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CASE REPORT

Serial evaluation of bosentan monotherapy in a patient with Eisenmenger syndrome during an 11-year period: A case follow-up report

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ABSTRACT
Eisenmenger syndrome is a rare disease primarily characterized by severe degrees of irreversible pulmonary arterial hypertension in the setting of congenital heart disease. In this report, we aim to report, on a yearly basis, the clinical, hemodynamic and echocardiographic parameters of a female patient with Eisenmenger syndrome who had been under bosentan treatment during an 11-year follow-up.

Keywords: bosentan, Eisenmenger syndrome, pulmonary hypertension

ÖZET
Eisenmenger sendromlu bir hastada 11 yıllık dönemde bosentan monoterapisinin seri değerlendirmesi: Olgu takip raporu
Eisenmenger sendromu, konjenital kalp hastalığı ortamında öncelikle geri dönüşümsüz pulmoner arteriyel hipertansiyon ile karakterize nadir bir hastalıktır. Bu raporda, 11 yıllık bir takip sırasında Bosentan tedavisi altında olan Eisenmenger sendromlu bir kadın hastanın yıllık olarak klinik, hemodinamik ve ekokardiyografik parametrelerini bildirmeyi amaçlıyoruz.

Anahtar kelimeler: bosentan, Eisenmenger sendromu, pulmoner hipertansiyon

INTRODUCTION

Eisenmenger syndrome (ES) is a rare disease primarily characterized by severe degrees of irreversible pulmonary arterial hypertension (PAH) in the setting of congenital heart disease (CHD). In this context, PAH invariably ensues as a result of systemic-to-pulmonary shunt, and is largely attributable to chronically elevated pulmonary blood flow and pressure eventually leading to enhanced pulmonary vascular resistance (PVR) along with consequent reversed shunt and systemic hypoxemia [1]. Furthermore, numerous life-threatening complications including cerebrovascular events, hemoptysis, syncope, that are all indicative of a poor quality of life, have been reported in patients with ES [2]. Based on World Health Organization (WHO) classification, ES belongs to group 1 PAH.

Bosentan is an orally active agent that exerts its effects through endothelin A and B receptors (ET-A and ET-B). In other terms, it inhibits endothelin-mediated activation of secondary messenger systems associated with vasoconstriction and smooth muscle cell proliferation. However, it is still unclear how bosentan reduces mortality and morbidity in group 1 PAH patients with Class II-III functional capacity [3]. In the general context, there are limited data regarding the management of patients with ES. Moreover, long-term results of bosentan treatment in this specific condition still remains to be established. In this report, we aim to report, on a yearly basis, the clinical, hemodynamic and echocardiographic parameters of a female patient with ES who had been under bosentan treatment during an 11-year follow-up.

CASE REPORT

Herein, we report a 50-year-old female with ES in whom PAH was initially detected 30 years earlier. In time, she was diagnosed as having ES associated with a ventricular septal defect (VSD) leading to consideration of a PAH-specific treatment. In 2009, vaso-reactivity testing was performed during cardiac catheterization (largely for reimbursement issues of specific PAH therapy), and was found to be non-reactive. Since the patient had been in a good functional status, bosentan monotherapy was deemed as a sufficient therapeutic option. Bosentan was initiated at a dose of 62.5 mg b.i.d at the onset of treatment with subsequent doubling of its dose (125 mg b.i.d) one month later after confirming

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Table 1. Clinical and echocardiographic parameters under bosentan monotherapy during an 11-year follow-up period.

Years	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
SaO_2 (%)	86	88	93	92	90	92	90	89	93	92	90
6 MWT (m)	165	340	400	480	460	450	500	450	460	450	440
Heart rate (min)	110	95	92	96	88	86	92	82	90	96	92
NYHA	III	II	II	II	II	II	II	II	II	II	II
EF (%)	70	66	67	65	68	65	64	68	65	62	59
sPAP (mmHg)	85	90	95	110	100	100	105	110	110	110	115
TAPSE (mm)	23	21	22	20	19	20	18	19	18	17	15
RV (mm)	43	44	47	45	48	46	45	46	48	48	50
RVsV (cm/sec)	-	-	-	-	-	-	11	10	9	10	7
RAA (cm^2)	16	18	17	19	20	20	19	22	20	23	22
RA (mm)	46	45	46	49	47	49	50	52	50	47	50
VCI (mm)	19	16	16	18	17	18	17	17	18	18	19
NT-pro BNP (pg/ml)	-	-	-	-	-	197	221	452	291	328	518
Hemoglobin (g/dl)	16.5	16.1	15.8	16	15.7	16.2	17.3	15.3	15.6	15.4	15.9
ALT (U/L)	23	18	12	10	6	18	23	14	12	14	16
AST (U/L)	37	28	19	15	21	26	22	18	22	23	24
Complications	-	-	-	-	-	-	-	-	-	-	-

SaO_2: Arterial oxygen saturation, 6 MWT: Six minutes walking test, NYHA: New York Heart Association functional class, EF: Ejection fraction, sPAP: Systolic pulmonary arterial pressure, TAPSE: Tricuspid annular plane systolic excursion, RV: Right ventricular diameter, RVsV: Right ventricular systolic velocity, RAA: Right atrium area, RA: Right atrium diameter, VCI: Vena cava inferior diameter, NT-pro BNP: N-terminal B-type natriuretic peptide, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase.

the absence of drug-specific adverse effects. Evaluation of hemogram, liver function and β-HCG tests at baseline and 6 months were performed. Thereafter, she had been under close follow- up with an annual evaluation of her clinical status and associated parameters. Importantly, there had been no deterioration in functional capacity along with no adverse effects of bosentan monotherapy during an 11-year follow-up. As adjunct to bosentan monotherapy, she also received acetyl salicylic acid (ASA) 100mg and ramipril 2.5mg on a daily basis along with initiation of furosemide 40mg daily during short periods of heightened peripheral edema. Of note, serial hemodynamic evaluation was not feasible as she did not consent to further invasive procedures. Table 1 demonstrates clinical, hemodynamic and echocardiographic parameters on a yearly basis during the follow-up period.

All procedures performed conform to the National Research Committee ethical standards, 1964 Helsinki Declaration and subsequent amendments.

DISCUSSION

In patients with ES, promising results have been reported with the use of PAH-specific agents [4, 5]. Among these, bosentan has been the most popular one. However, long-term follow-up results are largely unknown in ES patients under bosentan monotherapy.

As far as the prognostic factors mentioned in the PAH guidelines [4,5] are concerned, the patient did not suffer any syncopal episode, and did not demonstrate any signs of pericardial effusion on imaging. However, it seems noteworthy that echocardiographic parameters including right ventricular (RV) functions, tricuspid annular plane systolic excursion (TAPSE), pulmonary arterial pressure (PAP), status of neurohormonal activation (as measured with natriuretic peptides) worsened on follow-up. In contrast, functional capacity (six minutes walking test, NYHA functional class), hemodynamic parameters as well as oxygen saturation significantly improved in time [4]. In particular, longer follow-up period is needed to determine whether the above-mentioned deteriorations would reach a plateau, and stabilize in the long-term. Nevertheless, subjective findings including functional capacity might be more crucial as compared with other parameters in risk-stratification of patients with ES. Accordingly, the study by Hascoet et al. demonstrated a significant association between functional capacity and rate of adverse events in adult patients with ES managed with specific PAH drugs [6]. This notion also applies to our case who did not suffer any adverse events possibly owing to the temporal improvement of her functional status. Of note, largely owing to the signs of improved quality of life that possibly seems as the most important prognostic marker, maintenance of monotherapy was deemed as a more plausible strategy. In this context, a systematic review by Li, et al suggested bosentan therapy as an efficient and safe option in the relatively early period of ES, and more importantly; as an optimal agent to preserve functional capacity in the long-term [7]. It is well known that ES has been considered as a life-threatening condition necessitating urgent initiation of PAH-specific strategies in an effort to improve overall prognosis. Therefore, bosentan monotherapy seems to be a promising option in the setting of ES, particularly for the stabilization of functional capacity that might also serve as an important prognostic marker in this setting. Importantly, avoiding unnecessary drug combinations

might have possibly obviated potential adverse effects in the patient. This case includes the longest follow-up period of bosentan monotherapy in patients with ES in the literature, and we think that it is important to show that in uncomplicated cases, the treatment can be followed without switching to multiple drug combinations and that drug side effects can be avoided.

Lastly; despite the use of multiple parameters on follow-up, serial hemodynamic evaluation was not feasible, and might be regarded as a potential limitation in the current report.

In this long follow-up report of bosentan monotherapy, we were able to demonstrate significant improvement in functional capacity and systemic arterial oxygen saturation in a patient with ES who had been under bosentan monotherapy during a 11-year period. Importantly, since functional capacity appears to be strongly associated with adverse event rates in patients with ES, bosentan therapy in these patients might have important prognostic implications in the long-term. However, further studies are still needed to establish clinical implications of bosentan monotherapy in patients with ES.

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