Imatinib Mesylate Has The Potential to Exert Its Efficacy by Down-Regulating The Plasma Concentration of Platelet-Derived Growth Factor in Patients With Pulmonary Arterial Hypertension

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Summary

Recently, platelet-derived growth factor (PDGF) has been implicated in the abnormal proliferation and migration of pulmonary artery vascular smooth muscle cells. Imatinib mesylate, a PDGF receptor antagonist, has been reported to dramatically improve pulmonary arterial hypertension (PAH) in some human cases as well as animal models.

Five patients with PAH (3 scleroderma-associated PAH and 2 idiopathic/familial PAH) taking no less than 2 PAH agents were treated with low-dose imatinib (100 mg/day) for 24 weeks. Imatinib was titrated up to 200 mg/day unless major complications were observed. Before and after the treatment, right heart catheterization, cardiopulmonary exercise test, respiratory function test, and plasma concentration measurements of PDGF-BB and vascular endothelial growth factor (VEGF) were performed. Plasma PDGF-BB levels were significantly decreased after 12 weeks of treatment ($P = 0.04$), while VEGF did not change. Although 24 week administration of imatinib did not show a significant effect on hemodynamics and exercise capacity, 2 patients with high plasma PDGF-BB levels showed a good initial response of more than a 15% decrease in pulmonary vascular resistance. Diffusion capacity of the lung for carbon monoxide significantly improved after 12 weeks of treatment ($P < 0.01$) and this improvement tended to be sustained for 24 weeks ($P = 0.05$). Renal dysfunction was observed in 3 patients during imatinib therapy.

The upregulated PDGF-BB in patients with PAH could be suppressed by imatinib treatment, and also seemed to be one of the determinant factors for its efficacy. (Int Heart J 2010; 51: 272-276)

Key words: Imatinib mesylate, Platelet-derived growth factor, Pulmonary arterial hypertension

Pulmonary arterial hypertension (PAH) is a disease with a poor prognosis. Three major pathways have been identified as playing important roles in the pathophysiology of PAH; the endothelin pathway, nitric oxide pathway, and prostacyclin pathway.1 These 3 pathways are associated with not only vasodilation, but also the unregulated proliferation of pulmonary artery vascular smooth muscle cells (PASMCs) in PAH patients. Several drugs which modulate each pathway are now available and have been shown to ameliorate PAH. Treatment with these drugs has been demonstrated to reverse intimal or medial thickening of the pulmonary artery in animal models.2-5 However, these effects are not so apparent in human PAH cases. In fact, the prognosis of PAH is improved to some extent with these drugs, but pulmonary vascular resistance (PVR) still remains over the normal range in almost all human PAH cases even after optimal treatment. Therefore, the development of drugs which regulate other pathways is still needed.

Recently, platelet-derived growth factor (PDGF) has been implicated in the abnormal proliferation and migration of PASMCs and seems to play a pivotal role in the pathophysiology of PAH.6,7 Plasma PDGF-BB levels have been shown to be higher in PAH patients than in healthy controls.9 Imatinib mesylate is known to inhibit the effect of PDGF as a receptor-tyrosine kinase inhibitor, and is widely used to treat chronic myeloid leukemia. In monocrotaline-induced PAH rats, treatment with imatinib reversed the elevated right ventricular pressure and dramatically improved the prognosis in a dose-dependent manner, accompanied by the regression of medial hypertrophy and muscularization in pulmonary vessels.6,9 This favorable result paved the way for administration of imatinib to human PAH patients. Following the report, the imatinib treatment has been reported to in fact improve the clinical outcomes of refractory PAH patients with World Health Organization (WHO) functional class IV.10,11 However, the number of reported cases is still small, and controversial results were also reported.12 Thus, the efficacy of imatinib has not yet been definitively established. In this study, we examined the effects of imatinib on 5 PAH patients who were in WHO functional class III and clinically stable for more than 12 weeks.

Methods

Patient selection and study design: Five patients with PAH were enrolled in this study from October 2008 to April 2009.
Table I. Baseline Characteristics of the Patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Pathogenesis</th>
<th>WHO FC</th>
<th>Duration of previous treatment (months)</th>
<th>WHO FC</th>
<th>Pathogenesis</th>
<th>BNP (pg/mL)</th>
<th>Peak VO2 (watt)</th>
<th>RAP (mmHg)</th>
<th>Mean PAP (mmHg)</th>
<th>CI (L/min/m^2)</th>
<th>%TLC</th>
<th>%TLC</th>
<th>DLCO (mL/min/m^2/mmHg)</th>
<th>PVR (dyne∙sec/cm^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>63</td>
<td>M</td>
<td>FPAH</td>
<td>II</td>
<td>16</td>
<td>III</td>
<td>SS-PAH</td>
<td>6.8</td>
<td>125 mg</td>
<td>250 mg</td>
<td>60 mg</td>
<td>592.4</td>
<td>11</td>
<td>85</td>
<td>34.9</td>
<td>24.5</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>F</td>
<td>SS-PAH</td>
<td>II</td>
<td>10</td>
<td>III</td>
<td>FPAH</td>
<td>3.8</td>
<td>0.25 mg</td>
<td>250 mg</td>
<td>60 mg</td>
<td>125 mg</td>
<td>11</td>
<td>35</td>
<td>368.4</td>
<td>30.4</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>F</td>
<td>SS-PAH</td>
<td>III</td>
<td>7</td>
<td>III</td>
<td>IPAH</td>
<td>13.1</td>
<td>0.5 mg</td>
<td>60 mg</td>
<td>60 mg</td>
<td>250 mg</td>
<td>11</td>
<td>60</td>
<td>866.1</td>
<td>6.8</td>
</tr>
<tr>
<td>4</td>
<td>67</td>
<td>F</td>
<td>IPAH</td>
<td>II</td>
<td>7</td>
<td>III</td>
<td>IPAH</td>
<td>19.9</td>
<td>0.4 mg</td>
<td>592.4</td>
<td>60 mg</td>
<td>125 mg</td>
<td>11</td>
<td>75</td>
<td>866.1</td>
<td>6.8</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>F</td>
<td>IPAH</td>
<td>III</td>
<td>10</td>
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<td>IPAH</td>
<td>19.9</td>
<td>0.4 mg</td>
<td>60 mg</td>
<td>60 mg</td>
<td>250 mg</td>
<td>11</td>
<td>75</td>
<td>866.1</td>
<td>6.8</td>
</tr>
</tbody>
</table>

Baseline patient characteristics: The baseline characteristics of the patients are shown in Table I. Three patients were diagnosed with scleroderma-associated PAH and 2 patients idiopathic/familial PAH, all of whom were classified as WHO functional class III. All patients had been administered no less than 2 PAH agents, and 2 (patients 1 and 5) had received intravenous epoprostenol therapy. Exercise capacity defined by
peak VO₂ was considerably low, ranging from 6.8 to 14.1 mL/min/kg. DLCO was impaired in all the patients, especially in those with scleroderma-associated PAH. Hemodynamic examination revealed wide variations in CI and PVR, which ranged from almost normal values (2.9 L/min/m² and 427 dyne·sec/m²) to severely impaired values (1.5 L/min/m² and 2161 dyne·sec/m²).

Effects of imatinib on hemodynamic parameters and exercise capacity: The effects of imatinib on hemodynamics and exercise capacity are shown in Table II. When a more than 5% decrease in mPAP or PVR, and a more than 5% increase in CI or peak VO₂ was regarded as being improved, at least one of the parameters worsened suddenly in patient 3 after the initiation of imatinib. However, the favorable effects were sustained at 24 weeks only in the patients with scleroderma-associated PAH. After 24 weeks or more, imatinib was titrated up to 200 mg in 4 patients in accordance with the study protocol. After up-titration, follow-up right heart catheterization and cardiopulmonary exercise testing were performed in 3 of these 4 patients. All of the parameters worsened suddenly in patient 3 after the up-titration. In the other 2 patients with idiopathic/familial PAH, the effects of the up-titration were equivocal. All patients remained in WHO functional class III throughout the study.

Laboratory testing and respiratory function test: Plasma PDGF-BB levels were significantly decreased after 12 weeks of treatment (P = 0.04) (Figure 1A). There were no significant or even slight changes in VEGF (Figure 1B) and BNP (data not shown) levels during imatinib treatment.

DLCO was also significantly improved after 12 weeks of treatment (P < 0.01) and this improvement was sustained to a slight degree for 24 weeks (P = 0.05) (Figure 2). DLCO could not be measured in patient 3 because her vital capacity was too small.

Safety: All patients tolerated 100 mg of imatinib, although transient renal dysfunction was observed in 1 patient (patient 1) a week after the initiation of imatinib. Mild renal dysfunction was observed in 2 patients (patients 2 and 4) after titration up to 200 mg. Their serum creatinine levels were elevated from 0.64 mg/dL and 0.85 mg/dL to 1.43 mg/dL and 1.54 mg/dL, respectively, and their renal function did not completely return to the baseline level even after discontinuation of imatinib. Peripheral edema was observed in 2 patients (patients 2 and 5).

### Table II. Effects on Hemodynamics and Exercise Capacity of Imatinib

<table>
<thead>
<tr>
<th>Patient</th>
<th>Δ% mean PAP (%)</th>
<th>Δ% CI (%)</th>
<th>Δ% PVR (%)</th>
<th>Δ% Peak VO₂ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12w 24w Post up-titration</td>
<td>12w 24w Post up-titration</td>
<td>12w 24w Post up-titration</td>
<td>12w 24w Post up-titration</td>
</tr>
<tr>
<td>1</td>
<td>0 -15 -5 -0</td>
<td>5 -7 -5 -0</td>
<td>10 0 -17 -17</td>
<td>3 11 -5 -5</td>
</tr>
<tr>
<td>2</td>
<td>-16 -14 -6 -5</td>
<td>13 15 -1  -1</td>
<td>3 9 -10 -8</td>
<td>8 -17 0 5</td>
</tr>
<tr>
<td>3</td>
<td>9 0 46 13</td>
<td>37 7 8 12</td>
<td>-27 12 -1 -1</td>
<td>1.9 -1.0 3.4 14.0</td>
</tr>
<tr>
<td>4</td>
<td>-2 6 13</td>
<td>10.6 1.9 -7.6 -2.4</td>
<td>14.5 -3.0</td>
<td>13.8 3.4 14.0</td>
</tr>
<tr>
<td>5</td>
<td>-3 3 25</td>
<td>16.3 0.9</td>
<td>-27 12 -1 -1</td>
<td>3.4 1.9 14.0</td>
</tr>
<tr>
<td>Mean</td>
<td>-2.4 -3.8</td>
<td>10.6 1.9 -7.6 -2.4</td>
<td>14.5 -3.0</td>
<td>13.8 3.4 14.0</td>
</tr>
<tr>
<td>SD</td>
<td>8.7 9.8</td>
<td>16.3 0.9</td>
<td>-27 12 -1 -1</td>
<td>3.4 1.9 14.0</td>
</tr>
</tbody>
</table>

Each value is expressed as % change from the baseline. CI indicates cardiac index; PAP, pulmonary arterial pressure; PVR, pulmonary vascular resistance; 12w, 12 weeks after the initiation of imatinib; 24w, 24 weeks after the initiation of imatinib; and Post up-titration, 12 weeks after titrated up to 200 mg.

### Figure 1. Changes in the plasma concentration of PDGF-BB (A) and VEGF (B). Data for individual patients are shown. Blue, black, green, black-dot, and red lines are the data for patients 1, 2, 3, 4, and 5, respectively. Mean ± SD is expressed as square symbols with vertical lines. [PDGF-BB]: plasma concentration of PDGF-BB. [VEGF]: plasma concentration of VEGF. Pre: before the initiation of imatinib. 4w, 12w, 24w: 4, 12, 24 weeks after the initiation of imatinib, respectively. Post up-titration: 12 weeks after increase up to 200 mg.

### Figure 2. Changes in %DLCO. Data for individual patients are shown. Blue, black, black-dot, and red lines are the data for patients 1, 2, 4, and 5, respectively. DLCO could not be measured in patient 3 because her vital capacity was too small. Mean ± SD is expressed as square symbols with vertical lines. Pre: before the initiation of imatinib. 12w, 24w: 12, 24 weeks after the initiation of imatinib, respectively. Post up-titration: 12 weeks after increase up to 200 mg.
after titration up to 200 mg. No other adverse events, including any digestive symptoms, were observed.

**Discussion**

To the best of our knowledge, this is the first study to report that imatinib decreases the plasma concentration of PDGF-BB in patients with PAH. We have also observed that DLCO is improved during imatinib treatment, while the improvement in hemodynamic parameters was transient.

Recently, PDGF signaling pathways have been shown to lead to promoting the abnormal proliferation and migration of PASMCs, which is thought to induce the obliteration of resistance vessels and the muscularization of arterioles in association with the pathophysiology of PAH. Schermuly, et al have shown that imatinib suppresses the overexpression of PDGF receptor, and reverses the medial hypertrophy and muscularization of arterioles in monocrotaline-induced PAH rats. They have also shown that vascular negative remodeling is attributable to the inhibition of PASMC proliferation and the induction of PASMC apoptosis. Nakamura, et al have recently reported that imatinib induces apoptosis of PASMCs only in the presence of PDGF-BB. Considering that PDGF-BB was significantly decreased soon after the initiation of imatinib (ie, within 4 weeks) as observed in our study, imatinib might induce apoptosis only in the early period of treatment when plasma PDGF-BB levels were relatively high. Therefore, this might be the reason why the efficacy of imatinib for PAH was equivocal after 24 weeks of treatment, although hemodynamic parameters and exercise capacity showed temporal improvement in the early phase. Consistent with this idea, patients with higher plasma PDGF-BB levels (patients 2 and 5) had a better initial response in the reduction of PVR, while patients with lower plasma PDGF-BB levels (patients 3 and 4) had a poorer initial response. There has been one report that imatinib did not have favorable effects in 3 cases, however, the plasma PDGF-BB levels were not measured in those patients. Once the plasma concentration of PDGF-BB is decreased, imatinib may not have the ability to reverse vascular remodeling. Further investigation is required to determine the relation between the effect of imatinib and plasma PDGF-BB levels.

Usually, a receptor antagonist up-regulates ligand production, for example, administration of an angiotensin II type 1 receptor blocker increases circulating angiotensin II. However, we have found that a PDGF receptor antagonist down-regulates circulating PDGF levels. In several tumor cells, an autocrine regulatory loop of PDGF has been reported to play a crucial role in maintaining their growth. In these abnormal cells produce PDGF and express PDGF receptors simultaneously. In this situation, once PDGF receptors are blocked by imatinib, proliferation of these cells is terminated, which may result in decreases in PDGF production. This scenario might be the case in PASMCs in our PAH patients. The plasma concentration of PDGF-BB is normally undetectable, and we believe that the main source of PDGF-BB production is attributable to abnormally proliferating pulmonary vasculature. Undoubtedly PASMCs express PDGF receptors, and termination of the autocrine loop by imatinib may inhibit cellular growth which consequently decreases PDGF production by PASMCs.

Although hemodynamic parameters and/or exercise capacity showed only transient improvement, DLCO was significantly improved after 12 weeks of treatment, and this improvement appeared to be sustained for 24 weeks. This is the first report to show that DLCO is improved in human PAH cases treated with imatinib. Although DLCO is one of the markers for the severity of PAH, imatinib may also exert sustained favorable effects on lung function in human PAH cases.

Adverse events appeared to occur in a dose-related fashion. Renal dysfunction was observed in 3 patients, which emerged after up-titration in 2 of them. Two different mechanisms responsible for renal dysfunction have been reported. One was tumor lysis syndrome, the other was toxic tubular damage caused by the drug. The first one could occur when imatinib is used for patients with chronic myeloid leukemia, and was unlikely in our patients. Therefore, renal dysfunction observed in this study was most likely attributable to tubular damage, reported as acute tubular necrosis, tubular vacuolization, and partial Fanconi syndrome. Renal dysfunction induced by imatinib sometimes becomes severe enough so as to require hemodialysis or irreversible even after discontinuation. Careful monitoring of renal function should be conducted during the administration of imatinib, especially when a higher dose is selected. According to our study, a higher dose (200 mg/day) had no beneficial effects but seemed to increase the incidence of adverse events. Therefore, the indication for a higher dose should be carefully determined.

**Study limitations:** 1) The patient population was very small and the control group was not configured in this study. 2) All the patients with scleroderma had mild to moderate interstitial lung disease. Imatinib has been reported to improve interstitial lung disease itself and all of the improvement in DLCO may not be attributable to the effects on pulmonary vasculature. 3) Candidates had to be limited to patients who already had received optimal PAH treatment without satisfactory results, and it was very difficult to distinguish the efficacy of imatinib from that of combination therapy.

**Conclusions:** Imatinib mesylate may have some potential to improve hemodynamics and exercise capacity with an increase in DLCO in stable PAH patients as well as in patients in clinically critical situations. Also, imatinib mesylate decreases the upregulated plasma PDGF-BB level, the meaning of which remains to be elucidated. Further investigations, including global clinical trials, are necessary.

**Acknowledgment**

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**References**


