Pulmonary Arterial Hypertension in Systemic Sclerosis: Update on Current Treatment

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Abstract: This review covers the major therapeutic advances in treatment of pulmonary hypertension in systemic sclerosis patients in recent decade. Highlights on endothelin-1 antagonists, prostacyclin analogs and phosphodiesterase type 5 inhibitors are included.

Keywords: Pulmonary hypertension, Systemic sclerosis

Introduction

Systemic sclerosis is a major cause of pulmonary arterial hypertension (PAH). PAH associated systemic sclerosis is less responsive to therapy and usually has a worse overall survival. Recent estimates indicate that 10-15% of patients with systemic sclerosis will develop PAH and this contributes to a significant proportion (~30%) of all systemic sclerosis-related death.¹

PAH is defined as mean pulmonary pressure >25 mmHg at rest and >30 mmHg with exercise. The pathogenesis of PAH in systemic sclerosis involves endothelial cell injury. With endothelial cell dysfunction, there is reduced nitrous oxide and prostaglandin production, and increased endothelin-1 production. Vascular wall remodeling then follows with intimal and smooth muscle proliferation. Luminal narrowing results in slow blood flow, a hypercoagulable state with in-situ thrombosis.

Screening and Diagnosing Pulmonary Arterial Hypertension

The most common and widely used tool is echocardiography, which can estimate pulmonary artery systolic pressure.

Management

Basic therapy such as oxygen supplementation should be offered to patients with PAH if there is evidence of hypoxaemia. Anticoagulation is recommended for moderate to severe pulmonary hypertension patients, targeting to keep international normalized ratio (INR) between 1.5 and 2.5. Vasodilators such as calcium channel blockers are suggested. Specific therapies including prostacyclins, endothelin blockers and phosphodiesterase inhibitors are discussed below. In severe cases with class IV functional status, atrial septostomy and lung transplant can be considered.

Current Recommendation from Chest Physicians

According to the American College of Chest Physicians 2007 treatment algorithm for pulmonary arterial hypertension, the first-line therapy in functional class III patients includes bosentan, sildenafil, epoprostenol and inhaled iloprost (evidence strength class A). For functional class IV patients, most experts recommend intravenous epoprostenol as first-line therapy.
Endothelin-1 Receptor Antagonist

Endothelin-1 is a peptide which interacts with vascular smooth muscle to induce vasoconstriction. It stimulates cell proliferation, fibrosis and inflammatory responses. Endothelin-1 receptor expression is shown to be increased in systemic sclerosis, and is implicated as an important step in pathogenesis of PAH.

Bosentan is an oral non-selective endothelin-1 antagonist, which blocks both type A and B receptors. Bosentan Randomized trial of Endothelin Antagonist THERapy trial (BREATHE-1) recruited 213 class III-IV PAH patients: 72% had primary PAH and 21% suffered from systemic sclerosis or other connective tissue diseases. The primary endpoint was 6MWD with hemodynamics measured at week 12. Bosentan 62.5 mg twice daily was shown to significantly increase exercise capacity compared to placebo after one month of treatment, as bosentan group had a mean difference of 44 m on 6MWD (p<0.001). Distance walked in six minutes was increased by 36 m in the bosentan group, whereas a deterioration of 8 m occurred in the placebo group; baseline 6MWD for bosentan group was 330±74 m while placebo group was 344±76 m. Bosentan was also shown to delay the time to clinical worsening (p=0.0038) and improved both the dyspnea score (p=0.059) and WHO functional class (p=0.042). However, elevation of aminotransferase enzymes was relatively frequent in bosentan group (14%) with more than eight-fold elevation observed in five patients taking bosentan at dosage of 250 mg twice daily.

Sub-group analysis of 66 PAH patients secondary to connective tissue disease in BREATHE-1 study was separately reported. They were randomized into 2 groups: 44 patients were treated with bosentan and 22 patients were put on placebo. Exercise tolerance by week 12 as measured with 6MWD was maintained in bosentan group (+19.5 m) but deteriorated in placebo group (-2.6 m), with an absolute difference of 22.1 m (95% CI: -32 to 76 m; not statistically significant).

Another retrospective study on outcomes of systemic sclerosis patients with PAH and idiopathic PAH on bosentan showed systemic sclerosis patients had a lower survival trend with most of them either maintained stable or declined in WHO functional class.

Indications for bosentan use include PAH with WHO class III (or IV) with dosage of 62.5 mg twice daily for 4 weeks, then 125 mg twice daily thereafter if liver function is normal. The estimated cost is around US$48,000/year.

Selective Type A Endothelin-1 Receptor Antagonists - Sitaxsentan and Ambrisentan

They are selective type A endothelin-1 receptor antagonists in oral form. Preliminary data showed it can increase exercise tolerance, WHO functional class, haemodynamics and quality of life in PAH patients. Both selective blockers require dosing of once daily and they have lower liver toxicity compared to bosentan.

In a recently published STRIDE-2X trial, which is an extension from an 18-week Phase III randomized controlled trial to one year including 229 patients at 55 centers. The estimated risk for a clinical worsening event at one year was 34% in the sitaxsentan 100 mg group and 40% in the bosentan group, (hazard ratio, 0.73; 95% CI, 0.45 to 1.2). Clinical worsening was defined as on-study death, hospitalization for PAH, addition of any chronic PAH therapy, atrial septostomy, transplantation or a combined decline in WHO functional class and >15% reduction in 6MWD from baseline. The one-year survival in sitaxsentan group was higher than bosentan group (96% vs. 88%). A subgroup analysis was performed post-hoc which suggested PAH-CTD patients (n=52) may demonstrate a differential response to two therapies. The 1-year risk of reporting a clinical worsening event for PAH-CTD subgroup was 27% for sitaxsentan and 56% for bosentan, as opposed to 27% for sitaxsentan and 28% for bosentan in non-CTD subgroup. Survival rates at 1 year for patients with PAH-CTD were 96% with sitaxsentan and 80% with bosentan, as opposed to 95% for sitaxsentan and 91% for bosentan in non-CTD subgroup.

Prostacyclins – Epoprostenol, Iloprost and Treprostinil

It is postulated that they can relax the smooth muscle cells and inhibit smooth muscle proliferation on top of an anti-platelet effect. In a 12-week randomized controlled trial, 111 class III-IV PAH patients from 17 centers were randomized
to intravenous epoprostenol group and conventional treatment group (calcium channel blockers, anticoagulation, diuretic, digoxin and oxygen). Intravenous epoprostenol was able to improve exercise capacity and hemodynamics with median 6MWD 316 m at 12 weeks versus 270 m at baseline. For conventional treatment, the 6MWD decreased from 240 m to 192 m. However survival advantage or mortality benefit was not demonstrated in this trial. For long-term usage of epoprostenol, Hickman catheter may need to be inserted. Annual cost can be over US$100,000.

In a 3-month iloprost randomized controlled trial, 35 out of 203 patients had systemic sclerosis. Iloprost was administered via inhalation, around 6-9 times per day. In iloprost group, 17% had absence of clinical deterioration and death compared to 5% in placebo group (p=0.007). Inhaled iloprost was approved by FDA in December, 2004. It is used in class III and IV PAH patients. The duration of hemodynamic effect lasts only 90 minutes. Therefore, frequent administration such as at least 6 times per day is required. The cost is also high ranging from US$ 60,000 - 70,000 per year.

Treprostinil can be administered by continuous infusion using an ambulatory pump designed for subcutaneous infusions. It has a longer half life than epoprostenol. A double-blind, randomized control trial investigated subcutaneous infusion of treprostinil in class II-IV PAH patients. It was shown to improve 16 m in 6MWD (p=0.006). The effect was dose related, and was limited by infusion site pain and reaction. Around 85% of patients complained of infusion site pain. Intravenous form of treprostinil was also shown to have improvement in class III and IV PAH patients in terms of hemodynamic parameters such as 6MWD, pulmonary arterial pressure, cardiac index and pulmonary vascular resistance. It was approved by FDA in January, 2005. The advantages are long half life around 3-4 hours, no requirement of mixing or cold packs and smaller pumps compared to intravenous epoprostenol. The improvement in haemodynamics and functional status are similar to epoprostenol. However, the drug is also expensive.

For experimental prostacyclins, inhaled treprostinil was studied in TRIUMPH trial with results released in ACR 2007 showing improvement in 20 m median 6MWD. Oral treprostinil (FREEDOM) trial is still in patient recruitment phase.

Phosphodiesterase (PDE) 5 Inhibitors – Sildenafil

PDE 5 is found abundantly in lung. Inhibitors increase cGMP and act as effective pulmonary vasodilators. FDA approved use of sildenafil in June, 2005 in PAH WHO Group 1 patients (PAH which is idiopathic, familial or associated with connective tissue disease, congenital heart disease, portopulmonary hypertension, HIV and drugs/toxins). It is in oral form and is relatively inexpensive (US$12,000/yr). In Sildenafil Use in Pulmonary Arterial Hypertension-1 Study (SUPER-1), 278 patients including idiopathic and connective tissue disease patients with PAH were recruited in this double-blind randomized controlled trial. Significant 6MWD change from baseline to week 12 was shown in sildenafil group (45 m in 20 mg TDS, 46 m in 40 mg TDS, 50 m in 80 mg TDS, p<0.0001). FDA only approved the use of 20 mg TDS dose but not higher. For connective tissue sub-group, 20 mg TDS showed highest gain in 6MWD of 42 m among the other dosages of sildenafil. For 20 mg TDS group, 29% improved in WHO functional class at week 12. Concerning the side effects, 46% had headache, 13% dyspepsia, 10% flushing, 9% epistaxis and 7% insomnia.

Combination Trials

Trials are undergoing to study the effects of different combinations of drugs:
- Iloprost + Bosentan: STEP JACC 2007
- Sildenafil + Epoprostenol: ATS 2006
- Inhaled Treprostinil + Bosentan/Sildenafil: TRIUMPH in progress
- Bosentan + Sildenafil: COMPASS 2
- Inhaled Iloprost + Sildenafil: VISION
- Oral Treprostinil + Bosentan/Sildenafil: FREEDOM

Survival in PAH-SSc

Williams et al measured survivals in patients with systemic sclerosis associated pulmonary arterial hypertension in two treatment eras. In historical control group, in addition to diuretics, digoxin, oxygen and warfarin, patients were given prostanoids as advanced therapy. In current treatment era group, patients were given bosentan. A total of 92 patients were studied (45 patients in bosentan group, 47 patients in placebo group). Kaplan-Meier survival in historical control
group was 68% at one year and 47% at two years. Survival in current treatment era group was 81% and 71% (p=0.016) at one and two years respectively. It is the first trial to document improved survival in systemic sclerosis patients with PAH. Denton et al. investigated long-term effects of bosentan in PAH-CTD patients exclusively. A total of 53 patients with class III PAH received bosentan for 44 weeks. Survival at week 48 was 92%. In STRIDE-2X, there was 96% overall survival shown in patients treated with sitaxsentan at 100 mg per day, compared to 88% in patients treated with bosentan 125 mg per day, though the difference did not reach statistical significance yet (sitaxsentan-to-bosentan hazard ratio, 0.34; 95% CI, 0.11 to 1.10).

Future Directions in PAH Management

There are many potential new therapeutic approaches being under investigated. For example, Rho kinase inhibitors, tyrosine kinase/growth factor receptor inhibitors with reports of successful treatment with imatinib in refractory patients, gene therapy, vasoactive intestinal peptide, HMG-Co A reductase inhibitors (e.g. statins) and serotonin transporter/receptor blockers.

In conclusion, systemic sclerosis with pulmonary arterial hypertension carries poor prognosis and is difficult to treat. In the past decade, new treatments of PAH were found to improve symptoms and possibly mortality, though they are prohibitory expensive at this moment. A number of novel vasodilator therapies showed promising results and combination therapy may become a reality. Early detection of PAH is advocated to improve the clinical outcome of this group of patients.

References