Interferon (IFN) therapy has an important role in the treatment of multiple sclerosis and chronic hepatitis C infection. A few case reports have described an association between IFN therapy and the development of irreversible pulmonary arterial hypertension (PAH), and it is currently listed as a possible drug-induced cause of PAH in the most recent classification of pulmonary hypertension. A causal link between IFN use and PAH remains to be elucidated; many reports of PAH resulting from IFN occur in individuals with some other risk factors for PAH, who developed severe PAH after exposure to IFN therapy. The patient experienced significant clinical and hemodynamic improvement, with normalization of her pulmonary pressures after the initiation of combination therapy for PAH. At 28 months after diagnosis, she remains asymptomatic with no hemodynamic evidence of PAH and has been off all PAH therapy for 10 months.

Key Words: Diagnosis; Interferon treatment; Multiple sclerosis; Pulmonary artery hypertension

Learning Objectives

• To discuss the clinical presentation of a patient with a new diagnosis of pulmonary arterial hypertension (PAH).
• To recognize interferon (IFN) therapy as a potential cause of PAH.

CanMeds Competency: Medical Expert

Pretest

• What initial tests are recommended in the diagnostic work-up of a patient with suspected PAH?
• When is dual therapy indicated for the treatment of PAH?

Interferon (IFN) therapy has been associated with the development of PAH in rare cases. In all cases, prolonged use was associated with a severe and irreversible form of the disease. We report a patient who developed severe PAH after undergoing IFN-beta therapy for three years. The present report is the first description of a patient with potential IFN-induced PAH whose symptoms and hemodynamics normalized after the introduction of upfront combination therapy.

CASE PRESENTATION

A 45-year-old woman with a history of multiple sclerosis (MS) was admitted to the coronary care unit for hypoxemia, chest pain and shortness of breath. This patient was diagnosed with MS three years previously and was placed on IFN-beta for the management of her MS symptoms at that time. The patient had a history of syncope in December 2011 and April 2012, with progressive shortness of breath, fatigue and atypical chest pain culminating in an admission to hospital for hypoxemia in September 2012 with New York Heart Association (NYHA) class III symptoms. Her initial examination revealed a blood pressure of 121/58 mmHg, with a heart rate of 100 beats/min and an oxygen saturation of 90% on 5 L of oxygen by nasal prongs. She was found to have a jugular venous pressure of 5 cm above the sternal angle, with a split second heart sound and a loud P2. Her other medical history was otherwise unremarkable except for mild hypertension, with no vascular, connective tissue or thromboembolic disease. The initial echocardiogram showed a significant pattern of right ventricular dysfunction with moderate dilation and moderate systolic dysfunction of the right ventricle, moderate to severe tricuspid regurgitation, a flattened septum consistent with right ventricular overload and an elevated right ventricular systolic pressure (RVSP) of 64.9 mmHg. There was also a patent foramen ovale contributing to her hypoxia. A diagnostic right heart catherization (RHC) revealed a pulmonary artery pressure of 71/33 mmHg with a mean of 47 mmHg, mean right atrial pressure of 6 mmHg, pulmonary wedge pressure of 3 mmHg, cardiac output of 3.25 L/min, cardiac index of 2.45 L/min/m² and pulmonary vascular resistance of 13.5 Wood units with no response to nitric oxide. Coronary angiogram revealed normal coronary arteries. Pulmonary function testing was unremarkable, with a forced vital capacity (FVC) of 2.83 L (100% predicted), a forced expiratory volume in 1 s (FEV₁) of 2.47 L (102% predicted) and an FEV₁/FVC ratio of 87%. A computed tomography scan was consistent with PAH, with no evidence of pulmonary emboli or evidence of pulmonary vascular occlusive disease. A diagnosis of severe PAH was established. At this time, the IFN was stopped and the patient was treated aggressively with upfront oral combination therapy of ambrisentan 5 mg daily and tadalafil 40 mg daily. Intravenous prostacyclins were not initiated at that time due to...
Discontinuance of PAH therapy.

A mechanistic link between IFN and PAH has been suggested in previous experimental research. Hanaoka et al (6) demonstrated that in the thromboxane cascade, a mediator of inflammation, is directly involved in the effect of IFN on the lungs and may be a mediator of PAH. Links between endothelin-1 and IFNs have also been described (7). It has recently been demonstrated that IFN-alpha and IFN-beta stimulation can activate pulmonary vascular cells to release endothelin-1 (8).

Treatment of PAH with combination therapy of endothelin-receptor antagonist, prostacyclin derivatives or phosphodiesterase type 5 inhibitors is becoming increasingly common in the setting of lack of clinical improvement or deterioration on a monotherapy. Sequential combination therapy is strongly recommended for PAH patients who exhibit an inadequate clinical response to monotherapy (grade IA recommendation) based on current recommendations (9). The evidence for upfront combination therapy has not been well established (current recommendation grade IIb) but can be considered in certain clinical scenarios (10), and preliminary results from the A Study of First-Line Ambisentan and Tadalafil Combination Therapy in Subjects With Pulmonary Arterial Hypertension (AMBITIOn) trial (11), the largest double-blind randomized control trial investigating this question to date, appear to be promising. In a comparison of upfront combination therapy with ambisentan and tadalafil to first-line monotherapy with either ambisentan or tadalafil in FC II or III PAH patients, the AMBITIOn trial has demonstrated a reduction in the risk of clinical failure by 50% with combination therapy compared with monotherapy with no significant difference in the rates of serious adverse events and events leading to discontinuation of therapy (11). Since published, this trial may ultimately contribute to a paradigm shift in terms of how patients initially presenting with PAH are managed.

Despite the absence of a prospective case control study establishing a link between IFN and PAH, IFN use is considered to be a possible risk factor for PAH. Previous reports have suggested that the resultant PAH is often irreversible and progressive. The marked clinical improvement and sustained normalization of pulmonary pressures 28 months after diagnosis has not been previously described and has allowed for discontinuation of all PAH therapies. Whether this was due to cessation of IFN therapy or upfront combination therapy cannot be determined. Further study is needed to identify the precise pathophysiology of the problem and determine whether clinical/physiological markers can

### DISCUSSION

There have been few case reports published suggesting a link between PAH and the use of IFN-alpha or IFN-beta; some illustrate irreversible progressive PAH, while others demonstrate modest improvement in functional capacity and symptoms with ongoing PAH treatment (1-5). However, to date, none have described complete resolution of pulmonary hemodynamics to normal values with discontinuation of IFN and aggressive upfront combination therapy for PAH, nor such a robust resolution of symptoms (which has been sustained even with discontinuation of PAH therapy).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Diagnosis (September 2012)</th>
<th>January 2013</th>
<th>March 2013</th>
<th>March 2014</th>
<th>June 2014</th>
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<tbody>
<tr>
<td>Medication(s)</td>
<td>None</td>
<td>Tadalafil and ambisentan</td>
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<td>Echocardiography</td>
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<tr>
<td>Systolic PAP, mmHg</td>
<td>RVSP 65 mmHg</td>
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<td>RVSP 26 mmHg</td>
<td>RVSP 26 mmHg</td>
<td>RVSP 27 mmHg</td>
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<td>Cardiac output, L/min</td>
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<td>Pulmonary artery oxygen saturation, %</td>
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<td>New York Heart Association class</td>
<td>III</td>
<td>III</td>
<td>I</td>
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</table>

PAP Pulmonary arterial pressure; PCWP Pulmonary capillary wedge pressure; RV Right ventricle; RVSP RV systolic pressure; TR Tricuspid regurgitation
predict or explain a more favourable short-term prognosis or potentially identify targets for different treatment strategies.

**Post-test**

- **What initial tests are recommended in the diagnostic work-up of a patient with suspected PAH?**
  This patient presented with progressive shortness of breath, hypoxia and signs of right heart strain. Given her clinical presentation, pulmonary hypertension is high on the differential list. An initial echocardiogram supports the diagnosis but further testing was needed to confirm the etiology. The computed tomography scan and pulmonary function tests were performed to rule out intrinsic lung disease. While a ventilation/perfusion lung scan was not performed in the present case, it is the preferred imaging modality if chronic thromboembolic disease is suspected due to its higher sensitivity relative to computed tomography pulmonary angiogram. An RHC was essential to confirm the diagnosis, evaluate the severity of PAH and rule out any elevation of left-sided filling pressures that would suggest a cardiac cause.
- **When is dual therapy indicated for the treatment of PAH?**
  This is a case of two PAH-specific medications used simultaneously in the upfront treatment of patients with PAH. The current guidelines endorse the use of combination therapy in a sequential fashion in patients not meeting treatment goals with monotherapy. It is not certain whether the patient’s clinical improvement was due to cessation of the IFN or upfront combination therapy. However, no previous reports have identified this degree of sustained response after discontinuation of long-term IFN therapy. There has been significant recent discussion regarding the growing role of upfront combination therapy, and initial results from the AMBITION trial appear to be promising.

**DISCLOSURES:** Gibbons, Promislow, Dunne – No conflicts to disclose. Davies, Chandy, Stewart, Contreras-Dominguez, Puliese, Mielenzczuk have all received consulting and/or speaking fees from Actelion and Bayer, Mielenzczuk has had research funding from Actelion and Bayer.

**REFERENCES**
