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Early View

Research letter

Initial combination therapy of macitentan and tadalafil in pulmonary arterial hypertension

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Initial combination therapy of macitentan and tadalafil in pulmonary arterial hypertension

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Take-home message (256 characters including spaces; current 174): Initial combination therapy with macitentan and tadalafil is well tolerated and improves cardiopulmonary haemodynamics and functional capacity in newly-diagnosed PAH patients

To the Editor:

Initial combination therapy plays a central role in managing pulmonary arterial hypertension (PAH) [1–4]. Patients with low- or intermediate-risk of 1-year mortality at diagnosis should be treated with initial combinaton therapy with an endothelin receptor antagonist (ERA) and phosphodiesterase type-5 inhibitor (PDE5i) [2–4]. Benefits of initial therapy with the ERA ambrisentan and PDE5i tadalafil were demonstrated in AMBITION [1]; prospective evidence for other treatment combinations within these drug classes is needed.

In SERAPHIN, macitentan, a dual ERA, improved long-term outcomes in PAH patients [5], including those receiving background treatment (predominantly PDE5i) [5, 6]. OPTIMA (NCT02968901) was a prospective, multicentre, single-arm, open-label, phase IV study that explored the efficacy and safety of macitentan administered as initial oral combination therapy with tadalafil, in newly-diagnosed treatment-naïve PAH patients.

Treatment-naïve adult patients diagnosed with PAH within the previous 6 months were eligible if they had idiopathic, heritable, or associated PAH (drug/toxin-induced, connective tissue disease [CTD], human immunodeficiency virus, corrected congenital heart disease). Patients were World Health Organization functional class (FC) II to III, with 6-minute walk distance (6MWD) ≥50 m and the following haemodynamics at screening: resting mean pulmonary arterial pressure (mPAP) ≥25 mmHg, pulmonary arterial wedge pressure (PAWP) or left ventricular end diastolic pressure ≤15 mmHg, and pulmonary vascular resistance (PVR) ≥5 Wood units if PAWP was <12 mmHg or PVR ≥6.25 Wood units if PAWP was 12–15 mmHg. Written informed consent was obtained from all patients and the study conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

The study included a 16-week period during which efficacy and safety were assessed followed by an optional extension period assessing safety. Within 28 days after screening, macitentan 10mg once daily (o.d.) and tadalafil 20mg o.d. were initiated; at day 8±3, the tadalafil dose was increased to 40mg o.d. The dose of tadalafil could be decreased for tolerability reasons. Study treatment continued until week 16 (W16), or until PAH progression required administration of other PAH drugs. Patients who completed 16 weeks of treatment could enter an extension period with macitentan, tadalafil or both drugs until the Sponsor stopped the trial, or patient/investigator decision to discontinue both

treatments. Patients who discontinued both treatments had an end-of-treatment safety visit within 7 days. All patients had an end-of-study safety visit 30 days after the end of treatment.

Clinical assessments and right heart catheterisation (RHC) were performed at baseline and W16. Safety laboratory testing was performed monthly during the first 6 months, after which it was recommended monthly and performed at the discretion of the treating physician. Adverse events (AEs) were monitored until 30 days after the end of treatment. The primary endpoint was the ratio of W16 to baseline PVR assessed by RHC. Secondary endpoints were: percentage of patients with PVR decrease ≥30% from baseline to W16; change from baseline to W16 in mean right atrial pressure, mPAP, cardiac index, total pulmonary resistance, mixed venous oxygen saturation, 6MWD, FC, and N-terminal pro-brain natriuretic peptide (NT-proBNP); and percentage of patients with improvement/worsening FC from baseline to W16. A pre-specified exploratory endpoint was the number of low-risk criteria at baseline and W16. Two sets of parameters were assessed and the thresholds used to define low-risk were updated *post hoc* to align with those recommended in the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines [2, 3] and validated in a French registry analysis [7]. For PVR and NT-proBNP, ratios of W16 versus baseline were log-transformed and the geometric mean of the ratio and its 95% two-sided confidence interval (CI) obtained by exponentiation. Other parameters were summarised descriptively.

From November 2015 to December 2017, 50 patients were screened at 15 sites in France. Forty-six patients were enrolled and 44 completed 16 weeks of treatment (2 discontinued both drugs due to: aetiology revision [n=1]; AE and suspicion of veno-occlusive disease [n=1]). Forty-four patients entered the extension period and 39 completed the study (5 discontinued both drugs due to: AE and aetiology revision [n=1]; AE and death [n=1]; death [n=2]; patient decision [n=1]). Patients were predominantly female (65.2%) with idiopathic (63.0%) or CTD-associated (19.6%) PAH, and were FC II (21.7%) or III (78.3%). Mean±standard deviation (SD) age was 57.4±14.9 years and mean±SD time from PAH diagnosis was 29.6±55.2 days (n=45). All patients were titrated to tadalafil 40mg o.d., the majority within 8±3 days. Tadalafil dose reductions to 20mg o.d. occurred in two patients, both between day 15 and W16.

The geometric mean ratio (95% CI) of W16 to baseline PVR was 0.53 (0.47–0.59), representing a 47% reduction (Table). A ≥30% decrease in PVR between baseline and W16 occurred in 87.0% (95%

CI 73.7–95.1) of patients. Changes in other haemodynamic parameters, 6MWD, NT-proBNP concentration, FC, and the number of low-risk criteria are shown in the Table.

Median (Q1, Q3) exposure to macitentan and tadalafil was 86.5 (53.0, 115.1) weeks. At least one AE was reported in 43 (93.5%) patients and serious AEs were reported in 13 (28.3%) patients. Three (6.5%) patients had an AE leading to study treatment discontinuation (both study drugs) (one AE of lack of efficacy before W16, one AE of treatment inefficiency after W16, and one AE of PAH worsening after W16). Most frequent AEs were peripheral oedema (28.3%), headache (23.9%), diarrhoea (19.6%), dyspnoea (15.2%), anaemia (13.0%) [2] and asthenia (13.0%). Haemoglobin decreases to >8 and ≤10 g/dL were reported for 5 (10.9%) patients (who had baseline values ranging from 10.9 to 13.4 g/dL), with no decreases to ≤8 g/dL. No patients discontinued study treatment due to decreased haemoglobin. Aspartate aminotransferase levels above 3x the upper limit of normal (ULN) without bilirubin elevation above 2xULN were reported in one patient but did not lead to treatment discontinuation. Three patients died (one due to multiorgan failure on day 764 and two due to underlying disease, on days 127 and 588). Kaplan-Meier survival estimates (95% CI) were 97.7% (84.9%–99.7%) at 12 months, 93.7% (75.7%–98.5%) at 24 months and 87.8% (64.5%–96.2%) at end of study (2.7 years).

Our findings are aligned with those from previous randomised controlled trials and real-world studies where haemodynamic and functional improvement was observed following initial ERA and PDE5i combination therapy [1, 8–12]. Safety and tolerability were generally consistent with previous data for macitentan in combination with PDE5i [5, 6, 13]. The main limitations of our study were the open-label uncontrolled nature of the design and the small sample size.

Overall, in the prospective OPTIMA study, initial double combination therapy with macitentan and tadalafil led to a significant improvement, from baseline to W16, in cardiopulmonary haemodynamics, functional parameters NT-proBNP and risk profile in newly-diagnosed, treatment-naïve patients with PAH. There were no unexpected safety findings during long-term follow-up. In line with recommendations in the ESC/ERS guidelines [2, 3] and proceedings from the 6th World Symposium on Pulmonary Hypertension [4], the data presented here support early use of double oral combination therapy with an ERA and PDE5i to optimally manage PAH.

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Table. Haemodynamic parameters, 6MWD, NT-proBNP concentrations, FC and low-risk criteria

	Baseline N=46	W16* N=46	Change from baseline to W16*	
			Mean (95% CI)	p-value
Pulmonary vascular resistance, Wood units	11.7±4.7	6.5±3.6	0.53 (0.47, 0.59)** 47% reduction from baseline	<0.0001
Mean pulmonary arterial pressure, mmHg	50.0±12.3	42.2±14.7	−7.83 (−11.71, −3.94)	0.0002
mRAP, mmHg	8.1±4.7	7.8±5.3	−0.28 (−1.94, 1.37)	0.7321
Cardiac index, L/min/m^2	2.2±0.6	3.1±0.8	0.91 (0.71, 1.11)	<0.0001
Total pulmonary resistance, Wood units	13.9±5.3	8.5±4.3	−5.4 (−6.5, −4.3)	<0.0001
Mixed venous oxygen saturation, %†	63.0±7.1	68.2±7.2	5.53 (2.80, 8.27)	0.0003
6MWD, m	352.2±134.9	388.1±142.1	35.8 (15.8, 55.9)	0.0008
NT-proBNP, ng/L‡	1456.8 (646.6, 2119.5)‡‡	404.2 (147.5, 873.7)‡‡	0.32 (0.23, 0.44)** 68% reduction from baseline	<0.0001
FC: patients, n (%)	FC I: 0 (0) FC II: 10 (21.7) FC III: 36 (78.3)	FC I: 9 (19.6) FC II: 23 (50.0) FC III: 14 (30.4)	Improved: 29 (63.0) Worsened: 0 (0) No change: 17 (37.0)	NA
Number of low-risk criteria: patients, n (%)††				
Low-risk criteria: invasive and non-invasive variables defined as FC I/II, 6MWD > 440 m, mRAP < 8 mmHg, and cardiac index > 2.5 L/min/m^2 [7]	0 criteria: 11 (23.9) 1 criterion: 20 (43.5) 2 criteria: 7 (15.2) 3 criteria: 5 (10.9) 4 criteria: 3 (6.5)	0 criteria: 5 (10.9) 1 criterion: 8 (17.4) 2 criteria: 9 (19.6) 3 criteria: 16 (34.8) 4 criteria: 8 (17.4)	Increased: 34 (73.9) Decreased: 8 (17.4) No change: 4 (8.7)	NA
Low-risk criteria: non-invasive variables defined as FC I/II, 6MWD > 440 m, and NT-proBNP < 300 ng/L [7]	0 criteria: 29 (63.0) 1 criterion: 7 (15.2) 2 criteria: 9 (19.6) 3 criteria: 1 (2.2)	0 criteria: 10 (21.7) 1 criterion: 8 (17.4) 2 criteria: 21 (45.7) 3 criteria: 7 (15.2)	Increased: 30 (65.2) Decreased: 2 (4.3) No change: 14 (30.4)	NA

Data are mean (SD) unless otherwise stated. *At W16, missing data were imputed: 2 patients for pulmonary vascular resistance (baseline value carried forward); 2 patients for mean pulmonary arterial pressure, mRAP, cardiac index, total pulmonary resistance and FC (baseline value carried forward); 5 patients for mixed venous oxygen saturation (baseline value carried forward for 4 patients; for 1 patient who died the day after W16, the value imputed at W16 was calculated from baseline using the worst evolution between baseline and W16 in the analysed population); 3 patients for 6MWD (baseline value carried forward for 2 patients; for 1 patient who died the day after W16, the value imputed at W16 was calculated from baseline using the worst evolution between baseline and W16 in the analysed population); 6 patients for NT-proBNP (LOCF); for risk assessment, missing parameters were considered “not low risk”; **Change expressed as the ratio of W16 versus baseline (geometric mean [95% CI]); [†]N=29 at baseline, N=33 at W16, N=29 for change from baseline; [‡]N=43; [‡‡] Median (Q1, Q3); [††]Percentages may not add to 100% due to rounding. 6MWD: 6-minute walk distance; CI: confidence interval; FC: World Health Organization functional class; LOCF: last observation carried forward; mRAP: mean right atrial pressure; NA: not applicable; NT-proBNP: N-terminal pro-brain natriuretic peptide; Q1, Q3: interquartile range; SD: standard deviation; W16: week 16.