Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: _Pulmonary Arterial Hypertension_
-May 2019-

Background:

Pulmonary hypertension is a disease characterized by elevated pulmonary artery pressure with a mean pulmonary artery pressure ≥25 mmHg at rest.[1] The World Health Organization classifies patients with Pulmonary Hypertension into five groups based upon etiology. Group 1, or pulmonary arterial hypertension (PAH) refers to pulmonary hypertension in which the disease process includes the pulmonary arteries themselves. PAH predominantly affects the small resistance pulmonary arteries, characterized by intimal hyperplasia, medial hypertrophy, adventitial proliferation, in situ thrombosis, and inflammation. Following a comprehensive review of advanced therapies for PAH, **no agents were recommended for addition to the National Core Formulary**.

Discussion:

There are three general categories of pulmonary arterial hypertension, including heritable, idiopathic, and that associated with other conditions. Associated and idiopathic pulmonary arterial hypertension have roughly equivalent prevalence, although when considering the variety of associated causes, as a single category of disease, idiopathic pulmonary hypertension is by far the most common cause. The leading causes of associated pulmonary arterial hypertension are: connective tissue disease (especially scleroderma), congenital heart disease, and pulmonary hypertension due to chronic liver disease.[2]

Testing for pulmonary arterial hypertension includes right heart catheterization or echocardiogram, though these are not commonly performed in asymptomatic individuals. The initial pathophysiology, consisting of pulmonary arterial vasoconstriction, typically does not produce symptoms. However, when identified early in the disease course, it may be amenable to vasodilators such as calcium channel blockers. Responders to vasodilators have a better prognosis. As the disease progresses to pulmonary arterial remodeling and fibrosis, it becomes irreversible. At this stage symptoms may lead to diagnosis, although often this is delayed. Treatment at this stage, comprised of various advanced therapies does improve quality of life and may substantially improve survival duration. Ultimately, the end stage of the disease process is right heart failure leading to cor pulmonale.

Current standard of care for patients with PAH (WHO group 1) includes; oral calcium channel blockers for patients who respond to acute vasoreactive testing (which is approximately 10% of patients), diuretics for fluid retention, digoxin to improve cardiac output and slow ventricular rate, and anticoagulants to decrease risk for thromboembolic events. Other supportive care includes oxygen, supervised physical activity, and rehabilitation.[3] Advanced therapy consists of four medication classes, which are; prostacyclin agents, endothelin agents, phosphodiesterase type 5 (PDE5) inhibitors, and a soluble guanylate cyclase stimulant. These agents may be used alone or in combination.

Prostacyclin is an endogenous bioactive lipid with potent antithrombotic and vasodilatory effects. A variety of prostacyclin agents have been introduced for the advanced management of pulmonary arterial hypertension, including epoprostenol, treprostinil, iloprost, and selexipag.

Epoprostenol is the best studied among the various advanced PAH therapies. It has been shown to improve hemodynamic parameters, functional capacity, and probably survival (although studies are insufficiently powered to determine statistically significant improved survival due to low sample sizes).[4] Epoprostenol is indicated for affected patients with NYHA Class 3 or 4 symptoms for improvement of exercise tolerance and capacity and should be considered first-line for those with class 4 symptoms.

Endothelin receptor antagonists (ERAs), including ambrisentan, bocentan, and macicentan have been shown to improve exercise capacity, dyspnea, and hemodynamic measures (including pulmonary artery pressure, pulmonary vascular resistance, and cardiac index). There is some evidence that the magnitude of the response to ERAs may vary according to sex and race, with a greater magnitude of effect in terms of functional status improvement, seen in women and whites compared to men and persons of African descent. The main adverse effects of concern for ERAs are hepatotoxicity and peripheral edema.

The PDE5 inhibitors, including sildenafil and tadalafil cause vasodilation in the lung by blocking the breakdown of cyclic guanosine monophosphate, which results in prolongation of the action of mediators of vasodilation including nitric oxide.

Riociguat is an oral soluble guanylate cyclase stimulant. In the PATENT Trial, the drug was associated with a modest increase in the six-minute walking distance.[5] Improvements in pulmonary vascular resistance, symptoms, WHO functional class, and time to clinical worsening were also reported in patients receiving the study drug.

The 2014 CHEST guideline regarding management of PAH is comprised of consensus recommendations due to the lack of available high-quality evidence.[6] For treatment-naïve patients with WHO functional class 2 or 3 symptoms who fail or cannot tolerate a calcium channel blocker, monotherapy with an endothelin receptor antagonist, PDE5 inhibitor, or riociguat is recommended. Likewise, for treatment-naïve patients with WHO functional class 4 symptoms who fail or cannot tolerate a calcium channel blocker, monotherapy with a parenteral prostanoid is considered first line and an inhaled prostanoid is considered second line therapy. For those on monotherapy who have advanced disease and unacceptable symptom control, combination therapy including various regimens of two or three agents is advised. In the 2018 update to the CHEST guidelines, two new recommendations were added relative to advanced therapies.[7] For treatment naïve patients with functional class 2 or 3 symptoms, initial combination therapy with ambrisentan and tadalafil was recommended to improve 6-minute walking distance. For stable or symptomatic patients on background therapy with ambrisentan, the addition of tadalafil is recommended to improve 6-minute walking distance.

A meta-analysis published in Lancet in 2016 included 17 studies comparing combination therapy with various agents for pulmonary arterial hypertension with monotherapy.[8] Combination therapy was associated with significant risk reduction for clinical worsening compared with monotherapy. Also in 2016, a meta-analysis of 18 randomized control trials comparing monotherapy to combination therapy was published in the Canadian Journal of Cardiology.[9] Combination therapy included an endothelin receptor antagonist with a PDE5 inhibitor or prostacyclin or a PDE5 inhibitor with prostacyclin. The primary endpoint was combined clinical worsening, including but not limited to death or hospitalization. Combination therapy significantly reduced the risk of combined clinical worsening events by 38% (RR 0.62, 95% CI: 0.50-0.77) compared to monotherapy.

Findings:
World Health Organization Category 1 Pulmonary Arterial Hypertension is fortunately quite rare. Standard therapy is mostly geared toward symptom control and reducing additional risk unrelated to the primary disease process, with the exception of the small subset of vasoreactive patients with a better prognosis. Advanced therapy improves functional status and may confer survival benefit.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References:
1. Simonneau G, Gatzoulis MA, Adatia I, et al. Updated clinical classification of pulmonary hypertension. *J Am Coll Cardiol.* 2013; 62(25 Suppl):D34.
2. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension: A Report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association. *Journal of the American College of Cardiology.* 2009; Vol. 53. Issue 17.
3. Galie N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology and the European Respiratory Society. *Eur Heart J.* 2016; 37(1):67-119.
4. Barst RJ, Rubin LJ, McGoon MD, et al. Survival in primary pulmonary hypertension with long-term continuous intravenous prostacyclin. *Ann Intern Med.* 1994; 121:409.
5. Ghofrani HA, Galie N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension. *NEJM.* 2013; 369(4):330-40.
6. Taichman D, Ornelas J, Chung L, et al. Pharmacologic Therapy for Pulmonary Arterial Hypertension in Adults, CHEST Guideline and Expert Panel Report. *CHEST.* 2014; 146(2):449-475.
7. Klinger JR, Elliot CG, Levine DJ, et al. Therapy for Pulmonary Arterial Hypertension in Adults 2018, Update of the CHEST Guideline and Expert Panel Report. *CHEST.* 2019.
8. Lajoie A, Lauziere G, Lega JC, et al. Combination therapy versus monotherapy for pulmonary arterial hypertension: a meta-analysis. *Lancet Respir Med.* 2016; 4:291–305.
9. Fox B, Shtraichman O, Langleben D, et al. Combination Therapy for Pulmonary Arterial Hypertension: A Systematic Review and Meta-analysis. *Canadian Journal of Cardiology.* 2016; 32(12):1520-30.