

## Experience With Imatinib to Treat Pulmonary Arterial Hypertension

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Despite advances in the treatment of patients with pulmonary arterial hypertension (PAH), survival has not improved greatly. Imatinib, an antagonist of platelet-derived growth factor with antiproliferative activity, has been effective in experimental models and clinically in several published reports. We report the results of imatinib therapy in 4 patients with PAH (functional class IV) who were refractory to treatment with drug combinations for this condition. The final outcome was favorable in only 1 of the 4 cases. In this case, the patient was in functional class III and his hemodynamic parameters had improved significantly within 5 months after starting therapy. However, the patient died as a result of severe toxic hepatitis in which imatinib may have played a role. The present report adds to the few already in the literature (4 cases) and suggests that care should continue to be shown when using imatinib to treat PAH.

**Key words:** *Imatinib. Pulmonary arterial hypertension. Toxicity.*

### Introduction

Pulmonary arterial hypertension (PAH) is characterized by constriction and occlusion of the pulmonary vessels, conditions which lead to increased vascular resistance. The disease may be idiopathic or associated with various processes. Although the prognosis of idiopathic PAH has improved in the past decade thanks to new drugs,<sup>1-10</sup> 5-year survival is still around 50%.<sup>11</sup> Experimental evidence of the efficacy of imatinib<sup>10,12-14</sup> has been corroborated by several case descriptions of favorable responses.<sup>15-17</sup> Our group has treated 4 patients with imatinib. A MEDLINE search carried out using the search terms imatinib and pulmonary hypertension between January 2000 and

### Experiencia en el tratamiento de la hipertensión arterial pulmonar con imatinib

A pesar de los avances en el tratamiento de los pacientes con hipertensión arterial pulmonar (HAP), su supervivencia sigue estando muy afectada. El imatinib, un antagonista del factor de crecimiento derivado de las plaquetas con acción antiproliferativa, ha sido eficaz en modelos experimentales y en algunos casos comunicados. Se describe el resultado del tratamiento con imatinib en 4 pacientes con HAP en clase funcional IV y refractarios al tratamiento con asociaciones de medicamentos para la HAP. La respuesta final fue favorable sólo en uno de los 4 casos, que 5 meses después de iniciado el tratamiento estaba en clase funcional III y con mejoría significativa de los parámetros hemodinámicos. Sin embargo, el paciente falleció por hepatitis tóxica grave en la que el imatinib pudo haber participado. Estos resultados se añaden a la escasa experiencia clínica comunicada (sólo otros 4 casos) e indican que debemos mantener la cautela sobre la utilidad del imatinib en el tratamiento de la HAP.

**Palabras clave:** *Imatinib. Hipertensión pulmonar. Toxicidad.*

October 23, 2007 found only 4 other treated patients. The present report adds to the few already in the literature.

### Case Descriptions

#### *Patient 1*

A 50-year-old woman had been diagnosed 3 years previously with PAH associated with scleroderma and hypothyroidism. At the time of diagnosis, she was in functional class IV and had a 6-minute walking distance of 300 m. Systolic pulmonary arterial pressure (sPAP) was 79 mm Hg measured by echocardiogram and mean PAP (mPAP) was 58 mm Hg measured by catheterization; the vasodilator test was negative. The patient was started on intravenous iloprost (maximum dose, 2.5 ng/kg/min), diuretics, and anticoagulants; she then improved to functional class II. Ten months after starting treatment, she developed central catheter-related septic thrombophlebitis and was switched to subcutaneous treprostinil. The dose was limited to 6 ng/kg/min due to local intolerance. The patient's condition progressively deteriorated and by June 2005, she was in functional class IV. Bosentan (250 mg/d) and sildenafil (up to 300 mg/d) were

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successively added, but with no improvement. In February 2006 treprostinil was switched to inhaled iloprost. In November 2006 the patient was in functional class IV with refractory right-sided heart failure, had an sPAP of 95 mm Hg, and was unable to do the 6-minute walk test. Imatinib was added at a dose of 200 mg/d. She died 1 month later from right-sided heart failure.

#### *Patient 2*

A 52-year-old woman diagnosed with idiopathic PAH 4 years earlier developed autoimmune polyglandular syndrome during the course of her disease. At the time of diagnosis, she was in functional class IV and had a 6-minute walking distance of 35 m. The sPAP was 75 mm Hg measured by echocardiogram and the mPAP was 48 mm Hg measured by catheterization; the vasodilator test was negative. Intravenous epoprostenol, diuretics, and anticoagulants were started and the epoprostenol dose was increased as the patient's situation deteriorated (maximum dose, 41 ng/kg/min in August 2006). Sildenafil (up to 300 mg/d),<sup>9</sup> bosentan (250 mg/d), and inhaled iloprost were also successively added. In November 2006 the patient was in functional class IV with refractory right-sided heart failure, had an sPAP of 125 mm Hg, and was unable to do the 6-minute walk test. Atrial septostomy was felt to be contraindicated, and imatinib was added (200 mg/d). She died 1 month later from right-sided heart failure.

#### *Patient 3*

A 50-year-old woman had been diagnosed 8 years earlier with PAH associated with collagen disease (lupus erythematosus overlap syndrome-dermatomyositis with associated antiphospholipid syndrome) and chronic venous thromboembolic disease. At the time of diagnosis, the patient was in functional class III, had a 6-minute walking distance of 400 m, an sPAP of 70 mm Hg measured by echocardiogram and an mPAP of 67 mm Hg measured by right catheterization; the vasodilator test was negative. She improved with intravenous epoprostenol, diuretics, and anticoagulants. During follow-up, the patient was diagnosed with hyperthyroidism due to Graves disease, which was adequately controlled with propylthiouracil. The epoprostenol dose was increased as the patient's clinical situation deteriorated (maximum dose, 42 ng/kg/min in June 2005), and sildenafil (up to 350 mg/d),<sup>9</sup> bosentan (up to 500 mg/d), and inhaled iloprost were successively added. In early December 2006 she was in functional class IV with refractory right-sided heart disease, had an sPAP of 118 mm Hg, and was unable to do the 6-minute walk test. Atrial septostomy was felt to be contraindicated and lung transplantation had previously been ruled out. Imatinib was added (200 mg/d). From that moment, the patient experienced gradual improvement, with decreased need for diuretics, and was able to walk short distances. In January 2007 epoprostenol infusion was discontinued due to persistent infection caused by the catheter, but the patient's situation did not deteriorate. In March 2007 the laboratory workup revealed elevated transaminases (aspartate transaminase, 135 U/L; alanine aminotransferase, 131 U/L). Bosentan (500 mg/d) was discontinued for 1 month, then resumed at 125 mg/d once the transaminase values were normal. Five months after imatinib was started, the patient was in functional class III, had a 6-minute walking distance of 35 m, and had an sPAP of 75 mm Hg (36.5% decrease). On 22 May she went to the hospital with stable PAH symptoms but with associated general malaise and jaundice. She was admitted and bosentan, imatinib, and propylthiouracil were

discontinued due to possible hepatotoxicity. The laboratory workup showed aspartate transaminase, 2115 U/L; alanine aminotransferase, 2087 U/L; alkaline phosphatase, 1697 U/L;  $\gamma$ -glutamyl transpeptidase, 269 U/L; total bilirubin, 15.3 mg/dL; direct bilirubin, 13.7 mg/dL; normal complete blood count, erythrocyte sedimentation rate, creatinine, lipids, proteins, thyrotropin hormone, and thyroxine, and negative viral hepatitis markers and hepatic autoantibodies. The patient died 1 week later. The autopsy revealed submassive liver necrosis with lymphoplasmacytic and polymorphonuclear inflammatory infiltrate, but no evidence of viral hepatitis, thus indicating toxicity to be the cause. The lungs presented plexiform lesions and concentric hyperplasia of the intima, but no thrombosis. The heart was also considerably enlarged, with right ventricular dilation and hypertrophy.

#### *Patient 4*

A 42-year-old woman diagnosed with pulmonary arterial hypertension 1 year previously and treated 2 years earlier for breast cancer (in remission) was in functional class IV in July 2006, despite having started treatment with bosentan, digoxin, furosemide, and acenocoumarol 1 month earlier. She had an sPAP of 90 mm Hg measured by echocardiogram and an mPAP of 52 mm Hg measured by right catheterization, with a negative vasodilator test and a 6-minute walking distance of 250 m. She improved to functional class II once intravenous treprostinil was added (with progressive dose increases up to a maximum dose of 22 ng/kg/min in February 2007). In March 2007 she deteriorated to functional class III; treprostinil was switched to epoprostenol (progressively increased to 52 ng/kg/min). However, she was in functional class IV again by April and had an sPAP of 85 mm Hg, considerable right ventricular dilation, and pericardial effusion. Lung transplantation was ruled out due to the patient's history of cancer. She developed refractory right-sided heart failure, despite successively adding sildenafil (300 mg/d) and inhaled iloprost. Imatinib (200 mg/d) was also added, but the patient died 20 days later from refractory right-sided heart failure.

## Discussion

Distal extension of the smooth muscle cells of the vasculature toward the small nonmuscular pulmonary arterioles is characteristic of PAH.<sup>13</sup> Platelet-derived growth factor (PDGF) has been implicated in this process and acts *in vitro* as a potent mitogen and chemoattractant.<sup>14</sup> Expression of both PDGF and PDGF receptors is increased in the medial layer of the small pulmonary arteries in experimental PAH models and in the lungs of patients with IPAH. Imatinib, a PDGF antagonist, reversed PAH in experimental models, improved the cardiac index, reduced right ventricular hypertrophy, increased the percentage of nonmuscular pulmonary arteries and the survival rate up to 100%, and reduced PDGF and PDGF-receptor expression in the pulmonary vessels.<sup>12,14</sup> Ghofrani et al<sup>15</sup> first reported the results obtained from imatinib in a patient with IPAH in functional class IV after exhausting all therapeutic options. The patient's response was favorable and maintained after 6 months. Patterson et al<sup>16</sup> and Souza et al<sup>17</sup> also reported satisfactory results in 3 cases. Our experience was favorable in only 1 of the 4 patients treated, all of whom were desperate cases with a poor prognosis.

Imatinib is not free of adverse effects. Liver toxicity may be severe in 2% to 5% of treated patients. It usually appears 2 to 8 months after the treatment is started and reverts once the treatment is discontinued, but it can occur again with rechallenge.<sup>18</sup> To our knowledge, 2 cases of imatinib-induced fulminant hepatitis have been described: in the first case the patient had received treatment for chronic myeloid leukemia and was also taking paracetamol, which indicated combined toxicity,<sup>19</sup> and in the second case the patient was being treated for polycythemia vera.<sup>20</sup> Autopsy revealed submassive acute liver necrosis, with fibrin thrombi also located in the spleen and lungs. These abnormalities were attributed to a prothrombotic state associated with polycythemia. Abnormalities indicative of an immune mechanism have been described more often, with focal necrosis, inflammatory infiltrates,<sup>18,21-23</sup> and favorable response to corticosteroids.<sup>18</sup> In the patient in our series who developed hepatitis, the evidence suggested a toxic origin of the condition. She was taking other potentially hepatotoxic drugs (bosentan and propylthiouracil) and had already had an episode of transaminase elevation that resolved with temporary discontinuation of bosentan, despite continuation of imatinib. This makes it difficult to discern the extent to which imatinib is responsible.

Additional experience and clinical trials are needed to establish the role of imatinib in the treatment of PAH. The optimistic data reported to date were not confirmed in our experience; however, our patients had very advanced disease.

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