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ORIGINAL ARTICLE

Targeted Treatments for Pulmonary Arterial Hypertension: Interpreting Outcomes by Network Meta-analysis

Brigitta Badiani, PharmD, Andrea Messori, PharmD *

HTA Unit, ESTAV Toscana Centro, Regional Health Service, 50100 Firenze, Italy

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Background No meta-analysis for indirect comparisons has been conducted to study the effectiveness of treatments for pulmonary arterial hypertension (PAH).

Methods Our search covered the literature up to December 2014. The following five classes of agents indicated for PAH were evaluated: 1) oral endothelin receptor antagonists (ERAs); 2) oral phosphodiesterase type 5 inhibitors (PDE-5Is); 3) prostanoids administered by oral, intravenous, subcutaneous or inhalatory route; 4) selective non-prostanoid prostacyclin receptor (IP receptor) agonists (sPRAs); 5) soluble guanylate cyclase stimulators (sGCSs). Our methodology was based on standard models of Bayesian network meta-analysis. The end-point of our analysis was clinical worsening. Odds ratio was the outcome measure along with 95% credible intervals.

Results Our search identified 17 randomised controlled trials (4,465 patients). There were 15 head-to-head comparisons (five direct, 10 indirect). As expected, nearly all values of odds ratio estimated for the direct comparisons versus placebo favoured the treatment arm at levels of statistical significance. More interestingly, none of the 10 head-to-head indirect comparisons between active agents showed any statistically significant difference.

Conclusion Our results indicate that these five classes of agents for PAH are more effective than placebo and show no significant difference in effectiveness from one another. In this context, choosing the treatment for an individual patient is a quite difficult task.

Keywords Meta-analysis • Pulmonary arterial hypertension • Endothelin receptor antagonists • Phosphodiesterase type 5 inhibitors • Prostanoids • Soluble guanylate cyclase stimulators • Prostacyclin

Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease with high morbidity and mortality. The progression of the disease can lead to limited exercise capacity, right heart failure and eventually death [1]. The rate of survival of PAH patients at five years from diagnosis is only 57% [2]. The main treatments currently available for PAH have vasodilatory and/or antiproliferative effects.

The most commonly used targeted therapies for PAH include prostacyclin analogues (administered by oral, intravenous, inhaled and subcutaneous routes), oral endothelin receptor antagonists (ERAs), and oral phosphodiesterase type 5 inhibitors (PDE-5Is) [3,4]. Because the oral route is

*Corresponding author at: HTA Unit, Area Vasta Centro Toscana, Regional Health System, Via San Salvi 12, 50100 Firenze (Italy). Fax: +39 0574 701319, Email: andrea.messori.it@gmail.com

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the most convenient and usually the safest and least expensive, it is the one most often used. Intravenous, inhaled and subcutaneous routes can only be recommended in patients with WHO functional class III/IV [1,2].

Meta-analyses have suggested that oral pulmonary vasodilators are beneficial in decreasing clinical worsening and increasing 6-min walk distance [5]. However, many new oral agents have been made available for PAH in recent years [including new oral prostanoids, e.g. treprostinil; selective non-prostanoid prostacyclin receptor (IP receptor) agonists, e.g. selexipag; soluble guanylate cyclase stimulators, e.g. riociguat] that deserve to be assessed in meta-analyses or systematic reviews.

In the present study, we performed an updated meta-analysis on PAH treatments including the information from recently published randomised controlled trials (RCTs).

Methods

Our literature search was conducted in PubMed (last query on 31 December 2014) and covered the period from January 2000. A single search term (''pulmonary hypertension'' OR ''pulmonary arterial hypertension'') was employed in combination with the filter ''randomized controlled trials''. Since the number of citations was small (less than 600), we analysed all of these articles by examining the abstract or, when necessary, the full text, and we identified the RCTs that met our inclusion criteria. These criteria comprised: a) adult patients diagnosed as PAH (including associated pulmonary arterial hypertension, APAH, and idiopathic pulmonary arterial hypertension, IPAH); b) clinical material represented by a RCT; c) targeted therapies administered to at least one study arm; d) follow-up of eight weeks or more. Our PubMed search was supplemented by searching two other sources of information (EMBASE and Cochrane reviews).

The end-point of our analysis was clinical worsening. This composite endpoint was defined as one of six different events/conditions: death, lung transplantation, inter-atrial fistulisation, hospitalisation due to decompensated PAH, initiation of a new therapy, or worsening WHO functional classes

For each trial, we extracted the basic information needed for our analysis as well as the information on the primary

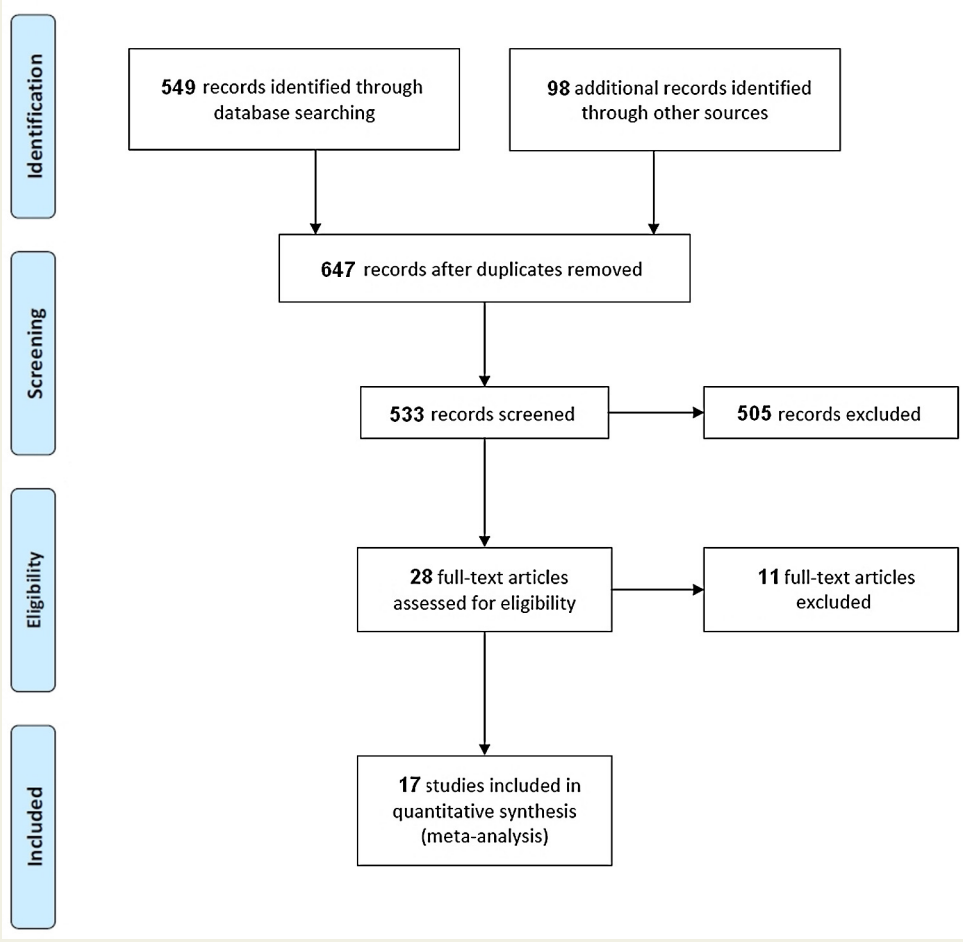

Figure 1 PRISMA schematic. This flow chart summarises the literature search and the selection process that identified the 17 RCTs included in our analysis.

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end-point; extraction was performed separately by both authors and was then double-checked. Data on the primary end-point were meant to reflect the intention-to-treat population; however, there were some occasional post-randomisation exclusions in some trials, and so the clinical material actually adopted the so-called modified intention-to-treat population [6].

For our statistical analysis, we employed a Bayesian model of network meta-analysis [7–11]. This approach is advantageous because all treatments under comparison are incorporated into a single model; another advantage is that the Bayesian technique enables rank ordering of each treatment. This Bayesian model (available as fixed-effect model or random-effect model) [11] has been developed by the NICE Support Unit (UK).

In running our analysis, the following treatment classes were evaluated: ERAs, PDE-5Is, selective non-prostanoid prostacyclin receptor (IP receptor) agonists (sPRAs), soluble guanylate cyclase stimulators (sGCSs). Control arms were assumed to receive either placebo (PLA) or an active treatment included in the above-mentioned pharmacological classes.

In our analysis, we firstly determined whether the clinical worsening for each active treatment was significantly different from that of the controls based on the pooled trial data. Then, the rank order was calculated for each treatment according to the endpoint of clinical worsening. Next, we estimated the statistics for pairwise comparisons (five direct comparisons and 10 indirect comparisons) by determining the odds-ratio (OR) for each comparison. Hence, the main output of our analysis consisted of the meta-analytic ORs with credible intervals (CrIs) along with ranking statistics. Heterogeneity was estimated by application of the ''common variance'' approach; accordingly, heterogeneity was determined by estimating precision, where the latter is defined as follows [12]: precision = (1/between-trial variance).

Finally, as a sensitivity analyses, we changed the initial values from which each Markov chain Monte Carlo simulation began, as is customary in the Bayesian framework.

The procedure described above of application of Bayesian meta-analysis was run twice according to the fixed-effect and the random-effect model, respectively. Thereafter, we selected the model providing the best fit which was the one that ensured the lowest value of Deviance Information Criterion (DIC) [11].

All of our analyses were conducted by using the software package WinBUGS 1.4.3 (Cambridge, United Kingdom) in combination with the meta-analysis code developed by the National Institute for Health and Care Excellence [11].

Table 1 Characteristics of the randomised studies included in the meta-analysis; all control groups of these trials received placebo.

Study Acronym	Mean Age (yrs)	Class Functional WHO FC	Deaths Active Treatment Group vs Control Group	Active Treatment	Treatment Group Event Rate (n/N)	Control Group Event Rate (n/N)	Reference
BREATH-1	48.7	III,IV	1 vs 2	Bosentan	9/144	14/69	Rubin et al. (2002) [24]
ALPHABET	45.8	II,III	Not reported	Beraprost	4/65	3/65	Galie et al. (2002) [14]
ARIES 1	49	II,III	1 vs 2	Ambrisentan	3/67	6/67	Galie et al. (2008) [4,17]
ARIES-2	52	II,III	2 vs 3	Ambrisentan	3/64	14/65	Galie et al. (2008) [17]
Barst et al.	42	II,III	10 vs 15	Beraprost	10/60	15/56	Barst et al. (2003) [12]
BREATH-5	44.2	III (Eisenmenger syndrome)	Not reported	Bosentan	1/37	1/17	Galie et al. (2006) [16]
Channink et al.	52.2	III, IV	0 vs 0	Bosentan	0/21	3/11	Channik et al. (2001) [2]
EARLY	45.2	II	1 vs 1	Bosentan	3/93	13/92	Galie et al. (2008) [18]
EVALUATION	32	II, III	0 vs 2	Vardenafil	1/44	4/20	Jing et al. (2011) [21]
FREEDOM-C	51	II, III	0 vs 1	Treprostinil	8/174	12/176	Tapson et al. (2012) [25]
FREEDOM-C2	51.5	II, III, IV	6 vs 4	Treprostinil	11/157	10/153	Tapson et al. (2013) [26]
FREEDOM-M	40.6	II, III	13 vs 8	Treprostinil	22/233	15/116	Jing et al. (2013) [22]
PATENT-1	51	II, III	2 vs 3	Riociguat	5/317	8/126	Ghofrani et al. (2013) [20]
PHIRST	53.5	II, III	1 vs 1	Tadalafil	7/80	13/82	Galie et al. (2009) [19]
SERAPHIN	45.5	II, III, IV	21 vs 17	Macitentan	72/250	93/250	Pulido et al. (2013) [23]
GRIPHON	From 18 to 75	II,III	Not reported	Selexipag	67/578*	110/57*	Actelion (2014) [27,28]
SUPER	51	II,III	1 vs 1	Sildenafil	3/69	7/70	Galie et al. (2005) [15]

*The event rates for this trial were estimated according to the approximate method described by Altman and Bland [32].

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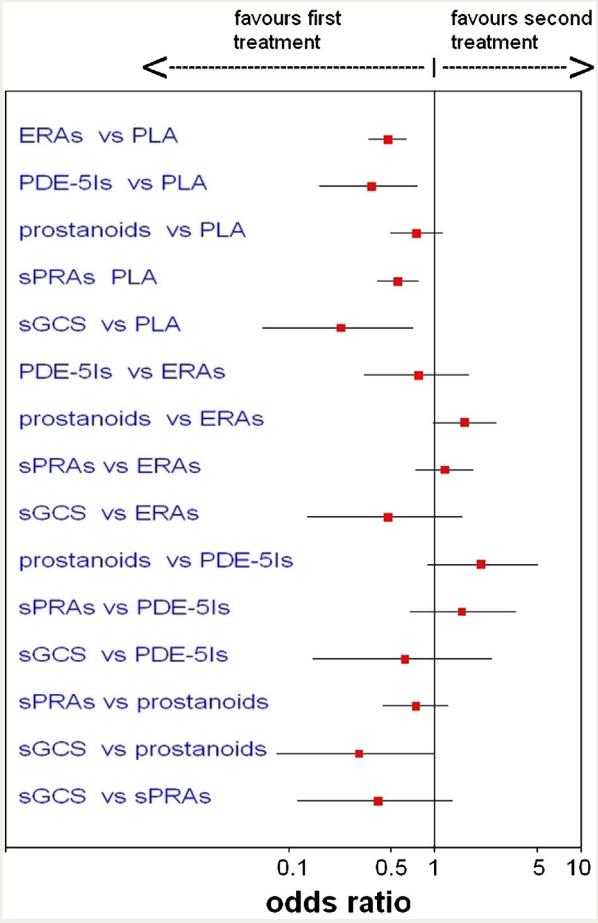

Figure 2 Meta-analytical values of OR estimated for five direct comparisons (ERAs, PDE-5Is, prostanoids, sPRAs, or sGCSs versus placebo) and for 10 head-to-head indirect comparisons between the five treatment classes.
Each horizontal bar indicates the two-sided 95%CrI for the OR (solid square). Direct comparisons are those for which at least a single clinical trial was available whereas indirect comparisons are those for which a ''real'' trial is lacking. The numerical values of all ORs are presented in our Supplementary Material.
Abbreviations: OR odds-ratio; CrI credible interval; PAH pulmonary arterial hypertension; PLA placebo; ERAs endothelin receptor antagonists; PDE-5Is phosphodiesterase type 5 inhibitors; sPRAS selective prostacyclin receptor antagonists; sGCSs soluble guanylate cyclase stimulators.

Results

Our literature search is summarised in Figure 1 according to the PRISMA schematic. After the initial selection of 549 articles, we examined the full text of 28 articles and we finally identified 17 studies that met our inclusion criteria [13,2,14–29]. The main characteristics of these 17 studies are shown in Table 1. A total of seven RCTs assessed the effect of ERAs (bosentan, ambrisentan and macitentan), three RCTs assessed the effect of PDE-5Is (sildenafil, tadalafil and vardenafil), five assessed the effect of prostanoids (namely, the prostacyclin analogues beraprost and teprostenil), and one assessed the effects of sGCS (riociguat) and of selective non-prostanoid prostacyclin receptor agonists (selexipag). Overall, these 17 RCTs enrolled 4,465 patients.

According to the DIC criterion, the results of our meta-analysis showed a better fit with the fixed-effect model than with the random-effect one. Only the results obtained with the former model are presented herein while those obtained with the random-effect model are not reported.

The results of our network meta-analysis based on the fixed-effect model (Figure 2) revealed a statistically significant difference in all direct comparisons between active treatments vs placebo with one exception in that prostanoids did not differ significantly from placebo. More interestingly, no differences in the 10 indirect head-to-head comparisons reached the threshold of statistical significance. Overall, heterogeneity was found to be low as indicated by the small value of precision (median, 0.030; mean, 0.158). Further details on our analysis are described in our Supplementary Material.

Figure 3 illustrates the ranking histograms generated by the Bayesian probabilistic analysis. Individual rankings for the five pharmacological classes plus placebo were the following (lowest rank=highest effectiveness, highest rank=lowest effectiveness; 95%CrI in parenthesis): sGCS, 1 (1 to 4); PDE-5Is, 2 (1 to 5); ERAs, 3 (1 to 4); sPRAs, 4 (2 to 5); prostanoids, 5 (3 to 6); placebo, 6 (5 to 6).

Discussion

Our results provided a synthesis of the effectiveness data of the main pharmacological classes indicated for the treatment of PAH and was successful in determining the statistical significance of differences between active treatments and in defining their respective rankings. In a context where five different pharmacological classes are available and have in fact been tested in placebo-controlled RCTs, our comprehensive picture of current therapeutic evidence can be of interest under several viewpoints.

The information on relative rankings (along with the probabilistic analysis) represents - in our view - the most interesting result of our analysis. Among the five active treatments, sGCS, ERAs, and PDE-5Is had the best rankings (with little differences from one another), sPRAs had an intermediate ranking, and prostanoids ranked last; while these indirect comparisons between active agents did not reach the threshold of statistical significance, some of these head-to-head comparisons were however close to this threshold.

It is well-known that Bayesian models provide a two-fold key for interpreting the results. On the one hand, the probabilistic analysis on which ranking histograms are based provides a unique key for interpreting the results in which the descriptive component tends to prevail on the statistical component. On the other hand, statistical testings resulting from Bayesian analysis can also be interpreted according to the traditional rules of interpretation commonly employed in

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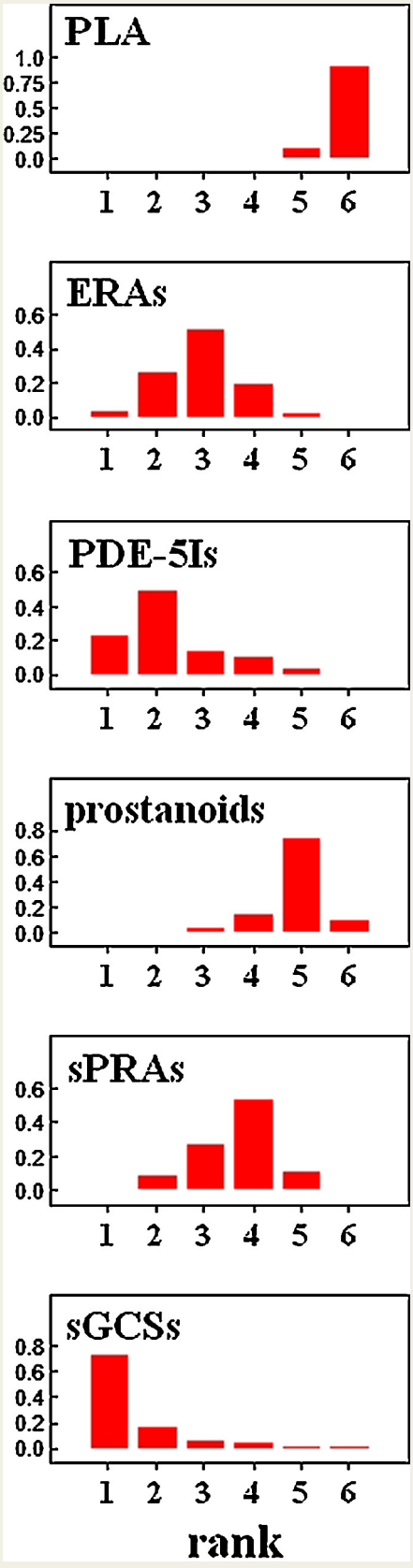

Figure 3 Histogram of rankings generated by Bayesian network meta-analysis.

The graphs reflect a total of 20,000 iterations and consist of as many histograms as the treatment classes (N=5 plus placebo) included in the analysis. In each panel, the histogram shows the per cent distribution of the simulations across rank 1 (lowest effectiveness) through 5 (highest effectiveness). The y-axis shows probability on 0 to 1 scale; according to the characteristics of Winbugs, the highest values on this axis across the histograms are not set constant at y=1, but depend on the results of individual simulations.
Abbreviations: see Figure 2.

frequentist analysis (e.g. the dichotomy between significant and non-significant results).

If one compares the results of our Bayesian network meta-analysis with those reported by the traditional meta-analyses previously published on the same topic [30,31], the main difference lies in the different objectives pursued by these two techniques. The two traditional meta-analysis [30,31] evaluated a single binary comparison (i.e. the comparison between the effectiveness of treatments vs the effectiveness of placebo) and concluded that treatments are more effective than placebo. Some points of controversy included the different effect of treatments on different end-points, the uncertainty of the long-term effects, the lack of clinical head-to-head trials comparing active agents with one another. Our network meta-analysis essentially had a different purpose because, by using the ''all-in-one'' Bayesian model, we tried to offer a comprehensive picture of all information currently available on comparative effectiveness and therefore we focussed our analysis much more on indirect comparisons between active agents than on the comparison of treatments vs placebo.

Overall, the message arising from our analysis is, to some extent, disappointing because, while numerous treatments aimed at PAH have been developed over the past decade, no significant improvement in effectiveness has been obtained with time. One exception to this lack of differences is possibly represented, on the side of reduced effectiveness, by prostanoids that showed a less favourable effectiveness profile in comparison with the other agents; on the side of increased effectiveness, the exception might be represented by sGCSs. In this context, selecting a specific treatment for a new patient with PAH remains a quite difficult task because, while numerous options are available, the criteria for selecting the best treatment for an individual patient are, at best, largely subjective, and trials of direct head-to-head comparison between active treatments have not been performed.

The strengths of our study include, in the first place, the originality of the methodological approach inasmuch this is the first ''all-in-one'' Bayesian meta-analysis conducted on this specific topic. Another advantage is represented by our choice to evaluate the main pharmacological classes currently available for PAH, without focussing the analysis on individual agents (as in other published papers).

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Our study had some limitations. Firstly, while further end-points are implicated in the effectiveness profile of these treatments, these end-points were not studied in our analysis. Secondly, since we adopted the end-point definition for clinical worsening employed in the original studies, we cannot rule out that some differences existed in these definitions.

In conclusion, our results convey original information to better interpret the effectiveness profile of these five pharmacological classes. Finally, a number of innovative treatments are currently being studied for PAH and several phase 2 and phase 3 trials are ongoing or are close to be completed. When mature data on these new treatments become available, the results of the present analysis will be useful to better define the place in therapy also for the innovative treatments.

Conflict of Interests

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.hlc.2015.05.020.

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