Clin Res Cardiol 98:265–267 (2009)
DOI 10.1007/s00392-009-0752-3

Henrik ten Freyhaus
Daniel Dumitrescu
Henning Bovenschulte
Erland Erdmann
Stephan Rosenkranz

Significant improvement of right ventricular function by imatinib mesylate in scleroderma-associated pulmonary arterial hypertension

Sirs: Pulmonary arterial hypertension (PAH) is a devastating disease that harbours a poor prognosis, particularly in patients with scleroderma-associated PAH. Although modern therapies such as endothelin receptor antagonists (ERA), phosphodiesterase type-5 inhibitors (PDE5i) and prostanoids have improved the clinical situation and outcome of affected patients [5], the current medical treatment of PAH is not satisfactory. Recent experimental data suggest that platelet-derived growth factor (PDGF) plays a pivotal role in the pathobiology of PAH by initiating and maintaining the underlying pulmonary vascular remodelling [9]. Consistently, inhibition of PDGF receptor (PDGFR) signalling by the tyrosine kinase inhibitor imatinib mesylate was recently shown to reverse PAH in animal models and to improve the clinical situation in selected patients [3, 7, 9, 10].

Received: 8 September 2008
Accepted: 8 January 2009
Published online: 13 February 2009

H. ten Freyhaus · D. Dumitrescu
E. Erdmann · S. Rosenkranz, MD (✉)
Klinik III für Innere Medizin
Universität zu Köln
Kerpener Str. 62
50937 Köln, Germany
Tel.: +49-221/478-32402
Fax: +49-221/478-32400
E-Mail: stephan.rosenkranz@uk-koeln.de

H. Bovenschulte
Klinik für Radiologie
Universität zu Köln
Köln, Germany

However, imatinib was also shown to exert significant cardiotoxicity in animals and humans through its inhibitory effect on the non-receptor Abelson tyrosine kinase (c-Abl) [4]. Further analyses of clinical studies revealed that congestive heart failure is a rare event in patients receiving imatinib therapy, but occurs more frequently in patients with pre-existing cardiac conditions [1]. The latter fact may be of particular significance in patients with PAH and impaired right ventricular function since the right ventricle responds particularly sensitive to hemodynamic and/or cardiotoxic impairment. In addition, patients with scleroderma-associated PAH harbour a lower right ventricular contractility as compared to those with idiopathic PAH [6].

Case report

We report the case of a 58-year-old female with severe scleroderma-associated PAH (functional class III) in whom right ventricular function was severely compromised as a consequence of chronically elevated afterload. While inhaled iloprost was not tolerated due to significant side effects (headache, dizziness), a sequential combination therapy with the ERA bosentan (125 mg bid) and the PDE5i sildenafil (50 mg tid) was initiated. Despite this therapeutic regimen, the patient rapidly deteriorated to functional class IV, but refused intravenous prostanoid treatment. In this situation, imatinib mesylate (400 mg/day) was added to the therapeutic regimen and maintained for a period of 2 years. The patient was closely monitored for right ventricular function, clinical parameters, and physical performance. NTproBNP serum levels which

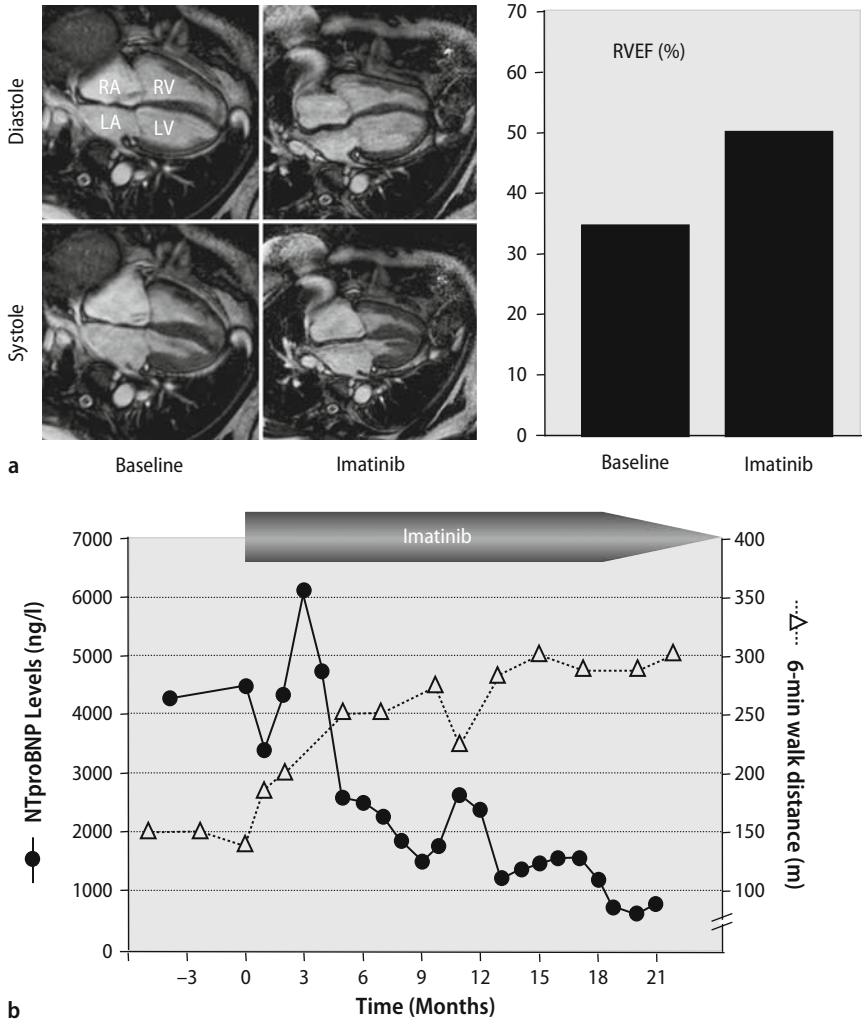

Fig. 1 Effects of chronic imatinib mesylate treatment on **a** right ventricular function as assessed by cardiac magnetic resonance imaging (MRI); and **b** 6-min walk distance (6MWD) and NTproBNP serum levels in a patient with severe scleroderma-associated PAH. *RVEF* right ventricular ejection fraction

indicate the extent of right heart overload/dysfunction in PAH patients were measured in monthly intervals. Furthermore, right heart catheterization (RHC) and magnetic resonance imaging (MRI) were performed before (baseline) and after 2 years of imatinib treatment. Repeat RHC showed a significant improvement of hemodynamic parameters: the systolic/mean pulmonary artery pressure declined from 97/56 to 75/44 mmHg, and pulmonary vascular resistance (PVR) decreased from 816 (10.2) to 552 (6.9) dyn × s/cm^5 (wood units). At the same time, MRI measurements revealed a dramatic improvement of right ventricular function, as RVEF increased from 36% to 50% (Fig. 1a). Consistent with these hemodynamic improvements, there was a continuous increase of physical performance (as assessed by the 6-min walk distance), and a constant decline of NTproBNP levels (Fig. 1b). These findings collectively indicate that chronic treatment with imatinib mesylate was associated with a significant improvement of functional class, exercise tolerance, hemodynamic parameters, and right ventricular function in a patient with PAH and severe right heart failure.

Discussion

This is the first case that demonstrates an improvement of PAH and right ventricular function by imatinib in PAH associated with scleroderma. Given that scleroderma-associated PAH is a chronic progressive disease, the current treatments mainly aim to slow the disease process and delay the time to clinical worsening. Hence, the dramatic improvement of clinical and hemodynamic parameters over a period of 2 years as shown in the present case is rather impressive and demonstrates the therapeutic potential of tyrosine kinase inhibitors in PAH, representing an anti-proliferative rather than a vasodilative approach. The therapeutic effect may be attributable to

inhibition of PDGFR signalling and reversal of vascular remodelling in the pulmonary vasculature [9], and/or to interference with stimulatory autoantibodies to the PDGFR that have recently been described in scleroderma patients [2]. A concern with imatinib is, however, cardiotoxicity, particularly in patients with pre-existing heart failure [1, 4]. While the beneficial effects of imatinib mesylate in PAH are due to PDGFR inhibition [9], the cardiotoxic effects that are attributed to inhibition of c-Abl were shown to be dose-dependent [1]. Here, long-term imatinib mesylate at a dose of 400 mg/day—through reduction of PVR—did not compromise but actually improve right ventricular function, as shown by cardiac MRI and a decline in NTproBNP levels. This is of particular importance as the degree of right ventricular dysfunction determines the prognosis in patients with PAH [8], and right ventricular function is particularly impaired in scleroderma-associated PAH [6]. Although these findings are based on a single case, they indicate that imatinib mesylate may be beneficial in scleroderma-associated PAH, even when right ventricular function is severely compromised. Nevertheless, cardiac function must be monitored closely, and the safety and efficacy of tyrosine kinase inhibitors in PAH should exclusively be investigated in clinical trials that are currently under way.

Conflict of interest All authors report that no significant conflicts of interest exist.

References

1. Atallah E, Durand JB, Kantarijan H, Cortes J (2007) Congestive heart failure is a rare event in patients receiving imatinib therapy. Blood 110:1233–1237
2. Baroni SS, Santillo M, Bevilacqua F, Luchetti M, Spadoni T, Mancini M, Fraticelli P, Sambo P, Funaro A, Kazlauskas A, Avvedimento EV, Gabrielli A (2006) Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis. N Engl J Med 354:2667–2676
3. Ghofrani HA, Seeger W, Grimminger F (2005) Imatinib for the treatment of pulmonary arterial hypertension. N Engl J Med 353:1412–1413
4. Kerkelä R, Grazette L, Yacobi R et al (2006) Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. Nat Med 12:908–916
5. Olschewski H, Höper MM, Borst MM et al (2007) Diagnostik und Therapie der chronischen pulmonalen Hypertonie. Leitlinien der Deutschen Gesellschaft für Pneumologie, der Deutschen Gesellschaft für Kardiologie und der Deutschen Gesellschaft für Pädiatrische Kardiologie. Clin Res Cardiol 96:301–330
6. Overbeek JM, Lankhaar JW, Westerhof N et al (2008) Right ventricular contractility in systemic sclerosis-associated and idiopathic pulmonary arterial hypertension. Eur Respir J 31:1160–1166
7. Patterson KC, Weissmann A, Ahmadi T, Farber HW (2006) Imatinib mesylate in the treatment of refractory idiopathic pulmonary arterial hypertension. Ann Intern Med 145:152–153
8. Rosenkranz S (2007) Pulmonary hypertension: current diagnosis and treatment. Clin Res Cardiol 96:527–541
9. Schermuly RT, Dony E, Ghofrani HA, Grimminger F et al (2005) Reversal of experimental pulmonary hypertension by PDGF inhibition. J Clin Invest 115:2811–2821
10. Souza R, Sitbon O, Parent G, Simonneau G, Humbert M (2006) Long term imatinib treatment in pulmonary arterial hypertension. Chest 61:736