Combination Therapy in Pulmonary Arterial Hypertension: Single Centre Long-term Experience

G Taçoy, A Çengel, Y Alsancak, S Ünlü, S Turkoğlu

ABSTRACT

Background: *Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vascular bed and causes right heart failure and death. Combination therapy which targets three different pathways is necessary due to the progressive nature of the disease. In patients with PAH, there are two approaches in combination therapy: "first-line up-front" and "sequential add-on" treatment. In "first-line up-front" treatment, patients receive double or triple drug therapy from the start. In the "sequential add-on" approach, a single drug is initially started and then according to the patient's requirements, a second or third drug is added. There is insufficient evidence about the efficiency and safety of treatment approaches. In this study, we aimed to evaluate the treatment approach in patients with PAH at a tertiary centre.*

Methods: *Pulmonary arterial hypertension was diagnosed according to clinical, echocardiographic and right heart catheterization findings. The patients received bosentan, sildenafil and iloprost treatment in accordance with guidelines recommendations. Clinical worsening in patients was defined as death, requirement of hospitalization for PAH, a 15% decline in the six-minute walk test (6MWT) distance, deterioration in functional capacity, and symptoms and findings of right heart failure.*

Results: *At the end of the follow-up period, clinical and echocardiographic findings, brain natriuretic peptide (BNP) levels and oxygen saturation were similar between patients who completed the study with monotherapy and with combination therapy. The follow-up period was significantly longer in patients who required combination treatment. Two patients (6.9%) died and four patients (13.8%) were hospitalized due to recurrent symptoms and findings of right heart failure. At the end of follow-up, 10 patients (34.5%) completed the study with a single drug, 15 patients (51.7%) with two drugs and four patients (13.8%) with three drugs.*

Conclusion: *In this study, combination therapy was given to patients as "sequential add-on therapy". At the end of the follow-up period, monotherapy was sufficient in 34.5% of patients of the study group and in eight patients, sildenafil or prostaglandin analogues were added; a total of 15 patients (48.4%) completed the study under dual therapy. Four patients (12.9%) received combination therapy with three drugs.*

Keywords: Combination therapy, hypertension, pulmonary artery

Terapia Combinada en la Hipertensión Arterial Pulmonar: Experiencia a Largo Plazo en un Solo Centro

G Taçoy, A Çengel, Y Alsancak, S Ünlü, S Turkoğlu

RESUMEN

Antecedentes: *La hipertensión arterial pulmonar (HAP) es una enfermedad progresiva del lecho vascular pulmonar, que causa insuficiencia cardíaca derecha y muerte. La terapia de combinación que apunta a tres diferentes vías, es necesaria debido a la naturaleza progresiva de la enfermedad. Para los pacientes con HAP, existen dos enfoques de terapia combinada: el tratamiento "inicial de primera línea" y el tratamiento "combinado secuencial". En el tratamiento de "inicial de primera línea inicial", los pacientes reciben terapia doble o triple desde el principio. En el enfoque "combinado secuencial", se comienza*

From: Cardiology Department, Faculty of Medicine, Gazi University, Ankara, Turkey.

Correspondence: Dr G Tacoy, Cardiology Department, Faculty of Medicine, Gazi University, Ankara, Turkey. Fax: 03122129012; e-mail: gtacoy@gmail.com

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con un solo medicamento, y luego según los requerimientos del paciente, se añade un segundo o tercer fármaco. No existen suficientes evidencias sobre la eficacia y seguridad de los enfoques de tratamiento. En este estudio, el objetivo fue evaluar el enfoque del tratamiento en pacientes con HAP en un centro terciario.

Métodos: *La hipertensión arterial pulmonar fue diagnosticada según los hallazgos clínicos, los ecocardiográficos, y los cateterismos cardíacos derechos. Los pacientes recibieron bosentán, sildenafil e iloprost de tratamiento, siguiendo las recomendaciones de las guías médicas. El empeoramiento clínico en los pacientes se definió como muerte, necesidad de hospitalización por HAP, disminución de un 5% en la prueba de caminata de seis minutos (PC6M), deterioro de la capacidad funcional, y síntomas y hallazgos de insuficiencia cardíaca derecha.*

Resultados: *Al final del período de seguimiento, los resultados clínicos y ecocardiográficos, los niveles de péptido natriurético cerebral (PNC), y la saturación de oxígeno, fueron similares entre los pacientes que completaron el estudio con monoterapia y terapia combinada. El período de seguimiento fue significativamente mayor en los pacientes que requirieron tratamiento combinado. Dos pacientes (6.9%) murieron y cuatro pacientes (13,8%) fueron hospitalizados debido a síntomas recurrentes y hallazgos de insuficiencia cardíaca derecha. Al final del seguimiento, 10 pacientes (34.5%) completaron el estudio con un solo medicamento, 15 pacientes (51.7%) con dos fármacos y cuatro pacientes (13.8%) con tres fármacos.*

Conclusión: *En este estudio, la terapia de la combinación fue administrada a los pacientes como "terapia combinada secuencial". Al final del período de seguimiento, la monoterapia fue suficiente en 34.5% de los pacientes del grupo estudio y en ocho pacientes, sildenafil o análogos de la prostaglandina fueron agregados; un total de 15 pacientes (48.4%) completaron el estudio bajo terapia dual. Cuatro pacientes (12.9%) recibieron terapia combinada con tres fármacos.*

Palabras claves: Terapia combinada, hipertensión arterial, arteria pulmonar

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vascular bed, and right heart failure is the leading cause of death (1). Although it can arise due to many different reasons, the pathological finding of the pulmonary vascular bed is similar in the patient groups (2). Numerous factors such as female gender, accompanying comorbid conditions, decreased exercise capacity and impaired haemodynamic parameters are prognostic factors in patients with PAH (3–5).

Three groups of drugs are approved for use in PAH: 1) endothelin receptor antagonists (bosentan, ambrisentan), 2) phosphodiesterase inhibitors (sildenafil, tadalafil) and 3) prostaglandin analogues [epoprostenol, treprostinil and iloprost] (6–12). Studies have demonstrated that combination therapy improved symptoms and haemodynamic findings and prolonged the time to clinical worsening. In current clinical practice, combination therapy is necessary for patients who do not respond adequately to treatment with a single drug (13–15). In PAH patients, there are two approaches in combination therapy: "first line up-front" and "sequential add-on" treatment. In "first line up-front" treatment, the patients receive double or triple drug therapy from the beginning. In the "sequential add-on" approach, a single drug is initially started and then, according to the patient's requirements, a second or third drug might be added. There is insufficient evidence about the efficacy and safety of treatment approaches. In this study, we aimed to evaluate the treatment approach in patients with PAH at a tertiary centre.

SUBJECTS AND METHODS

This descriptive and retrospective study was approved by the Ethics Committee. The study subjects were selected from patients older than 18 years of age with PAH due to Eisenmenger syndrome, idiopathic, connective tissue disease (Group I according to pulmonary hypertension [PH] classification) who were admitted to the Cardiology Clinic between 2008 and 2013. All participants provided written informed consent before study entry. Patients who met the haemodynamic right heart catheterization criteria for PAH were enrolled into the study: mean pulmonary artery pressure (PAP) $\geq$ 25 mmHg, pulmonary capillary wedge pressure (PCWP) < 15 mm Hg and pulmonary vascular resistance > 3 Wood units (240 dyns/s/cm^{-5}). Pulmonary artery pressure specific vasoreactivity testing prior to treatment was assessed by adenosine infusion. Exclusion criteria was described as left ventricular systolic (left ventricular ejection fraction [LVEF] < 45%) and diastolic dysfunction, severe valvular heart disease, coronary artery disease, severe liver and renal disease, and pregnancy. Exercise capacity was evaluated with the six-minute walk test (6MWT). Transcutaneous arterial oxygen saturation was monitored by pulse oximetry during 6MWT. Transthoracic echocardiogra-

phy w performed on all patients at diagnosis. Mortality, need for hospitalization and additional treatment of PAH were evaluated as clinical worsening. Conventional treatment with diuretics and digoxin was continued in patients with right heart failure symptoms and findings.

Pulmonary arterial hypertension-specific treatment was started in accordance with guidelines recommendations (1). At the beginning of the study period, patients were receiving PAH-specific therapy for at least three months.

Transthoracic echocardiographic examination

Transthoracic echocardiography was performed with the subjects in the left lateral decubitus position according to the guidelines of the American Society of Echocardiography (16) [Vivid 7, GE Vingmed, Horton, Norway].

Two-dimensional (2D) images were obtained from standard windows (parasternal short-, long axis, apical four- and two-chamber views). The estimated pulmonary artery systolic pressure was calculated as the sum of the transtricuspid gradient and the estimated right atrial pressure. From the apical four-chamber view, continuous-wave Doppler echocardiography was used to assess the peak tricuspid regurgitant velocity. Pulsed-wave tissue Doppler myocardial velocities were measured in the apical four-chamber view from the lateral mitral annulus and the right ventricular wall at the level of the tricuspid annulus. Pulsed tissue Doppler imaging (TDI) was characterized by a myocardial systolic wave (S) and two diastolic waves – early diastolic (E_m) and atrial contraction (A_m). Right ventricular (RV) dimension at base was measured at end-diastole in a right ventricle-apical four-chamber view. Right atrial (RA) major and minor dimensions were calculated in the apical four-chamber view. Right atrial area was measured at end-systole. Tricuspid regurgitant velocity was determined at the apical four-chamber view. Right ventricular fractional area change (RVFAC) was measured as: end-diastolic area (cm^2) – end-systolic area (cm^2)/end-diastolic area in apical four-chamber view. Right ventricular myocardial performance index (RVMPI) or Tei index was calculated as: isovolumic contraction time (ICT) + isovolumic relaxation time (IRT)/RV ejection time (RVET). Tricuspid annular plane systolic excursion (TAPSE) is a measure of longitudinal RV function and was determined with M-mode cursor aligned through the anterior tricuspid annulus in the apical four-chamber view and recorded as longitudinal displacement of the annulus toward the apex during systole.

Statistical analysis

Statistical analysis was performed using the statistical package SPSS 16. Definitive statistics were expressed as the mean ± standard deviation for normally distributed data and as the number and percentage for categorical variables. Results were evaluated using 95% confidence intervals, and $p < 0.05$ was considered statistically significant. The compliance of numerical variables to a normal distribution was assessed using the Kolmogorov-Smirnov test. Nonparametric data were compared with Kruskal-Wallis and the Mann-Whitney U test.

RESULTS

A total of 33 patients – 19 patients with Eisenmenger syndrome (11 patients with ventricular septal defect [VSD], two with aorticopulmonary window, two with patent ductus arteriosus [PDA], two with primum atrial septal defect [ASD], one with great vessels transposition, one with atrioventricular canal defect), five patients with idiopathic PAH, five patients with connective tissue disease (due to scleroderma-PAH), in addition to four patients with PH due to pulmonary thromboembolism – were enrolled into the study (Table 1).

Table 1: Causes of pulmonary hypertension in the study group

	Patients n (%)
Eisenmenger syndrome	19 (57.5) VSD, 11 PDA, 2 Aorticopulmonary window, 2 Primum ASD, 2 Down syndrome – AV canal defect, 1 Great vessel transposition, 1
IPAH	5 (5)
Connective tissue disease – scleroderma	5 (5)
Thromboembolic disease	4 (12.5)

VSD: ventricular septal defect; PDA patent ductus arteriosus, ASD: atrial septal defect; AV: atrioventricular; IPAH: idiopathic pulmonary arterial hypertension

Baseline standard echocardiographic findings are shown in Table 2. Patients were followed for an average of 57 months. There was sudden death in two patients with idiopathic PAH who were receiving monotherapy. Total mortality was calculated as 6.9%.

Table 2: Comparison of standard transthoracic echocardiographic findings before and after follow-up

	Before	**After**	***p***
LVEDD (mm)	42.76 ± 4.44	41.51 ± 9.38	0.543
LVESD (mm)	26.71 ± 3.34	26.30 ± 6.62	0.784
LVEDV (ml)	81.47 ± 19.73	80.47 ± 18.58	0.785
LVESV (ml)	28.47 ± 8.15	29.76 ± 8.12	0.199
EF (%)	63.47 ± 5.16	64.61 ± 8.69	0.665
LA (mm)	34.54 ± 7.62	34.68 ± 6.60	0.884
RA (mm)	44.22 ± 9.54	45.00 ± 9.32	0.588
RA/LA	1.25 ± 0.35	3.24 ± 9.33	0.332
RV (mm)	42.47 ± 7.76	41.52 ± 7.51	0.451
PAP (mmHg)	94 ± 33.05	93.66 ± 30.92	0.959

LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; EF: ejection fraction; LA: left atrium; RA: right atrium; RV: right ventricle diameter; PAP: pulmonary artery pressure

The majority of patients had Eisenmenger syndrome (57.5%), with the most common cause being VSD, 57.8% and female patients (82.2%) were more than male patients. Ini-

tially, 21 patients (63.6%) were New York Heart Association (NYHA) class II and 12 patients (36.4%) class III functional capacity, while in the last follow-up, two patients (6.5%) had class I , 14 patients (45.2%) class II, 11 patients (44.2%) class III and one patient (3.25 %) class IV functional capacity. There were no differences in the brain natriuretic peptide (BNP) levels, oxygen saturation and echocardiographic findings which were compared at the beginning and at the end of the study. At baseline, 26 patients (78.7%) were receiving monotherapy and seven patients (21.3%) were receiving dual therapy (Table 3). At the end of the follow-up period, two patients died and PAH-specific treatment was discontinued in two patients with thromboembolic PH due to myeloproliferative disease; thus, 29 patients completed the study. In eight patients, sildenafil or prostaglandin analogues were added and they completed the study under dual therapy. Four patients (12.9%) received combination therapy with triple drugs. During the five-year study period, 10 patients (34.5%) completed the study under monotherapy; no patient had any serious side effect due to PAH-specific treatment.

Table 3: Treatment before and after the follow-up period

Drugs	**Before n (%)**	**After n (%)**
Monotherapy	26 (78.7)	10 (32.2)
Dual combination (bosentan + sildenafil or bosentan + iloprost)	7 (21.3)	15 (38.7)
Triple combination (bosentan + iloprost + sildenafil)	–	4 (22.3)
Functional capacity		
Class I	–	2 (6.5)
Class II	21 (63.6)	14 (45.2)
Class III	12 (36.4)	11 (35.5)
Class IV		4 (13)

Patients who received monotherapy and combination therapy had similar clinical and echocardiographic findings, pro-BNP levels and oxygen saturation. Only disease duration was longer in patients who required combination therapy [$p < 0.05$] (Table 4).

Table 4: Comparison of clinical, echocardiographic and catheterization findings of patients who received monotherapy and combination therapy

	Monotherapy	**Combination therapy**	***p***
Age (year)	40.25 ± 16.28	41.68 ± 17.96	0.814
Duration (months)	36.25 ± 9.52	71.93 ± 13.78	0.037
Oxygen saturation (%)	88.24 ± 8.62	83.31 ± 9.02	0.162
6MWT distance (m)	434.8 ± 80.6	409.5 ± 99.11	0.455
Pro-BNP mg/L	466.4 ± 161.85	539.0 ± 108.4	0.717
LVEDD (mm)	40.28 ± 13.41	42.20 ± 3.22	0.665
LVESD (mm)	24.64 ± 9.39	27.60 ± 1.71	0.340
LVEDV (ml)	80.10 ± 23.43	80.0 ± 14.48	0.991
LVESV (ml)	29.70 ± 10.22	29.10 ± 6.00	0.875
EF (%)	67.0 ± 11.49	62.10 ± 4.72	0.229
LA	35.30 ± 6.23	33.09 ± 6.36	0.432
RA	44.20 ± 5.73	44.90 ± 12.02	0.867
RA/LA	5.53 ± 13.87	1.35 ± 0.40	0.329
RV	41.90 ± 4.55	40.70 ± 10.07	0.736
LAA (cm^2)	11.60 ± 3.06	13.09 ± 2.45	0.246
RAA (cm^2)	18.81 ± 5.32	23.00 ± 10.68	0.282
RAA/LAA	1.75 ± 0.94	1.71 ± 0.64	0.913
RVEDV (ml)	79.60 ± 23.05	92.44 ± 32.78	0.333
RVESV (ml)	50.60 ± 20.54	60.66 ± 27.50	0.375
RVFAC (%)	34.69 ± 8.26	32.82 ± 9.07	0.645
TAPSE (mm)	16.27 ± 3.58	16.00 ± 3.09	0.854
M E_m (cm/s)	7.5 ± 2.91	8.0 ± 3.26	0.722
M A_m (cm/s)	6.28 ± 0.95	5.88 ± 1.96	0.632
M S (cm/s)	6.80 ± 1.75	6.90 ± 2.02	0.907
T E_m (cm/s)	8.70 ± 2.31	9.11 ± 2.57	0.718
T A_m (cm/s)	9.14 ± 2.03	9.87 ± 2.79	0.578
T S (cm/s)	10.50 ± 2.91	9.11 ± 0.08	0.237
PAT (msn)	89.60 ± 16.69	89.00 ± 19.89	0.945
PAP (mmHg)	89.27 ± 26.99	105.66 ± 26.60	0.191
d PAP (mmHg)	59.66 ± 12.70	55.50 ± 11.47	0.668
RVOT (mm)	33.80 ± 3.99	35.35 ± 6.10	0.533
PVR	16.10 ± 11.68	24.75 ± 22.35	0.414
SVR	28.16 ± 5.15	30.20 ± 13.80	0.819
PET (msn)	280.28 ± 102.7	250.33 ± 76.45	0.569
RVWT (mm)	11.11 ± 3.05	12.10 ± 2.79	0.562

6MWT: six-minute walk test; BNP: brain natriuretic peptide; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVEDV: left ventricular end diastolic volume; LVESV: left ventricular end systolic volume; EF: ejection fraction; LA/RA: left/right atrium; RV: right ventricle; RAA/LAA: right/left atrial appendage; RVEDV: right ventricle end diastolic volume; RVESV: right ventricle end systolic volume; RVFAC: right ventricular fractional area change; TAPSE: tricuspid annular plane systolic excursion; M: mitral annulus; T: tricuspid annulus; pulsed tissue Doppler imaging was characterized by a myocardial systolic wave (S) and two diastolic waves – early diastolic (E_m) and atrial contraction (A_m); PAT: pulmonary acceleration time; PAP: pulmonary artery pressure; d PAP: diastolic pulmonary artery pressure; RVOT: right ventricular outflow tract; PVR: pulmonary vascular resistance; SVR: systemic vascular resistance; PET: pulmonary ejection time; RVWT: right ventricular wall thickness

DISCUSSION

Pulmonary arterial hypertension is a progressive disease and causes right heart failure and death. In patients with PAH, combination treatment is required for improving of symptoms and exercise capacity. Pulmonary arterial hypertension-specific drugs have different action mechanisms. The most important advantages of combination therapy are improving the efficiency and the reduction of possible side effects. There are numerous studies which have demonstrated the useful effects of combination therapy. The BREATHE-2 study found that combination treatment with bosentan and epoprostenol caused non-significant haemodynamic recovery (17). In the TRIUMPH study, adding treprostinil to bosentan or sildenafil improved the quality of life and 6MWT distance (15). There are different results in some studies that evaluated the effect of combination therapy due to a low proportion of NYHA functional class IV patients (14, 15, 18–29). The PACES study is different in this respect; 6% of the patients had class IV functional capacity. The study showed that with the addition of sildenafil to long-term intravenous epoprostenol, 6MWT distance, time to clinical worsening and quality of life were improved (14). Initially, in our study group, 26 patients (78.9%) were receiving monotherapy and at the end of follow-up period, combination therapy with two drugs was given to 15 patients (46%). In addition, four patients (10.1%) received combination therapy with triple drugs. Our results are consistent with other study findings and, due to the chronic and progressive nature of the disease, combination treatment was necessary for patients. There are different studies which suggest that combination therapy should be given to patients at the beginning of treatment to prevent the progression of the disease (25–27). A meta-analysis showed that combination treatment improved 6MWT distance, haemodynamic data and reduced the incidence of clinical worsening (28).

The first registration study in 194 patients with PAH was performed by NIH (National Institutes of Health) in 1980 and survival time after diagnosis was determined as 2.8 years (29). Subsequently, in a French registry, one-year survival in 674 patients with PAH was found to be 88% (30). In the REVEAL study, one- and three-year survival rate was found as 91% and 74% (31). Advances in diagnostic method and treatment approaches may explain the improvement of the survival rates of patients with PAH in follow-up programmes. In our study, mortality rate was 6.9% in the five-year follow-up. Low ratio of NYHA functional class IV patients and high ratio of patients with Eisenmenger syndrome, who have better prognosis than other PAH patients, might have contributed to the better survival rate in our study.

In a meta-analysis of seven randomized studies, Zhu *et al* showed that combination therapy improved 6MWT and time of clinical worsening (32). They compared combination therapy with monotherapy and found that the rate of clinical deterioration was 12% in monotherapy group and 5.2% in combination therapy group and they could not find any mortality benefit due to the small number of patients with class IV functional capacity in which combination therapy has the most important mortality benefit (32).

Bosentan, ambrisentan, macitentan and phosphodiesterase type 5 (PDE-5) inhibitors are orally used drugs, and combination therapy with these agents is accepted as a convenient and easy approach. In the COMPASS study, binary pharmacodynamic effect was achieved with the addition of sildenafil to bosentan therapy (33). Macitentan with sildenafil treatment in SERAPHIN study caused significant beneficial effects in PAH patients (34).

In our patient population, clinical, echocardiographic and catheterization findings were similar between patients who received monotherapy and combination therapy at the end of the follow-up. Follow-up duration was longer in the com-bination group, which might reflect the chronic course of the disease and, thus, requirement for combination treatment. Also, in our study, the "sequential add-on" approach was pre-ferred. At the end of follow-up, 34.5% of patients were still re-ceiving monotherapy. The "sequential add-on" approach prevented the addition of unnecessary medications, increased the cost-effectiveness and reduced side effects.

Limitations

A major limitation of the study was small patient population. Another limitation was the low ratio of high-risk individuals with class IV functional capacity. At the beginning of the follow-up period, the echocardiographic indices, which are prognostic for right ventricle performance, were not measured, therefore, we could not compare these parameters.

CONCLUSION

In long-term follow-up of patients with PAH, depending on the progressive nature of the disease, combination therapy became necessary and the "sequential add-on" approach provided beneficial results. The study identified lower mortality rates, probably due to lower rates of high-risk patients in the study group.

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