RESEARCH ARTICLE

Prospective clinical assessment of patients with pulmonary arterial hypertension switched from bosentan to macitentan (POTENT)

Abdullah M. Aldalaan[1] ⦿ | Sarfraz A. Saleemi[1] | Ihab Weheba[1] |
Abeer Abdelsayed[1] | Maha M. Aleid[2] | Fatima Alzubi[1] | Hamdeia Zaytoun[1] |
Nadeen Alharbi[1]

[1]Department of Medicine, Pulmonary Hypertension Program, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

[2]Department of Biostatistics, Epidemiology & Scientific Computing, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia

Correspondence
Abdullah M. Aldalaan, Department of Medicine, Pulmonary Hypertension Program, King Faisal Specialist Hospital & Research Center, Riyadh 11211 Saudi Arabia.
Email: aldalaan@kfshrc.edu.sa

Abstract

Even though pulmonary arterial hypertension (PAH) remains an incurable disease, the combination of PAH-specific therapies allowed evolving from symptom-based strategies to others aiming to move patients to low-risk conditions. Endothelin-1 (ET-1) receptor antagonists emerged as specific-PAH drugs that can be used in combination with other specific therapies. This work aimed to perform a prospective clinical assessment of patients with PAH that switched from bosentan to macitentan (POTENT), due to inadequate response. POTENT is a prospective, open-label, single-arm, uncontrolled study including PAH patients from our ongoing SAUDIPH registry. It enrolled 50 PAH patients divided as follows: idiopathic/heritable pulmonary arterial hypertension (I/HPAH); $n = 24$; PAH associated with congenital heart disease, $n = 19$; PAH associated with connective tissue diseases, $n = 5$; and pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis (PVOD/PCH), $n = 2$. At baseline, most patients were in World Health Organization Functional Class (WHO FC) II/III (52.0%). After switching to macitentan, patients were more likely to be in WHO FC I/II (78%) and 22% of the overall cohort moved to a lower risk condition, with three low risk stratification parameters. Mean 6-min walking distance increased about 34 m after

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Abbreviations: ALT, alanine aminotransferase; AST, aspartame aminotransferase; CHD, congenital heart disease; CI, confidence interval; CTD, connective tissue disease; dPAP, pulmonary artery diastolic pressure; FC, functional class; GGT, gamma-glutamyl transferase; iPVR, incremental pulmonary vascular resistance; iTPR, incremental total pulmonary resistance; iTPR, incremental total pulmonary resistance; I/HPAH, idiopathic/heritable pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; 6MWD, 6-min walking distance; NT-proBNP, N-terminal pro b-type natriuretic peptide; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVOD/PCH, pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RHC, right heart catheterization; SAUDIPH, The systematic prospective follow-up for better understanding of clInical characteristics of patients with pulmonary hypertension disease; sPAP, pulmonary artery systolic pressure; TPR, total pulmonary resistance; WHO FC, World Health Organization Functional Class.

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12 months, with a significant mean change over time (12.63 ± 11.69 at month 3 vs. 40.75 ± 12.57 at month 12, $p = 0.002$). Most haemodynamic parameters decreased over time, with corresponding negative mean changes ($p < 0.001$). The safety of macitentan was confirmed by the absence of anaemia and liver injury; clinical worsening was observed only in a small group of patients. In general, macitentan might be a valid alternative to bosentan in PAH stable patients on combination therapy with insufficient clinical response, and presenting intermediate and high-risk parameters. We anticipate that studying this strategy in PAH subgroups would further clarify its potential and limitations.

INTRODUCTION

Pulmonary hypertension (PH) encompasses a group of conditions, with distinct etiologies, symptoms and causes, characterized by an increase in pulmonary artery pressure.[1] The most recent classification of PH identifies 5 diagnostic groups, comprising several subgroups.[2] Amongst these groups, pulmonary arterial hypertension (PAH)–group 1 PH–is a rare and progressive disease, with high morbidity and mortality.[3,4]

In the last decades, the therapeutic options for PAH evolved from strategies based on the treatment of symptoms to PAH-specific drugs with enhanced efficacy.[3] Nowadays, the objective of PAH treatment is to conduct patients to a low risk condition, in accordance with the 2015 ERS/ERC treatment guidelines.[5] Despite the different etiologies, PAH is characterized by a progressive cellular proliferative process resulting in significant remodeling of pulmonary blood vessels, a reduced production of prostacyclin and decreased NO synthase function, along with vasoconstriction and increased mitogenesis due to upregulation of ET-1 signaling.[6] In fact, the hallmark of PAH is the disruption of three main signaling pathways: (i) endothelin-1 (ET-1); (ii) nitric oxide (NO); and (iii) prostacyclin and thromboxane A2.[4,7] Interfering on the downregulation of the prostacyclin and NO pathways, and on the upregulation of the ET-1 pathway can provide effective treatments for PAH.

In this context, ET-1 receptor antagonists (ERAs) emerged as specific-PAH drugs with remarkable results in terms of exercise capacity, World Health Organization Functional Class (WHO FC) and time to clinical worsening.[4,6,8] Bosentan was the first drug of this class to be approved for the treatment of PAH.[9] Even though it demonstrated to have impact on disease progression and survival (clinical trials BREATHE-1, BREATHE-2, BREATHE-5, and EARLY),[10–12] it has been associated with a significant increase in transaminase enzymes

levels, which can demand treatment cessation or dose reduction. As so, the structure of bosentan was modified and the new ERA macitentan emerged.[13] The SERA-PHIN trial demonstrated the efficacy of macitentan in reducing the progression of PAH (significant reduction of morbidity and mortality).[14,15] In addition, its hepatoxicity is negligible, and the once daily dosage is far more attractive. Considering that, nowadays, PAH therapy is defined to achieve a low-risk status, preserving the quality of life of patients, and minimizing mortality, it seems that macitentan might be a more adequate option to include in monotherapy or in combination strategies. The evolution of PAH patients starting macitentan, after discontinuation of bosentan, has been evaluated retrospectively only in small cohorts.[16–18] Prospective studies are only available for children and young adults[19] and CHD associated PAH.[20]

This work aimed to evaluate the impact of replacing bosentan with macitentan in PAH patients with inadequate response. For this, we performed a prospective clinical assessment of patients with PAH that switched from bosentan to macitentan (POTENT). This evaluation was based on disease progression and focused mainly on the assessment of non-stabilized parameters and additional medication, to ascertain the impact of macitentan on treatment goals.

METHODS

Study design

POTENT is a prospective, open-label, single-arm, uncontrolled study including patients from our ongoing SAUDIPH registry.[21] We enrolled 50 patients between October 22, 2014 and July 23, 2018. The last follow-up visit took place on December 03, 2019.

The study included patients with generally stable disease but that did not fully meet the low-risk stratification criteria. The inclusion criteria were: (i) adults with >18 years of age diagnosed with PAH (idiopathic/heritable pulmonary arterial hypertension [I/HPAH]; PAH associated with congenital heart disease [CHD]; PAH associated with connective tissue diseases [CTD]; and pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis [PVOD/PCH]), according to current guidelines, based on right heart catheterization (RHC), showing mean pulmonary artery pressure (mPAP) >25 mmHg, pulmonary capillary wedge pressure (PCWP) <15 mmHg, and pulmonary vascular resistance (PVR) >3 wood; (ii) PAH patients in WHO FC I and II and some stable patients in class III that refused intravenous therapy; (iii) patients presenting a 6-min walking distance (6MWD) between 165 and 400 m; and (iv) patients on combination therapy (including bosentan 250 mg), for at least 3 months. Patients in WHO FC IV and pregnant women were excluded from this study as their conditions required more careful or aggressive treatment approaches.

SAUDIPH includes patients with diagnosis of PH under clinical management at our Hospital, which is a tertiary care government academic hospital where patients are accepted from all over the Kingdom following electronic referral through a centralized referral system. The SAUDIPH registry and the POTENT study, herein presented, received favorable opinion from the Research Ethics Committee and of the Institutional Review Board of our Hospital (#2171148). The study was carried out in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided their written informed consent before enrollment in the registry and in the study.

Clinical management

Patients underwent a comprehensive clinical evaluation, according to the current WHO/ERS/ESC guidelines, including RHC, to establish the diagnosis of PH (mPAP ≥25 mmHg). Upon diagnosis, patients were invited to participate in the registry and received treatment according to routine clinical practice. Patients fulfilling the inclusion criteria were included in this study and had their treatment changed, by switching from bosentan to macitentan, in an attempt to fully meet the low-risk stratification criteria. Patients were allowed to continue other background therapy with other drugs. Baseline assessments were obtained while patients were still receiving bosentan, which was stopped in the day of the first dose of macitentan. The drugs included in the previous combination strategy were kept as well as other support interventions. Patients started macitentan at a daily dose of 10 mg.

Follow-up visits were scheduled according to routine clinical practice, typically a visit every 3 months, or more frequently depending on the clinical condition.

Assessments

For this study, all patient data were collected in a disease-specific electronic medical record (PAH Tool™, Inovultus Lda, Santa Maria da Feira, Portugal). In the analysis, the following baseline and follow-up variables were considered: demographic (age, gender), clinical characteristics (PH aetiology, follow-up time, WHO FC, Borg fatigue scale, 6MWD, N-terminal pro-B-type natriuretic peptide [NT-proBNP]), haemodynamic parameters (cardiac index, cardiac output [using Fick method], heart rate, pulmonary artery dyastolic pressure [dPAP] mPAP, O_2saturation, pulmonary artery systolic pressure [sPAP], pulmonary capillary wedge pressure [PCWP], PVR, incremental pulmonary vascular resistance [iPVR], right atrial pressure [RAP], stroke volume), and safety parameters (hemoglobin, haematocrit, uric acid, total bilirubin, alanine aminotransferase [ALT], aspartame aminotransferase [AST], gamma-glutamyl transferase [GGT], alkaline phosphatase, urea, and creatinine).

Among these, WHO FC (class I and II), 6MWD (>440 m), and NT-proBNP (<300 ng/L) were considered as low-risk parameters for the analysis, in the setting of low-risk stratification.[5] Patients were classified according to the number of low-risk criteria present at baseline and at the fourth visit.[22]

Clinical worsening was defined as: (i) death; (ii) need for atrial septostomy and lung transplantation; (iii) PAH-related hospitalization; (iv) addition of other nonintravenous/subcutaneous (IV/SC) PAH therapy; (v) addition of IV/SC prostanoids therapy; (vi) persistent decrease in 6MWD (>15% from baseline or >30% from last measurement); (vii) persistent worsening of WHO FC; or (viii) appearance or worsening of signs/symptoms of right heart failure.

Statistical analysis

Demographic and clinical characteristics were summarized as mean (*SD*), for continuous variables, and *n* (%), for categorical variables. A *p* value is presented according to Kruskal–Wallis for continuous variables and chi-square test for categorical variables. Previous and current medication was summarized with count and percentage.

Pulmonary Circulation

A Generalized Additive Mixed Model assuming a gaussian distribution for continuous variables was used to estimate the mean and the mean change from baseline, and a binomial distribution for dichotomous variables to estimate the probability of having the outcome of interest and its 95% confidence intervals (CI) over time. Time (months) was assumed as fixed-effect and subject as random-effect to control for nonindependence over time. A one-dimensional non-parametric function, using spline functions (smoothers), was incorporated in the model to allow for possible nonlinearities in the effect of time and to deal with irregularly spaced sampling times, regulating the sampling scheme; this form of interpolation was used to consider time as equally spaced.

The cumulative probability of an individual achieving clinical worsening at any time after baseline was estimated using the Kaplan–Meier method. Individuals that did not experience the event during the study period were censored to the time of the last contact date. Clinical worsening time was defined as the time to reach one of the following conditions: death, need for atrial septostomy and lung transplantation, PAH-related hospitalization, addition of other non-IV/SC PAH therapy, addition of IV/SC prostanoids therapy, persistent decrease in 6MWD (>15% from baseline or >30% from last measurement); persistent worsening of WHO FC; or appearance or worsening of signs/symptoms of right heart failure.

Statistical analysis was performed using R version 3.6.2 (R Foundation for Statistical Computing), using a 5% significance level.

RESULTS

Baseline characteristics of the study population

Our study enrolled 50 patients (previously included in the SAUDIPH registry) diagnosed with PAH and receiving bosentan, in mono or combination therapy. Table 1 shows the baseline characteristics of the cohort that included patients with I/HPAH ($n = 24$), CHD ($n = 19$), CTD ($n = 5$), and PVOD/PCH ($n = 2$). In the setting of CHD, three patients were surgically repaired; two with post tetralogy of Fallot repair and one with post-pulmonary artery reconstruction and placement of pulmonary homograph. Mean age at diagnosis was 35 ± 11 years and most patients were in WHO FC I/II (52.0%). A female predominance was observed (78%)

TABLE 1 Baseline demographic and clinical characteristics of the study population

	Study population ($n = 50$)
Age, years	35 (11)
Sex, n (%)	
Female	39 (78.0%)
Male	11 (22.0%)
WHO FC, n (%)	
I/II	4/22 (52.0%)
III/IV	24/0 (48.0%)
6MWD, m	331.3 (130.1)
PAH subgroup, n (%)	
I/HPAH	24 (48%)
CHD	19 (38%)
CTD	5 (10%)
PVOD/PCH	2 (4%)
Heart rate—bpm	83.8 (12.4)
Borg fatigue, Borg units	3.2 (1.8)
O2 Sat, %	95.0 (2.8)
TTE sPAP, mmHg	95.2 (22.7)
TTE TR Vmax, m/s	4.5 (0.7)
RAP, mmHg	11.9 (10.2)
sPAP, mmHg	105.4 (20.1)
dPAP, mmHg	45.1 (13.6)
mPAP, mmHg	68.3 (15.7)
PCWP, mmHg	12.8 (6.1)
Cardiac output, l/min	3.6 (1.3)
Cardiac index, L/min	2.2 (0.8)
Stroke volume, ml/beat	48.9 (19.43)
PVR, WU	17.1 (7.6)
iPVR, WU.m^2	28.0 (12.1)
Hemoglobin, g/dl	138.9 (27.9)
NT-proBNP, pg/ml	972.2 (1411.6)
Uric acid, umol/L	350.9 (125.7)
Total Bilirubin, umol/L	11.6 (8.4)
ALT, UI/L	17.0 (7.8)
AST, U/L	21.2 (6.7)
Creatinine, umol/L	68.4 (12.6)
Treatment, n (%)	
Single therapy	3 (6.0%)

TABLE 1 (Continued)

	Study population ($n = 50$)
Double therapy	32 (64.0%)
Triple therapy	15 (30.0%)

Note: Results are presented as mean (*SD*) for continuous variables and *n* (%) for categorical variables.

Abbreviations: ALT, alanine aminotransferase; AST, aspartame aminotransferase; CHD, congenital heart disease; CTD, connective tissue disease; dPAP, diastolic pulmonary arterial pressure; I/HPAH, idiopathic heritable pulmonary arterial hypertension; iPVR, incremental pulmonary vascular resistance; mPAP, mean pulmonary arterial pressure; 6MWD, 6-min walking distance; n, number of subjects; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAH, pulmonary arterial hypertension; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVOD/PCH, pulmonary veno-occlusive disease/pulmonary capillary haemangiomatosis; PVR, pulmonary vascular resistance; RAP, right atrial pressure; sPAP, systolic pulmonary arterial pressure; TTE, transthoracic echocardiography; WHO FC: World Health Organization Functional Class.

among our patients. At baseline, mean 6MWD was 331.3 ± 130.1 m, with 9 patients presenting values below 200 m. Mean NT-proBNP was 972.2 ± 1411.6 5 pg/ml for the whole cohort, with a median value of 393.5 (Q1: 186.5, Q3: 1318.0); 30% of the patients presented values above 1000 pg/ml. In terms of haemodynamic parameters, 20% of the patients presented mPAP above 80 mmHg, with a mean value of 68.3 ± 15.7 mmHg; the cardiac index was 2.2 ± 0.8 L/min, for the overall cohort.

Regarding treatment strategy, the cohort included 47 (94%) patients in combination therapy regimens (all of them including bosentan 250 mg), and 3 patients (2 of them with CHD and 1 with I/HPAH) that, even though were stable on monotherapy, manifested the will to change to macitentan (for more convenience) or had one risk parameter not meeting the low-risk criteria. From the patients in combination regimens, 64% were on double therapy. Double therapy regimens were based on the combination of bosentan 250 mg with sildenafil 60, 120, or 180 mg ($n = 30$) or inhaled iloprost 120 μg ($n = 1$). In triple therapy regimens, bosentan 250 mg was combined with sildenafil 60, 120, or 180 mg ($n = 15$), inhaled iloprost 120 μg ($n = 13$), treprostinil 59, 70, or 71 ng/kg/min, intravenous or subcutaneous ($n = 3$) or riociguat 1.5 mg ($n = 1$).

Switching from bosentan to macitentan: clinical and safety outcomes

Table 2 shows the estimated over time clinical and safety outcomes of the overall cohort, before and after replacing bosentan with macitentan, during a period of 12 months.

One year after switching, 26% of the patients shifted from WHO FC III/IV to WHO FC II/III (Figure 1); the probability of a patient being on WHO FC III/IV decreased from $0.41 \pm 0.09\%$ to $0.11 \pm 0.04\%$, from baseline to month 12 ($p = 0.002$). Mean 6MWD increased about 34 m (327.8 ± 16.7 m at baseline vs. 361.7 ± 16.4 m at month 12, $p = 0.006$), with a significant mean change over time (12.63 ± 11.69 m at month 3 vs. 40.75 ± 12.57 m at month 12, $p = 0.002$) (Table 2 and Figure 2). Most haemodynamic parameters (RAP, PAP, PAWP, Stroke volume, PVR, iPVR,) decreased over time with corresponding negative mean changes and statistical significance ($p < 0.001$) (Table 2 and Table S1). Cardiac index and cardiac output increased overtime with significant mean changes ($p < 0.001$). Hemoglobin and haematocrit did not change significantly ($p = 0.339$ and $p = 0.125$, respectively); the hemoglobin of 2 patients with values below 100.0 g/dl started increasing 3 months after switching and reached values above 120 g/dl, at month 12. Regarding liver enzymes, GGT decreased 11.8 U/L from baseline to month 12 (39.1 ± 3.1 U/L, 95% CI: 32.9, 45.3 vs. 27.3 ± 2.8 U/L, 95% CI: 21.7–32.9), with a significant negative mean change (-16.19 ± 3.76 at month 12, $p < 0.001$) (Table S1). NT-proBNP decreased from 898.6 ± 178.7 pg/ml to 761.9 ± 177.8 pg/ml but without statistical significance ($p = 0.075$); the mean change was also not significant ($p = 0.054$) (Table 2 and Figure 3). Other noteworthy nonsignificant trends, registered after switching, include: (i) decrease of heart rate, Borg fatigue, O_2 Sat, and alkaline phosphatase; and (ii) increase of uric acid, total bilirubin, urea, and creatinine (Table S1).

Figure 4 represents the cumulative proportion of patients achieving clinical worsening. The number of patients with events of clinical worsening after 3, 6, 9, and 12 months was 3, 9, 9, and 9, respectively. These patients started other non-IV/SC PAH therapy ($n = 8$) and/or IV/SC prostanoids therapy ($n = 1$) or experienced PAH related hospitalization ($n = 7$); 4 of the patients that started therapy with other drugs were hospitalized. We did not register cases of lung transplantation, atrial septostomy, or death. During the period under analysis, the drop-out rate was 0% with all the patients attending the four predicted visits (at 3, 6, 9, and 12 months).

In terms of risk assessment, the results showed an increase of 22%, from baseline to the 4th visit, in the number of patients meeting three low-risk parameters (WHO FC, 6MWD, or NT-proBNP) ($p = 0.005$; Figure 5). At the same time, we observed a decrease in the number of patients meeting one or two high (58% vs. 26% and 20% vs. 2%, respectively) risk parameters, from baseline to the 4th visit.

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TABLE 2 Estimated changes over time in clinical characteristics after switch from bosentan to Macitentan

	Baseline	Month 3	Month 6	Month 9	Month 12	p value
6MWT, m	—					
Mean (SE; 95% CI)	327.8 (16.7; 294.4, 361.2)	336.3 (15.8; 304.7, 367.9)	344.8 (15.4; 313.9, 375.6)	353.2 (15.6; 321.9, 384.5)	361.7 (16.4; 328.9, 394.5)	0.006
Mean change (SE; 95% CI)		12.63 (11.69; (−10.76, 36.01)	22.00 (11.21; 0.41, 44.42)	31.38 (11.52; 8.33, 54.42)	40.75 (12.57; 15.60, 65.90)	0.002
Borg fatigue, Borg units						
Mean (SE; 95% CI)	3.1 (0.2; 2.6, 3.6)	3.1 (0.2; 2.6, 3.5)	3.0 (0.2; 2.6, 3.4)	3.0 (0.2; 2.6, 3.4)	2.9 (0.2; 2.5, 3.4)	0.553
Mean change (SE; 95% CI)	—	−0.13 (0.19; −0.52, 0.25)	−0.19 (0.18; −0.54, 0.17)	−0.24 (0.19; −0.61, 0.14)	−0.29 (0.22; −0.73, 0.14)	0.406
RAP, mmHg						
Mean (SE; 95% CI)	11.8 (1.5; 8.9, 14.7)	—	—	—	12.9 (1.6; 9.6, 16.1)	0.211
Mean change (SE; 95% CI)	—	—	—	—	−5.5 (0.1; (−5.6, −5.3)	<0.001
mPAP, mmHg						
Mean (SE; 95% CI)	68.1 (2.2; 63.6, 72.6)	—	—		65.4 (2.7; 60.0, 70.9)	0.137
Mean change (SE; 95% CI)	—	—	—		−8.1 (1.8; −11.8; −4.4)	<0.001
Cardiac index, L/min						
Mean (SE; 95% CI)	2.2 (0.1; 2.0, 2.4)-	—	—		2.3 (0.1; 2.1, 2.6)	0.097
Mean change (SE; 95% CI)	—	—	—		0.3 (0.1; 0.2, 0.4)	<0.001
PVR, WU						
Mean (SE; 95% CI)	17.1 (1.1; 14.9, 19.2)	—	—		14.8 (1.5; 11.9, 17.8)	0.069
Mean change (SE; 95% CI)	—	—	—		−4.1 (1.5; −7.0, −1.2)	<0.001

Pulmonary Circulation

TABLE 2 (Continued)

	Baseline	Month 3	Month 6	Month 9	Month 12	p value
NT-proBNP, pg/ml						
Mean (SE; 95% CI)	898.6 (178.7; 541.2, 1256.0)	864.4 (175.4; 513.7, 1215.2)	830.2 (174.1; 482.0, 1178.4)	796.1 (174.9; 446.2, 1145.9)	761.9 (177.8; 406.3, 1117.5)	0.075
Mean change (SE; 95% CI)	-	−105.41 (64.89; −235.18, 24.36)	−142.26 (61.36; −264.99, −19.53)	−179.11 (63.63; −306.37, −51.86)	−215.96 (71.12; −358.21, −73.72)	0.054

Abbreviations: CI, confidence interval; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; SE, standard error; WHO FC, World Health Organization Functional Class.

DISCUSSION

In this study, we performed a prospective evaluation of the clinical and safety outcomes resulting from replacing bosentan with macitentan in PAH patients. Our cohort included 50 patients that were on combination therapy with bosentan and were changed to a similar treatment strategy with macitentan, due to inadequate response (persistence of high-risk parameters). The analysis was based on a multiparametric risk stratification approach and added relevant clinical information to the growing body of evidence on PH management, in Saudi Arabia. Due to the improved safety and efficacy profile of macitentan over bosentan,[15,23] this strategy is becoming usual in clinical practice. The impact of this change has been evaluated before through prospective studies in pediatric and young adult PAH populations,[19] and in PAH-CHD adults.[20] Retrospective studies in small PAH cohorts are also available.[16–18,24] Still, as far as we know, this is the first prospective study addressing this analysis on an adult PAH cohort, through a multiparametric risk stratification approach, in Saudi Arabia. Similar studies, with similar inclusion criteria (up to WHO FC III), were performed with patients with intermediate risk on treatment with drugs of other classes like phosphodiesterase type 5 (PD5) inhibitors and riociguat (REPLACE and RESPITE studies).[25,26]

Our results showed that the switch from bosentan to macitentan resulted in improvements in relevant clinical outcomes, like WHO FC and 6MWD, with a good safety profile. These results confirm the observations of Verlinden and co-workers in a safety and efficacy study of the transitioning from the combination of bosentan and sildenafil to alternative therapy (macitentant or riociguat), in PAH patients.[24]

The demographic characteristics of the study population are in agreement with those reported in previous studies on the Saudi PAH population.[21,27] As usual in PH literature, we could notice a female predominance in our cohort.[28] At baseline, the mean age of our population was substantially lower (35 years) than that reported in studies from other regions, in which age at diagnosis is usually between 50 and 70 years. This tendency has already been reported in other Saudi PH studies[21,27,29,30] and may be associated with the fact that the overall Saudi population is younger (about 69% of the population is below 40 years old) than populations of Western countries (data from the General Authority for Statistics of the Kingdom of Saudi Arabia).

As expected, most patients (94%) were on combination therapy at baseline. In fact, in PAH patients with nonstabilized parameters, combination therapy is the most common approach and patients are kept on
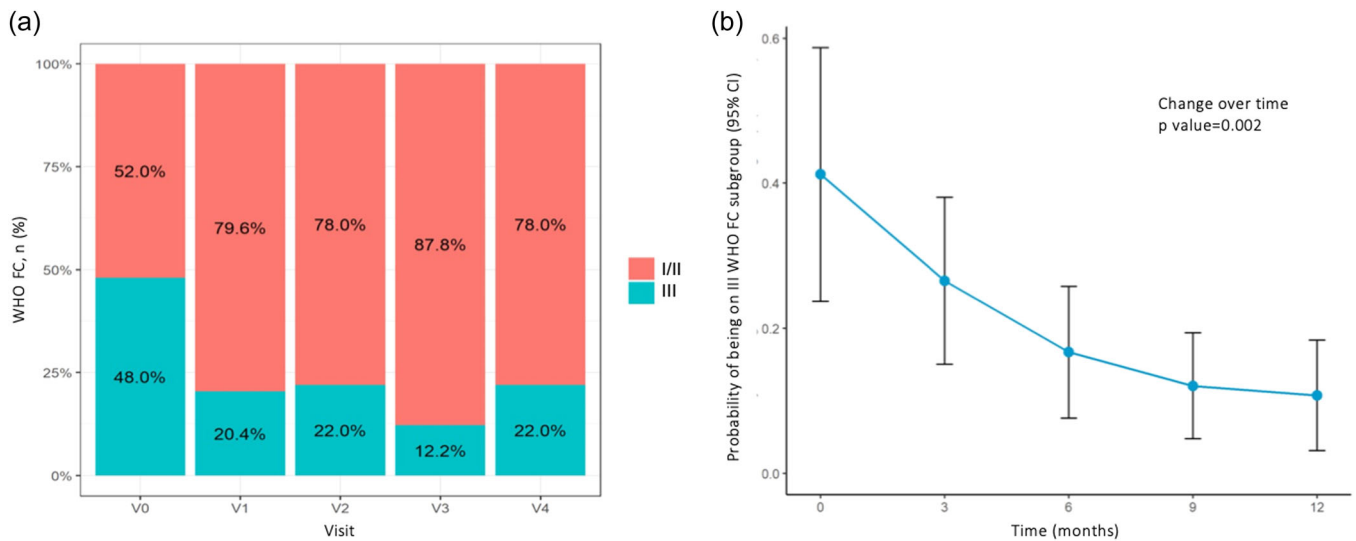
(a)

(b)

FIGURE 1 Change of WHO FC after switching from bosentan to macitentan. (a) Distribution of patients (%) in WHO FC I/II and III/IV, over time. (b) Probability of a patient being on WHO FC III/IV, over time. WHO FC, World Health Organization Functional Class
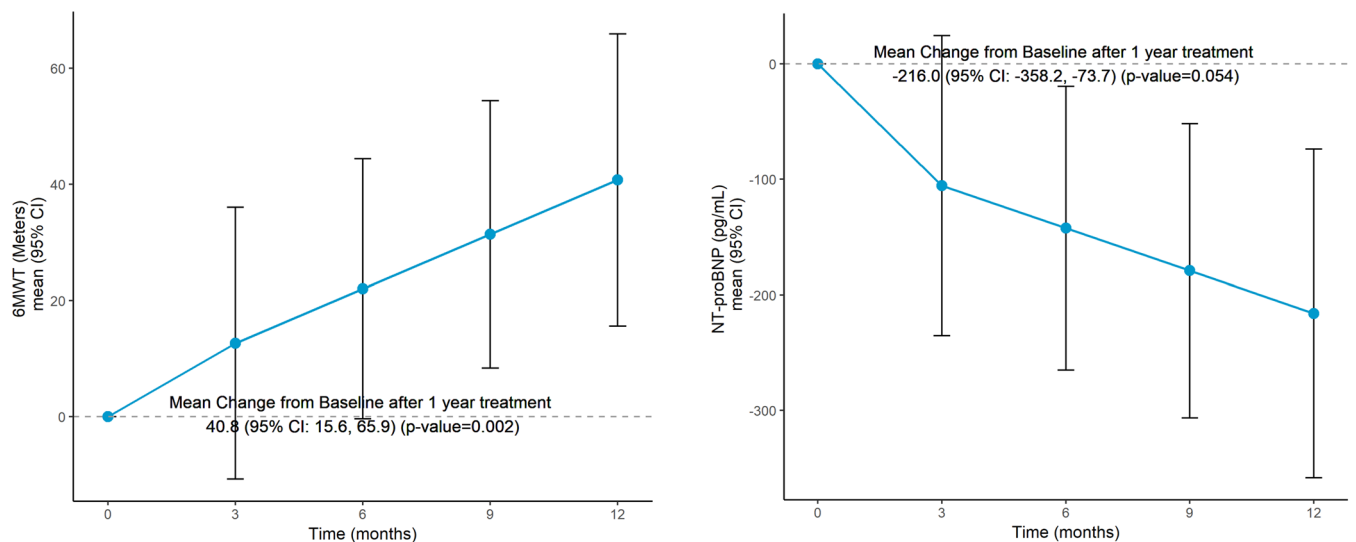

FIGURE 2 Estimated change of 6MWD over time, after switching from bosentan to macitentan. CI, confidence interval; 6MWD, 6-min walking distance

FIGURE 3 Estimated change in NT-proBNP over time, after switch from bosentan to macitentan. CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide

monotherapy or subjected to other nondrug treatment options only in exceptional situations.[4,11] Switching between drugs, belonging to the same group or other, is, in general, explored if the previously implemented combination strategy does not show efficacy; it can also be a valid option to increase patients' adherence to treatment, if the new drug is advantageous in terms of daily dosage or administration mode.

At baseline, disease severity, measured by WHO FC, showed to be lower than that reported in other registries and reports for PAH populations.[31–34] This trend is a result of the defined inclusion criteria that

imposed relative disease stability before changing the treatment.

Overall, after switching to macitentan, patients were more likely to be in WHO FC I/II (78% in WHO FC I/II), which indicates a reduction in disease severity, related to the change of the therapeutic approach. This improvement is in good agreement with the results of previous studies in PAH patients treated with macitentan[14,16,17,20] and, even though it was more evident in patients in double (40.0%) and triple (43.8%) therapy, it was also noticed in patients in monotherapy (33.3%). Lower disease severity was also evidenced by an overall increase
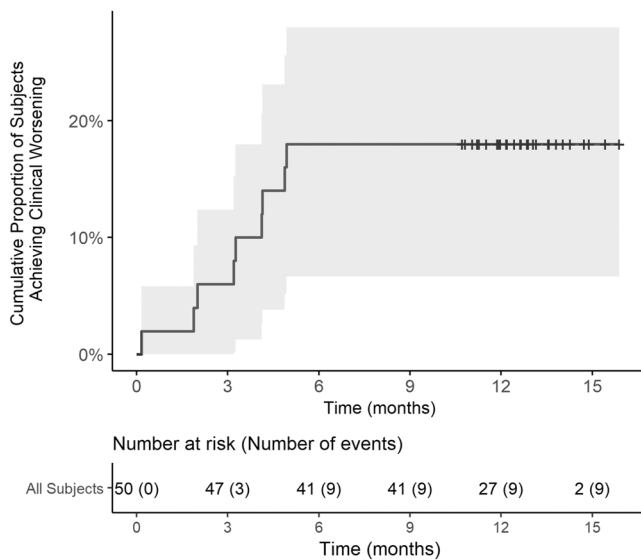
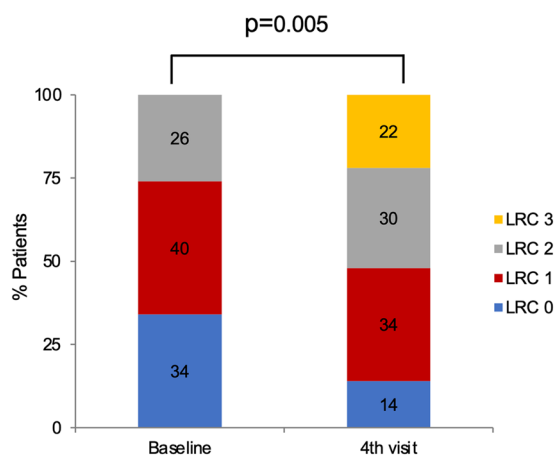**FIGURE 4** Clinical worsening after switching from bosentan to Macitentan

FIGURE 5 Patients with low-risk criteria* at baseline and 4th visit. *WHO FC (classes I and II), 6MWD (>440 m), and NT-proBNP (<300 ng/L). LRC, low risk criteria; WHO FC, World Health Organization Functional Class

in 6MWD, with 40% of the patients achieving distances in a range that has been associated with reduced risk of death and hospitalization (>400 m).[35] Haemodynamic improvements overtime, such as the significant decrease of mPAP, dPAP, sPAP, and RAP and the increase of cardiac index, cardiac output, and stroke volume, were also evidence of better clinical condition. The registered decrease of NT-proBNP was nearly statistically significant confirming somehow the benefits of the change. All these results are in line with previous reports on the performance of macitentan in PAH patients.[16,17,19]

The significant decrease of GGT, after switch, associated with the nonsignificant effect on the levels of ALT, AST, total bilirubin and hemoglobin, excluded the risk of liver damage and significant anaemia, and confirmed that macitentan is well tolerated and constitutes a valid alternative to bosentan.[15,19,23]

Our analysis found that only 18% of the patients had signs of clinical worsening, like the need to start additional drug treatments or hospitalization, until the 6th month of treatment. We could also show that hospitalization occurred in about 33% of these patients, confirming their poor clinical condition. It seems that, for these group of patients, switching from bosentan to macitentan was not the more adequate approach, as their clinical condition demanded additional interventions, such as the addition of non-IV/SC PAH therapy or IV/SC prostanoids therapy.

Overall, the study showed that a significant number of patients was moved to a lower risk condition after switching the treatment from bosentan to macitentan. This was evidenced by a significant increase in the number of patients with three low risk stratification criteria (WHO FC, 6MWD, and NT-proNBP) and by the decrease in the number of patients with one and two high-risk criteria. This change to lower risk conditions is caused by the reported significant increase in 6MWD and by the decrease in NT-proBNP levels, along with a significant shift of patients to WHO FC I/II. In addition, the clinical condition of CHD patients did not worsen during after 12 months, with registered slight non-significant changes in 6MWD (mean change at baseline: 369.1 m; mean change at month 12: 374.0 m) and NT-proNBP (mean change at baseline: 922.2 pg/ml; mean change at month 12: 752.6 pg/ml).

The main strengths of the present study include its prospective design, the assessment of clinical and safety outcomes (before and after switching) with overtime measurements, and evaluation of clinical worsening events. However, significant limitations shall also be discussed. First, the sample size was limited, reducing the statistical power of the study and the extrapolation to the overall PAH population. Second, in this study we presented only the results for the overall population. It would be interesting to evaluate the effects of switching from bosentan to macitentan in patients of PAH subgroups. Third, the absence of a control group hindered the discussion around long term survival. To finalize, the unblinded design might have been responsible for analysis bias.

In conclusion, replacing bosentan with macitentan is generally safe and may be a feasible treatment option in selected PAH patients who did not fully meet the low-risk stratification criteria on bosentan as monotherapy or in combination with others pulmonary vasodilator therapy. We anticipate that studying this strategy in

PAH subgroups would further clarify its overall potential and limitations.

AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

The SAUDIPH registry and the POTENT study, herein presented, received favorable opinion from the Research Ethics Committee (REC) and of the Institutional Review Board (IRB) of the King Faisal Specialist Hospital (#2171148). The study was carried out in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. All patients provided their written informed consent before enrollment in the registry and in the study.

ORCID

Abdullah M. Aldalaan http://orcid.org/0000-0001-9658-081X

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.