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ORIGINAL ARTICLE

Influence of Age on Outcome in Patients with Pulmonary Arterial Hypertension

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Background The development of effective orally administered medical therapy for pulmonary arterial hypertension (PAH) has made a significant impact on outcome in patients with PAH. Identification of patient groups likely to derive optimal benefit is important, given cost and potential side effects; the clinical effectiveness of these therapies in older patients with PAH is unclear as the presence of co-morbidity may limit benefits of therapy.

Aims We evaluated the epidemiology of PAH in a contemporary cohort to assess the influence of age on long-term outcome using PAH-specific therapies.

Results A total of 119 patients (88% female; mean age 65±12 years) were reviewed, comprising 52% with underlying connective tissue disease. Bosentan was the PAH specific agent most frequently used. The baseline 6MWT distance in the entire cohort was 304m with age associated with a significant decline in 6MWT.

Conclusions In a large cohort of patients treated with PAH-specific therapies, patients less than 55 years of age showed improvement in 6MWT with older patients demonstrating stabilisation or decline.

Keywords Pulmonary arterial hypertension • Endothelin receptor antagonist • Phosphodiesterase inhibitor • Right heart failure • Cardiac transplant

Advances in the treatment of pulmonary arterial hypertension (PAH) have resulted in improved clinical outcomes. The advent of endothelin receptor antagonists and the recognition of the benefits of phosphodiesterase inhibitors, in addition to the established role of prostacyclin analogues, have made an important contribution in terms of both morbidity and mortality for patients with PAH. As experience with these agents increases, identification of patient groups who are likely to derive optimal benefit is important. As such, screening high-risk groups, such as those with connective tissue disease, has been advocated, as has initiation of therapy early in patients with WHO functional class II symptoms [1–4]. The elderly are typically underrepresented in clinical trials, with the clinical effectiveness of these therapies in older patients with PAH less well established. The co-existence of co-morbidity may limit the efficacy of these agents and influence the anticipated benefit in terms of outcome.

We sought to evaluate the course of PAH and assess the influence of age on long-term outcome in a cohort of patients maintained on PAH–specific therapies.

Methods

All patients maintained on PAH–specific therapies (endothelin receptor antagonists, phosphodiesterase inhibitors or intravenous or inhaled prostanoids) treated at the John Hunter Hospital since 2004 were reviewed.

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Table 1 Baseline characteristics.

Variable	Class / Statistic	Total (N=119)
Gender	Males	22 (18%)
Smoker	Yes	49 (47%)
Hypertension	Yes	60 (51%)
Diabetes	Yes	16 (14%)
COPD	Yes	15 (13%)
Calcium channel blocker (CCB)	Yes	19 (16%)
Warfarin	Yes	43 (37%)
Change in Therapy	Yes	23 (19%)
Admission / Transplant / Death	Yes	24 (20%)
Diagnosis class	Idiopathic PAH (IPAH)	56 (47%)
Diagnosis class	CTD	62 (53%)
WHO class	II	4 (3.4%)
WHO class	III	106 (90%)
WHO class	IV	8 (6.8%)
Age (years)	Mean (std)	65.01 (12.64)
Weight (kg)	Mean (std)	79.22 (21.76)
BMI (kg/cm^2)	Mean (std)	29.55 (7.24)
Baseline 6 min walk test (m)	Mean (std)	304.06 (114.29)

The review was approved by the Hunter New England Area Health District Research Ethics Committee.

Clinical outcome data was obtained from the prospectively maintained PAH treatment database established for patients maintained on subsidised PAH therapies. All patients maintained on PAH specific therapies underwent a six-minute walk test (6MWT) and transthoracic echocardiography every six months, with the majority of echocardiograms reviewed by two experienced echocardiologists with an interest in PAH. Minimum follow-up time was one year and maximum eight years.

Baseline and follow-up diagnostic right heart catheterisation was performed at the discretion of the treating physician, with serial assessment typically performed in cases of clinical deterioration. The need for additional (add on) PAH specific therapies was prospectively documented.

We evaluated the influence of age on outcome in terms of serial change in 6MWT distance, the need for change in medical therapy due to lack of efficacy, hospitalisation, death and transplantation.

Analysis for change in 6MWT was performed using a linear regression model within the generalised estimating equation framework. Age was treated as a continuous variable except when exploring interaction, where groups were classified as younger than 55 years of age, 55 – 65 years, 65 – 75 years and older than 75 years. Covariates included other interventions (calcium channel blockers, warfarin), smoking, WHO functional class, pulmonary hypertension complicating connective tissue disease (CTD) and gender. Comparison for other outcomes, such as the need for change in medical therapy, hospitalisation, death and transplantation, was performed using Cox regression models; all of these models observed the proportional hazards assumption.

Results

A total of 119 patients (88% female; mean age 65±12 years) have been followed since 2004. Baseline characteristics of the total cohort are outlined in Table 1. This cohort comprised 53% having connective tissue disease, reflecting the rigorous screening of patients with auto-immune disease at our institution. Of those patients with underlying autoimmunity, 55% (n=38) had a diagnosis of either systemic sclerosis or CREST syndrome. Bosentan was the PAH specific agent most frequently used, with 37% receiving warfarin treatment.

Six-minute Walk Test

The baseline mean 6MWT distance in the entire cohort was 304m. Age had a significant effect on decline in 6MWT in the unadjusted model and this difference remained significant after adjustment for smoking, calcium channel blockade use, warfarin therapy and gender (Table 2); each year older at entry was associated with a five metre greater decline in 6MWT over the following year.

After adjusting for age, each year of follow-up led to a slight increase in 6MWT although this was not significant; this presumably indicates a stabilisation of these values while on treatment. The age by time interaction term was also significant indicating that the effect of treatment follow-up on age was not consistent across all age groups. To understand this interaction further, we plotted 6MWT values over time for different age group bands which demonstrated the following: those aged younger than 55 years noted a significant improvement in 6MWT over time, compared to the stabilisation or slight decline in those older than 55 years old (Figure 1). This difference remained significant after adjustment for smoking, calcium channel blockers, warfarin