

Initial combination therapy with macitentan and tadalafil in pulmonary arterial hypertension: a retrospective cohort study

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Abstract

Purpose: Initial combination therapy with ambrisentan and tadalafil has been demonstrated superior to either agent alone in pulmonary arterial hypertension (PAH). More recently, the OPTIMA trial showed efficacy of another combination of endothelin receptor antagonist and phosphodiesterase 5-inhibitor, macitentan and tadalafil, as initial therapy for PAH. The objective of this study was to assess the effectiveness, tolerability, and safety of macitentan and tadalafil in a real-world clinical setting.

Methods: This single centre, retrospective cohort study identified adult patients newly diagnosed with PAH between January 2014 and December 2017 who were started on macitentan and tadalafil. Patients were retrospectively followed for one year. Effectiveness was evaluated via change from baseline in disease risk profile based on a validated score incorporating World Health Organization functional class, 6-minute walk distance (6MWD), B-type natriuretic peptide (BNP), and hemodynamics on follow-up right heart catheterization. Secondary endpoints included change in 6MWD, BNP, and hemodynamic variables. Drug tolerability and adverse events were assessed.

Results: The cohort included 46 patients, 8 of whom (17%) did not tolerate and discontinued either macitentan or tadalafil. Median time to follow-up was 161 days (IQR 72). 42% of patients with an initially moderate or high risk disease profile improved to low risk. Secondary endpoints showed a reduction in the geometric mean of pulmonary vascular resistance of 45% (95% CI 29, 57%) and improvement in 6MWD of 88m (95% CI 27, 148m).

Conclusion: In a real-world setting, macitentan and tadalafil as initial combination therapy for PAH was well tolerated and yielded clinical benefit.

Background

Pulmonary arterial hypertension (PAH) is a disease characterized by vascular remodelling leading to progressive elevation of pulmonary vascular resistance, right heart failure and death [1]. While there is no cure to the proliferative pulmonary arteriopathy, three mechanistically different pathways are known that may be targeted pharmacologically to delay disease progression [2]. The AMBITION trial demonstrated that, in treatment-naïve patients, upfront combination therapy targeting two such pathways via ambrisentan (an endothelin receptor antagonist, ERA) and tadalafil (a phosphodiesterase type 5 inhibitor, PDE-5i) was superior to either drug as monotherapy, with most of this benefit derived from a lower rate of hospitalization for worsening PAH [3, 4].

Based in part on these findings, initial combination therapy with ERA/PDE-5i has become a recommended treatment strategy in patients newly diagnosed with PAH, although the interchangeability of different ERA/PDE5-i agents is not certain [5, 6]. Macitentan is a relatively newer ERA with higher biochemical antagonistic potency, longer half-life and suggested improved adverse effect profile compared to ambrisentan [7]. Most recently, the prospective OPTIMA trial showed macitentan and

tadalafil were well tolerated and resulted in a 47% reduction in the geometric mean of pulmonary vascular resistance after 16 weeks of therapy compared to baseline [8].

While the OPTIMA trial demonstrated the relative efficacy of macitentan and tadalafil, we sought to add to this experience by assessing the effectiveness of macitentan and tadalafil in a real-world clinical setting over longer follow-up and with particular focus on improvement in validated, guideline-based disease risk category [5].

Methods

We conducted a single-centre, retrospective cohort study. Consecutive patients referred to the Pulmonary Hypertension Program at the Toronto General Hospital between January 2014 and December 2017 were eligible for inclusion. A manual chart review identified patients started on upfront combination therapy with macitentan and tadalafil. Patient records were reviewed for treatment effect, safety, and tolerability of macitentan and tadalafil over one year of follow-up. The study was approved by the institutional Ethics Board (UHN17-5845).

Inclusion and Exclusion Criteria

Individuals aged 18 years and older were included if they were newly diagnosed with PAH in the previous 6 months and started on macitentan and tadalafil within 6 weeks of one another. Full doses consisted of macitentan 10mg and tadalafil 40mg daily. PAH etiologies included idiopathic, heritable, and PAH associated with anorexigen use, connective tissue disease (CTD), congenital heart disease, or human immunodeficiency virus infection. A diagnosis of PAH was established by right heart catheterization (RHC) demonstrating mean pulmonary arterial pressure (mPAP) of $\geq 25\text{mm}_{\text{Hg}}$, pulmonary capillary wedge pressure (PCWP) $\leq 15\text{mm}_{\text{Hg}}$, and pulmonary vascular resistance (PVR) of ≥ 3 Wood Units (WU). Exclusion criteria consisted of PAH secondary to portopulmonary hypertension, concurrent therapy with a prostacyclin, or any prior PAH-specific therapy.

Effectiveness

Treatment effects of macitentan and tadalafil were assessed in all individuals who received at least one dose of each drug, similar to an intention-to-treat analysis. Effectiveness was evaluated over one year of follow-up based on the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) risk assessment table for prognostication in PAH [5]. We examined change in World Health Organization (WHO) Functional Class (FC), 6-minute walk distance (6MWD), B-type natriuretic peptide (BNP), and hemodynamics on follow-up RHC, including right atrial pressure (RAP), cardiac index (CI), and mixed venous oxygen saturation (S_{VO_2}). Each patient was classified as low, intermediate, or high risk for each of the aforementioned variables according to the 2015 ESC/ERS risk categories (low risk, 1; intermediate risk, 2; high risk, 3). For three patients who expired during the one-year study, highest risk categories were imputed on follow-up. Overall risk profiles at baseline and follow-up were calculated by taking the mean value among all prognostic variables rounded to the nearest integer. The primary endpoint was

percentage of patients improving to the low overall risk category following treatment with macitentan and tadalafil. Secondary endpoints were changes in WHO FC, 6MWD, BNP, and hemodynamic variables on follow-up RHC. For the three patients who expired, the worst value recorded in the study was imputed for each variable on follow-up. For all other individuals, each patient's baseline data was imputed on follow-up wherever the latter was missing (**Table S1**).

Tolerability and Safety

Safety endpoints assessed were the occurrence of hypotension (systolic blood pressure $<85\text{mmHg}$ or diastolic blood pressure $<50\text{mmHg}$), edema (new or worsening peripheral edema), headache, anemia (hemoglobin decline $\geq 15\text{g/L}$ from baseline to an absolute value $<100\text{g/L}$) or liver enzyme elevation (transaminases greater than 3 times the upper limit of normal) within one year of follow-up. Tolerability endpoints included agent discontinuation as well as reason for and time to discontinuation.

Statistics

Simple descriptive statistics were used to express patient characteristics and the primary endpoint. Change in categorical variables before and after treatment was assessed using a Chi squared/Fisher's exact test, as appropriate. Secondary endpoints consisting of change in continuous variables were estimated by simple linear regression; BNP, PVR, and CI data were lognormally distributed and the ratio of geometric means at baseline and follow-up was used to assess change.

Results

Between January 2014 and December 2017, 46 patients newly diagnosed with PAH were started on combination therapy with macitentan and tadalafil, receiving at least one dose of each medication. Demographic data and disease etiology are presented in **Table 1**. The median age was 56 years and 85% of patients were female. The etiology of PAH was relatively evenly divided between idiopathic PAH (50%) and PAH associated with connective tissue disease (43%), most commonly scleroderma (26%).

Table 1: Baseline Characteristics of Study Population

Cohort characteristics	
Subjects, <i>n</i>	46
Age, median (Q1, Q3), years	56 (36, 68)
Sex, <i>n</i> (%)	
Male	7 (15)
Female	39 (85)
BMI, mean (SD), m/kg²	27 (7)
Pulmonary Hypertension WHO Classification, <i>n</i> (%)	
Idiopathic	23 (50)
Connective tissue disease	19 (41)
Scleroderma	12 (26)
Mixed connective tissue	3 (7)
Systemic lupus erythematosus	2 (4)
Myositis	1 (2)
Rheumatoid arthritis	1 (2)
Congenital heart disease	3 (7)
Human immunodeficiency virus	1 (2)

BMI=body mass index.

Effectiveness

Cohort composition by overall risk category at baseline and follow-up is shown in **Figure 1**. The median time from start of therapy to follow-up and reassessment via RHC was 161 days (IQR 72). Forty-three of 46 patients (93%) were at high or intermediate risk at baseline, of whom 18 patients (42%) met the primary endpoint and improved to low risk category on follow-up. Three patients died within 6 months of starting treatment: 2 were initially at moderate risk and did not tolerate macitentan, discontinuing the drug within one week of initiation, and 1 was initially high risk and remained so despite dual therapy. All 3 individuals who died were women with scleroderma aged >65 years.

Changes in PAH prognostic variables at baseline and follow-up are described in **Table 2**. Twenty-nine individuals (63%) improved in functional class while 2 (4%) worsened. Average 6MWD improved by 88m (95% CI 27, 148m) and BNP was reduced by 65% (geometric mean ratio 0.35, 95% CI 0.15, 0.82). With respect to hemodynamic variables, PVR decreased by 45% (geometric mean ratio 0.55, 95% CI 0.43, 0.71) and CI improved by 30% (geometric mean ratio 1.3, 95% CI 1.16, 1.46). Results remained similar when

analysis was restricted to the subset of patients who tolerated and did not discontinue macitentan or tadalafil (**Table S2**). Change in risk category for individual PAH prognostic variables as per 2015 ESC/ERS guidelines are shown in **Table S3**.

Table 2: PAH Prognostic Variables at Baseline and Follow-up

	Baseline	Follow-up	Change from baseline to follow-up	
			Mean (95% CI)	<i>p</i>
Subjects, <i>n</i>	46	46		
Functional Class, (%)				
I	0	6 (13)	Improved: 29 (63)	<0.0001
II	6 (13)	25 (54)	No change: 15 (33)	
III	36 (78)	12 (26)	Worsened: 2 (4)	
IV	4 (9)	3 (7)		
Baseline 6MWD^a	322 (139)	409 (151)	88 (27, 148)	<0.01
Baseline BNP, pg/mL^b	421 (82, 840)	77 (24, 210)	0.35 (0.15, 0.82) ^d	0.02
Baseline RHC				
PVR, WU	12.6 (9.4, 16.1)	7.0 (4.7, 10.3)	0.55 (0.43, 0.71) ^d	<0.0001
mPAP, mm _{Hg}	49.6 (12.0)	41.8 (17.2)	-7.8 (-13.9, -1.7)	0.01
RAP, mm _{Hg}	9.7 (5.5)	6.0 (5.0)	-3.7 (-5.9, -1.5)	<0.01
PCWP, mm _{Hg}	8.1 (3.5)	8.1 (3.5)	0 (-1.4, 1.4)	0.98
CI, L/min/m ²	1.9 (1.6, 2.3)	2.5 (2.1, 2.9)	1.3 (1.16, 1.46) ^d	<0.0001
Sv _{O2} , % ^c	58.1 (9.8)	64.5 (10.1)	6.4 (2.0, 10.9)	<0.01

Median follow-up of 161 days (IQR 72 days). Variables expressed as mean (SD) with the exception of BNP, PVR and CI, which are lognormally distributed and expressed as median (IQR). Change from baseline expressed as arithmetic difference in means (95% confidence interval), with the exception of BNP, PVR and CI, which are expressed as a geometric mean ratio of follow-up and baseline values (95% confidence interval).

6MWD=6-minute walk distance, BNP=B-type natriuretic peptide, RHC=right heart catheterization, PVR=pulmonary vascular resistance, mPAP=mean pulmonary arterial pressure, PCWP=pulmonary capillary wedge pressure, CI=cardiac index, Sv_{O2}=mixed venous oxygen saturation.

^a Based on 45 measurements

^b Based on 32 measurements

^c Based on 40 measurements

^d Geometric mean ratio with CI

Tolerability and Safety

Adverse events and drug discontinuations are summarized in **Table 3**. In total, 8 of 46 patients (5 macitentan and 3 tadalafil; 17% total) discontinued therapy due to an adverse effect or intolerance. Baseline characteristics of individuals who discontinued either macitentan or tadalafil are shown in **Table S4**. Of these 8 patients, 2 expired within one year due to progressive disease, having only tolerated tadalafil monotherapy. Two other patients who discontinued macitentan or tadalafil went on with monotherapy; the remaining 4 had the ERA or PDE-5i substituted with a different drug of the same class.

The most common adverse events associated with combination therapy were headache and edema, occurring in 50% and 30% of individuals, respectively. Headache occurred within days of starting therapy, resulting in discontinuation of tadalafil in 2 individuals (4%). A further 4 cases required transient stopping and gradual re-introduction of tadalafil. Edema led to discontinuation of macitentan in 3 cases (7%), of which two patients required admission to hospital for intravenous diuresis.

Anemia occurred in 6 cases (13%) between 20 to 171 days of starting macitentan. Three of these cases were complicated by superimposed confounding factors felt to be the primary drivers of the anemia. One case required red blood cell transfusion, but anemia did not lead to discontinuation of macitentan in any of the 6 cases. Transaminitis greater than 3 times the upper limit of normal occurred in one patient 22 days after initiation of macitentan, reaching an ALT of 230 IU and AST of 456 IU from previously normal baseline values. Macitentan was discontinued and the patient was later started on ambrisentan without recurrence of transaminitis.

An additional 2 patients discontinued PAH therapy due to other adverse effects. One patient elected to stop tadalafil 18 days from initiation due to significant epistaxis, though this was also in the setting of a supratherapeutic INR of 5 and felt unlikely to be related to tadalafil. In another case, macitentan was discontinued within 8 days due to unremitting nausea and decreased appetite, possibly confounded by worsening PAH.

Table 3: Adverse Events and Discontinuation of Macitentan or Tadalafil

Adverse event	<i>n</i> (%)	Agent discontinued, <i>n</i>
Headache	23 (50)	2
Edema	14 (30)	3
Anemia	6 (13)	0
Hypotension	3 (7)	0
Transaminitis	1 (2)	1
Epistaxis	1 (2)	1
Muscle cramps	1 (2)	0
Nausea	1 (2)	1

Discussion

Our study describes a Canadian experience with macitentan and tadalafil as initial therapy for newly diagnosed PAH. Among this cohort, a majority of individuals (83%) tolerated macitentan and tadalafil, and 42% of patients with initially moderate or high risk disease improved to low risk based on a validated prognostic score composed of WHO functional class, 6MWD, BNP, and hemodynamic parameters [5, 9]. These findings provide real-world effectiveness data supporting the use of this particular ERA/PDE5-i combination, which has only been specifically studied in one previous trial [8].

While the AMBITION trial demonstrated that initial combination therapy with ambrisentan and tadalafil reduced the composite endpoint of death or worsening PAH compared to either drug in monotherapy [3], generalizability to all ERA/PDE-5i combinations is not guaranteed. Indirect data from the SERAPHIN trial suggests benefit of macitentan and PDE-5i. The addition of macitentan to background PDE-5i therapy (62% of trial patients) in this study reduced the primary endpoint of morbidity and mortality by 38%, similar to those not on background therapy [10]. However, of those individuals on background therapy, most were on sildenafil and had been stabilized on this drug for at least 3 months, limiting the information that can be extrapolated regarding the particular combination of macitentan and tadalafil [11]. This led to the French OPTIMA trial designed specifically to examine macitentan and tadalafil in newly diagnosed PAH over 16 weeks [8]. This prospective, open-label, single-arm, multicentre trial enrolled 46 patients and found treatment with macitentan and tadalafil led to a 47% reduction in the geometric mean of PVR and 36m improvement in 6MWD [8]. Only 2 individuals discontinued drug therapy before 16 weeks due to either a revision in etiology of PAH or an adverse event.

Our findings confirm the results of the OPTIMA trial outside of the rigorous trial setting. Specifically, we observed a near-identical reduction in PVR of 45%, as well as an improvement in 6MWD of 88m. Compared to OPTIMA, we found more individuals discontinued either macitentan or tadalafil due to adverse effects (17% compared to 4%). While the lower number of discontinuations in OPTIMA likely

reflects selection bias in the highly motivated patients who took part in the trial, the current study continues to suggest that this combination is well-tolerated in most individuals with relatively minor adverse effects. We observed headache considerably more frequently in the current study compared to OPTIMA (50% vs 24%), while instances of edema, anemia, and transaminitis were similar (30% vs 28%, 13 vs 13%, 2% vs 2%, respectively). All adverse effects were comparable to previous major trials [3, 10], and there were no cases of treatment discontinuation due to anemia or transaminitis.

The current study has several strengths, including a real-world setting, lengthy follow-up time of one year that exceeds most trials in PAH, and application of the validated ESC/ERC prognostic score for assessing response to therapy and low-risk disease status as a primary outcome. This prognostic score has been independently validated in three studies [12-14] and constitutes an endpoint that is increasingly recognized and clinically relevant to long-term outcomes in PAH [9]. Furthermore, follow-up assessment of hemodynamics on RHC was available for a vast majority of individuals in the current study, demonstrating meaningful improvement in physiologic variables shown to be directly related to improved clinical outcomes [15]. Although a retrospective trial design, analysis was conducted as intention-to-treat and missing data was handled as conservatively as possible, either carrying forward baseline values or imputing the worst value observed across the entire study for those patients who died. This lends credibility to the significant beneficial effect observed. The limitations of the study include its retrospective nature, small number of participants, lack of control group, and possible bias in clinician selection of those individuals to start on dual oral therapy. While the study was restricted to a single Canadian centre, the close agreement of the current results with the French OPTIMA trial is reassuring with regards to the generalizability of the findings.

Conclusions

Our retrospective analysis suggests that macitentan and tadalafil are a viable ERA/PDE-5i combination in a real-world setting. Drug tolerability remained high and 42% of individuals who started as intermediate or high risk had improved to a low risk profile, which has been associated with excellent 5-year transplant-free survival. However, approximately 60% remained intermediate or high risk, highlighting the limitations of initial oral combination therapy.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Conflicts of interest: The authors declare that they have no competing interests.

Availability of data and materials: The datasets generated and/or analysed during the current study are not publicly available but are available from the corresponding author on request.

Code availability: The code generated for analysis in the current study are not publicly available but are available from the corresponding author on request.

Ethics approval: The study was approved by the University Health Network's Ethics Board (UHN17-5845).

Consent to participate: Not applicable.

Consent for publication: Not applicable

Abbreviations

6MWD: 6-minute walk distance

BMI: body mass index

BNP: B-type natriuretic peptide

CI: cardiac index

CHD: congenital heart disease

CTD: connective tissue disease

ERA: endothelin receptor antagonist

ERS: European Respiratory Society

ESC: European Society of Cardiology

FC: functional class

HIV: human immunodeficiency virus

mPAP: mean pulmonary arterial pressure

PAH: pulmonary arterial hypertension

PCWP: pulmonary capillary wedge pressure

PDE-5i: phosphodiesterase type 5 inhibitor

PVR: pulmonary vascular resistance

RA: rheumatoid arthritis

RAP: right atrial pressure

RHC: right heart catheterization

SLE: systemic lupus erythematosus

S_{V02}: mixed venous oxygen saturation

IQR: inter-quartile range

WHO: World Health Organization

WU: Wood units

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Figures

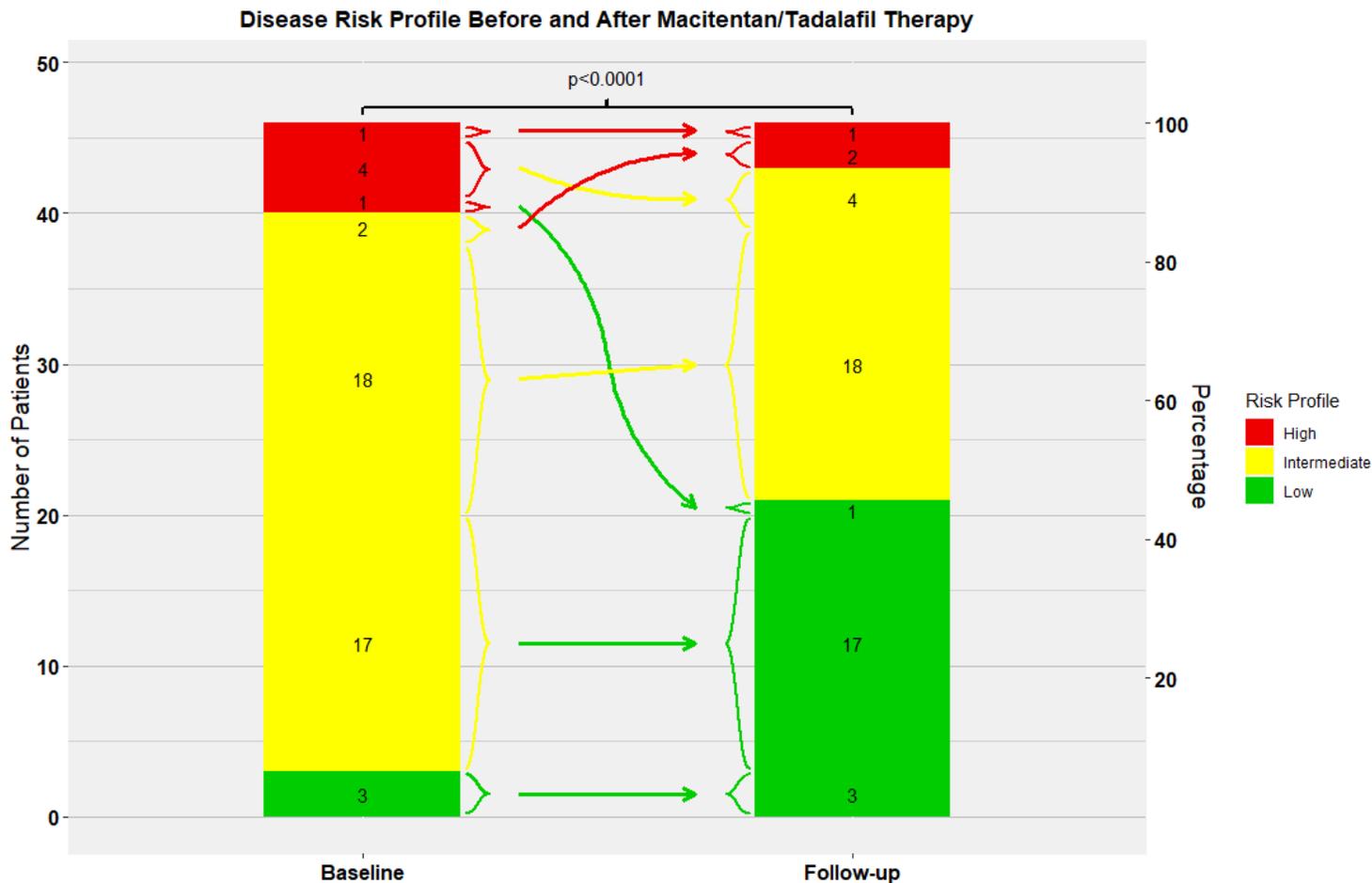


Figure 1

Number of study patients classified by pulmonary arterial hypertension risk category as per 2015 European Society of Cardiology/European Respiratory Society guideline criteria, at baseline and upon follow-up of median 161 days (IQR 72 days). Overall risk score is based on combination of World Health Organization functional class, 6-minute walk distance, B-type natriuretic peptide, right atrial pressure, cardiac index, and mixed venous oxygen saturation. X2 test for significance.

Supplementary Files

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