Everolimus in patients with severe pulmonary hypertension: a safety and efficacy pilot trial

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Abstract: Despite the availability of vasodilating compounds, pulmonary hypertension (PH) of various origins remains a disease with a poor prognosis. In recent years, pulmonary arterial hypertension (PAH) has been recognized as a predominantly proliferative process. Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), inhibits cellular protein synthesis and growth not only in lymphocytes but also in cells of the vascular wall. Ten patients suffering from PAH ($n = 8$) or chronic thromboembolic PH ($n = 2$) with progressive disease despite therapy with at least 2 vasodilating drugs were included in a prospective open-label pilot study. All patients were treated with everolimus in addition to their prior medication. Safety and tolerability were observed throughout the study. Pulmonary vascular resistance (PVR) and 6-minute walk distance (6MWD) were considered coprimary end points. In 2 patients, study medication was stopped prematurely because of an adverse event. One patient had acute bronchitis, and the other had right heart decompensation. The remaining 8 patients exhibited a significant 31% decrease in PVR (median [interquartile range], 1,012 [688–1,344] vs. 663 [546–860] dyn s cm^{-5}; $P = 0.018$) and an increase in 6MWD (median [interquartile range], 236 [139–350] vs. 298 [207–450] m; $P = 0.069$) after 6 months of treatment with everolimus. In conclusion, in this pilot study antiproliferative therapy with everolimus was well tolerated in patients with PH. The observed improvements in PVR and 6MWD may stimulate further consideration of mTOR inhibition with everolimus for the treatment of PH.

Keywords: pulmonary hypertension, treatment, mTOR inhibitor, exercise, hemodynamic.

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INTRODUCTION

Precapillary pulmonary hypertension (PH) is a hemodynamic condition that is associated with poor prognosis.[1] The hemodynamic impairment may be either idiopathic or associated with various medical conditions, including scleroderma, pulmonary embolism, or liver cirrhosis.[2-7]

The increase in pulmonary pressure and pulmonary vascular resistance (PVR) is caused by vaso-

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constriction as well as structural changes in small pulmonary arteries. The current medical treatment of pulmonary arterial hypertension (PAH) is based on 3 classes of vasodilative compounds: prostanoids, endothelin receptor antagonists, and phophodiesterase type 5 inhibitors.[8,9] In addition to the confirmed vasodilative activities of these compounds, antiproliferative effects of varying extent may explain the long-term effects of these drugs over and above their short-term vasodilative action. Because both inflammation and (to an even greater extent) proliferation of vascular smooth muscle cells and other components of the vascular wall may be pivotal in the development of PH in most situations, it has been suggested that newer therapies for PH should be targeted to pathways involved in these events.[10]

Case reports have suggested that the selective platelet-derived growth factor receptor (PDGFR) antagonist imatinib, a tyrosine kinase inhibitor of PDGFR α and β kinases, Abl, DDR, and c-KIT, may be beneficial in patients with PH, and this antiproliferative drug has consequently been investigated in large trials for the treatment of PAH.[10,11] Results of the first randomized, double-blind, placebo-controlled trial seem to confirm a benefit of this compound on PVR and pulmonary arterial pressure, but the 6-minute walk distance (6MWD) did not improve in the small group of patients.[12]

The subsequent phase 3 trial (IMPRES) demonstrated comparable hemodynamic effects as well as a significant placebo-corrected improvement in 6MWD of 32 m.[13] Similarly, the multikinase inhibitor sorafenib has been shown to improve pulmonary hemodynamics and right ventricular remodeling in rats with monocrotalin-induced PH.[14]

As long as 12 years ago, Nishimura et al.[15] reported a beneficial effect of sirolimus on PH in an experimental animal setting. In this trial, 40-O-(2-hydroxyethyl)-rapamycin attenuated PH in a model of left pneumonectomy and subsequent monocrotaline injection in rats. Interestingly, treatment with rapamycin, administered at the same time as monocrotaline, resulted in both a significantly lower rise in pulmonary arterial pressure and a significantly lower vascular occlusion score in comparison with untreated controls. Moreover, rapamycin also reduced right ventricular hypertrophy. This effect was less pronounced when rapamycin was started more than a week after monocrotaline administration. In a similarly designed experiment, triptolide, an inhibitor of transcriptional activation of nuclear factor κB in numerous cell types, showed a comparable effect.[16]

Everolimus, a compound closely related to sirolimus, binds intracellularly to the immunophilin FK506 binding protein 12. The resulting complex inhibits a central signaling protein, the mammalian target of rapamycin (mTOR), and thereby hinders several signaling pathways directed at protein synthesis and cellular growth and leads to the arrest of the cell cycle in the G_1 phase.[17] In recent years, it has been demonstrated by many authors that not only lymphocytes but also other cell types, such as vascular smooth muscle cells, respond similarly to this compound.[18-20] Everolimus was approved for immunosuppression following heart and kidney transplantation several years ago.[21,22] Because of its specific properties, it is presently in experimental use for various clinical conditions.

Results of animal experiments as well as the favorable safety profile of the compound in patients with renal or heart graft suggested that a pilot trial of the mTOR inhibitor everolimus be conducted in patients with PH. We therefore examined the effect of everolimus on exercise capacity and hemodynamic parameters, such as PVR, in patients with idiopathic PAH (IPAH) or chronic thromboembolic PH (CTEPH) who did not benefit significantly from combination therapy containing at least 2 specific vasodilative agents.

METHODS

Study objectives and design

The aim of this prospective single-center open-label pilot study was to investigate the safety and tolerability of everolimus in patients with PH and existing combination therapy. In addition, we intended to estimate the effect of everolimus on 6MWD and PVR in these patients.

Patients with IPAH or CTEPH not eligible for pulmonary endarterectomy (as stated by an experienced surgeon) were included if progression of the disease had been observed despite receipt of combination therapy consisting of at least 2 different vasodilative com-

pounds. Progressive disease was assumed if at least 2 of the following criteria were fulfilled: (*a*) cardiac index ≤2.1 L min^{-1} m^{-2}, (*b*) 6MWD ≤380 m, (*c*) systolic blood pressure during cycle ergometry ≤120 mmHg, (*d*) maximum oxygen uptake ($\dot{V}o_2max$) during cycle ergometry ≤11 mL min^{-1} kg^{-1}, (*e*) central venous oxygen saturation ≤60%, and (*f*) heart rate ≥90 bpm.

Patients with clinically apparent right heart failure were excluded, as were patients with hepatic insufficiency (liver cirrhosis Child stage B or C; liver enzymes exceeding the upper limit of normal more than threefold). Patients classified as World Health Organization (WHO) functional class IV were accepted if lung transplantation was not an option. Patient characteristics are summarized in Table 1.

The study was approved by the local ethics committee and institutional review board. All patients provided written informed consent. The study was designed and conducted in full compliance with the principles of the most recent amendment to the Declaration of Helsinki as well as with the ICH Guideline for Good Clinical Practice E6 from June 1996. It was registered with EudraCT (2006-004224-37).

Intervention

Everolimus was administered at 0.75 mg twice a day for 2 days and was adjusted to serum levels thereafter. Target serum levels were 5–8 ng mL^{-1} and were measured on days 2, 3, and 4 and every 2 weeks thereafter throughout the duration of the study.

Safety assessments

Patients were seen at 2-week intervals. Study visits were used to check for adverse events and request updates for concomitant medication. Blood was an-

Table 1. Patient characteristics at baseline

Patient	Age, years	Gender	Type of PH	First diagnosis, months	Therapy (months)	PAPm, mmHg	CI, L min^{-1} m^{-2}	6MWD, m	NYHA class	NTproBNP, pg mL^{-1}
1	30	Female	IPAH	31	Bosentan (31), inhaled iloprost (24), sildenafil (13)	74	2.43	112	IV	2,094
2	66	Male	CTEPH	75	Bosentan (65), sildenafil (54)	57	1.72	308	III	4,237
3	57	Female	IPAH	10	Sildenafil (9), sitaxsentan (5)	50	2.63	315	III	743
4	56	Female	IPAH	12	Sildenafil (10), sitaxsentan (7)	53	1.66	196	IV	4,693
5	50	Male	IPAH	69	Bosentan (65), sildenafil (13)	31	2.10	260	III	4,470
6	74	Male	IPAH	55	Bosentan (47), inhaled iloprost (39), sildenafil (27)	46	1.96	252	IV	4,014
7	46	Female	IPAH	77	Bosentan (76), inhaled iloprost (50), sildenafil (14)	63	1.42	392	III	2,438
8	39	Male	IPAH	48	Inhaled iloprost (40), sildenafil (37)	53	2.06	362	III	1,133
9	55	Female	IPAH	53	Bosentan (47), sildenafil (27)	69	3.24	212	III	670
10	43	Female	CTEPH	111	Inhaled iloprost (90), bosentan (85), sildenafil (8)	52	1.58	120	IV	9,586

Note: PH: pulmonary hypertension; PAPm: mean pulmonary arterial pressure; CI: cardiac index; 6MWD: 6-minute walk distance; NYHA: New York Heart Association; NTproBNP: N-terminal pro–brain natriuretic peptide; IPAH: idiopathic pulmonary arterial hypertension; CTEPH: chronic thromboembolic pulmonary hypertension.

alyzed for red and white blood cell counts, platelet counts, C-reactive protein, levels of cholesterol and triglyceride, and serum levels of everolimus. Lung function tests and echocardiography were performed at 4-week intervals.

Measurements

Baseline assessment comprised the following: physical examination, including vital signs (blood pressure, heart rate); 6-minute walk test (6MWT); pulmonary function test (PFT); cardiopulmonary exercise test (CPET); echocardiography; right heart catheterization; and blood samples. Thereafter, echocardiography was performed every 14 days, and 6MWTs and PFTs were repeated monthly. The objective of these diagnostics was to detect side effects or clinical worsening at an early stage. After 6 months of treatment with everolimus, additional right heart catheterization and CPET were carried out. Right heart catheterization, 6MWT, and CPET were performed according to standards at our institution and published guidelines.

Changes in 6MWD and PVR after 6 months of therapy compared with baseline were considered coprimary end points. Secondary end points were maximum oxygen uptake during exercise ($\dot{V}o_2max$), serum N-terminal pro–brain natriuretic peptide (NTproBNP) levels, and clinical worsening (hospitalization due to right heart failure, decrease in 6MWD >30%, or change in WHO functional class).

Statistical analysis

The results obtained from this pilot study were evaluated on the basis of a per-protocol analysis. Data were presented as median (interquartile range). The 2-sided distribution-free exact Wilcoxon test was applied for comparison of baseline parameters and parameters after 6 months of therapy with everolimus. Significance was considered at $P \leq 0.05$.

All analyses were performed using SPSS Statistics (ver. 19; IBM). In addition, results of intention-to-treat analysis are listed in the text.

RESULTS

Ten patients were enrolled in this pilot series. One patient (patient 6; Table 1) was hospitalized after 5 months with clinical signs of right heart failure. Study medication was stopped, and diuretic therapy with intravenous furosemide was initiated.

Safety

Of the remaining 9 patients, 1 reported an adverse event (patient 2; Table 1). This patient had severe cough that he interpreted to be related to the study medication and therefore decided to stop the study medication. On examination, an episode of acute bronchitis was diagnosed. The relationship between the study treatment and the onset of acute bronchitis might have been attributed to the immunosuppressive effect of everolimus. No further adverse events occurred.

No patients experienced changes in peripheral blood counts. On average, cholesterol levels rose by 37% (range, 10%–116%). Four patients had an elevated cholesterol level at baseline. After 6 months of treatment with everolimus, the cholesterol levels of 6 patients were above the normal range (mean: 4.54 ± 1.6 mmol L^{-1} at baseline and 5.49 ± 1.1 mmol L^{-1} after 6 months; $P = 0.03$), and an additional 3 patients had increased triglyeceride levels (mean: 1.24 ± 0.7 mmol L^{-1} at baseline and 1.64 ± 0.56 mmol L^{-1} after 6 months; $P = 0.02$).

To achieve predefined serum levels of everolimus (5–8 ng mL^{-1}), an average daily dose of 2.1 mg (range, 0.75–4.5 mg d^{-1}) was administered.

Efficacy outcomes

Eight patients completed 6 months of everolimus therapy. Seven of these 8 patients displayed an improvement in PVR, ranging between 15% and 54%, and 1 patient did not exhibit a change in PVR (Fig. 1). Altogether, we observed a significant improvement in PVR after 6 months of treatment, with a mean decrease of 31% (median [interquartile range], 1,012 [688–1,344] vs. 663 [546–860] dyn s cm^{-5}; $P = 0.016$).

Six of the 8 patients had an increase in 6MWD, ranging between 28 and 240 m (mean increase, 100 ± 66 m). Two patients had a decreased 6MWD (8 and 52 m). Altogether, the average 6MWD increased in patients treated with everolimus; however, the increase was not significant (median [interquartile range], 236 [139–350] vs. 298 [207–450] m; $P = 0.078$; Fig. 1). Accordingly, only 1 of the 2 coprimary end points in terms of efficacy was met in this 10-patient pilot trial.

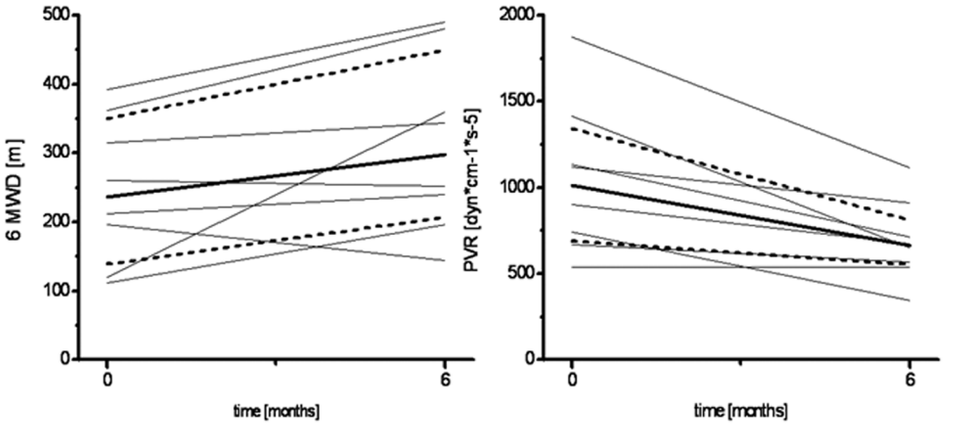

Figure 1. Six-minute walk distance (6MWD) and pulmonary vascular resistance (PVR; $P = 0.016$) at baseline and after 6 months of therapy with everolimus. Each individual patient completing the study is depicted by a separate line (per-protocol analysis; $n = 8$). Thick black lines represent medians, and dashed lines show interquartile ranges.

In addition, among patients who completed the study period, mean pulmonary arterial pressure (PAPm) and cardiac index improved significantly in comparison with baseline after 6 months of therapy with everolimus, whereas right atrial pressure, pulmonary capillary wedge pressure, $\dot{V}o_2max$, workload, and NTproBNP revealed only a trend toward improvement (Table 2).

For the intention-to-treat analysis, patient hemodynamics and parameters of exercise tests of all patients were considered. Improvements in PVR and PAPm after 6 months of treatment with everolimus were still significant using the intention-to-treat approach. The remaining parameters exhibited a trend toward improvement, but significance was not reached (Table 2).

DISCUSSION

In this pilot study, we investigated for the first time the safety and efficacy of the mTOR inhibitor everolimus over a 6-month period in a small group of 10 patients with advanced PH who had been previously unresponsive to standard medication. Everolimus was well tolerated in these patients. One patient (patient 2) dropped out of the study of his own accord following an episode of acute bronchitis.

Table 2. Results of exercise tests and hemodynamic parameters

	Per-protocol analysis			Intention-to-treat analysis		
Parameter	Baseline	6 months	*P*	Baseline	6 months	*P*
Hemodynamics						
PVR, dyn s cm^{-5}	1,012 (688–1,344)	663 (546–860)	0.016	1,065 (725–1,291)	694 (560–961)	0.035
PAPm, mmHg	53 (50.5–67.5)	48.5 (37–61.3)	0.023	53 (49–65)	49 (40–60)	0.012
CI, L min^{-1} m^{-2}	2.08 (1.48–2.58)	2.36 (2.05–2.92)	0.039	2.01 (1.60–2.48)	2.19 (1.87–2.73)	NS
RAP, mmHg	17.0 (8.75–18.75)	9.0 (7.0–21.0)	NS	17 (8–18)	11.0 (8.0–18.0)	NS
PCWP, mmHg	7.0 (5.3–11.0)	9.0 (9.0–11.0)	NS	8.0 (6.9–11.0)	9.0 (8.0–11.0)	NS
CPET						
$\dot{V}o_2max$, mL min^{-1} kg^{-1}	9.9 (7.5–11.8)	10.4 (9.1–11.3)	NS	9.4 (7.8–11.5)	10.4 (7.0–11.3)	NS
Workload, W	51 (43–51)	57 (33–59)	NS	51 (44–51)	56 (35–59)	NS
6MWD, m	236 (139–350)	298 (207–450)	NS	256 (177–327)	266 (183–390)	NS
NTproBNP, pg mL^{-1}	3,417 (1,384–4,637)	1,994 (988–5,541)	NS	4,126 (1,857–4,526)	2,109 (1,235–7,193)	NS

Note: Data are median (interquartile range). PVR: pulmonary vascular resistance; PAPm: mean pulmonary arterial pressure; CI: cardiac index; RAP: right atrial pressure; PCWP: pulmonary capillary wedge pressure; CPET: cardiopulmonary exercise test; $\dot{V}o_2max$: maximum oxygen uptake; 6MWD: 6-minute walk distance; NTproBNP: N-terminal pro–brain natriuretic peptide.

Everolimus is an immunosuppressive agent, and this may increase the risk of infectious events. In a 3-year study in nearly 400 patients receiving everolimus (1.5 or 3 mg d^{-1}) in combination with cyclosporin and steroids, bacterial infections were observed in up to 50% of patients.[23] Although in the present study everolimus was given as the only immunosuppressive drug and this patient experienced bronchitis both before and after the treatment period, a causal relationship between the study drug and this adverse event must be considered. A second patient (patient 6) had to be eliminated from the study group after 5 months of treatment because of progressive right heart failure, one of the safety end points of the trial. It is unlikely that everolimus caused the worsening of right heart function, merely that it was unable to prevent it. Altogether, we observed 2 serious adverse events in 2 of 10 patients over 6 months.

Among the remaining 8 patients, no unexpected side effects were observed. In these patients we found a significant improvement in PVR but only a trend toward improved 6MWD (Table 2).

In our small study population, we observed an improvement in 6MWD and PVR comparable to that in placebo-controlled studies examining the safety and efficacy of imatinib in PAH patients.[12,13] Interestingly, patients in both studies displayed similar hemodynamic impairment, suggesting that everolimus in addition to standard PAH therapy results in improvement comparable to that with imatinib.

Even though our coprimary efficacy end point was not reached, our data may indicate a trend toward an improved outcome and justify a confirmatory trial. Of particular note is the fact that the 2 patients who did not complete the study protocol were older than the other participants of this pilot study: 66 and 74 years versus 47 (mean) and 30–57 (range) years. In addition, with respect to hemodynamics, exercise tolerance, and time since diagnosis, these 2 patients had the most unfavorable prognostic findings. In general—as required by the inclusion criteria—patients in this trial were characterized by an advanced stage of the disease. None of the patients was able to walk >400 m in 6 min at baseline. Therefore, the reduced performance status at baseline indicating advanced PH may in part explain the lack of improvement in workload and $\dot{V}O_2max$ during exercise.

These observations are supported by data from an experimental model of PH in which early treatment with rapamycine was proven to be more effective than late treatment.[15] Proliferation of the layers of the vascular wall has already occurred in advanced PH. Inhibition of proliferation may therefore be a goal to achieve very early in PAH, and thus patients with advanced PAH may not have been an ideal study population for this compound. It might be speculated that treatment with everolimus at an earlier stage of the disease and for longer periods of time would result in greater effects.

The observed increases in cholesterol and triglyceride levels were consistent with those reported for renal transplant patients taking everolimus.[21,23] On the basis of the finding that cardiac and renal transplant recipients with a blood trough level $\geq$3 ng mL^{-1} had a significantly lower incidence of rejection and that the upper limit of therapeutic range had been previously established in those patients at 8 ng mL^{-1}, the target blood trough level of everolimus in our study patients was 5–8 ng mL^{-1}.[13] The dose of everolimus required (2.1 mg d^{-1}, on average) to achieve this target was similar to that required for renal transplant recipients.[21]

The main limitations of our study were the small number of patients and the selection of patients with an advanced stage of PH and a very limited exercise capacity. Nevertheless, the encouraging results of our study suggest that treatment with everolimus in patients with IPAH or CTEPH is safe and tolerable. Furthermore, the improvement of 6MWD and PVR indicate that therapy with everolimus in addition to the established treatment of PH may lead to more favorable outcomes. The results of this exploratory study indicate that an innovative antiproliferative therapeutic approach for the treatment of PH should be examined further. In light of the findings of this pilot study, the effect of everolimus in patients with PH should be investigated in a larger number of patients in a confirmatory trial.

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