Outcome measures in pulmonary arterial hypertension associated with systemic sclerosis

O. Kowal-Bielecka¹, M. Delcroix², A. Vonk-Noordegraaf³, M. M. Hoeper⁴ and R. Naeije⁵

SSc is complicated in ~10% of the patients by pulmonary arterial hypertension (PAH), a rare dyspnoea–fatigue syndrome caused by an increase in pulmonary vascular resistance. The prognosis of SSc-PAH is particularly poor, with estimated survival rates of ~50% at 2 yrs without pulmonary circulation-targeted therapies. Prostacyclins, endothelin receptor antagonists and phosphodiesterase-5 inhibitors have been shown to be efficacious in PAH, with persistent long-term benefit and approximate doubling of survival rate, and these encouraging results appear transposable to the SSc-PAH subcategory. However, PAH as well as SSc-PAH remain incurable, with insufficient functional improvement in many patients. More progress is needed, and this will require more effective drugs and adapted outcome measures.

KEY WORDS: Pulmonary arterial hypertension, Systemic sclerosis, Outcome measure, Exercise capacity.

Introduction

Pulmonary arterial hypertension (PAH) is a rare dyspnoea–fatigue syndrome caused by an increase in pulmonary vascular resistance (PVR) and eventual right ventricular failure [1]. The condition is either idiopathic (iPAH), or occurs in association with a variety of conditions including SSc (SSc-PAH). Screening strategies based on a combination of clinical suspicion, echocardiography and right heart catheterization allow for a diagnosis of PAH in up to 10% of the patients with SSc [2]. In spite of advances brought about during the last decade by the introduction of prostacyclins, endothelin receptor antagonists (ERAs), and phosphodiesterase-5 inhibitors (PDE5is) [3], PAH remains incurable, with a median survival still limited to 5–6 yrs, which decreases to 2–3 yrs in SSc-PAH [4].

Efficacy of PAH therapies

Most randomized controlled trials (RCTs) of new therapies in PAH have relied on exercise capacity measured by the distance walked in 6 min as a primary end-point. The logic of this approach is that the aerobic exercise capacity or maximum oxygen uptake in heart failure is predominantly determined by maximum cardiac output [5]. The symptomatology of PAH is explained by right ventricular failure caused by an increased PVR [6]. Because of the tight linear relationship between oxygen uptake and muscle work, which translates into maximum average running or walking speed, exercise capacity can be reliably estimated by a distance run or walked in 6 or 12 min as submaximal exercise tests [5, 6]. The 6-min walk distance (6MWD) is a simple, cheap, safe and reproducible measurement, which has been extensively used to assess the effects of drugs in PAH patients [5, 6]. The 6MWD has been shown to be well correlated to New York Heart Association (NYHA) functional class, maximum oxygen uptake, PVR and survival [7] in chronic obstructive pulmonary disease (COPD) and iPAH and is sensitive to pharmacological interventions [8].

This reasoning has been questioned by a recent meta-analysis. The authors examined 10 RCTs of the ERAs bosentan and sitaxsentan and of the PDE5i sildenafil in a total of 613 patients with PAH, of whom 186 with SSc-PAH received the active treatment and 72 SSc-PAH received placebos [9]. The effect size, which is the ratio of the treatment effect (mean difference in treatment group minus mean difference in placebo group) to the pooled s.d. of these differences, was 0.31 for bosentan, 0.26 for sitaxsentan and 0.53 for sildenafil in SSc-PAH, while for the whole PAH population, these values were of 0.61, 0.33 and 0.58, respectively. By convention, effect sizes of <0.2 are usually considered trivial, 0.2–0.5 as small, 0.5–0.8 as moderate and >0.8–1.2 as important to very important [9]. Therefore, the study concluded that the 6MWD seemed to indicate a poor therapeutic response of SSc-PAH to currently used therapies in PAH patients. However, whether effect sizes for 6MWD are really different between PAH subcategories remains uncertain. Small effect sizes for the 6MWD may simply reflect the limited, but still clinically relevant, efficacy of available PAH therapies or it may, indeed, reflect lack of responsiveness to these therapies in SSc. On the other hand, PAH as a disease entity is described by more than just exercise capacity, and one could consider other measures of improvement based on signs and symptoms scores, the NYHA functional class, more extensive dyspnoea scores, echocardiographic or haemodynamic measurements and chemical biomarkers [10]. There may be in addition a need for more specific outcome measures and validation in SSc-PAH [11].

How do outcome measures used in PAH apply to SSc-PAH?

RCTs of new therapies in PAH have included a majority of idiopathic PAH and a variable, though dominant minority of SSc-PAH patients [8]. Only one of the trials was specifically devoted to SSc-PAH [12]. We re-examined the changes in 6MWD and in other outcome variables reported in SSc-PAH (or extended to CTD-associated PAH) and compared them with those reported in PAH in general. As illustrated in Fig. 1, the 6MWD as primary end-point, and as secondary end-points NYHA functional class and PVR all changed directionally (although not usually statistically significantly) in SSc-PAH, CTD-PAH or global PAH, without suggestion of specificities.

There are of course important methodological limitations to this analysis. Secondary end-points are only exploratory, and repetition of a posteriori analysis of subgroups is challenging because of rapidly increasing risk of false-positive and -negative
results [13]. Even more difficult is the assessment of long-term effects of drugs shown efficacious in short-term RCT, where one remains limited to registries with associated suboptimal levels of evidence. It is nevertheless remarkable that a recent 6-yr longitudinal, single-centre study of 92 patients with SSc-PAH reported an improved 2-yr survival from 47% (historical controls) to 71% with the introduction of efficacious oral therapies for PAH [14].

Future studies
There is an on-going debate as to whether the 6MWD is the ideal primary end-point in PAH, especially in SSc-PAH. While there has been no study specifically aimed at the determination of the minimal change in 6MWD clinically meaningful in PAH, the presence of systemic disease would be expected to decrease the sensitivity of the measure. In patients with COPD, in whom exercise capacity limitation is multifactorial, the minimal-change 6MWD perceived by the patients as being clinically meaningful is ~54 m [15]. However, in PAH including SSc-PAH, a mean change in 6MWD of 8 m was reported to be associated with significant changes in dyspnoe–fatigue rating and clinical scores after only 6 weeks of subcutaneous treprostinil therapy [16].

Alternative end-points are being investigated and actively built into trials [10, 11]. Time to deterioration is an interesting alternative to the 6MWD as it measures clinical stability, which is a desirable result to achieve in the less severely ill patients. Chemical biomarkers are being closely examined. Whether more specific end-points are to be considered when PAH is associated with SSc is a challenging question, which will be answered only with properly designed RCTs using new expert consensus-derived outcome measures.

Acknowledgements
Supplement: This paper forms part of the supplement entitled ‘Update in systemic sclerosis’. This supplement was supported by an unrestricted grant from Encysive.

Disclosure statement: M.M.H. has received fees for speaking at conferences and is a consultant for Actelion, Encysive, GlaxoSmithKline, Bayer and Pfizer. All other authors have declared no conflicts of interest.

References


