World Journal of Cardiology

Online Submissions: http://www.wjgnet.com/1949-8462office
wjc@wjgnet.com
doi:10.4330/wjc.v2.i3.68

World J Cardiol 2010 March 26; 2(3): 68-70
ISSN 1949-8462 (online)

CASE REPORT

Long term combination treatment for severe idiopathic pulmonary arterial hypertension

Flora Affuso, Plinio Cirillo, Antonio Ruvolo, Guido Carlomagno, Serafino Fazio

Flora Affuso, Plinio Cirillo, Antonio Ruvolo, Guido Carlomagno, Serafino Fazio, Department of Internal Medicine, Cardiovascular and Immunologic Sciences, University of Naples Federico II School of Medicine, via S. Pansini 5, 80131 Naples, Italy
Author contributions: Affuso F performed clinical follow-up, analysis of data, manuscript drafting and review; Cirillo P performed right heart catheterization and drafting of the manuscript; Ruvolo A performed FMD and lung function testing, collection and analysis of data; Carlomagno G performed clinical follow-up, echocardiograms, manuscript drafting and review; Fazio S conceived the study, and was involved in the clinical follow-up and final review of manuscript.
Correspondence to: Serafino Fazio, MD, Department of Internal Medicine, Cardiovascular and Immunologic Sciences, University of Naples Federico II School of Medicine, via S. Pansini 5, 80131 Naples, Italy. fazio@unina.it
Telephone: +39-81-7463737 Fax: +39-81-7463737
Received: February 18, 2010 Revised: March 17, 2010
Accepted: March 22, 2010
Published online: March 26, 2010

Abstract

We report the long-term follow-up of 3 cases of severe idiopathic pulmonary arterial hypertension, in whom tadalafil plus sitaxentan combination therapy improved the clinical condition and exercise performance without any relevant adverse event.

Key words: Pulmonary hypertension; Tadalafil; Sitaxentan; Endothelin receptors

Peer reviewers: Dirk Skowasch, MD, Department of Cardiology, University of Bonn, Sigmund-Freud-Str. 25, 53105 Bonn, Germany; Juan C Grignola, PhD, Department of Pathophysiology, Hospital de Clinicas, Facultad de Medicina, Universidad de la República. Avda Italia s/n, Piso 15. Montevideo, PC 11600, Uruguay

Affuso F, Cirillo P, Ruvolo A, Carlomagno G, Fazio S. Long term combination treatment for severe idiopathic pulmonary arterial hypertension. *World J Cardiol* 2010; 2(3): 68-70 Available from: URL: http://www.wjgnet.com/1949-8462/full/v2/i3/68.htm DOI: http://dx.doi.org/10.4330/wjc.v2.i3.68

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a devastating disease with a median life expectancy, without appropriate therapy, of 2.8 years from diagnosis[1]. The better understanding of the pathologic processes responsible for the increase of pulmonary vascular resistance in PAH has led, in the past 10 years, to the development of new oral substances that have significantly improved the prognosis and the quality of life (QoL) of PAH patients[2]. The 3 main mechanisms involved in the pathogenesis of PAH are vasoconstriction, proliferation and remodeling of the pulmonary arteries, and thrombosis. An imbalance among key neurohormonal mediators leads to the progression of the disease. Oral drugs are now available, targeting the different pathways involved in the pathobiology of PAH; it appears therefore likely that a prompt combination approach in the treatment of the disease may result in a synergistic action, with consequent slowing of disease progression and improvement of prognosis. However, the role and exact timing of initiation of multiple drug therapy are still debated.

Tadalafil is a long-acting phosphodiesterase type-5 inhibitor. By increasing the levels of cGMP, the final mediator in the nitric oxide pathway, tadalafil exerts vasodilatatory and antiproliferative effects on pulmonary vascular smooth cells. Although only recently approved in Europe for PAH, tadalafil has proven to improve exercise capacity and QoL in patients[3,4]. Endothelin-1 is a potent endothelium-derived vasoconstrictor peptide endowed with mitogenic properties. Its overexpression in PAH can be counteracted by endothelin receptor antagonists. Sitaxentan is an approved selective endothelin receptor antagonist that is selective for ET_A over ET_B

Table 1 Parameters at baseline (T0), after 1 year of therapy with tadalafil 40 mg/d (T1) and after 6 (T2) and 12 mo (T3) of a combination of tadalafil 40 mg/d plus sitaxentan 100 mg/d

	Patient 1 F (74 yr)				Patient 2 F (44 yr)				Patient 3 F (45 yr)			
RHC PAP S/M/D (mmHg)	97/52/31				95/53/34				116/68/44			
RHC CI (L/min per m^2)	2.25				2.00				2.94			
RHC PVR (WU)	7.8				12.9				11.0			
Timepoint	T0	T1	T2	T3	T0	T1	T2	T3	T0	T1	T2	T3
WHO functional class	Ⅲ-Ⅳ	Ⅲ	Ⅲ	Ⅲ	Ⅲ-Ⅳ	Ⅱ-Ⅲ	Ⅱ-Ⅲ	Ⅳ	Ⅲ	Ⅱ	Ⅰ	Ⅰ
6MWT (m)	251	276	305	330	245	285	311	90	316	456	462	470
Borg score	8	8.5	8	7	5	7	6	9	2	0.5	0	0.5
SF-36	83	89	93	91	82	96	100	n/a	91	107	119	115
PAP (mmHg)	97	94	70	75	110	80	80	75	118	97	60	70
NT-proBNP (pg/mL)	989	951	785	654	2094	1650	1812	2834	503	172	106	102
TLCO-SB (%)	23	41	42	46	60	68	68	n/a	58	74	68	70
VO2max (mL/min per kilogram)	n/a	n/a	n/a	n/a	n/a	10.0	11.1	n/a	10.6	16.8	16.9	15.3
FMD (%)	6.6	7.3	7.6	n/a	6.6	11.2	12.6	n/a	7.35	13.3	14.3	n/a

RHC: Right heart catheterization data at baseline; PAP: Pulmonary artery pressure (systolic/diastolic/mean); CI: Cardiac index; PVR: Pulmonary vascular resistance; WHO: World Health Organization; 6MWT: 6 min walking test; SF-36: Short Form-36 questionnaire; PAP: Doppler estimate of systolic pulmonary arterial pressure; NT-proBNP: N-terminal pro-brain natriuretic peptide; TLCO-SB: Transfer factor of the lung for carbon monoxide; VO2max: Peak oxygen consumption on cardiopulmonary exercise testing; FMD: Flow mediated dilation.

receptors and has about a 6000-fold higher affinity than non-selective endothelin receptor antagonists. It is also associated with a lower incidence of hepatic abnormalities, and with a comparable improvement in the 6-min walking test[5].

As a result of their long half lives, both tadalafil and sitaxentan can be administered once a day. In addition, they are not associated with the pharmacokinetic interactions reported with other combinations of the same drug classes[6].

CASE REPORT

Three patients with severe idiopathic PAH, assessed by right heart catheterization (baseline data shown in Table 1), had been treated for 1 year with tadalafil 40 mg/d. Subsequently, an oral dose of sitaxentan 100 mg was added to the therapy. All patients had negative coronary angiograms and no segmental defects on a lung perfusion scan. While patient 1 had longstanding disease, both patients 2 and 3 had been diagnosed within 1 year of the start of tadalafil therapy.

Clinical status, exercise capacity, QoL, vascular reactivity [measured by flow-mediated dilation (FMD)], diffusion capacity of the lung (DLCO), Doppler PA pressure estimates and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were assessed at baseline (T0), after 1 year of therapy with tadalafil alone (T1), after 6 mo of treatment with a combination of tadalafil plus sitaxentan (T2) and after 12 mo follow-up of combined therapy (T3). Liver function tests and hemoglobin were evaluated monthly. Patients also received supportive therapy, as indicated, including warfarin, digoxin, furosemide, and supplemental O_2. Adverse events were monitored throughout the period.

After 1 year of treatment with tadalafil, the 3 patients showed a clear improvement in their clinical condition, exercise capacity and QoL (Table 1). Subsequently, sitaxentan (100 mg/d) was added to the tadalafil treatment, despite the stable clinical conditions and the improvement of pulmonary pressure. The combination was well tolerated and, after 6 mo, there was an additional improvement in the patients' clinical status, exercise capacity, DLCO, FMD, WHO functional class, QoL, NT-proBNP levels and estimated PA pressure (Table 1). After 12 mo, patient 2 deteriorated to WHO class IV and was promptly started on epoprostenol therapy, with good clinical and hemodynamic response. In this patient, sitaxentan was withheld, while tadalafil therapy was continued. Patient 3 improved further, whereas patient 1 remained stable. No adverse event and no hemoglobin or liver enzyme abnormalities were recorded. As recommended, when initiating sitaxentan**,** doses of warfarin were halved in all 3 patients.

Invasive follow-up of hemodynamics was not performed because of objective and subjective symptomatic improvement and satisfactory Doppler-echocardiographic measurements, in a "clinical strategy" approach. Interestingly, measurements of vascular reactivity by means of FMD correlated well with clinical benefit and changes in NT-proBNP in the 3 subjects.

DISCUSSION

The results obtained in our 3 patients affected by severe idiopathic PAH show that an *ab initio* combination treatment strategy might be effective, well tolerated and safe in the long-term. To our knowledge, only one case series has been published to date on this combination therapy[7]. In fact, the combination of tadalafil and sitaxentan improved QoL and exercise capacity in these patients, and, because of the simple dose schedule, the compliance was very good, and no side effects were recorded.

There is an ongoing debate as to whether to initiate patients with PAH directly on combined therapy or to wait for clinical deterioration. The recent guidelines from the 4th World Conference on Pulmonary Hypertension report that a combinative approach may be proposed only when the clinical response to monotherapy is not adequate[8]. However, clinical studies suggest that delaying the start of therapy may lead to a loss of efficacy with respect to prompt therapy, and, probably, this could be considered particularly true in a combination strategy[9]. We believe that early treatment with a combination of 2 or more drugs, acting on different pathologic pathways at the base of the disease, could prevent or slow the further progression, limiting the costs in terms of clinical worsening; we look forward to the results of large controlled trials exploring this intriguing hypothesis with a more powerful study design.

REFERENCES

1 **D'Alonzo GE**, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med* 1991; **115**: 343-349

2 **Thenappan T**, Shah SJ, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Contemporary survival in patients with pulmonary arterial hypertension: a Reappraisal of the National Institutes of Health Risk Stratification Equation. *Eur Respir J* 2009; Epub ahead of print

3 **Galiè N**, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, Frumkin L, Barst RJ. Tadalafil therapy for pulmonary arterial hypertension. *Circulation* 2009; **119**: 2894-2903

4 **Affuso F**, Palmieri EA, Di Conza P, Guardasole V, Fazio S. Tadalafil improves quality of life and exercise tolerance in idiopathic pulmonary arterial hypertension. *Int J Cardiol* 2006; **108**: 429-431

5 **Barst RJ**, Langleben D, Badesch D, Frost A, Lawrence EC, Shapiro S, Naeije R, Galie N. Treatment of pulmonary arterial hypertension with the selective endothelin-A receptor antagonist sitaxsentan. *J Am Coll Cardiol* 2006; **47**: 2049-2056

6 **Wrishko RE**, Dingemanse J, Yu A, Darstein C, Phillips DL, Mitchell MI. Pharmacokinetic interaction between tadalafil and bosentan in healthy male subjects. *J Clin Pharmacol* 2008; **48**: 610-618

7 **Faruqi S**, Fathi H, Morice AH. Combination of sitaxentan and tadalafil for idiopathic pulmonary arterial hypertension following relapse on bosentan. *Int J Cardiol* 2009; Epub ahead of print

8 **Galiè N**, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, Beghetti M, Corris P, Gaine S, Gibbs JS, Gomez-Sanchez MA, Jondeau G, Klepetko W, Opitz C, Peacock A, Rubin L, Zellweger M, Simonneau G, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, McGregor K, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, Sechtem U, Al Attar N, Andreotti F, Aschermann M, Asteggiano R, Benza R, Berger R, Bonnet D, Delcroix M, Howard L, Kitsiou AN, Lang I, Maggioni A, Nielsen-Kudsk JE, Park M, Perrone-Filardi P, Price S, Domenech MT, Vonk-Noordegraaf A, Zamorano JL. Guidelines for the diagnosis and treatment of pulmonary hypertension: The Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2009; **30**: 2493-2537

9 **McLaughlin VV**, Badesch DB, Delcroix M, Fleming TR, Gaine SP, Galiè N, Gibbs JS, Kim NH, Oudiz RJ, Peacock A, Provencher S, Sitbon O, Tapson VF, Seeger W. End points and clinical trial design in pulmonary arterial hypertension. *J Am Coll Cardiol* 2009; **54**: S97-S107

S- Editor Cheng JX **L- Editor** Cant MR **E- Editor** Zheng XM