EDITORIAL

PULMONARY HYPERTENSION – TREATMENT OPTIONS

Pulmonary Hypertension refers to abnormal increase in pulmonary pressure (mean PA pressure > 25 mmhg and > 30 mmhg), it can be caused by or associated with variety of conditions). The treatment of Pulmonary Hypertension depends upon the underlying factors precipitating or causing the disease process. In recent years many advanced treatment options has been developed to improve the functional class and even survival of pulmonary hypertension patients.

Pharmacological therapy comprises of primary and advanced therapy. Primary or standard or supportive therapy is usually used in all pulmonary hypertension groups for symptomatic relief[1]. Advanced therapies focus on preventing the underlying disease progression. Patients refractory to all treatment options may require heart lung transplant.

Supportive therapies include diuretics, digoxin, oral anticoagulation and supplemental oxygen. Fluid retention is common and diuretics gives substantial relive by decreasing the volume overload. Oral anticoagulation with warfarin is used in observational studies espsially in patients with thromoembolic pulmonary hypertension, idiopathic, drug induced and anorexiogenic induced pulmonary hypertension. The target International normalizing ration is 1.5 to 3 depending upon the indication[2]. Supplemental oxygen of 1-4 litre is used to improve hypoxemia and keep oxygen saturation above 90%.Digoxin is usually used to treat atrial fibrillation, especially useful in PH due to chronic obstructive pulmonary disease and Biventricular failure.

Calcium channel blockers were considered the most effective pharmacotherapy prior to the advent of newer pharmacotherapies. Responders to calcium channel blockers, who usually demonstrate acute nifedipine, sustained release diltiaziam and amlodipine. Verapamil should be avoided due to negative inotropic effects.

Newer and more effective therapies for pulmonary hypertension are available starting from prostacyclin analogs, initially used in early 1980 to more recently endothelin receptor antagonist and phosphodiesterase-5 inhibitors. Several randomized control trial have demonstrated significant functional class and survival benefit but they all have their merits and demerits, so should be used judiciously.

Three prostacyclin analogs are currently available–epoprostenol (intravenous formulation), treprostinil (intravenous, subcutaneous and inhaled formulation), and iloprost (Inhaled formulation). The efficacy and safety profile of prostacyclin analogues have been extensively reviewed and discussed in PAH treatment guidelines[4]. In addition to the improvements in exercise capacity, haemodynamics and functional class, the use of prostacyclin analogues provided a landmark in terms of providing survival benefit[5,6].

Endothelin receptor blockers (ERA), block the activation of endothelin receptors on endothelial or smooth muscle cells, thereby inhibiting the vasoconstriction and cellular proliferation mediated by endothelin. Bosentan is an oral nonselective ERA indicated for PAH with NYHA class II, III, and IV symptoms to improve exercise capacity and decrease clinical worsening of disease based on randomized, double-blind, placebo-controlled trials. One concern with bosentan treatment is the dose-dependent elevation of liver enzymes in about 10% of cases[8], which necessitates monthly monitoring of liver enzyme levels during

treatment. Ambrisentan is also a selective ETA receptor antagonist indicated for PAH patients with NYHA class II and III symptoms to prolong time to clinical worsening and improve exercise capacity and hemodynamic parameters[9].

Phosphodiesterease 5-catalyses the hydrolysis of cyclic guanosine monophosphate (cGMP) to its inactive 5-nucleotide monophosphate. Inhibitors of PDE5 prevent the breakdown of cGMP, thereby enhancing nitric oxide (NO)-dependent vasodilation mediated by cGMP. PDE-5 inhibitors, Sildenafil and tadalafil demonstrate improved exercise capacity in patients with PAH.

Patients treated with sildenafil had statistically significant increases in their 6MW test compared to those treated with placebo (>38 m). Most patients were NYHA functional class 2 or 3 at baseline. As compared to placebo, patients treated with sildenafil improved by at least one NYHA functional class after the 12-week treatment period. Effects were unchanged after 12 months of treatment. The changes in the 6MW distance with sildenafil are comparable to changes observed in patients treated with IV epoprostenol (47 m), inhaled iloprost (36 m), and oral bosentan (44 m), although these agents have not been directly compared[10]. Galiè et al found patients randomized to tadalafil 40 mg once daily for 16 weeks had a mean increase in 6MW distance by 44 more meters than placebo ($P < .01$)[11].

The potential complementary mechanism of all theses advanced therapies provides the rationale for investigating the combination therapy of these novel agents. Data both support and refute statistically significant improvement in functional capacity. Several studies failed to demonstrate statistical significance due to lack of power due to small sample size or insignificant improvement in functional class using combination therapy[12,13].

Combinations studied include prostacyclin plus an ERA, prostacyclin plus a PDE-5 inhibitor, and an ERA plus a PDE-5 inhibitor. The Bosentan Randomised trial of Endothelin receptor Antagonist THErapy (BREATHE)-2 study compared 16 weeks of treatment with epoprostenol alone versus combination epoprostenol plus bosentan in 33 patients with PAH[14]. Although there was a trend towards clinical and haemodynamic improvements with combination therapy, statistical significance was not met.

The 6MW distance increased 29.8 meters in PAH patients on epoprostenol plus sildenafil versus epoprostenol plus placebo ($P < .001$)[13].

In last two decades dramatic improvement in treatment options for pulmonary hypertension has occurred but still lots of question needed to be answered like which patient population benefits most from which particular therapy, determining when to initiate treatment and establishing optimal treatment sequence or combination therapy. Still improved disease awareness in addition to novel treatment options has lead to improve outcome both in terms of functional class and survival for this previously uniformly fatal disease.

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