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Pulmonary arterial hypertension outcomes upon endothelin-1 receptor antagonist switch to macitentan

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Abstract

Objectives: To assess whether switching patients with suboptimally controlled pulmonary arterial hypertension from bosentan or ambrisentan to macitentan would improve six-minute walk test (6MWT) distance and World Health Organization functional class.

Methods: This was a retrospective cohort analysis of 37 patients from a single center. Patients were separated into three heterogeneous treatment groups and followed for 18 months: switch group (n = 14): patients switched to macitentan from bosentan/ambrisentan; added group (n = 11): patients who began macitentan as de novo therapy (n = 5) or who added macitentan to an existing sildenafil regimen (n = 6); and control group (n = 12): patients for whom sildenafil and/or bosentan/ambrisentan therapy was unchanged.

Results: Mortality was observed in two patients (one each, switch and added groups). Patients in the control group had one hospital admission and 100% survival. There was significant improvement in functional class for the switch and added groups. Statistically significant improvement was observed in 6MWT distance in the added group alone. Overall, 92% of patients continued macitentan throughout the study.

Conclusion: Macitentan was well tolerated. For bosentan/ambrisentan-treated patients with suboptimally controlled pulmonary arterial hypertension, switching to macitentan may facilitate an improvement in functional class.

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Introduction

Pulmonary hypertension (PH) is associated with impaired quality of life, poor functional capacity, reduced survival, and mean pulmonary artery pressure (mPAP) ≥ 25 mmHg at rest.[1] There are five types of PH.[2,3] Pulmonary arterial hypertension (PAH), a rare form of PH, comprises PAPm ≥ 25 mmHg, combined with pulmonary capillary wedge pressure ≤ 15 mmHg.[3] PAH affects pulmonary circulation, but can occur secondary to other medical conditions.[3] The Armadale PH study suggested a prevalence of 15/100,000 people with PAH in a Western Australian population.[4] Traditionally, patients with PAH have had very high morbidity and mortality.[5] However, the prognosis of PAH has improved with the advent of targeted PAH therapies.[4]

The World Health Organization (WHO) categorizes PH into four classes of functional limitation: I (nil) to IV (severe).[2] Patients with WHO functional Class II and higher are generally eligible for targeted therapies,[5] including endothelin-1 receptor antagonists (ERAs), phosphodiesterase-5 inhibitors (PDE5) and synthetic prostacyclin/prostaglandin analogs.[6] Other therapies include prostanoid receptor agonists.[7] A recent meta-analysis showed that therapy with prostacyclin, an ERA, or a PDE5 inhibitor improved mortality, compared with controls.[8,9] Nonetheless, morbidity and mortality from PAH remain high.

In September 2014, a new ERA—macitentan—was made available under the Pharmaceutical Benefits Scheme in Australia.[10] Macitentan demonstrates enhanced receptor binding, potency, and receptor occupancy half-life, compared with other ERAs.[8] Thus, macitentan may be superior to either ambrisentan or bosentan for treatment of PAH. Compared with placebo, participants on macitentan have shown improved exercise capacity and WHO functional class;[11] macitentan significantly reduced morbidity and mortality, even among patients who received macitentan as an addition to established PAH therapy.[12] There is no notable increase in the risk of hepatotoxicity or peripheral edema on macitentan.[13] Despite these theoretical benefits of macitentan, to our knowledge, no studies have directly compared macitentan with other available ERAs, or any other targeted therapies. Thus, an analysis is needed to determine whether a switch of ERAs to macitentan is associated with functional improvement in patients with suboptimal response to first-line therapy.

We hypothesized that in adult patients with clinician-determined suboptimal response to bosentan or ambrisentan, a switch to macitentan would be associated with improved outcomes as measured by WHO functional class, six-minute walk test (6MWT), and echocardiographic parameters as well as reduced number of hospitalizations, irrespective of concurrent PDE5 inhibitor use. Furthermore, we hypothesized that drug tolerability would be improved in patients switched to macitentan.

Materials and methods

Study design

Ethics approval was granted through a low-risk application to the Human Ethics Research Committee through the University of Notre Dame Australia. This retrospective cohort study involved the analysis of cardiopulmonary, clinical, and exercise parameters from the records of patients who underwent treatment for PAH by one clinician in a private clinic in Australia. A public notification was posted in the examination rooms of the clinic to notify patients of the study.

The patients were classified into three treatment groups (described in "Participants" subsection, below) based on treatment status, which was determined prior to the study. The treating clinician used a combination of objective measures to determine which patients were stable and which patients showed a lack of response to first-line therapy; these included WHO functional class, 6MWT distance, echocardiography, tolerance to medication, and hospitalization requirement. Patients were then allocated to the appropriate treatment groups.

Data were retrospectively collected from patient records for the period from January 2014 through September 2016. All data reflected conventional clinical practice and clinical management decisions, which were not impacted by the current study. Patients with either prevalent (length of diagnosis ≥ 6 months) or incident (length of diagnosis < 6 months) PAH were included.

Participants

Records of patients $\geq$18 years of age who were diagnosed with Group 1 PH (i.e., PAH), and who were eligible for Pharmaceutical Benefits Scheme-subsidized targeted therapies, were included in the study. For the purpose of analysis, patients were divided into three groups based upon management decisions. The treating clinician made these decisions prior to beginning any research with regard to treatment of the patients.

The group of interest (switch group) consisted of patients who were switched from bosentan or ambrisentan, based on the clinician's assessment of suboptimal response.

The first comparator group (added group) consisted of patients who began macitentan as first-line therapy or who added macitentan therapy to existing sildenafil therapy.

The second comparator group (control group) consisted of patients who were judged by the treating clinician to have stable PAH; in these patients, therapy with sildenafil and/or bosentan/ambrisentan was unchanged.

Variables

In addition to survival data, information was collected from all patient records regarding demographic variables (age, sex), clinical diagnosis (type of PAH), and duration since diagnosis. Both WHO functional class and the 6MWT distance in meters were recorded as functional outcomes. Furthermore, the following echocardiography measures were recorded for each patient: right ventricular size, right ventricular systolic function, and pulmonary artery systolic pressure (PASP). The frequencies of all-cause hospitalization and mortality were recorded, as were the incidences of all known side effects of macitentan and other ERAs (e.g., abnormal liver function tests, gastrointestinal upset, and anemia). The use of other therapies, including diuretics, was also noted.

Data analysis

Demographic data (de-identified) for all patients were recorded in an Excel spreadsheet and coded appropriately. Stability of PAH was determined via the analysis of the outcome measures listed in variables. Differences among groups were identified using analyses of variance and analyses of covariance for continuous variables. Post hoc analyses involving small sample numbers and repeated measures data were performed using Friedman's nonparametric test for related samples. The nonparametric Wilcoxon signed-rank test was used to compare changes in categorical rank data. Measures of association for categorical data were tested using chi-squared analyses. SPSS for Windows (version 25.0.0.1; IBM Corp., Armonk, NY, USA) was used to perform statistical comparisons. A p-value of < 0.05 was considered to be significant.

Missing data were addressed as follows. Initially, all demographic information was collected. If information regarding 6MWT was unavailable, this parameter was left blank. For patients with insufficient tricuspid regurgitation, no numerical value was assigned for PASP. Regarding echocardiography, some reports did not describe systolic function and size; thus, this information was coded as absent. Patients who had missing data were excluded from analyses involving those parameters.

Results

This exploratory study enrolled a convenience sample of 37 patients, which is considerable for a rare disease. All had PAH confirmed by right heart catheterization. Non-PAH causes of pre-capillary PH were excluded, based on known diagnostic and assessment protocols.[1] There were 14 patients in the switch group, 11 patients in the added group, and 12 patients in the control group. One patient each in the switch and added groups died. The three groups were similar in age, sex distribution, and type of PAH (Table 1).

Regarding WHO Functional Class, Figure 1 shows the changes in actual rank for each patient. Wilcoxon signed rank test between functional class at baseline and at 6 months showed significant changes for the switch ($z = -2.91$, $p = 0.004$) and added

Table 1. Demographic characteristics.

	Switch (n = 14)	Added (n = 11)	Control (n = 12)	p-value
Age (years, ± SD)	63 ± 13	65 ± 5	74 ± 9	0.114
Female sex (%)	86%	73%	83%	0.927
PAH etiology				0.818
Idiopathic	64%	55%	67%	
Scleroderma	36%	45%	33%	
PAH type				Not compared
Incident	3	8	2	
Prevalent	11	3	10	
Prior medication				Not compared
Bosentan	12	0	9	
Ambrisentan	2	0	0	
None	0	5	0	
Sildenafil	0	6	1	
Bosentan + sildenafil	0	0	2	

SD, standard deviation; PAH, pulmonary arterial hypertension.

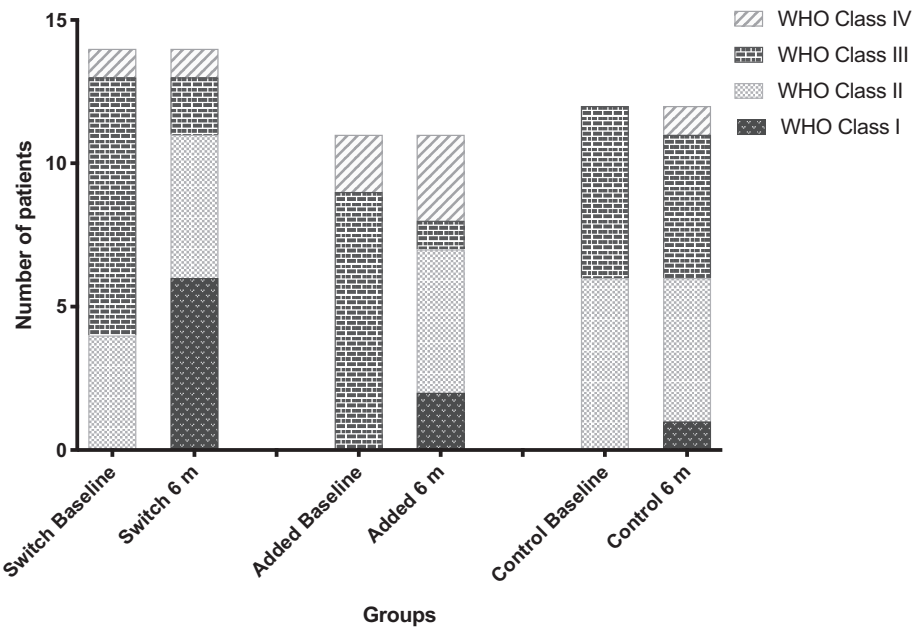

Figure 1. World Health Organization functional class. WHO, World Health Organization; 6 m, 6 months.

Table 2. Six-minute walk test distance.

Group	Time point	Distance (m, mean ± SD)	p-value
Switch	Baseline	371 ± 28	0.17
	3 months	415 ± 29	
	6 months	404 ± 42	
Added	Baseline	334 ± 28	0.01
	3 months	393 ± 29	
	6 months	415 ± 42	
Control	Baseline	484 ± 28	0.88
	3 months	464 ± 29	
	6 months	461 ± 42	

SD, standard deviation.

groups ($z = -2.12$, $p = 0.03$), but not for the control group ($z = 0.00$). For 6MWT (Table 2), by 6 months there was a 37-m improvement in the switch group (not statistically significant), a 98-m improvement in the added group ($p=0.01$), and no significant change in the control group. There was no difference between the switch and control groups, whereas there was a difference between the added and control groups ($p = 0.03$). There was weak statistical evidence for a difference between the switch and added groups (Figure 2).

Given the small study numbers, a Friedman's statistic was calculated to determine whether echocardiography scores differed among the three measurement points for each group. The χ^2 test did not show significant differences in right ventricular size or right ventricular systolic function for any of the groups (Figures 3 and 4). PASP at echocardiography was only recorded for patients with sufficient tricuspid regurgitation (Figure 5). In the switch group, eight patients at baseline had insufficient tricuspid regurgitation; thus, no data were available for analysis in these patients. Similarly, two patients in the control group and one patient in the added group had insufficient tricuspid regurgitation and were excluded from analysis. There was no

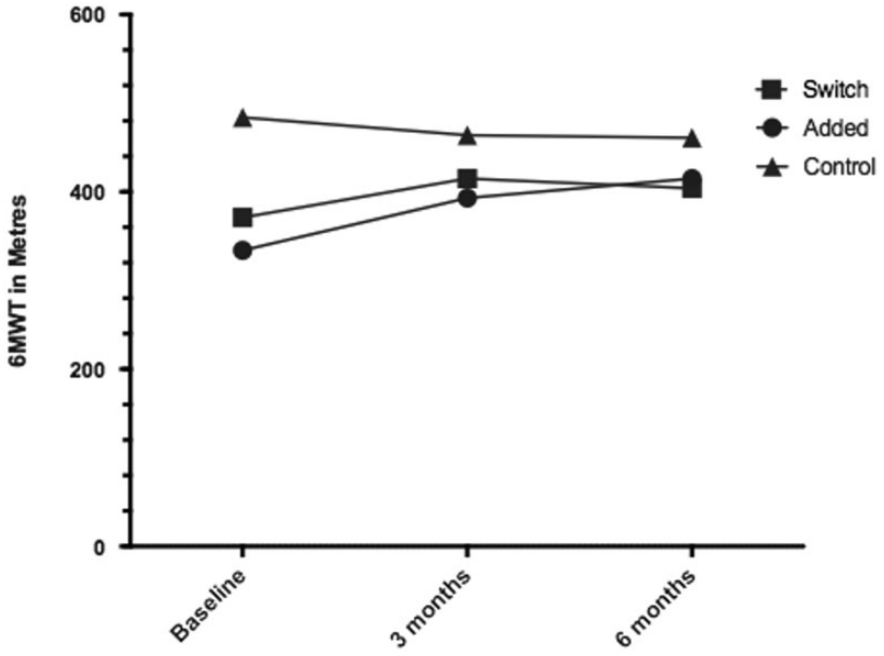

Figure 2. Mean six-minute walk test distance in meters.

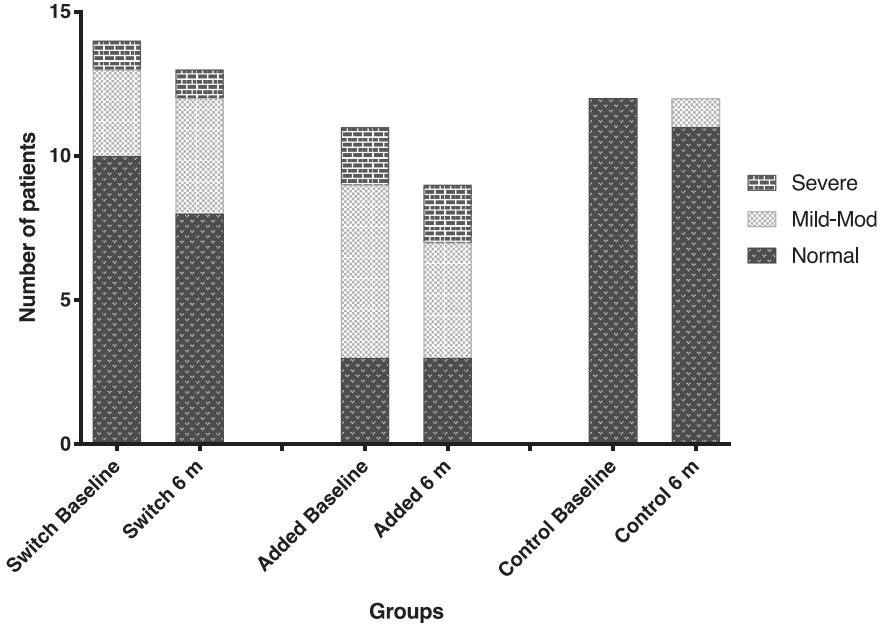

Figure 3. Echocardiography analysis of right ventricular systolic function. 6 m, 6 months; Mild-Mod, mild to moderate dysfunction.

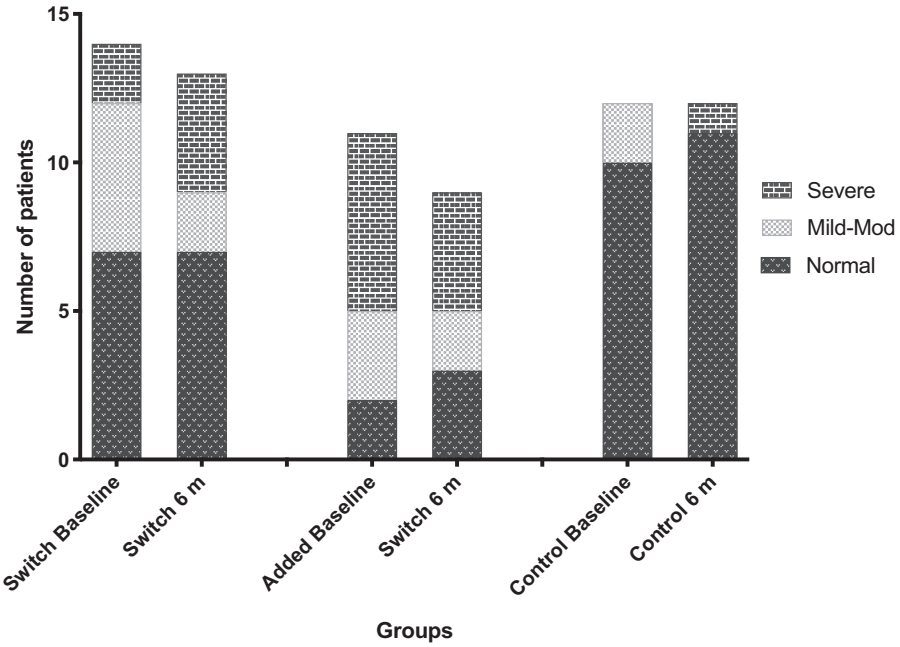

Figure 4. Echocardiography analysis of right ventricle size. 6 m, 6 months.

statistically significant difference in PASP for the switch ($\chi^2 = 3.5$), added ($\chi^2 = 1.6$), and control groups ($\chi^2 = 2.1$).

Eleven patients had at least one hospital admission. Mortality was 2/37 (one each in the switch and added groups) with an annualized mortality of 3.6%. Patients in the control group remained stable with one hospital admission and 100% survival. Overall, 92% of patients continued macitentan throughout the study. One patient in the switch group stopped macitentan due to anemia; another patient in the switch group stopped all therapy, received palliative therapy, and died shortly thereafter (Table 3).

Discussion

This study found that, in ERA-treated patients who did not show well-controlled PAH (based on WHO Functional Class, 6MWT distance, and echocardiography features of right ventricular failure), switching to macitentan was associated with a statistically significant improvement in functional class. These findings confirmed that macitentan is well tolerated and effective for treatment of PAH.

There was an improvement in the WHO functional class in the switch group. Notably, the WHO functional class is a robust measure and has been used to guide therapy.[3,14,15] To our knowledge this is the first study to show an improvement in WHO functional class following a switch from an existing ERA regimen to macitentan. Additionally, the 6MWT is a widely used, simple, and non-invasive test that measures reduced exercise capacity and provides an estimate of aerobic fitness in patients with PAH.[2,15] In this study, there was a 37-m improvement in the 6MWT distance in patients who switched to macitentan, compared with no change in patients

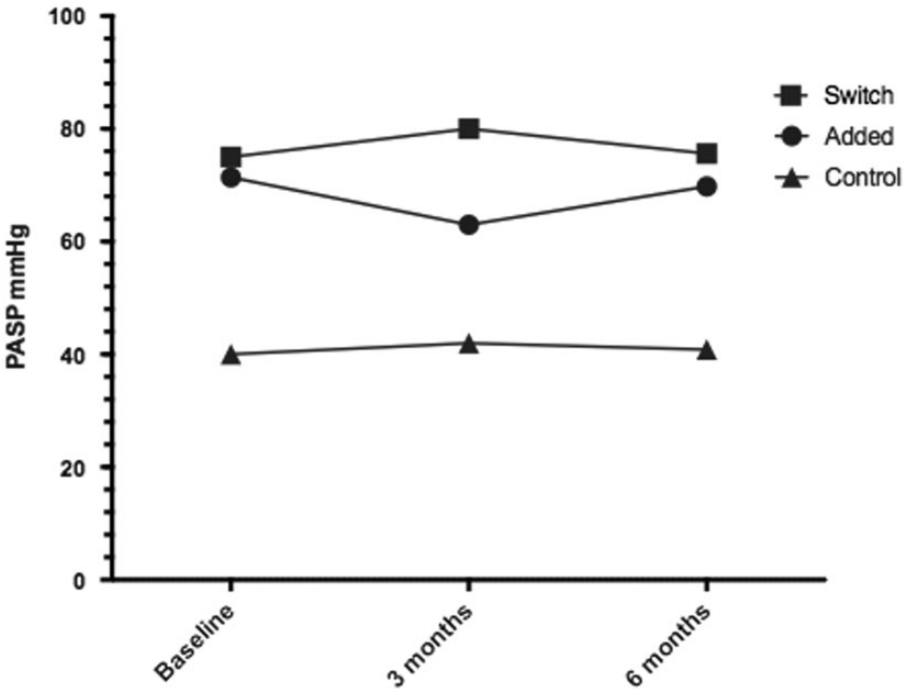

Figure 5. Mean echocardiography analysis of pulmonary artery systolic pressure. PASP, pulmonary artery systolic pressure.

Table 3. Frequency of side effects for each group at 6 months*.

	Switch (n = 14)	Added (n = 11)	Control (n = 12)
Discontinued drug due to side effects	1	0	0
Stopped or changed medication	2	0	1
Side effects			
GIT	0	0	0
Liver derangement	2	2	2
Anemia (Hemoglobin < 100)	2	3	1
New treatment required			
Diuretics	4	6	2
Hospitalizations	5	4	2
Mortality†	1	1	0

†Both patients who died were World Health Organization functional Class IV at baseline.
*Because of the small numbers of reported side effects, no data analysis was performed using data shown in this table.

who remained on their previous therapy; however, this improvement was not statistically significant.

Echocardiographic assessment of right ventricular function is routine for disease monitoring; however, its value in following patients—to determine response to therapy—has not been established.[16–18] Our findings also showed no clear value of right ventricular function for determining

response to therapy: there were no measurable differences in the switch or added groups with regard to right ventricular systolic function or size, nor were there differences in PASP. Clinicians should exercise caution in the use of echocardiography for monitoring disease progression; further investigation is needed regarding non-invasive assessments of disease in patients with PAH.[13,19]

This study had several limitations. Most importantly, it was retrospective and some data were missing. Furthermore, the sample size was relatively small, such that it was not powered to determine differences in mortality. Notably, mortality and hospitalizations for PAH occurred only in macitentan-treated patients. This was expected, as these groups contained patients who had shown poor response to first-line therapy, suggesting poorer overall health at baseline. Two patients died, both from progressive heart failure; moreover, both were in WHO functional class IV at the beginning of the study period. Additionally, more patients in the switch and added groups required hospitalization and the addition of diuretic treatment; this may also have been because these patients had poorer overall health at baseline; however, we cannot rule out that these effects may have been directly caused by macitentan. Finally, this was not a randomized study; thus, the highly heterogeneous patient groups were not directly comparable at baseline. However, this study reflects real-life situations, in that clinicians often encounter difficulty with regard to management of disease in patients with suboptimal response to therapy. Importantly, however, we have shown that in a group of patients with poorly controlled PAH on existing ERA regimens, switching to a plausibly more effective ERA (macitentan) may facilitate clinically meaningful improvements.

In summary, we found a significant improvement in WHO functional class and 6MWT in patients who switched from bosentan/ambrisentan to macitentan. To our knowledge, this has not been previously studied. We believe that the strength of this study is that the parameters used in the study are equivalent to those routinely used in clinical practice, such that they are available when determining the course of treatment in patients with PAH. Switching from bosentan or ambrisentan to macitentan is a therapeutic option available to clinicians who treat patients with suboptimal response to therapy for PAH.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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