

Macitentan in the treatment of pulmonary hypertension in Gaucher's disease

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Introduction

Gaucher's disease (GD) is a rare disease characterized by a lysosomal β glucosidase enzyme deficiency. Although the etiology of pulmonary hypertension in this condition cannot be clearly determined, the disease itself, splenectomy treatment and enzyme treatment are blamed for it. Upon a physiopathological examination, it is emphasized that the vaso-occlusion caused by Gaucher cells may be the mechanism of precapillary pulmonary arterial hypertension (PAH) observed in GD (1). Although the World Health Organization (WHO) classification is similar to Group 1 PAH, PAH due to GH or splenectomy is considered the WHO Group 5.

Macitentan is an orally active agent having effect on the endothelin A (ET-A) and endothelin B (ET-B) receptor. It inhibits the endothelin-mediated activation of second messenger systems resulting in vasoconstriction and smooth muscle cell proliferation. It is unclear how it (Macitentan) benefits from mortality and morbidity in patients with the functional capacity Class II-III in the WHO Group 1 PAH patients (2).

Since it is a very rare condition, there are limited data in the literature regarding the treatment of pulmonary hypertension in patients with GD. Although macitentan, is an effective agent in the WHO Group 1 pulmonary hypertension, it was evaluated whether it would contribute to the treatment of GD.

Case Report

Pulmonary hypertension was first detected 9 years ago in a 44-year-old female patient diagnosed with GD 15 years before. In her history, it was found that the patient receiving the enzyme replacement therapy (imigluserase, 40 IU/kg or 2000 IU/day) had not come to the cardiology follow-up since then and that her pulmonary arterial pressure was found to be 65 mm Hg in her echocardiography some 5 years ago (Table 1).

While the functional capacity was New York Heart Association (NYHA) II until 2 years ago, it reapplied as NYHA III 2 years ago. On physical examination, the blood pressure was 120/75 mm Hg, pulse was 100/min, S2 hard on pulmonary focus and 2/6 systolic murmur on tricuspid focus. There was no pretibial edema and ascites. Electrocardiography showed the sinus rhythm, a

Table 1. Zimran score and follow-up values for 4-year imigluserase treatment

	Pre-treatment	Post-treatment
Leukocytes (4000–10.000/mm ³)	16.400/mm ³	11.480/mm ³
Hemoglobin (12–18 gr/dL)	7.8 gr/dL	13.3 gr/dL
Platelet (150.000–400.000 U/L)	189.000 U/L	218.000 U/L
AST (0–34 U/L)	35 U/L	25 U/L
ALT (0–42 U/L)	12 U/L	12 U/L
ALP (0–125 U/L)	92 U/L	85 U/L
LDH (210–425 U/L)	196 U/L	190 U/L
Creatinine (0.57–1.1 mg/dL)	0.35 mg/dL	0.48 mg/dL
Volume of liver (1500–2500 cm ³)	5370 cm ³	2250 cm ³
Splenectomy	+	+
Bone fractures	-	-
Aseptic necrosis	+	+
Zimran score	20	17
(mild: 0–10, moderate: 10–25, severe: >25)		
Echocardiography		
LVDD (mm)	49 mm	48 mm
LVSD (mm)	29 mm	27 mm
EF (%)	67%	70%
E/A	0.89	0.84
RV (mm)	39 mm	42 mm
RA (mm)	44 mm	46 mm
PAP (mm Hg)	45 mm Hg	65 mm Hg
Pericardial effusion	-	-

AST - aspartate aminotransferase; ALT - alanine aminotransferase; ALP - alkaline phosphatase; LDH - lactate dehydrogenase; LVDD - left ventricular end-diastolic diameter; LVSD - left ventricular end-systolic diameter; EF - ejection fraction; E/A - early diastolic myocardial velocity/late diastolic myocardial velocity; RV - right ventricular diameter; RA - right atrial diameter; PAP - pulmonary arterial pressure

rate 100/min and trigeminal ventricular extrasistole (VES). Echocardiography revealed a normal left ventricular systolic function and type 1 diastolic dysfunction, severe enlargement of the right heart chambers, moderate tricuspid regurgitation, and an estimated pulmonary artery pressure (PAP) of 110 mm Hg. A systolic PAP 97 mm Hg, the mean PAP 68 mm Hg, right ventricular (RV) pressure 105/10 mm Hg, right atrial pressure 17 mm Hg, aortic pressure 120/75 mm Hg, left ventricular systolic pressure/left ventricular end-diastolic pressure 115/10 mm Hg and pulmonary vascular resistance 17.05 wood were detected on cardiac catheterization. The vasoreactivity test was negative. The patient in the PAH WHO Group 5 was decided to be start on macitentan. All procedures performed in our study involving human participants were performed in accordance with the ethical standards of the National Research Committee (Ministry of Health) and the

Table 2. Evaluation results of macitentan pre-treatment, at 6 months and 1 year

	Pre-treatment	6 th month	1 st year
Echocardiography			
LVDD (mm)	48 mm	43 mm	44 mm
LVSD (mm)	33 mm	32 mm	30 mm
EF (%)	53%	60%	62%
E/A	0.82	0.85	0.83
RV (mm)	55 mm	48 mm	46 mm
RA (mm)	60 mm	54 mm	53 mm
TAPSE (mm)	21 mm	24 mm	29 mm
PAP (mm Hg)	95 mm Hg	100 mm Hg	90 mm Hg
Pericardial effusion	-	-	-
Cardiac catheterization			
Systolic/Diastolic PAP (mm Hg)	97/45 mm Hg	91/39 mm Hg	-
Mean PAP (mm Hg)	68 mm Hg	59 mm Hg	-
PCWP (mm Hg)	10 mm Hg	10 mm Hg	-
PVR (wood)	17.05 wood	10.44 wood	-
CO (L/min)	3.4 L/min	4.69 L/min	-
RAP (mm Hg)	25/18 (17) mm Hg	20/9 (10) mm Hg	-
RVP (mm Hg)	105/10 (20) mm Hg	100/10 (18) mm Hg	-
6 min treadmill distance (m)	90 m	450 m	475 m
NT-ProBNP (0-125 pg/mL)	1695 pg/mL	573 pg/mL	347 pg/mL
O ₂ saturation (%)	96%	97%	98%
NYHA class	III	II	II
<small>LVDD - left ventricular end-diastolic diameter; LVSD - left ventricular end-systolic diameter; EF - ejection fraction; E/A - early diastolic myocardial velocity/late diastolic myocardial velocity; RV - right ventricular diameter; RA - right atrium diameter; TAPSE - tricuspid annular plane systolic excursion; PAP - pulmonary arterial pressure; PCWP - pulmonary capillary corner pressure; PVR - pulmonary vascular resistance; CO - cardiac output; RAP - right atrial pressure; RVP - right ventricular pressure; NT-proBNP - N-terminal (NT) prohormone B-type natriuretic peptide; NYHA - New York Heart Association</small>			

1964 Helsinki Declaration and subsequent amendments or comparable ethical standards.

The patient was follow-up in the cardiology clinic (functional capacity, 6 minute treadmill test, echocardiography, laboratory tests and catheterization). At 3 months, 6 minute treadmill test and functional capacity were improved [6 minute treadmill test was 90 meters (m) and oxygen saturation was 96% before treatment]. 3 months 6 minute treadmill test was 450 m and oxygen saturation was 97%. NYHA changed from Class III to Class II. Cardiac catheterization was repeated 6th month following treatment. A mild improvement in hemodynamic data and at least progression was observed. A significant improvement was achieved in functional capacity (Table 2). The treatment was completed after 1 year. In the 1st year, oxygen saturation was found to be 98% with the NYHA Class II and 6-minute treadmill test at 475 m. However, because the patient's consent was not obtained for cardiac catheterization, catheter data could not be obtained in the 1st year and they were evaluated clinically and echocardiographically (Table 2).

Discussion

Type 1 GD is the most common form of the disease. Type 1 GD is also called the adult or non-neuropathic GD where the brain is unaffected. Patients with type 1 GD have an enlarged spleen and liver, anemia, and a low platelet count and they may also experience bone pain and bone deterioration. Symptoms can occur at any age.

The enzyme replacement therapy has been widely used in GD. Good results are obtained without irreversible damage to the signs and symptoms, especially when started early. The best and fastest response was found to be an elevation in hemoglobin (Hb) and platelet (PLT) counts and reduction of organomegaly, but there was no improvement in pulmonary and skeletal findings (3). Our case also had similar clinical outcomes (Table 1).

Previously, in some cases, PAH-specific therapies have been shown as beneficial in PAH in GD, but available data are insufficient to develop a treatment algorithm for these patients (4, 5).

PAH has an increased incidence in these patients, the cause of which is unknown.

A prostacyclin pathway inhibitor epoprostenol has been used intravenous infusions for the treatment of PAH in GD and it has been reported that it may be useful in treatment (6). However, serious side effects associated with the drug delivery system may develop. Therefore, oral drugs may be preferred in terms of both side effects and ease of use.

Macitentan was developed as dual endothelin receptor blockers (ERB) by changing its structure to increase the effectiveness and safety of Bosentan, the first molecule used orally and found in ERB. In a randomized controlled trial, it was shown to reduce the combined endpoint of morbidity and mortality among patients with PAH, to increase the exercise capacity, and to benefit patients who had not previously received treatment or those who received other treatment (7). However, to the best of our knowledge, it has first been reported in our case that it was used in the treatment of PAH in GD. In our case, we observed that macitentan treatment could reverse the progression of PAH and that the patient's functional capacity and 6 minute treadmill test results improved without serious side effects. We also found an improvement in the N-terminal (NT) prohormone B-type natriuretic peptide (NT-proBNP) and tricuspid annular plane systolic excursion (TAPSE) values, proportional to the increase in functional capacity. We think that these parameters should be followed to evaluate the response to treatment.

We believe that the clinical results of macitentan in the treatment of PAH in GD; are due to an activation of the endothelin system and an increase of the plasma level in PAH and suppression of vasoconstrictor and mitogenic effects on pulmonary vascular smooth muscle cells (8, 9).

Conclusion

In conclusion, although the risk of PAH increases in GD, it may lead to both morbidity and mortality. An intermittent echocardiography follow-up in these patients and macitentan treatment after advanced examination in patients with PAH can be used to improve the functional capacity of the patients and to prevent the progression of PAH. Improvement of NT-proBNP

and TAPSE values should be considered during the treatment follow-up.

Informed consent: Informed consent was obtained from all individual participants included in the study.

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