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Article Summary by: Mohammad Dalabih MBBS, MHA

ARTICLE

Comparative Efficacy and Safety of Targeted Therapies for Chronic Thromboembolic Pulmonary Hypertension: A Systematic Review and Network Meta-Analysis. Can Respir J. 2021 Sep 1; 2021:1626971. doi: 10.1155/2021/1626971

CLINICAL QUESTION

How do the available PAH-targeted therapies rank in their efficacy of treating CTEPH?

SUMMARY

Chronic thromboembolic pulmonary hypertension (CTEPH) - group 4 in the PH classification - is a rare form of pulmonary hypertension that results from the obstruction of pulmonary arteries by organized thromboembolic material and subsequent small vessel remodeling of the pulmonary arterial tree. These changes cause a progressive increase in the resistance to flow in the pulmonary arteries and if untreated, right-sided ventricular failure. CTEPH is the only form of PH that can be potentially cured surgically with pulmonary endarterectomy (PEA). Not all patients with CTEPH, however, are surgical candidates. Surgical intervention may fail to resolve the hemodynamic abnormalities, possibly due to the role small vessel disease plays in the pathophysiology of CTEPH. The role of PAH-targeted therapies in patients who are not surgical candidates has been the subject of much investigation.

A previous meta-analysis analyzed how different PAH-targeted therapies compare to placebo. In this meta-analysis the authors aimed to evaluate the comparative efficacy and safety of PAH-targeted therapy in CTEPH as no such analysis is available.

Methods:
The authors reviewed available data in randomized-controlled trials (RCT) of PAH-therapies in CTEPH and performed a traditional as well as network meta-analysis. The authors included all studies published before January 2020 in patients 18 years or older with symptomatic CTEPH treated with one agent: a prostacyclin analogue, an endothelin receptor antagonist (ERA), a phosphodiesterase type 5 (PDE5) inhibitor or soluble guanylate cyclase stimulator (sGC). Single or double-blinded studies were included. Trials included had to report at least one of the following outcomes: 6-minute walk distance (6MWD), BNP or NT-proBNP, change in WHO functional class (FC), pulmonary vascular resistance (PVR), or clinical worsening. Studies with duplicate data or subjects with other forms of PH were excluded.

Pairwise meta-analysis was used to compare homogenous studies. Network meta-analysis (NMA) was conducted using a multivariate meta-analysis function. Comparative efficacy based on primary and secondary outcomes was obtained by using surface under cumulative ranking (SUCRA) method.

Results:
The database search retrieved 566 records with 8 fitting the inclusion and exclusion criteria and included in the final analysis. Seven agents were used in these RCT: iloprost, bosentan, sildenafil, riociguat, macitentan, ambrisentan, and treprostinil. The total number of participants was 703, with 394 assigned to a treatment group and 309 assigned to a placebo. All studies were double-blinded except for one of two bosentan trials, in which only the investigators were blinded. Heterogeneity among the studies was found to be low allowing for pooling of quantitative data.

In pairwise meta-analysis, weighted mean 6MWD was significantly improved by riociguat (45 m), macitentan (34 m), and ambrisentan (41.6) m. Only bosentan significantly lowered BNP/NT-proBNP (-0.51 pg/mL). Functional class improvement was correlated with riociguat (OR = 2.8) and treprostinil (OR = 4.88). PVR was reduced by iloprost, bosentan, riociguat and ambrisentan. Clinical worsening was not significantly affected by any of the therapies.

NMA showed that, using SUCRA ranking, 6MWD improved on riociguat, treprostinil and macitentan to a lesser degree. For BNP and NT-proBNP reduction, SUCRA ranking showed that bosentan (84.3%), treprostinil (65.9%), and macitentan (49.8%) were the most effective therapies. FC improved in SUCRA analysis by sildenafil (87.3%), treprostinil (72.5%), and bosentan (63.2%). PVR was most reduced by treprostinil (SUCRA 86.2%), riociguat (77.4%), and sildenafil (54.9). Clinical worsening was most affected by macitentan (SUCRA 79.2%), riociguat (63.3%), treprostinil (52.6%), and bosentan (42.8%).

Discussion:
In this meta-analysis, several PAH-targeted therapies were compared in CTEPH patients. Changes in different outcomes were ranked and treprostinil performed well in all aspects, ranking first in reducing PVR, second in reducing BNP, and third in reducing clinical worsening. Riociguat also performed well, ranking first in improving 6MWD, and second in probability of reducing PVR. From the ERAs included, macitentan exhibited the highest probability of reducing incidence of clinical worsening and ranked 3rd in improving 6MWD and BNP overall.

Conclusion:
Treprostinil and riociguat were superior to iloprost, sildenafil, macitentan, bosentan, and ambrisentan in improving several outcomes in the treatment of CTEPH.

Table 2: Ranking of PAH-targeted drugs for CTEPH assessed by estimated and predictive probabilities using SUCRA values.

Intervention	SUCRA				
	6MWD (%)	BNP (%)	NYHA/WHO FC improvement (%)	PVR (%)	Clinical worsening (%)
Placebo	14.7	11.2	9.0	5.0	12.1
Bosentan	24.2	84.3	63.2	48.4	42.8
Sildenafil	45.6	43.4	87.3	54.9	—
Riociguat	80.4	45.4	50.7	77.4	63.3
Macitentan	64.0	49.8	17.3	33.9	79.2
Ambrisentan	46.4	—	—	—	—
Treprostinil	74.6	65.9	72.5	86.2	52.6
Iloprost	—	—	—	44.2	—

Higher estimated probabilities of SUCRA close to 100% indicate superiority over other therapies, whereas lower values close to 0% indicate inferiority.

GROUP OPINION

Several studies have looked at the efficacy of PAH-targeted therapies in CTEPH. No comparative studies are available, and this retrospective analysis might provide some guidance in the selection of medical therapy for patients with CTEPH. In clinical practice, medical therapy is used in inoperable patients, those with severe disease that might need “rescue” therapy before surgery, and for persistent PAH after PEA or balloon pulmonary angioplasty. Riociguat is the only medication specifically approved for this condition, based on the results of the CHEST-1 trial, and demonstration of long-term benefits in the extension study CHEST-2. Of the studies included in this meta-analysis, CHEST-1 was the largest RCT trial with 261 participants. The other studies were smaller, with one being single-blinded, and one with the placebo arm including a low dose (3ng/kg/min) of the treatment medication, treprostinil. The study that evaluated sildenafil was particularly small, with only19 participants, which may explain the relative inferiority of sildenafil in this meta-analysis despite targeting the nitric oxide pathway like riociguat. The study is further limited by the small number of RCTs available for comparison. The NMA relied on indirect evidence for comparison, as there were no studies comparing two treatments directly. Furthermore, ERAs are considered clinically interchangeable by many, and in this NMA lumping them as one group may have been more informative than analyzing each separately. Lastly, the meta-analysis did not include any oral prostacyclin pathway agents. In the absence of comparative studies, however, this analysis might represent the best evidence available to date when selecting medical therapy in CTEPH patients, especially if more than one agent is considered or when riociguat is not tolerated.

Reference:

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On behalf of the National Jewish Health PH Program Providers:

Mohammad Dalabih, MBBS, MHA
Assistant Professor of Medicine
Pulmonary Hypertension Section
Division of Pulmonary, Critical Care, and Sleep Medicine

Suraj Sunder, MD, MPH
Assistant Professor of Medicine
Pulmonary Hypertension Section
Division of Pulmonary, Critical Care and Sleep Medicine

Andrew M. Freeman, MD, FACC
Associate Professor of Medicine
Pulmonary Hypertension Section
Division of Cardiology

Tim Lahm, MD, ATSF
Professor of Medicine
Pulmonary Hypertension Section
Division of Pulmonary, Critical Care and Sleep Medicine

Darlene Kim, MD
Associate Professor of Medicine
Division of Cardiology

Vera Pillitteri, DNP, FNP-BC
Division of Cardiology

M. Patricia George MD
Associate Professor of Medicine
Pulmonary Hypertension Section
Division of Pulmonary, Critical Care and Sleep Medicine