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Effect of Pulmonary Arterial Hypertension-Specific Therapies on Health-Related Quality of Life

A Systematic Review

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BACKGROUND: Health-related quality of life (HRQoL) is severely impaired in pulmonary arterial hypertension (PAH). We aimed to assess the effect of PAH-specific therapies on HRQoL.

METHODS: A literature search was performed in MEDLINE and Embase databases (January 1990 to September 2013) to retrieve prospective placebo-controlled randomized trials of at least 6 weeks duration reporting the effect of PAH-specific therapies on HRQoL in adult patients with PAH. The articles were independently reviewed, and the validity of the trials was assessed using the Cochrane's Risk of Bias Tool.

RESULTS: The literature search identified 1,172 titles. Seventeen articles reporting on 14 trials were retrieved, all of which were associated with a low risk of bias. The median study duration of the different trials was 12 weeks. Most patients had idiopathic PAH or PAH associated with connective tissue disease. A variety of HRQoL questionnaires were used in these trials, and most were generic. HRQoL results were most commonly minimally detailed, and some pivotal trials did not even assess HRQoL. Nevertheless, these trials consistently demonstrated statistically significant improvements in HRQoL with PAH-specific therapies, especially for the physical domains. In most cases, however, these improvements were smaller than the minimal important difference in HRQoL previously reported in PAH.

CONCLUSION: This review shows that PAH-specific therapies improve HRQoL in PAH. However, it remains difficult to draw any firm conclusion about the clinical significance of these improvements. Further work is mandatory to validate PAH-specific questionnaires that are responsive to clinical changes as well as to establish their interpretability.

CHEST 2014; 146(3):686-708

Manuscript received November 13, 2013; revision accepted February 24, 2014; originally published Online First March 13, 2014.

ABBREVIATIONS: CAMPHOR = Cambridge Pulmonary Hypertension Outcome Review; CHFQ = Chronic Heart Failure Questionnaire; EQ-5D = EuroQol 5D; HR = hazard ratio; HRQoL = health-related quality of life; LPHQ = Living with Pulmonary Hypertension Questionnaire; MID = minimal important difference; MLHFQ = Minnesota Living with Heart Failure Questionnaire; NHP = Nottingham Health Profile; PAH = pulmonary arterial hypertension; RCT = randomized controlled trial; SF-12 = Medical Outcomes Study 12-item Short Form; SF-36 = Medical Outcomes Study 36-item Short Form

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FUNDING/SUPPORT: The authors have reported to *CHEST* that no funding was received for this study.

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DOI: 10.1378/chest.13-2634

Pulmonary arterial hypertension (PAH) is a progressive but fatal vascular disease characterized by a pathologic increase in pulmonary vascular resistance.[1] PAH may be idiopathic, heritable, or associated with connective tissue disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection, and anorexigen exposure.[2] The clinical consequences of these pulmonary vascular changes include dyspnea, exercise intolerance, right-sided heart dysfunction, loss of health-related quality of life (HRQoL), and ultimately death.[1] Over the last two decades, PAH-specific therapies have been developed[3] and led to improvements in pulmonary hemodynamics, exercise capacity, and survival.[4] However, despite newly developed therapies, most patients display persistent exercise intolerance, and long-term prognosis remains poor.[1,5-9]

Thus, in addition to better survival and exercise capacity, these drugs are intended to improve patients' HRQoL. As a result, many randomized controlled trials (RCTs) included HRQoL as a secondary or exploratory end point. However, the heterogeneity of the HRQoL measures and the small sample size of each of these individual RCTs precluded any firm conclusions about the effects of treatment on HRQoL in PAH. The aim of this systematic review was to assess the effect of recently developed therapies on HRQoL in PAH.

Materials and Methods

Literature Search

We performed a literature search using MEDLINE and Embase databases (January 1990 to September 2013) to identify randomized placebo-controlled trials published in any language evaluating PAH-specific therapies. Search strategy combined the following terms: ("pulmonary hypertension" OR "pulmonary arterial hypertension") AND (therapy OR therapies OR treatment OR treatments OR therapeutics) AND ("quality of life" OR "exercise tolerance" OR "exercise capacity" OR "daily living" OR "daily life activities") AND (trial OR trials OR controlled OR randomized) NOT (children OR child OR infant OR neonates OR neonatal OR pediatric)) OR ("Hypertension, Pulmonary/drug therapy"[Medical Subject Headings (Mesh)] OR "Hypertension, Pulmonary/therapy"[Mesh]) AND ("Quality of Life"[Mesh] OR "Activities of Daily Living"[Mesh] OR "Exercise Tolerance"[Mesh]) AND (Clinical Trial OR Randomized Controlled Trial). We also searched for additional articles from the reference list of relevant articles obtained from the electronic search. In addition, the gray literature was explored by hand searching the conference abstracts of the American Heart Association, American College of Cardiology, European Society of Cardiology, American Thoracic Society, American College of Chest Physicians, European Respiratory Society, and British Thoracic Society from January 1999 to September 2013.

Inclusion Criteria for Studies

Only prospective placebo-controlled RCTs of >6 weeks duration evaluating the effect of PAH-specific therapies in adult patients with PAH from January 1990 to September 2013 and evaluating HRQoL using questionnaires were included. Studies recruiting both treatment-naive and treated patients at baseline were considered as evaluating monotherapy, unless subgroup analyses allowed the assessment of the effect of PAH-specific therapy in addition to baseline therapy (add-on combination therapy) on HRQoL. Studies involving overlapping cohorts of patients, pediatric populations, and studies evaluating patients without PAH and nonpharmacologic interventions were excluded.

Study Selection and Assessment of Risk of Bias

The retrieved articles were independently reviewed and were considered eligible if the two reviewers (G. R., S. P.) independently decided that they met the inclusion criteria described previously. Disagreements were resolved by consensus or by consulting a third reviewer (Y. L.). Throughout this process, the reviewers were blinded to authors' names, journal, and year of publication of the articles. If studies that had been reported in multiple articles were identified, the analysis was limited to the largest cohort, unless the necessary data had appeared only in another article. A log of reasons for rejection of citations identified from the searches was kept. The agreement between the two primary reviewers was measured using the quadratic weighted κ statistic.[10]

Validity of trials was independently assessed by two reviewers (G. R., S. P.) using the Cochrane's Risk of Bias Tool[11] that assesses sequence generation, allocation concealment, blinding, and incomplete outcome data. Studies were classified into "low risk," "unclear," or "high risk" of bias. Only low-risk studies were considered. Disagreement between reviewers was resolved by consensus.

Data Extraction and Synthesis

Two reviewers (G. R., S. P.) abstracted information from the original articles selected for inclusion in the review. The abstracted information included the following: (1) the baseline characteristics of the participants, (2) the number of included patients, (3) the active drugs and the comparator, (4) the duration of the study, and (5) the HRQoL measures and their associated results. In each trial and for each outcome, whenever possible, the difference in HRQoL measure from baseline and the end of study between active drugs and placebo was assessed. Results from the studies for which the treatment effect could not be computed were represented as a "0" (no significant difference), "+," or "−" (statistically significant difference between groups favoring the treatment group or the control group, respectively).[12] Unless otherwise specified in the primary studies included in the overview, statistical significance was set at the .05 level. Whether statistical analysis was properly corrected for multiple comparisons was assessed.

Results

General Characteristics of Included Studies

The literature search identified 1,172 titles (Fig 1). Seventeen articles[13-29] reporting on 14 trials[13-17,19,21-26,28,29] were retrieved by the two independent authors, with an excellent agreement (quadratic weighted κ statistic at 0.8867). Of those 17 articles, three represented subgroup analyses of patients with PAH associated with connective tissue disease,[18,20,27] whereas three were specifically reporting HRQoL data[23,25,28] from previous pivotal RCTs.[30-32] Included articles are described in Table 1. The study duration of the different trials ranged from 6 to up to 104 weeks (median, 12 weeks). Most patients had idiopathic PAH or PAH associated with connective tissue disease. Eleven articles compared PAH monotherapy to