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Research Brief

A randomized, double-blind, placebo-controlled study to evaluate sildenafil, ambrisentan combination therapy in pulmonary hypertension, particularly of Eisenmenger syndrome

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ABSTRACT

Pulmonary arterial hypertension (PAH) - a complex and progressive disease that carries significant morbidity and mortality despite optimal medical treatment. Combination therapy for PAH can be more effective than monotherapy. The present randomized trial compared the safety and efficacy of sildenafil ambrisentan combination therapy with sildenafil monotherapy. Twenty-two patients of Eisenmenger syndrome and five patients of idiopathic PAH were randomized to two arms. There was a significant improvement in NYHA functional class and mean pulmonary artery pressure, while an insignificant improving trend was observed for 6-min walk distance and oxygen saturation, following the 12 weeks of combination therapy. An upfront combination therapy was found to be safe and effective in the management of PAH patients.

1. Introduction

Pulmonary arterial hypertension (PAH) is a complex and progressive disorder caused by diverse etiologies. It carries significant morbidity and mortality despite optimal medical treatment. As multiple pathways can be involved in the pathogenesis of PAH, a combination therapy targeting different pathways can be of a potential benefit than monotherapy. Most of the available data about combination therapy is based on sequential addition to ongoing single-agent therapy,[1–3] rather than upfront combination therapy.[4–6] We in the present study had compared monotherapy with upfront combination therapy targeting two signalling pathways of nitric oxide and endothelin in patients with idiopathic pulmonary hypertension (iPH) and Eisenmenger Syndrome (ES).

2. Methods

It was a prospective, randomized, double-blind, placebo-controlled study to compare the safety and efficacy of sildenafil monotherapy versus ambrisentan sildenafil combination therapy in patients of iPH and ES. Twenty-seven patients - 5 of iPH and 22 of ES, were enrolled in the study. Pulmonary arterial hypertension was defined as a mean pulmonary artery pressure (PAP) of ≥25 mm Hg. Patients of secondary PAH and chronic pulmonary thromboembolism and those with deranged hepatic and renal functions, coronary artery disease, or contraindication to the studied drugs were excluded from the study. Various parameters such as New York Heart Association (NYHA) functional class, oxygen saturation, 6-min walk distance (6-MWD), hemoglobin, liver function tests, and echocardiographic parameters were measured at baseline and repeated after 12 weeks of drug therapy. Patients were divided into 2 groups by block randomization method. Both the groups received sildenafil (20 mg thrice a day, Cipla India). In addition, Group 1 received a placebo tablet (once a day); and Group-2 received an ambrisentan tablet (5 mg once a day, Cipla India). A baseline oxygen saturation, pulse rate, and blood pressure were measured after 10 min of rest in a comfortable position and repeated after completion of the 6-min walk test (6 MWT). The primary outcomes were the change in 6 MWD and NYHA functional class. The secondary outcomes were the change in right ventricular (RV) functions using echocardiographic parameters such as RV dimensions, RV fractional area change (FAC), and tricuspid annular plane systolic excursion (TAPSE). The study protocol was approved by the

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institute ethics committee. The trial registration number was CTRI/2017/12/010,736 dated 4th December 2017.

Statistical Analysis: - It was performed using the SPSS software package for Windows version 22.0 (SPSS Inc, Chicago, IL). Descriptive statistics were used for demographic data. Correlations were estimated by the Pearson correlation coefficient. An independent *t*-test was used for comparison of differences. A *p*-value of <0.05 was considered statistically significant.

3. Results

Out of 27 patients, 13 were randomized to sildenafil monotherapy and 14 received combination therapy. The mean age of 27 patients (13-female and 14-male) was 28 ± 12 years. The underlying congenital heart disease in 22 ES patients was as follows - ventricular septal defect-16, atrial septal defect −2, atrioventricular canal defect- 2, and patent ductus arteriosus −2. The two groups were comparable with no significant differences in the baseline characteristics (Table 1), except oxygen saturation and NYHA class which was worse in the combination therapy group. The primary and secondary outcomes in both the groups were similar without any significant differences (Table 2). There was a significant improvement in the 6 MWD and oxygen saturation in the monotherapy group. Both the parameters had insignificant improvement in the combination therapy group (Table 3). The NYHA functional class had significant improvement in both groups. Mean pulmonary artery pressures significantly decreased in the combination therapy group. There was an insignificant improving trend of various echocardiographic parameters in both the groups. None of the patients had drug-induced adverse effects like aminotransferase elevation, headache, pedal edema or hypotension.

4. Discussion

The potential benefit of monotherapy - sildenafil or ambrisentan is well established in PAH management. Similar to our observation about sildenafil monotherapy, Galie et al,[7] and Singh et al,[8] also demonstrated its beneficial effects in PAH patients. Ambrisentan monotherapy is also found to be effective in improving 6 MWD, functional class, and right heart hemodynamics in PAH patients.[1,9–11]

The concept of combination therapy targeting different PAH pathways was evolved to achieve additional benefits in those patients who hada suboptimal response to monotherapy. Badesch DB, et al,[1] demonstrated that sequential add-on ambrisentan therapy for 24 weeks of duration, to preexisting sildenafil monotherapy, further improves the 6 MWD in PAH patients. Iversen et al,[12] found improvement in 6 MWD ($p = 0.48$) and oxygen saturation ($p < 0.01$) with add-on sildenafil to bosentan monotherapy in 21 ES patients. Galie et al,[6] found that 24 weeks of ambrisentan tadalafil combination therapy in comparison to ambrisentan or tadalafil monotherapy, was associated with significant improvement of NT-proBNP levels, 6 MWD and clinical improvement. Similarly, Hassoun et al,[13] also found significant improvement in 6 MWD and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels after 24-weeks of ambrisentan tadalafil combination therapy in scleroderma associated PAH patients. We observed an improving trend, though not significant in 6 MWD and oxygen saturation in the combination group. A shorter 12 weeks of combination therapy instead of 24–48 weeks[1,6,13] was the possible reason as an extended period of therapy was found to have a consistent and progressive improvement in various parameters.[1,9–11] Our study cohort consists of 81 % patients of ES, while almost all these studies included iPAH and connective tissue associated PAH patients, hence extrapolation of their results with the present study needs a cautious interpretation.

Hassoun et al,[13] had shown a significant improvement in TAPSE following 24-weeks of ambrisentan tadalafil therapy in scleroderma associated PAH patients. Kaya et al,[14] in their study of 23 ES patients treated with 24-months of bosentan therapy did not show a significant change in RV dimensions, though RV myocardial performance index had a significant improvement. Our study did not show a significant change in RV dimensions, TAPSE and FAC, possibly because of the short duration of therapy. The combination therapy was well tolerated in the present study, unlike others who had reported frequent drug-related adverse events.[6,15]

Limitation of the study: - A limited number of patients and a shorter duration of combination therapy were the limiting factors

Table 1
Baseline characteristics in the groups.

Baseline characteristics	Sildenafil monotherapy ($n = 13$)	Combination therapy ($n = 14$)	*p*-value
Age (years)	27.76 ± 11.76	29.78 ± 12.57	0.67
Body surface area (m^2)	1.49 ± 0.18	1.54 ± 0.13	0.43
Eisenmenger syndrome	10	12	0.7
Primary PAH	3	2	0.7
Pulse rate (beats/min)	88.14 ± 18.30	91.5 ± 14.31	0.60
Systolic blood pressure (mmHg)	101.38 ± 6.75	103.14 ± 6.06	0.48
Oxygen saturation (%)	90.69 ± 8.09	74.28 ± 15.05	0.002
Haemoglobin (g/dL)	15.09 ± 2.37	15.86 ± 4.43	0.58
Bilirubin (mg/dL)	0.93 ± 0.32	1.27 ± 0.95	0.23
Aspartate aminotransferase (Units/L)	34.76 ± 14.40	29.85 ± 8.94	0.29
Alanine aminotransferase (Units/L)	28.23 ± 8.56	33.29 ± 11.96	0.22
Alkaline phosphatase (Units/L)	109.72 ± 51.06	103.18 ± 34.90	0.69
6-min walk distance (meters)	480.56 ± 129.93	456.43 ± 108.53	0.60
Mean PA pressure (mmHg)	61.47 ± 20.39	61.97 ± 13.67	0.74
NYHA Class	2.31 ± 0.48	2.93 ± 0.26	<0.0001
TR velocity (cm/s)	454.76 ± 93.01	460.92 ± 62.33	0.84
RV basal diameter (cm)	3.74 ± 0.60	3.63 ± 0.54	0.63
RVOT PSAX Diameter (cm)	3.11 ± 0.70	3.06 ± 0.68	0.84
RVOT PLAX diameter (cm)	2.88 ± 0.80	2.82 ± 0.59	0.90
TAPSE (cm)	1.80 ± 0.20	1.70 ± 0.35	0.40
Fractional area change (%)	22.57 ± 8.62	24.07 ± 9.74	0.67

Values are in mean ± 1 standard deviation.
Abbreviations: NYHA - New York Heart Association, TR - Tricuspid regurgitation, RV - Right Ventricle, RVOT – Right ventricle outflow tract, PAH – Pulmonary artery hypertension, PSAX - Parasternal short-axis view, PLAX - Parasternal long-axis view, TAPSE - Tricuspid annular plane systolic excursion.

Table 2
Primary and secondary outcome analysis.

Characteristics	Sildenafil monotherapy ($n = 13$)	Combination therapy ($n = 14$)	p-value
Primary outcome			
6 min walk distance (meters)	523.84 ± 94.71	472.65 ± 122.09	0.23
NYHA class	2.00 ± 0.00	2.14 ± 0.36	0.16
Secondary outcome			
TR velocity (cm/s)	428.15 ± 79.92	434.28 ± 67.25	0.83
RV basal diameter (cm)	3.83 ± 0.62	3.61 ± 0.59	0.34
RVOT PSAX diameter (cm)	3.32 ± 0.82	3.14 ± 0.59	0.49
RVOT PLAX diameter (cm)	2.85 ± 0.80	2.82 ± 0.59	0.90
TAPSE (cm)	1.83 ± 0.33	1.69 ± 0.30	0.26
Fractional area change (%)	26.18 ± 7.09	25.44 ± 9.99	0.82

Values are in mean ± 1 standard deviation.
Abbreviations: NYHA - New York Heart Association, TR - Tricuspid regurgitation, RV - Right Ventricle, RVOT – Right ventricle outflow tract, PSAX - Parasternal short-axis view, PLAX - Parasternal long-axis view, TAPSE - Tricuspid annular plane systolic excursion.

Table 3
Comparison of outcomes in monotherapy and combination therapy group.

Characteristics	Sildenafil alone group ($n = 13$)			Combination therapy group ($n = 14$)		
	Baseline	Follow-up	p-value	Baseline	Follow-up	p-value
6-min walk distance (m)	480.56 ± 129.93	523.84 ± 94.71	0.004	456.43 ± 108.53	472.65 ± 122.09	0.22
NYHA Class	2.31 ± 0.48	2.00 ± 0.0	0.04	2.93 ± 0.26	2.14 ± 0.36	<0.0001
Oxygen saturation (%)	90.69 ± 8.09	93.53 ± 6.65	0.01	74.28 ± 15.05	78.21 ± 13.66	0.26
Mean PA pressure (mmHg)	61.47 ± 20.39	55.48 ± 16.97	0.1	61.97 ± 13.67	56.32 ± 13.67	0.02
TR velocity (cm/s)	454.76 ± 93.01	428.15 ± 79.92	0.12	460.92 ± 62.33	434.28 ± 67.25	0.02
RV basal diameter (cm)	3.74 ± 0.60	3.83 ± 0.62	0.24	3.63 ± 0.54	3.61 ± 0.59	0.80
RVOT PSAX diameter (cm)	3.11 ± 0.70	3.32 ± 0.66	0.1	3.06 ± 0.68	3.14 ± 0.59	0.59
RVOT PLAX diameter (cm)	2.88 ± 0.80	2.85 ± 0.80	0.85	2.87 ± 0.59	2.82 ± 0.59	0.71
TAPSE(cm)	1.80 ± 0.20	1.83 ± 0.33	0.5	1.70 ± 0.35	1.69 ± 0.30	0.82
Fractional area change (%)	22.57 ± 8.62	26.18 ± 7.09	0.15	24.07 ± 9.74	25.44 ± 9.95	0.71

Values are in mean ± 1 standard deviation.
Abbreviations: NYHA - New York Heart Association, PA- Pulmonary artery, TR - Tricuspid regurgitation, RV - Right Ventricle, RVOT – Right ventricle outflow tract, PSAX - Parasternal short-axis view, PLAX - Parasternal long-axis view, TAPSE - Tricuspid annular plane systolic excursion.

to demonstrate the beneficial effects. The majority of the published data is about iPAH or connective tissue related PAH, the results of which should be cautiously extrapolated to the present study which had 81 % of ES patients.

5. Conclusion

An upfront combination therapy of sildenafil ambrisentan was associated with significant improvement in functional class and mean PA pressure, and improving trends for 6 MWD and oxygen saturation in PAH patients. The combination therapy was not associated with any drug-related adverse effects.

What is already known

The safety and efficacy of the single drug and sequential combination drugs therapy are well established in PAH management.

What this study adds

The present study is the first one to demonstrate the safety and efficacy of upfront combination therapy of sildenafil and ambrisentan in PAH patients, mainly comprising of Eisenmenger Syndrome.

Author's contribution

All the authors were involved in [1] substantial contributions to research design, acquisition, analysis, or interpretation of data; [2] drafting the paper or revising it critically; [3] approval of the submitted and final versions.

Declaration of competing interest

There is no conflict of interest on any of the authors about the present study.

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