Comparative Effectiveness of Oral Medications for Pulmonary Arterial Hypertension

Network Meta-Analysis

Ataru Igarashi,1 PhD, Sachie Inoue,2 PhD, Tomonori Ishii,3 MSc, Kiichiro Tsutani,1 PhD, and Hiroshi Watanabe,4 PhD

Summary

Pulmonary arterial hypertension (PAH) is a disease that imposes a significant burden on patients. Although multiple treatment options for PAH are available, head-to-head comparisons are difficult to conduct. Network meta-analysis (NMA) can be a useful alternative for direct comparison to estimate the relative effectiveness of multiple treatments. The objective of the present study was to conduct a systematic review and NMA to evaluate the relative effectiveness among oral PAH medications.

Data collection was performed by searching the Cochrane Central Register of Controlled Trials (CENTRAL) and Ichushi-Web. Randomized controlled trials (RCTs) assessing at least 1 of the following 3 outcome measurements; 6-minute walk distance test (6MWD), WHO functional class (WHOFC), and mean pulmonary artery pressure (mPAP) were included (PROSPERO registration number: CRD42015016557). Outcomes were evaluated by estimating the differences in the mean change from baseline or by estimating the odds ratios. Analyses were performed using WinBUGS 1.4.3.

Seven double-blind RCTs were eligible. NMA results showed similar improvements in 6MWD for all medications assessed. Bosentan and sildenafil caused a statistically significant improvement in WHOFC compared to other medications.

The relative effectiveness of oral PAH medications could be compared using NMA, which suggested the superiority of bosentan and sildenafil in the improvement of WHOFC. (Int Heart J 2016; 57: 466-472)

Key words: PAH, 6-minute walk distance test, Systematic review, WHO functional class

Pulmonary hypertension (PH) is characterized by the presence of major lesions within the pulmonary arteries and is defined as a mean pulmonary artery pressure ≥ 25 mmHg as measured by right heart catheterization. Pulmonary arterial hypertension (PAH) is defined as a subpopulation of patients with PH and is characterized hemodynamically by the presence of pre-capillary PH including pulmonary artery wedge pressure (PAWP) ≤ 15 mmHg and pulmonary vascular resistance (PVR) > 3 Wood units.1 Idiopathic PAH (IPAH) and heritable PAH (HPAH) account for about 50% of PAH cases; the rest are comprised of PAH associated with congenital heart disease (CHD-PAH), connective tissue disease (CTD-PAH), and portopulmonary hypertension (POPH).2

First-line therapeutic agents for PAH consist of pulmonary vasodilators such as endothelin receptor antagonists (ERAs), phosphodiesterase 5 inhibitors (PDE5Is), and other oral drugs such as beraprost (PGI2 derivative). In high-risk cases with a poor prognosis and failure of first-line therapy, continuous intravenous infusion of epoprostenol is considered.3

Several oral PAH medications including ERAs, PDE5Is, and PGI2 analogues are available for treatment of PAH in Japan; the medications and their dates listed are as follows: beraprost (September, 1999), bosentan (June, 2005), sildenafil (April, 2008), tadalafil (December, 2009), ambrisentan (September, 2010), riociguat (February, 2015), and macitentan (June, 2015). Some small-size randomized controlled trials (RCTs) have already been conducted to assess the efficacy and safety of these drugs, however, most of them were placebo-controlled trials. Therefore, little data is available for direct comparison among oral PAH medications. Lack of direct comparison is partly due to the characteristics of PAH itself, or its very low prevalence rate. Several meta-analyses of the therapeutic efficacy of PAH medications have been reported.4,5 However, only placebo or conventional therapies, not active drugs, were used as comparators in the studies included in
these meta-analyses. Although the Cochrane Collaboration Group has conducted a meta-analysis on ERAs, which are PAH therapeutic agents, the analysis lacked inclusion of other PAH medications such as PDE5is and prostacyclin. Indirect comparisons can be used if there is a paucity of data for head-to-head (direct) comparisons. However, simple indirect comparisons can be problematic, since the heterogeneity of target populations among studies, which can result in systematic errors, would not be adjusted.

Network meta-analysis (NMA) synthesizes the results of several clinical studies using statistical methods and enables indirect comparison, in which issues of heterogeneity can be handled with effective methodology. In the case of an indirect comparison, NMA has been introduced by the National Institute for Health and Care Excellence (NICE), a health technology assessment agency in the UK, and technical support documents on this method have been published. NMA has been used to characterize the relative effectiveness of therapies in many areas of disease and has become a well-known method to use when a direct drug comparison is not feasible. There have been no head-to-head clinical trials among PAH medications, and also no NMA on this area have been report-
ed.

Our objective was to conduct a systematic review and NMA to evaluate the relative effectiveness among oral PAH medications, combining the RCTs evaluating the efficacy with 6-minute walk distance test (6MWD), WHO functional class (WHOFIC), or mean pulmonary artery pressure (mPAP).

METHODS

Target medications: The protocol of this study was finalized in January 2014 and a literature search was conducted in February 2015. At that time, the following 5 PAH medications were used in actual clinical settings; beraprost (Dorner®, Procyclin®, Careload LA®, and Berasus LA®), bosentan (Tracleer®), sildenafil (Revatio®), tadalafil (Adcirca®), and ambrisentan (Volibris®).

Data collection: Data were collected from the Cochrane Central Register of Controlled Trials (CENTRAL) and Ichushi-Web. Search keywords included (“pulmonary arterial hypertension,” “PAH,” “ambrisentan,” “sildenafil,” “tadalafil,” “beraprost,” “bosentan,” “randomized controlled trial,” and “RCT”) in the Cochrane CENTRAL (search performed on February 6, 2015) and (“pulmonary hypertension,” “ambrisen-
tan,” “sildenafil,” “tadalafil,” “beraprost,” and “bosentan”) in Ichushi-Web (search performed on February 6, 2015); searches were limited to original papers or short reports on RCTs and human studies.

Inclusion criteria were as follows; 1) randomized controlled trials (RCTs) targeting PAH patients; 2) included any of 5 oral PAH medications; ambrisentan, bosentan, sildenafil, tadalafil, or beraprost; 3) at least 1 of following 3 outcome measurements were assessed; 6MWD, WHOFC, and mPAP; 4) the dosing ranges were within the approved range [ambrisentan ≤ 10 mg/day; sildenafil 60 mg/day; tadalafil 40 mg/day; beraprost ≤ 180 μg/day; and bosentan 125–250 mg/day]; 5) clinical outcomes were measured at 12 or 16 weeks; 6) published in Japanese or English; and 7) published in a peer-reviewed journal.

RCTs targeting pediatric PAH or groups with dosages above the approved ranges were excluded. Furthermore, data were combined by dose ranges and analyzed as a single dose group whenever possible.

Data extraction: Data were extracted by two independent reviewers for eligibility. Discrepancies between two reviewers were resolved by discussion among the reviewers.

For continuous outcomes measures 6MWD and mPAP, differences in the mean change from baseline (mean differences) for each drug and their standard errors (SEs) were extracted or calculated. Mean differences were extracted from the target publications and the SEs were either extracted from the same papers or calculated from the statistics described therein. For binary outcomes, the parameters of each group (N) and the number of events (n) were extracted or calculated. A full quality appraisal of these extracted articles was made using the Cochrane criteria list for the methodological quality assessment.

Statistical analysis: The NMA was conducted based on the Bayesian method, using two analytical models: the fixed-effects model assumed homogeneity, ie, absence of an intra-trial difference in mean changes from baseline among trials included; the random-effects model accounts for heterogeneity, ie, presence of systematic intra-trial differences. The model that yielded the smaller residual deviance was adopted. Outcomes were evaluated by using the estimated differences in the mean change from baseline or odds ratios (binary data) and their 95% credible intervals (95% CrIs). For the prior distribution of mean differences in treatment effects and log odds ratios, a non-informative normal distribution with mean of 0 and variance of 100 was assumed, and the posterior distribution of each parameter was estimated by the Gibbs sampling method. The simulation was repeated 10,000 times with 1,000 burn-in time. Since the purpose of this analysis was to assess the relative effectiveness of oral PAH medications, the NMA was conducted for the clinical outcomes used for at least 4 of the 5 targeted drugs. All statistical analyses were performed using WinBUGS1.4.3.

Research protocol registration and reporting format: This NMA was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO)[registration number: CRD42015016557]. This NMA was aligned with the PRISMA statement.

RESULTS

Data collection: The data collection process is summarized in Figure 1. The literature search yielded 969 targets for review of the title and abstract. After screening 969 reports, 95 reports remained the targets for original article review. The two-step original article review process included 7 double-blind RCTs for the NMA. The characteristics of the studies included are summarized in the Table.

Six of the reports were blinded placebo-controlled RCTs; the remaining one blinded RCT compared multiple doses for ambrisentan. The average of patient age for all trials was within 40–50 years, and there were fewer males than females. There were no other appreciable differences among the studies. No studies of beraprost met our inclusion criteria; the drug was thus excluded from our analysis. The result of the assessment of risk of bias is summarized in Figure 2.

6MWD: All 7 reports assessed 6MWD, including the 6 place-
bo-controlled RCTs of ambrisentan, sildenafil, tadalafil, and bosentan, and the dose-ranging RCT study of ambrisentan. A network diagram of clinical trials for 6MWD is shown in Figure 3. The comparison showed slight 6MWD improvement for tadalafil compared to the other 3 medications, but there were no significant differences (Figure 4) [Mean differences of tadalafil 40 mg to bosentan 125–250 mg (95% CrI): -8.1 (-37.9, 21.1), to sildenafil 60 mg: -11.3 (-48.2, 25.2), to ambrisentan 1 mg: -7.7 (-29.7, 14.0), to ambrisentan 2.5–10 mg: -10.7 (-32.6, 11.0); Mean differences between bosentan 125–250 mg and sildenafil 60 mg: -3.2 (-39.0, 32.9), ambrisentan 1 mg: 0.4 (-19.4, 20.0), ambrisentan 2.5–10 mg: -2.6 (-22.3, 17.0); Mean differences between sildenafil 60 mg and ambrisentan 1 mg: 3.6 (-26.3, 33.4), ambrisentan 2.5–10 mg: 0.6 (-29.4, 30.6); Mean difference between ambrisentan 1 mg and ambrisentan 2.5–10 mg: -3.0 (-5.0, -1.0)].

WHOFC: WHOFC was analyzed in 5 reports, including the placebo-controlled RCTs of ambrisentan, sildenafil, tadalafil, and bosentan. The network diagram of clinical trials for WHOFC is shown in Figure 5. Analysis showed the effectiveness of bosentan and sildenafil equaled or surpassed that of the other agents, and both agents produced a significant improvement in WHOFC in comparison to ambrisentan and tadalafil [Odds ratios of bosentan to tadalafil 40 mg (95% CrI): 7.3 (1.2, 27.4), to sildenafil 60 mg: 0.8 (0.2, 6.6), to ambrisentan 2.5–10 mg: 4.3 (1.5, 27.5); Odds ratios of sildenafil to tadalafil 40 mg: 5.9 (1.3, 18.4), to bosentan 125–250 mg: 1.3 (0.2, 5.0), to ambrisentan 2.5–10 mg: 4.3 (1.6, 17.4)] (Figure 6).

**Discussion**

This study applied NMA for the first time to compare the therapeutic effectiveness of 4 oral PAH medications in 7 RCT studies that met the inclusion criteria. The drugs included ERAs (ambrisentan, bosentan) and PDE5Is (sildenafil, tadalafil) and the outcomes included 6MWD and WHOFC. Beraprost, macitentan, and riociguat were not assessed in this analysis because no trial with beraprost met our inclusion criteria, and macitentan and riociguat were not on the market at the time of data collection.

Analysis showed the drugs produced similar improvements in 6MWD, although bosentan and sildenafil provided significantly greater improvements in WHOFC. A randomized prospective study comparing sildenafil, vardenafil, and tadalafil on pulmonary and systematic hemodynamics in PAH patients revealed that a significant improvement in arterial oxygenation was found only with sildenafil.\(^\text{22}\) Hence there is less chance of ventilation-perfusion mismatch with sildenafil\(^\text{22}\) and it is believed to improve gas-exchange. Bosentan is a dual endothelin receptor type A and –B antagonist (ERA),\(^\text{24}\) and ambrisentan is an ERA that preferentially binds with endothelin receptor type A. Thus, the potential mechanisms of action of these drugs may have affected the results of the study.

Two models, the fixed-effects model and random-effects model, were tested and the fixed-effects model was chosen since it yielded the least residual deviance. However, both models yielded similar results, which implied the robustness of...
<table>
<thead>
<tr>
<th>Author (Year of publication)</th>
<th>Study name</th>
<th>Study population</th>
<th>Subject PAH classification (Proportion of patients %)</th>
<th>Active drug Dose</th>
<th>Control drug Dose</th>
<th>Subject patients Age</th>
<th>Gender (male)</th>
<th>Outcome measure (12/16 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Galie N (2009)</td>
<td>PHIRST-1</td>
<td>Age 12 or older</td>
<td>IPAH: 61.0%, CTD-PAH: 23.5%, Dr/Tx-PAH: 4.0%, CHD-PAH: 11.6%</td>
<td>T, 2.5 mg/day 82</td>
<td>T, 10 mg/day 80 Placebo 82</td>
<td>P: 55 ± 15</td>
<td>P: 21%</td>
<td>6MWD: 16 weeks WHOFC: 16 weeks</td>
</tr>
<tr>
<td>Galie N (2006)</td>
<td>BREATHE-5</td>
<td>Age 13 or older</td>
<td>CHD-PAH (Eisenmenger): 100%</td>
<td>Bo, 125–250 mg/day 37 Placebo 17</td>
<td>P: 44.2 ± 8.5 Bo: 37.2 ± 12.0</td>
<td>P: 41%</td>
<td>Bo: 38%</td>
<td>6MWD: 16 weeks WHOFC: 16 weeks mPAP: 16 weeks</td>
</tr>
<tr>
<td>Galie N (2005)</td>
<td>SUPER-1</td>
<td>No criterion</td>
<td>IPAH: 63.2%, CTD-PAH: 30.3%, CHD-PAH: 6.5%</td>
<td>S, 60 mg/day 69</td>
<td>S, 120 mg/day 67 Placebo 70</td>
<td>P: 49 ± 7</td>
<td>P: 19%</td>
<td>6MWD: 12 weeks WHOFC: 12 weeks mPAP: 12 weeks</td>
</tr>
<tr>
<td>Shapiro S (2012)</td>
<td>ARIES-1</td>
<td>No criterion</td>
<td>IPAH: 64.1%, CTD-PAH: 31.8%, Other PAH: Unknown</td>
<td>A, 2.5–10 mg/day 261 Placebo 132</td>
<td>P: 49 ± 15 A: 51 ± 15</td>
<td>P: 22%</td>
<td>A: 20%</td>
<td>6MWD: 12 weeks WHOFC: 12 weeks</td>
</tr>
<tr>
<td>Badesch DB (2002)</td>
<td>Study-351</td>
<td>No criterion</td>
<td>IH-PAH: 84.4%, CTD-PAH (SSc): 15.6%</td>
<td>Bo, 250 mg/day 21 Placebo 11</td>
<td>P: 47.4 ± 14 Bo: 52.2 ± 12.2</td>
<td>P: 0%</td>
<td>Bo: 19%</td>
<td>6MWD: 12 weeks WHOFC: 12 weeks mPAP: 12 weeks</td>
</tr>
<tr>
<td>Galie N (2005)</td>
<td>-</td>
<td>Adult</td>
<td>IPAH: 61%, Dr/Tx-PAH: 6%, CTD-PAH: 30%, HR-PAH: 3%</td>
<td>A, 2.5 mg/day 19 A, 5 mg/day 16 A, 10 mg/day 13 A, All 48</td>
<td>A, 1: 53 ± 17 A, 2.5: 52 ± 17 A, 5: 48 ± 16 A, 10: 53 ± 12 A, All 51 ± 16</td>
<td>A, 1: 13%</td>
<td>A, 2.5: 5%</td>
<td>6MWD: 12 weeks mPAP: 12 weeks</td>
</tr>
<tr>
<td>Rubin LJ (2002)</td>
<td>BREATHE-1</td>
<td>No criterion</td>
<td>IH-PAH: 70.4%, CTD-PAH: 29.6%</td>
<td>Bo, 125 mg/day 74 Bo, 250 mg/day 70</td>
<td>Bo, All 69</td>
<td>P: 47.2 ± 16.2 Bo: 48.7 ± 15.8 Bo, Alt 50 ± 15.9</td>
<td>P: 22%</td>
<td>Bo, Alt 21%</td>
</tr>
</tbody>
</table>

PAH indicates pulmonary arterial hypertension; IPAH, idiopathic PAH; HPAH, heritable PAH; IH/PAH, IPAH/HPAH; CTD-PAH, connective tissue disease PAH; Dr/Tx-PAH, drug- and toxin-induced PAH; CHD-PAH, congenital heart disease PAH; HR-PAH, HIV-associated PAH; SSC, systemic sclerosis; T, tadalafil; Bo, bosentan; S, sildenafil; A, ambrisentan; P, placebo; 6MWD, six-minute walk distance test; WHOFC, WHO functional class; mPAP, mean pulmonary artery pressure. *mPAP was not planned in Galie, **Shapiro and Rubin. Although WHOFC was planned and analyzed in Galie,** it had analyzed for all dose groups only. Although WHOFC was planned and analyzed in Rubin,** the number with improvement reported was class 1 and 2 only. It is not clear whether mPAP was planned or not in Rubin.
Of 969 reports, only 7 met our inclusion criteria. This is partly due to limitations in performing RCTs with high levels of evidence, given the very-low prevalence of PAH. In this analysis, however, we used NMA to estimate the relative effectiveness of ERAs and PDE5Is within the approved dose range, using 6MWD and WHOFC as typical outcome measures of therapeutic efficacy in PAH.

We excluded mPAP from this analysis for the following reasons: 1) only two of the target drugs have been studied in this context; and 2) in 3 trials, ARIES (ambrisentan), PHIRST (tadalafil), and BREATHE-1 (bosentan), mPAP was not included in the outcome measures. Although mPAP is clinically important, implementation of the NMA on this measure was abandoned due to the limited amount of data.

NMA for the oral PAH medications has also been reported by Giuseppe, et al in 2013, although inclusion criteria such as the scope of the dosing range, assessment period of outcomes, and outcome measures were different from those of our findings.

Figure 2. Summary of risk of bias.

Figure 3. Network diagram (6MWD). Numbers indicate the number of articles. No number indicates only one article.

Figure 4. Forest plot (6MWD).

Figure 5. Network diagram (WHOFC). Numbers indicate the number of articles. No number indicates only one article.
this study. In addition, the study of Shapiro, et al. was not included in their analysis, while we did include it. Recently, a double-blind RCT evaluating the combination therapy of ambrisentan and tadalafil (AMBITION Clinical Trial) reported clinical improvement in 6MWD. However, because the timing of evaluating the clinical outcomes was different from that adopted in this study, which was 12-weeks and 16-weeks, this RCT was not included in the present study. Further NMA would be desired when data from direct comparison, with the efficacy of these two PAH medications or combination medication, become available. Therapeutic decision-making for individuals tends to be done in terms of clinical effectiveness/safety, rather than efficiency or cost-effectiveness. If an alternative provided a higher efficacy rate and lower incidence rate for adverse effects, such an option could naturally be chosen, regardless of its costs, in clinical settings. However, if the decision-making needs to be conducted from a broader perspective, such as the community level or establishment process of therapeutic guidelines, efficacy issues should be incorporated to maintain the rational/optimal distribution of limited healthcare resources. PAH therapy has been substantially improved by prostacyclin formulations, endothelin receptor antagonists, PDE5 inhibitors, and other medications.

Prognostic improvements are also associated with increasing total medical costs. The total cost of oral medications for PAH in Japan is approximately JPY 48 billion per year (© 2014 IMS Health, created based on the JPM Aug 2014 MAT, Unauthorized copying prohibited). Considering the economic conditions in Japan, where most health insurance programs are becoming financially insolvent, the efficiencies, or cost-effectiveness, of various medication options of PAH should be considered in the decision-making process, as should efficacy and safety issues. In this systematic review and NMA, we demonstrated similarity for several oral PAH medications, thereby justifying the use of drug cost to drive drug selection guidelines. Similar selections of appropriate drugs will continue to be based on cost-effectiveness analysis in health economics.

**Conclusion:** This NMA study of the effectiveness of 4 drugs used to improve 6MWD and WHOFC in PAH showed that ERA- and PDE5I-class drugs were essentially similar, and bosentan and sildenafil appeared to be superior.

**Acknowledgments**

Yosuke Fujii of Pfizer Japan Inc. contributed to the interpretation of data and critical revision of the study for important intellectual content.

**References**

5. Coeytaux RR, Schmit KM, Kraft BD, et al. Comparative effec-