TITLE: Combination Therapy for Pulmonary Arterial Hypertension: Clinical Effectiveness

DATE: 18 January 2011

RESEARCH QUESTIONS

1. What is the clinical effectiveness of combination therapy with PDE-5 inhibitors (sildenafil or tadalafil) + endothelin receptor antagonists (bosentan or ambrisentan) in patients with pulmonary arterial hypertension?

2. What is the clinical effectiveness of combination therapy with PDE-5 inhibitors (sildenafil or tadalafil) + prostaglandins (epoprostenol or treprostinil) for patients with pulmonary arterial hypertension?

3. What is the clinical effectiveness of combination therapy with endothelin receptor antagonists (bosentan or ambrisentan) + prostaglandins (epoprostenol or treprostinil) for patients with pulmonary arterial hypertension?

KEY MESSAGE

Limited evidence was identified regarding the clinical effectiveness of combination therapies with PDE-5 inhibitors, endothelin receptor antagonists or prostaglandins, in patients with pulmonary arterial hypertension.

METHODS

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 1, 2011), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2001 and January 7, 2011. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, and randomized controlled trials. Internet links were provided, where available.

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RESULTS

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment (HTA) reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials.

One HTA report\(^1\) and two RCTs\(^2,3\) were identified examining the clinical effectiveness of combination therapies with PDE-5 inhibitors, endothelin receptor antagonists or prostaglandins in patients with pulmonary arterial hypertension (PAH). No systematic reviews or meta-analyses were identified. Additional information that may be of interest has been included in the appendix.

OVERALL SUMMARY OF FINDINGS

Overall, there is little evidence to demonstrate the clinical effectiveness of combination therapies for PAH. The identified HTA report\(^1\) included 20 RCTs on epoprostenol, iloprost, bosentan, sitaxentan and sildenafil in monotherapy or in combination. Four RCTs in the assessment found that the current evidence on the combination therapies is inadequate and therefore, no conclusions were made pertaining to the clinical effectiveness for PAH.

One RCT\(^2\) found a significant median change from baseline in 6 minute walk distance (6MWD) at 12 weeks (14m, \(p=0.0066\)) in PAH patients who took a combination of inhaled treprostinil and either oral bosentan (70%) or sildenafil (30%). The active group was compared to patients given an inhaled placebo plus either bosentan/sildenafil. Quality of life measures also improved. A second RCT\(^3\) randomized patients to epoprostenol plus bosentan or epoprostenol plus placebo. This study found that there was a trend towards clinical improvement, but did not achieve statistical significance on, hemodynamics, the primary outcome measured.
REFERENCES SUMMARIZED

Health technology assessments


Randomized controlled trials


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APPENDIX – FURTHER INFORMATION:

Systematic reviews and meta-analyses

Note: The only RCT included in the review using the combination of interest has an irrelevant outcome measure.

Non-randomized studies


Guidelines and recommendations

See page 13: Combination Therapy.

PubMed: PM17565025

Review articles


Additional references

16. Pohar R, Clark M, Spry C. Drugs for pulmonary arterial hypertension: a systematic review of the clinical-effectiveness of combination therapy [Internet]. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2009. [cited 2011 Jan 07]. Available from: http://www.cadth.ca/media/pdf/M0004_Drugs_for_Pulmonary_Arterial_Hypertension_tr_e.pdf