of adults with PAH functioning in New York Heart Association class II–III (Europe, https://www.actelion.com/documents/en-rebranded/our-products/opsumit-smpc.pdf), in monotherapy or in combination therapy.

Teratogenicity is a well-known side effect shared by all ERAs. Macitentan is therefore contraindicated in pregnant women (US and Europe). In Europe its use is also contraindicated in breastfeeding women and in women of childbearing potential who are not using reliable contraception (however

reliable contraception is recommended in all women of childbearing potential with PAH because of the negative prognosis of pregnancy).

Clinical experience with macitentan

The place of macitentan in the therapeutic algorithm

The most recent treatment algorithm for PAH (2015 ESC/ERS guidelines,[1]) gives macitentan a I-B recommendation for monotherapy or sequential combination therapy in patients functioning in WHO FC II–III, based on a single RCT with time to clinical worsening as primary endpoint, and a IIa-C recommendation for initial combination therapy with PDE5i in patients functioning in WHO FC II–III.

There are no head-to-head comparisons of macitentan and other drugs approved for PAH treatment making it difficult to recommend one agent above another. All of the ERAs have shown clear clinical benefit in double-blind, randomized, placebo-controlled trials but as the trials have a different design it is difficult to compare one ERA with another. Comparative studies would be needed to demonstrate the incremental value of macitentan in the treatment of PAH.

However, since the SERAPHIN trial included a large number of patients already treated with PAH therapy (mostly PDE5 inhibitors) and since patients with and without background therapy were prespecified subgroups for analysis, combination therapy has been evaluated (although this was not the primary endpoint of the trial) in a *post hoc* analysis.[45] The risk of morbidity/mortality was reduced by 38% in patients on macitentan and background therapy compared with those on background therapy alone. Also, the risk of being hospitalized for PAH was reduced by 37.4% compared with patients receiving background therapy alone. Macitentan treatment in combination with background therapy was associated with improvements in exercise capacity, functional class, cardiopulmonary hemodynamics and HRQoL compared with background therapy alone.

Since the publication of the AMBITION trial (initial use of ambrisentan plus tadalafil in PAH[46]), which showed a significantly lower risk of clinical failure ($p < 0.01$) in patients receiving initial bi-therapy with ambrisentan and tadalafil compared with patients treated with ambrisentan or tadalafil in monotherapy, there is a growing interest for initial combination therapy. Actually, it is not known if these results can be extended to other drugs from the same classes. Used in combination, there is clear pharmacokinetic distinction between the three ERAs. In healthy volunteers the concomitant administration of bosentan and sildenafil showed a decrease in the AUC of sildenafil by 62.6% and an increase in the AUC of bosentan by 49.8%.[47] The concomitant administration of bosentan and tadalafil decreased the AUC of tadalafil with 41.5% and slightly increased the AUC of bosentan by <20%.[48] There were no significant interactions between ambrisentan and sildenafil,[49] ambrisentan and tadalafil,[50] and macitentan and sildenafil[51] in healthy volunteers.

A small trial evaluating the effects of first-line oral combination therapy of macitentan and tadalafil in patients with newly diagnosed PAH is currently recruiting (OPTIMA; ClinicalTrials.gov Identifier: NCT02968901, Table 2), and will give better insights in the place of macitentan in PAH treatment.

Moreover, as combination dual therapy strategies are becoming more and more standard of care, the question of initial triple therapy led to the initiation of the TRITON trial evaluating initial triple (tadalafil, macitentan and selexipag) *versus* dual oral therapy (tadalafil, macitentan and placebo) (ClinicalTrials.gov Identifier: NCT02558231).

Macitentan in daily practice: the post-marketing experience

Although there was no difference in incidence of elevated hepatic transaminases between the placebo and the macitentan arms in the SERAPHIN trial,[27] a first case of fulminant liver failure, with a probable autoimmune origin, was recently reported in a patient treated with macitentan,[52] prompting a modification to the US-approved labeling for macitentan. The European label was unchanged but already mentioned that liver enzymes should be measured before starting treatment by macitentan and monthly monitoring of AST and ALT was recommended. If sustained, unexplained clinically relevant increases in aminotransferases occurred or if these elevations are accompanied with a more than two-fold ULN

values of bilirubin or with a clinical symptoms of liver injury, macitentan should be discontinued. Once transaminase levels had normalized, re-introduction of macitentan could be considered in patients without clinical symptoms of liver injury (https://www.actelion.com/documents/en-rebranded/our-products/opsumit-smpc.pdf). The US FDA also mandated a long-term surveillance program, the OPUS registry (ClinicalTrials.gov Identifier: NCT02126943), which was initiated in 2014 to characterize the safety profile of macitentan and to describe clinical characteristics and outcomes of 5000 patients treated with macitentan in a real-world, post-marketing setting.

In the context of ERA hepatotoxicity, great caution has been applied to their use in patients with portopulmonary hypertension due to end-stage liver disease. However, small case series reported favorable results with bosentan and ambrisentan.[53,54] The PORtopulmonary Hypertension Treatment wIth macitentan, a randOmized clinical trial (PORTICO study; ClinicalTrials.gov Identifier: NCT02382016) that was presented at the 2018 ERS annual meeting, included 84 patients with mild-to-moderate hepatic impairment and showed a significant improvement in the primary endpoint of PVR without safety issues.[55]

As ERA therapy can cause anemia (also reported for macitentan), hemoglobin levels should be measured before starting treatment and macitentan should not be administrated in patients with severe anemia (https://www.actelion.com/documents/en-rebranded/our-products/opsumit-smpc.pdf). Hemoglobin measurements should be repeated during treatment as clinically indicated.

Drug interactions occur with strong CYP3A4-inducers or inhibitors resulting in reduced (CYP3A4 inducers such as rifampicin, carbamazepine, phenytoin) or increased (CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir) plasma concentrations of macitentan. However, macitentan seems to have less drug interactions compared with other ERAs[24] but this should be confirmed in larger populations in clinical practice.

Perspectives

Macitentan has been the first drug demonstrating an effect on long-term outcome in PAH in addition to improvements in functional class and exercise capacity. Multiple publications (from basic science to RCT) have illustrated and enforced the evidence on efficacy and safety of this drug. Some uncertainties still exist regarding the effects in children (TOMORROW study; ClinicalTrials.gov Identifier: NCT02932410), and the long-term effects in Eisenmenger patients (MAESTRO-OL trial; Table 2). In the absence of head-to-head comparison of the different ERAs it is obvious that hepatotoxicity is reduced in comparison with bosentan and that edema is less frequent than with bosentan and ambrisentan.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

M. Delcroix is an investigator, speaker, consultant or steering committee member for Actelion, Bayer AG, Bellerophon, Eli Lilly, GSK, MSD, Pfizer and Reata; and has received an institutional research grant from Actelion C. Belge is an investigator, speaker or consultant for Actelion, Bayer and GSK.

ORCID iD

Marion Delcroix https://orcid.org/0000-0001-8394-9809

References

1. Galie N, Humbert M, Vachiery JL, *et al.* 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension: the joint 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: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; 37: 67–119.
2. Humbert M, Sitbon O, Chaouat A, *et al.* Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006; 173: 1023–1030.
3. Frost AE, Badesch DB, Barst RJ, *et al.* The changing picture of patients with pulmonary arterial hypertension in the United States: how REVEAL differs from historic and non-US contemporary registries. *Chest* 2011; 139: 128–137.

4. Sitbon O and Morrell N. Pathways in pulmonary arterial hypertension: the future is here. *Eur Respir Rev* 2012; 21: 321–327.
5. Giaid A, Yanagisawa M, Langleben D, *et al.* Expression of endothelin-1 in the lungs of patients with pulmonary hypertension. *N Engl J Med* 1993; 328: 1732–1739.
6. Galie N, Manes A and Branzi A. The endothelin system in pulmonary arterial hypertension. *Cardiovasc Res* 2004; 61: 227–237.
7. Stewart DJ, Levy RD, Cernacek P, *et al.* Increased plasma endothelin-1 in pulmonary hypertension: marker or mediator of disease? *Ann Intern Med* 1991; 114: 464–469.
8. Yanagisawa M, Kurihara H, Kimura S, *et al.* A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988; 332: 411–415.
9. Arai H, Hori S, Aramori I, *et al.* Cloning and expression of a cDNA encoding an endothelin receptor. *Nature* 1990; 348: 730–732.
10. Sakurai T, Yanagisawa M, Takuwa Y, *et al.* Cloning of a cDNA encoding a non-isopeptide-selective subtype of the endothelin receptor. *Nature* 1990; 348: 732–735.
11. Iglarz M and Clozel M. At the heart of tissue: endothelin system and end-organ damage. *Clin Sci (Lond)* 2010; 119: 453–463.
12. Iglarz M, Steiner P, Wanner D, *et al.* Vascular effects of endothelin receptor antagonists depends on their selectivity for ETA versus ETB receptors and on the functionality of endothelial ETB receptors. *J Cardiovasc Pharmacol* 2015; 66: 332–337.
13. Kakoki M, Hirata Y, Hayakawa H, *et al.* Effects of hypertension, diabetes mellitus, and hypercholesterolemia on endothelin type B receptor-mediated nitric oxide release from rat kidney. *Circulation* 1999; 99: 1242–1248.
14. Clozel M. Endothelin research and the discovery of macitentan for the treatment of pulmonary arterial hypertension. *Am J Physiol Regul Integr Comp Physiol* 2016; 311: R721–R726.
15. Channick RN, Simonneau G, Sitbon O, *et al.* Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001; 358: 1119–1123.
16. Rubin LJ, Badesch DB, Barst RJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346: 896–903.
17. Treiber A, Aanismaa P, de KR, *et al.* Macitentan does not interfere with hepatic bile salt transport. *J Pharmacol Exp Ther* 2014; 350: 130–143.
18. Fattinger K, Funk C, Pantze M, *et al.* The endothelin antagonist bosentan inhibits the canalicular bile salt export pump: a potential mechanism for hepatic adverse reactions. *Clin Pharmacol Ther* 2001; 69: 223–231.
19. Bolli MH, Boss C, Binkert C, *et al.* The discovery of N-[5-(4-bromophenyl)-6-[2-[(5-bromo-2-pyrimidinyl)oxy]ethoxy]-4-pyrimidinyl]-N'-p ropylsulfamide (macitentan), an orally active, potent dual endothelin receptor antagonist. *J Med Chem* 2012; 55: 7849–7861.
20. Iglarz M, Binkert C, Morrison K, *et al.* Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist. *J Pharmacol Exp Ther* 2008; 327: 736–745.
21. Gatfield J, Mueller GC, Sasse T, *et al.* Slow receptor dissociation kinetics differentiate macitentan from other endothelin receptor antagonists in pulmonary arterial smooth muscle cells. *PLoS One* 2012; 7: e47662.
22. Gatfield J, Mueller GC, Bur D, *et al.* Distinct ETA receptor binding mode of macitentan as determined by site directed mutagenesis. *PLoS One* 2014; 9: e107809.
23. Sidharta PN, van Giersbergen PL, Halabi A, *et al.* Macitentan: entry-into-humans study with a new endothelin receptor antagonist. *Eur J Clin Pharmacol* 2011; 67: 977–984.
24. Dingemanse J, Sidharta PN, Maddrey WC, *et al.* Efficacy, safety and clinical pharmacology of macitentan in comparison to other endothelin receptor antagonists in the treatment of pulmonary arterial hypertension. *Expert Opin Drug Saf* 2014; 13: 391–405.
25. Bruderer S, Aanismaa P, Homery MC, *et al.* Effect of cyclosporine and rifampin on the pharmacokinetics of macitentan, a tissue-targeting dual endothelin receptor antagonist. *AAPS J* 2012; 14: 68–78.
26. Raghu G, Million-Rousseau R, Morganti A, *et al.* Macitentan for the treatment of idiopathic pulmonary fibrosis: the randomised controlled MUSIC trial. *Eur Respir J* 2013; 42: 1622–1632.
27. Pulido T, Adzerikho I, Channick RN, *et al.* Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 809–818.
28. Channick RN, Delcroix M, Ghofrani HA, *et al.* Effect of macitentan on hospitalizations: results from the SERAPHIN trial. *JACC Heart Fail* 2015; 3: 1–8.

29. Simonneau G, Channick RN, Delcroix M, *et al*. Incident and prevalent cohorts with pulmonary arterial hypertension: insight from SERAPHIN. *Eur Respir J* 2015; 46: 1711–1720.

30. Galie N, Jansa P, Pulido T, *et al*. SERAPHIN haemodynamic substudy: the effect of the dual endothelin receptor antagonist macitentan on haemodynamic parameters and NT-proBNP levels and their association with disease progression in patients with pulmonary arterial hypertension. *Eur Heart J* 2017; 38: 1147–1155.

31. Mehta S, Sastry BKS, Souza R, *et al*. Macitentan improves health-related quality of life for patients with pulmonary arterial hypertension: results from the randomized controlled SERAPHIN trial. *Chest* 2017; 151: 106–118.

32. Souza R, Channick RN, Delcroix M, *et al*. Association between six-minute walk distance and long-term outcomes in patients with pulmonary arterial hypertension: data from the randomized SERAPHIN trial. *PLoS One* 2018; 13: e0193226.

33. McLaughlin VV, Hoeper MM, Channick RN, *et al*. Pulmonary arterial hypertension-related morbidity is prognostic for mortality. *J Am Coll Cardiol* 2018; 71: 752–763.

34. Krause A, Zisowsky J and Dingemanse J. Modeling of pharmacokinetics, efficacy, and hemodynamic effects of macitentan in patients with pulmonary arterial hypertension. *Pulm Pharmacol Ther* 2018; 49: 140–146.

35. Ghofrani HA, Simonneau G, D'Armini AM, *et al*. Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1): results from the multicentre, phase 2, randomised, double-blind, placebo-controlled study. *Lancet Respir Med* 2017; 5: 785–794.

36. Vachiery JL, Delcroix M, Al-Hiti H, *et al*. Macitentan in pulmonary hypertension due to left ventricular dysfunction. *Eur Respir J* 2018; 51: 1701886.

37. Benza RL, Torbicki A, Uno H, *et al*. Using controlled and real-world data in concert to assess survival benefits in pulmonary arterial hypertension: insights from SERAPHIN and REVEAL. *Eur Respir J* 2017; 50: OA1986.

38. McGoon MD, Benza RL, Escribano-Subias P, *et al*. Pulmonary arterial hypertension: epidemiology and registries. *J Am Coll Cardiol* 2013; 62(Suppl. 25): D51–D59.

39. McLaughlin VV, Gaine SP, Howard LS, *et al*. Treatment goals of pulmonary hypertension. *J Am Coll Cardiol* 2013; 62(Suppl. 25): D73–D81.

40. Savarese G, Paolillo S, Costanzo P, *et al*. 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.

41. Gatzoulis MA, Landzberg M, Beghetti M, *et al*. Evaluation of macitentan in patients with eisenmenger syndrome: results from the randomized, controlled MAESTRO study. *Circulation*. Epub ahead of print 24 August 2018. DOI: 10.1161/CIRCULATIONAHA.118.033575.

42. Galie N, Beghetti M, Gatzoulis MA, *et al*. Bosentan therapy in patients with Eisenmenger syndrome: a multicenter, double-blind, randomized, placebo-controlled study. *Circulation* 2006; 114: 48–54.

43. Chin KM, Gomberg-Maitland M, Channick RN, *et al*. Psychometric validation of the pulmonary arterial hypertension-symptoms and impact (PAH-SYMPACT) questionnaire: results of the SYMPHONY trial. *Chest* 2018; 154: 848–861.

44. Issac M, Dingemanse J and Sidharta PN. Pharmacokinetics of macitentan in patients with pulmonary arterial hypertension and comparison with healthy subjects. *J Clin Pharmacol* 2017; 57: 997–1004.

45. Jansa P and Pulido T. Macitentan in pulmonary arterial hypertension: a focus on combination therapy in the SERAPHIN trial. *Am J Cardiovasc Drugs* 2018; 18: 1–11.

46. Galie N, Barbera JA, Frost AE, *et al*. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med* 2015; 373: 834–844.

47. Burgess G, Hoogkamer H, Collings L, *et al*. Mutual pharmacokinetic interactions between steady-state bosentan and sildenafil. *Eur J Clin Pharmacol* 2008; 64: 43–50.

48. Wrishko RE, Dingemanse J, Yu A, *et al*. Pharmacokinetic interaction between tadalafil and bosentan in healthy male subjects. *J Clin Pharmacol* 2008; 48: 610–618.

49. Spence R, Mandagere A, Dufton C, *et al*. Pharmacokinetics and safety of ambrisentan in combination with sildenafil in healthy volunteers. *J Clin Pharmacol* 2008; 48: 1451–1459.

50. Spence R, Mandagere A, Harrison B, *et al*. No clinically relevant pharmacokinetic and safety interactions of ambrisentan in combination with tadalafil in healthy volunteers. *J Pharm Sci* 2009; 98: 4962–4974.

51. Sidharta PN, van Giersbergen PL, Wolzt M, *et al*. Investigation of mutual pharmacokinetic interactions between macitentan, a novel endothelin receptor antagonist, and sildenafil in healthy subjects. *Br J Clin Pharmacol* 2014; 78: 1035–1042.

52. Tran TT, Brinker AD and Munoz M. Serious liver injury associated with macitentan: a case report. *Pharmacotherapy* 2018; 38: e22–e24.

53. Savale L, Magnier R, Le PJ, *et al*. Efficacy, safety and pharmacokinetics of bosentan in portopulmonary hypertension. *Eur Respir J* 2013; 41: 96–103.

54. Cartin-Ceba R, Swanson K, Iyer V, *et al*. Safety and efficacy of ambrisentan for the treatment of portopulmonary hypertension. *Chest* 2011; 139: 109–114.

55. Sitbon O, Bosch J, Cottreel E, *et al*. European respiratory journal 2018 52: OA267 late breaking abstract - efficacy and safety of macitentan in portopulmonary hypertension: the PORTICO trial. *Eur Respir J* 2018; 52: OA267.