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META-ANALYSIS OF MONOTHERAPY VERSUS COMBINATION THERAPY FOR PULMONARY ARTERIAL HYPERTENSION

PROTOCOL SYNOPSIS

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META-ANALYSIS OF MONOTHERAPY VERSUS COMBINATION THERAPY FOR PULMONARY ARTERIAL HYPERTENSION

(PROTOCOL SYNOPSIS)

1. BACKGROUND

Pulmonary arterial hypertension (PAH) is characterized by the progressive increase in pulmonary vascular resistance ultimately leading to right heart failure and death [1]. PAH may be idiopathic, familial or related to connective tissue disease, congenital systemic to pulmonary shunts, portal hypertension, HIV infection and anorexigen exposure [2]. These different subtypes are grouped together because of their similar physiopathology [3] and therapeutic approach [4]. PAH predominantly affect people between 20 and 60 years of age [5]. Patients most commonly complain of shortness of breath and exercise intolerance. On conventional therapy including oral anticoagulants, diuretics and oxygen, the median survival in idiopathic PAH is less than three years [1]. In recent years, PAH-specific therapies targeting the endothelial dysfunction associated with PAH have been developed [6]. The 4 main classes of drug currently licensed for PAH are prostaglandins, endothelin receptor antagonists, phosphodiesterase-5 inhibitors and soluble guanylate cyclase stimulators [6-8]. More recently, selective prostacyclin receptor (IP receptor) agonist has also been evaluated [9].

Short-term randomized controlled trials have documented monotherapy with these compounds improved pulmonary hemodynamics and exercise capacity (the primary efficacy outcome measure in most trials) [4]. A recent meta-analysis also documented improved survival with these therapies [10]. However, long-term survival remains poor, with a yearly mortality rate of 15% in idiopathic PAH [11, 12]. Long-term survival is even worse in PAH associated with scleroderma [13]. Combination therapy modulating disease pathways at multiple sites has been proposed to improve patient outcomes. Several randomized clinical trials have shown that combination therapy was safe. However, these trials had conflicting results in terms of efficacy. Fox et al [14] published a systematic review and meta-analysis of randomized controlled trials of combination therapy for PAH. They suggested that combination therapy does not offer minimal advantage over monotherapy. Nevertheless, the recent international guidelines have given a grade IA recommendation for combination therapy in PAH patients with inadequate clinical response to initial monotherapy [8].

Importantly, initial combination trials were of short-term duration [15-20]. Moreover, exercise capacity assessed using the six-minute walk test (6MWT) was the primary efficacy endpoint in most of these randomized controlled trials. While baseline 6MWT has good discriminative capacity to prognosticate patients at the time of diagnosis, changes in exercise capacity with therapy may not be associated with clinically relevant outcomes (death, hospitalization, clinical worsening) in PAH patients, especially in the setting of combination therapy or in patients less severely impaired (WHO functional class 2) [21, 22]. More recently, large-scale long-term randomized controlled trials using morbidity/mortality as the primary efficacy endpoint were published.

We thus decided to reassess the efficacy of combination therapy for PAH. The **aim** of this systematic review and meta-analysis is to assess the effect of combination therapy for PAH on clinically relevant outcomes including death, hospitalisation and clinical worsening compared to monotherapy.

We **hypothesized** that combination therapy will be associated with improvements in 1) time to clinical worsening; 2) hospitalisation rate; 3) death and; 4) 6MWT. Note that we preciously reported in a recent systematic review the effect of PAH therapies (including combination trials) on health-related quality of life [23]. This outcome will thus not be part of the objectives for the current systematic review.

2. STUDY OBJECTIVES

2.1. General objective

To determine the effect of combination therapy on outcomes compared to monotherapy in PAH patients.

2.2. Primary objectives

To assess whether combination PAH-specific therapies reduces the risk of clinical worsening compared to monotherapy alone in PAH. Although the definition of clinical worsening may slightly differ from one study to the other, these analyses will be completed for the definition applied in the manuscript.

2.3. Secondary objectives

2.3.1. To assess whether combination PAH-specific therapies improves outcomes compared to monotherapy alone in PAH, including:

- Occurrence of the following events as first event of clinical worsening
  - All-cause mortality
  - PAH-related hospitalization
  - Transplantation
  - Atrial septostomy
  - Treatment escalation
  - PAH symptomatic progression
- All-cause mortality (including deaths occurring after censoring)
- Changes in exercise capacity (6MWD) after 3-6 months of therapy
- Improvement in WHO function class
- Worsening in WHO function class
- Treatment discontinuation

2.3.2. To assess whether the reduction in the risk of clinical worsening (primary outcome of interest) with combination PAH-specific therapies are homogeneous amongst subgroups, including:

- Drug classes (prostaglandins, endothelin receptor antagonists, phosphodiesterase-5 inhibitors, soluble guanylate cyclase stimulators, selective prostacyclin receptor (IP receptor) agonist)
- Idiopathic (i.e. combination sporadic, heritable and drug and toxin-induced) PAH associated with concomitant conditions (i.e. combination of connective tissue disease, congenital heart disease, HIV infection and portal hypertension)
- Trial duration (< 6 months or > 6 months)
- Study design (sequential combination versus initial upfront combination)
- WHO functional class I-II and III-IV
- 6MWT below/above the median

2.3.3. To assess whether combination PAH-specific therapy is associated with an increased discontinuation rate (for any reason) as a surrogate for safety

3. METHODS

The methods for this meta-analysis are in accordance with “Methodological guidelines for systematic review of randomized control trials in health care from the Postdam consultation on meta-analysis” [24].

3.1. Finding relevant studies

3.1.1. Electronic database

MEDLINE (1990-May 2015), EMBASE (1990-May 2015) and Cochrane Library (1990-May 2015) will be searched for randomized placebo-controlled trials evaluating combination therapy compared to monotherapy with PAH-targeted therapies in PAH. Search terms will be designed to provide maximum sensitivity in detecting therapeutic trials in PAH. Search strategy for ***pubmed*** will combine ("hypertension, pulmonary"[MeSH Terms] OR "pulmonary hypertension" OR "pulmonary arterial hypertension" NOT "persistent fetal circulation syndrome"[MeSH Terms]) AND (therapy OR therapies OR therapeutic* OR treatment* OR medication* OR drug* OR pharmacother* OR monotherapy) AND ("clinical trial"[Publication Type] OR "meta analysis"[Publication Type] OR "randomized controlled trial"[Publication Type] OR "combined therapy" OR "combined therapies" OR "combination therapy" OR "combination therapies" OR "combination treatment" OR "combination treatments" OR "combined treatment" OR "combined treatments") NOT (child* OR infant* OR neonate* OR neonatal OR newborn OR "child"[MeSH Terms] OR "infant"[MeSH Terms]) AND ("1990/01/01"[PDat] : "3000/12/31"[PDat]). Search strategy for ***Embase*** will combine ('pulmonary hypertension'/de OR 'pulmonary hypertension' OR 'pulmonary arterial hypertension') AND (therapy OR therapies OR therapeutic* OR treatment* OR medication* OR drug* OR pharmacother* OR monotherapy) AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim OR 'combined therapy' OR 'combined therapies' OR 'combination treatment' OR 'combination treatments' OR 'combined treatment' OR 'combined treatments'**)** NOT **(**child* OR infant* OR neonate* OR newborn* **OR** fetus**)** AND [1990-2015]/py. Search strategy for ***Cochrane*** (Cochrane Central Register of Controlled Trials (CENTRAL): Issue 5 of 12, May 2015) will combine: "pulmonary hypertension" OR "pulmonary arterial hypertension" in Title, Abstract, Keywords and "monotherapy" OR "monotherapies" OR "monotherapeutic" OR "combined therapy" OR "combined therapies" in Title, Abstract, Keywords, Publication Year from 1990 to 2015 in Trials'.

3.1.2. Hand searches

Bibliographies of each included study as well as any review article or text found will be searched for additional papers that may contain further studies. Reference lists of retrieved articles and review search will be reviewed manually to implement our search. In addition, the grey literature will be 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 2000 to May

2015.

3.1.3. Languages

The search will be not limited to English language. When possible, non-English papers will be translated in English.

3.2. Study selection

The abstracts of all articles will be independently reviewed by two authors (G.L. and A.C.L). A study will be considered eligible if the two authors independently decide that it meets the inclusion criteria of design and participants below. Disagreements will be resolved by consensus or by consulting a third reviewer (S.P.). Throughout this process the reviewers will be blinded to authors' names, journal and year of publication of the papers. If studies that had been reported in multiple papers are identified, the analysis will be limited to the largest cohort unless the necessary data had appeared only in another paper. A log of reasons for rejection of citations identified from the searches will be kept. The agreement between the two primary reviewers will be measured using the quadratic weighted kappa statistic.

3.3. Assessment of methodological quality

The methodological quality of the selected studies will be evaluated by systematically considering three important aspects of randomized placebo-controlled trials [24, 25]: 1) adequacy of randomisation sequence precluding selection bias (e.g. random numbers generated by computer, table of random numbers, etc.); 2) adequate concealment of allocation sequences (e.g. central randomisation); 3) absence of attrition bias (lack of patients lost to follow-up or analysis according to the intention to treat).

3.4. Inclusion criteria for studies

3.4.1. Prospective placebo-controlled randomized trials evaluating the effect of PAH-specific combination therapies (both upfront and sequential add-on combination therapy trials) compared to PAH-specific monotherapy in adult PAH patients from January 1990 to May 2015.

3.4.2. Trials with a clear identification of a placebo comparator (monotherapy).

3.4.3. One of the outcomes of interest is reported (section 2).

3.4.4. Currently licensed (or expected to be shortly) PAH-specific therapies including prostaglandins (epoprostenol, treaprostinil, iloprost), endothelin receptor antagonists (ambrisentan, bosentan, macitentan), type-5 phosphodiesterase inhibitors (sildenafil, tadalafil, vardénafil), soluble guanylate cyclase stimulators (riociguat) and selective IP prostacyclin receptor agonist (selixipag). For studies in which multiple doses are tested, analyses will be restricted to the currently approved doses.

3.4.5. All types of PAH (group 1 from Dana Point classification) that may be idiopathic/familial or associated with connective tissue disease, anorexigen exposure, portal hypertension, HIV infection and congenital heart disease.

3.4.6. Studies of at least 12 weeks duration.

3.5. Exclusion criteria fro studies

3.5.1. Studies involving overlapping or duplicated cohorts of patients.

3.5.2. The publications specific to the paediatric populations (defined as age <18 years). Note that studies for which the vast majority of patients were adults despite an inclusion criteria allowing subjects 12 years of age or older will be eligible.

3.5.3. Studies evaluating non-PAH patients.

3.5.4. Studies evaluating non-pharmacological interventions (e.g. exercise training).

3.5.5. Other study designs (observational studies, review articles, editorials, etc.).

3.6. Data extraction

Two reviewers (G.L. and A.C.L.) will independently abstract information from all selected papers for inclusion in the meta-analysis. The abstracted information will include: 1) the study design (e.g. duration, definition of time to clinical worsening, time of endpoint assessment, events adjudication by an independent clinical event committee); 2) patient characteristics (number of included patients, mean age, gender, PAH types, WHO functional class proportion, mean baseline 6MWD, baseline hemodynamics); 3) mean treatment-effect on time to clinical worsening, hospitalisation (all-cause and PAH-related), lung transplantation rate death (all-cause and PAH-related), changes in WHO functional class and changes in 6MWT at 3-6 months.

Briefly, 2x2 table will be constructed based on treatment received (combination versus monotherapy) and available data for one of seven outcomes:

- Clinical worsening (as defined in each RCT)(the primary outcome)
- Occurrence of the following events as first event of clinical worsening
  - All-cause mortality
  - PAH-related hospitalization
  - Transplantation
  - Atrial septostomy
  - Treatment escalation (as defined in each RCT)
  - PAH symptomatic progression (as defined in each RCT)
- All-cause mortality (including deaths occurring after censoring)
- Changes in exercise capacity (6MWD) after 3-6 months of therapy
- Improvement in WHO function class
- Worsening in WHO function class
- Treatment discontinuation

Whenever possible, these data will be assessed according to pre-specified subgroups including drug classes, PAH type (idiopathic versus non-idiopathic), study duration (< or > 6months), study design (upfront vs. sequential), baseline WHO functional class (I-II vs. III vs. IV), baseline 6MWT (lower vs. higher than the median value of baseline 6MWt). If necessary, abstracts sponsors/steering committee of each trial will be contacted to obtain subgroup data.

When subgroup analyses will not be available, the active group will be considered on combination therapy when the majority of patients (≥80%) are on background therapy at study entry. Otherwise, the study was excluded from the analysis.

Validity of trials will be independently assessed by two reviewers (G.L., A.C.L.) using the Cochrane's Risk of Bias Tool [26] that assesses sequence generation, allocation concealment, blinding and incomplete outcome data. Studies will be classified into "low risk", "unclear" or "high risk" of bias. Only "low risk" studies will be considered. Disagreement between reviewers will be resolved by consensus.

3.7. Heterogeneity of selected studies

A priori potential explanations for heterogeneity will include:

3.7.1. PAH type (idiopathic versus non-idiopathic PAH)

3.7.2. Baseline functional capacity (WHO functional class I/II versus III/IV; baseline 6MWD lower versus higher than the median value)

3.7.3. Study design (upfront combination therapy versus sequential add-on therapy)

3.7.4. Type of added PAH-specific therapies (prostaglandins, endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, soluble guanylate cyclase stimulators and selective prostacyclin IP receptor agonist)

3.7.5. Duration of the trial (≤ 6 months vs. >6 months)

3.7.6. Whether events (clinical worsening and PAH-related hospitalisation or death) were adjudicated by an independent clinical event committee

3.8. Statistical analysis

3.8.1. Primary analysis: We will use the Mantel-Haenszel method based on a fixed-effects model to estimate pooled risk ratios (RRs) with their 95% confidence intervals (CIs) for each outcome of interest. Forest plots will be created for each outcome.

For continuous variables (e.g. 6MWT), we will compute the effect size of tested drugs by using the weighted mean difference, which will be calculated after subtracting from baseline the end-study values in treated and control groups. When studies do not directly supply the standard error of the mean (SEM) for the calculation of effect size, it will be estimated from the published data. When either the values at the end of follow-up or the SEM are not reported in the article, they will be manually calculated from figures (if available).

3.8.2. Sensitivity analyses: A sensitivity analysis will be performed using the random-effects model. Sensitivity analyses will also be performed using more homogeneous definitions for clinical worsening, including only deaths, hospitalization and symptomatic progression.

3.8.3. Heterogeneity: Cochran's X^2 test and the I^2 test for heterogeneity will be used to assess between study heterogeneity. Statistically significant heterogeneity will be considered present at $P<0.10$ and $I^2>50\%$.

3.8.4. Subgroup analyses: Subgroup analyses to identify sources of heterogeneity (if any) in the main analysis will be conducted according to potential explanations for heterogeneity defined a priori (see above). In addition, the following subgroups analyses will be performed for the primary outcome even in the absence of heterogeneity (drug classes, study design, study duration, WHO functional class I-II vs III-IV, 6MWT below vs above the

median, PAH type).

3.8.5. Publication bias: will be assessed visually by the use of funnel plots. We assume that the effect of publication bias should be minor if the plot of the magnitude of treatment effect in each study versus its precision estimate (ie, standard error) shows a roughly symmetrical funnel shape [27]. We will also formally test the presence of publication bias using the standard error- and study size-based funnel plot and related asymmetry tests [28]. The CIs of indexes accuracy will be calculated with 95% Gaussian intervals.

3.8.6. Meta-regression: To assess the relationship between changes in 6MWD and subsequent risk of clinical worsening, **meta-regression analysis will be performed correlating** changes in 6-minute walked distance between combination therapy and monotherapy (treatment effect) from baseline to 3-6 months of therapy and the subsequent risk of clinical worsening based on inverse variance weighting.

3.8.7. Multiarm studies: Multiarm studies will be assessed combining all active arms and comparing it with the control group. To overcome potential issues due to multiple, correlated comparisons, we will analyze the multi-armed trial using methods described in the Cochrane Handbook for Systematic Reviews of Interventions.[28] We will thus split the 'shared' group of multiple comparison groups into two groups with smaller sample size divided out evenly.

3.8.8. Others: Analyses will be performed with Review Manager (The Cochrane Collaboration, Oxford, England). The report will be drafted with reference to the Preferred Reporting Items for Systematic Reviews and Meta- analyses (PRISMA) statement [29].

4. STUDY TIMELINE

June 2015	Librarian search of all potential titles
June 2015 – September 2015	Selection of appropriate studies to be included in the meta-analysis and data extraction from studies
September – October 2015	Statistical analysis and redaction of the manuscript

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