



PULMONARY HYPERTENSION

IN SCLERODERMA



Scleroderma



PULMONARY HYPERTENSION



Pulmonary hypertension (PH) is high blood pressure in the blood vessels of the lungs. If the high blood pressure in the lungs is due to narrowing of the pulmonary arteries leading to increased pulmonary vascular resistance, it is known as pulmonary arterial hypertension (PAH). When the blood pressure inside the pulmonary vessels is high, the right side of the heart has to pump harder to move blood into the lungs to pick up oxygen. This can lead to failure of the right side of the heart. Patients with scleroderma are at increased risk for developing PH from several mechanisms. Patients with scleroderma have multiple causes of their PH.

Patients who have limited cutaneous scleroderma (formerly known as CREST syndrome) are more likely to have PAH than those patients who have diffuse cutaneous systemic sclerosis. PAH may be the result of the same processes that cause damage to small blood vessels in the systemic circulation of patients with scleroderma. When the lining cells of the blood vessels (endothelial cells) are injured, excessive connective tissue is laid down inside the blood vessel walls. The muscle that constricts the blood vessel may overgrow and narrow the blood vessel.

Other scleroderma patients may have PH because they have significant scarring (fibrosis) of their lungs. This reduces the blood oxygen level, which in turn, may cause a reflex increase in blood pressure in the pulmonary arteries.



WHAT ARE THE SYMPTOMS OF PULMONARY HYPERTENSION?



Patients with mild PH may have no symptoms. Patients with moderate or severe PH usually notice shortness of breath (dyspnea), especially with exercise. Patients may also notice unusual chest pains and symptoms of right-sided heart failure, such as worsening shortness of breath and swelling of the feet and legs. Other symptoms that patients cite include a cough, lightheadedness or fainting, palpitations (heart racing or fluttering), and swelling.

HOW IS PULMONARY HYPERTENSION DIAGNOSED?



In a patient with scleroderma, the development of unexplained shortness of breath should lead to consideration of possible PH.

A laboratory clue that a patient might have PH is a reduced diffusing capacity (DLCO) on pulmonary function tests (PFTs). The DLCO measures the ability of gas to move from the air, across the lung tissue and blood vessel wall, into the blood. In the absence of lung fibrosis, if the DLCO is less than 50 percent of its predicted value, this is a clue that PH may be present. Another test commonly used to screen patients for PH is the echocardiogram. It can estimate the pulmonary artery pressure fairly well in most patients in a noninvasive manner.

The physician may order a cardiac catheterization to measure the actual pressure in the pulmonary arteries. This invasive test is done to more accurately measure the pressures in the lung blood vessels; to assess the blood flow generated by the heart (the cardiac output); to exclude an underlying leak or shunt contributing to the PH; to assess the function of the left side of the heart. Right heart catheterization is the “gold standard” for diagnosing PAH.

An exercise test known as the six-minute walk test is often helpful in assessing exercise capacity in patients with PH. In addition, a WHO (World Health Organization) Functional Class is often assigned to patients based on their activity tolerance, ranging from Class I to IV (with I being mildest and IV the most severe).



The development of PAH in patients with scleroderma is associated with a poor prognosis. However, ongoing educational efforts regarding the risk of PAH in scleroderma has led to earlier diagnosis. Studies now suggest that patients identified with mild or early PAH will fare better if drug therapy is started before symptoms and exercise capacity worsen.

WHAT IS THE TREATMENT OF PAH?



Anticoagulation (blood thinners), and diuretics are often important parts of treatment for PAH. If the oxygen level at rest, with exercise, or during sleep is low, supplemental oxygen therapy may be given. The decision to treat with anticoagulation is made on an individual basis by the patient and their physician, based on the potential risk of bleeding.

Calcium channel blockers (such as amlodipine, diltiazem or nifedipine) can help a small proportion of patients with PAH. Such treatment is successful in only a minority of scleroderma patients with PAH.

PAH SPECIFIC MEDICATIONS



The list of drugs for treating PAH continues to expand and include the following Health Canada-approved drugs:

- Epoprostenol (Flolan®) IV, approved in Canada since 1997; and (Caripul®), approved in Canada since 2012;
- Treprostinil SQ or IV (Remodulin®). Approved in Canada since 2002 and 2005 respectively;
- Bosentan (Tracleer®).
Approved in Canada since 2001;
- Ambrisentan (Volibris®).
Approved in Canada since 2008;
- Macitentan (Opsumit®).
Approved in Canada since 2013;
- Sildenafil (Revatio®).
Approved in Canada since 2006;
- Tadalafil (Adcirca®).
Approved in Canada since 2009; and
- Riociguat (Adempas®).
Approved in Canada since 2014.

Each of these drugs falls within one of four separate categories based on different mechanisms of action. These drugs are used alone or in combination with drugs in one or more other classes. Each will be briefly reviewed hereafter.

Prostacyclin Analogs



This class includes 3 drugs administered by continuous infusion: sodium epoprostenol (Flolan[®], Caripul[®]) and treprostinil (Remodulin[®]).

They have been approved by Health Canada for the treatment of patients with WHO Functional Class III or IV PAH related to scleroderma who have not responded to conventional therapy.

Sodium epoprostenol is a prostacyclin. Treprostinil is a prostacyclin analog because of its closely related chemical structure. Prostacyclin plays an important role as a potent vasodilator and antiplatelet agent, which contributes to the health of blood vessels.

The beneficial effect of these drugs in the treatment of PAH can be explained by their direct vasodilator action on the arteries of the lungs, heart and of the entire body. Thus they decrease the resistance of the arteries and blood pressure, and increase blood flow. They also prevent platelets to adhere to each other to form blood clots.

Epoprostenol

Epoprostenol (Flolan® Caripul®) must be given by constant intravenous infusion and requires an indwelling central venous catheter and a special infusion pump.

Epoprostenol has been shown to significantly improve physical capacity, which is measured using a 6-minute walk distance test (6MWT). It also improves cardiac and pulmonary hemodynamics, as well as the functional class and the quality of life. It alleviates symptoms of dyspnea.

Common side effects reported with epoprostenol include headache, flushing, jaw pain, diarrhea and bone pain.

Other side effects include the potential risk for serious infection associated with the use of the catheter.

Epoprostenol is contraindicated in patients who have congestive heart failure caused by severe left-sided heart problems. It should not be chronically administered to patients who have fluid in the lungs (pulmonary edema) prior to initiating treatment.



Treprostinil

The treprostinil (Remodulin®) may be administered by subcutaneous or intravenous continuous infusion.

The intravenous and subcutaneous infusion of this drug has been shown to be bioequivalent. Although, treprostinil is most often administered via the subcutaneous route.

As with epoprostenol, treprostinil has been shown to improve exercise capacity, hemodynamics and reduce dyspnea and fatigue symptoms associated with the disease. Symptoms of PAH are alleviated and an improvement of the physical component of the health-related quality of life has also been observed.

Treprostinil can cause side effects such as headache, diarrhea, nausea, jaw pain, vasodilatation and edema.

ENDOTHELIN RECEPTOR ANTAGONISTS (ERA)



This class includes 3 drugs administered orally: bosentan (Tracleer®), ambrisentan (Volibris®) and macitentan (Opsumit®).

The indications are slightly different for each of these 3 drugs.

These drugs inhibit the action of endothelin, a hormone secreted by the inner layer of blood vessels, by preventing binding to its receptors and the narrowing of blood vessels. Thus, they decrease pulmonary arterial pressure and increase cardiac blood flow without affecting heart rate.

Bosentan

Bosentan (Tracleer®) is approved by Health Canada for the treatment of patients with WHO Functional Class III and IV PAH due to scleroderma who have not responded to conventional therapy. In addition, there is evidence of the effectiveness of bosentan as a treatment to delay clinical disease progression in patients with WHO Functional Class II PAH.

Bosentan was shown to increase exercise capacity and cardiopulmonary hemodynamics in these patients.

There is also an improvement in functional class and a significant reduction in clinical worsening.

Bosentan can cause side effects such as nausea, headache, flushing, and edema in the lower limbs.

Since bosentan may increase liver enzymes levels and cause anemia, patients must undergo monthly blood tests before and during treatment.

Bosentan is contraindicated for pregnant or childbearing age women who don't use a reliable method of contraception, as well as for patients with moderate to severe liver disorder or patients treated with cyclosporin A (CSA) or glyburide.

Ambrisentan

Ambrisentan (Volibris®) is approved by Health Canada for the treatment of patients with WHO Functional Class II or III PAH related to scleroderma.

Ambrisentan was shown to improve exercise capacity, the Borg dyspnea score, hemodynamics and time to clinical worsening.

Ambrisentan can cause side effects such as edema of the lower limbs, headache, nasal congestion, dyspnea, increased liver enzymes and anemia.

Like bosentan, ambrisentan patients must undergo monthly blood tests before and during treatment.

Ambrisentan is contraindicated in pregnant or lactating women, patients with preexisting chronic or severe liver disease, as well as pulmonary fibrosis with or without associated hypertension.

Macitentan

Macitentan (Opsumit®) is the latest drug of the ERA class to be approved by Health Canada for the long-term treatment of patients with WHO Functional Class II or III PAH related with scleroderma in order to reduce morbidity.

Macitentan is effective in monotherapy or in combination with phosphodiesterase-5 inhibitors.

Macitentan has been shown to significantly reduce the clinical worsening of PAH defined as the simultaneous presence of a consistent decreased in the 6-minute walk distance test, worsened PAH symptoms and the need for additional PAH treatment.

Macitentan reduces the need for PAH hospitalization, improves cardiopulmonary hemodynamics and functional class, as well as quality of life and exercise capacity.

This medication can cause side effects such as nasal congestion, headache, sore throats and flu-like symptoms.

Like other ERA drugs, macitentan may increase liver enzyme levels and cause anemia in some patients. Hence, regular blood tests to assess these parameters are required.

Macitentan can cause birth defects if taken during pregnancy; therefore it should not be used by pregnant women.

Phosphodiesterase-5 (PDE-5) Inhibitors



This class includes 2 drugs: sildenafil (Revatio®) and tadalafil (Adcirca®).

They have been approved for the treatment of patients with WHO Functional Class II or III PAH related to scleroderma who have not responded to conventional therapy.

They inhibit the phosphodiesterase type 5 enzyme which destroys cyclic GMP inducing relaxation of the pulmonary blood vessels.

Sildenafil

Sildenafil is approved for the treatment of erectile dysfunction under the trade name Viagra®, and for the treatment of PAH under the trade name Revatio®.

Revatio® can be administered orally or intravenously.

It has been shown to improve exercise capacity and hemodynamics. It also improves the quality of life and alleviates dyspnea, as measured on the Borg scale.

Potential side effects include headache, flushing, upset stomach, back pain, diarrhea and pain in the arms or legs and nasal congestion.

Sildenafil is contraindicated in patients with hypertension secondary to sickle-cell disease (SCD, aka drepanocytosis), nonarteritic anterior ischemic optic neuropathy (NAION) or serious heart and liver disorders; as well as patients taking medications that affect its elimination or containing nitrate derivatives.

Tadalafil

Tadalafil is approved for the treatment of erectile dysfunction under the trade name Cialis[®], and for the treatment of PAH under the trade name Adcirca[®].

Adcirca[®] is administered orally.

In addition to its positive effect on pulmonary arterial pressure, it improves exercise capacity and quality of life and was shown to reduce clinical worsening.

Potential side effects include headache, muscle pain, flushing, nausea, pain in the arms or legs, back pain, upset stomach and nasal congestion.

Tadalafil has the same contraindications than sildenafil. Both medications should not be used in conjunction with riociguat.

GUANYLATE CYCLASE STIMULATORS



Riociguat

Riociguat (Adempas®) is the first of a new class of drugs to be approved by Health Canada for the treatment of patients with WHO Functional Class II or III PAH, used alone or in combination with an endothelial receptor antagonist, as well as for the treatment of patients with chronic thromboembolic pulmonary hypertension.

Riociguat works by stimulating the soluble guanylate cyclase enzyme which binds to nitric oxide. This binding leads to an increased production of cyclic GMP and the relaxation of pulmonary blood vessels.

Riociguat is administered orally.

Riociguat has been shown to significantly improve exercise capacity, functional class, time to clinical worsening and Borg dyspnea score.

Potential side effects include headache, dizziness, peripheral edema, nausea and upset stomach.

It is contraindicated in patients who are using medications with a similar action mechanism (PDE-5) and pregnant or lactating women.

LUNG TRANSPLANTATION



Lung transplantation is reserved for patients with severe PAH who do not respond to medical therapy. Due to the relatively high operative and perioperative risks, as well as the significant long-term risks of infection and rejection, lung transplantation should not be considered as first-line therapy or a cure for PAH. Whether single-lung, bilateral-lung, or heart-lung transplantation is the procedure of choice is still the subject of controversy. Not all patients are suitable candidates for lung transplantation. Gastroesophageal reflux disease (GERD), or esophageal dysmotility occurs frequently in scleroderma, and may be a reason not to attempt lung transplantation due to the risk of aspiration and transplant rejection.

Putting it all together

Pulmonary hypertension is not the only type of lung disease that can occur in patients with scleroderma. Interstitial lung disease (ILD), also called pulmonary fibrosis, is another serious complication. Please contact Scleroderma Quebec for information on pulmonary fibrosis.

It is important to note that patients can have significant pulmonary involvement from their scleroderma before signs and symptoms appear. Therefore, it is important to have routine screening for possible pulmonary involvement, in particular pulmonary arterial hypertension and interstitial lung disease.

Due to the complexity of the diagnosis and treatment of scleroderma lung disease, strong consideration should be given to referral of patients to physicians with expertise in scleroderma, interstitial lung disease, and PH. This requires close collaboration between you, your rheumatologist, pulmonologist, and cardiologist.

Please note that this brochure is provided for educational purposes only. It is not intended to substitute for informed medical advice.

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Scleroderma Quebec

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