

Change in R wave in lead VI predicts survival of patients with pulmonary arterial hypertension

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Abstract

Clinical guidelines for pulmonary hypertension recommend evaluating treatment response through various methods; however, electrocardiography (ECG) is not included as one of the methods of choice. We aimed to identify ECG parameters that correlated with prognosis in patients with pulmonary arterial hypertension (PAH). A total of 112 consecutive patients with PAH were enrolled in this study. Among them, 83 with treatment escalation were studied for further analysis. Survival analyses were conducted using the Kaplan–Meier method with the log-rank test. Cox proportional hazards regression modeling was used to identify predictors of survival. Receiver operating characteristic analysis was used to determine cut-off values for selected variables. ECG parameters were changed from baseline to three months after treatment. Patients in whom the R wave amplitude in lead VI decreased by ≥ 1 mm (0.1 mV) within three months demonstrated significantly better survival ($P = 0.017$). Our results suggest that evaluation of ECG parameters can contribute to assessments of survival in patients with PAH.

Keywords

pulmonary hypertension, R wave amplitude, survival, treatment

Date received: 16 August 2017; accepted: 22 April 2018

Pulmonary Circulation 2018; 8(2) 1–7

DOI: 10.1177/2045894018776496

Pulmonary arterial hypertension (PAH) is a progressive disease involving elevated pulmonary vascular resistance (PVR) and pulmonary arterial pressure (PAP). Early diagnosis and early intervention with PAH-targeted drugs are recommended in the treatment guidelines.¹ However, the recognition of PAH and evaluation of treatment response can be challenging. The gold standard examination to diagnose pulmonary hypertension (PH) is right heart catheterization (RHC), but this technique is invasive and unsuitable for screening and frequent follow-up. Electrocardiography (ECG) is an essential tool for the diagnosis and treatment of patients with cardiovascular diseases. It is a non-invasive, easy, and inexpensive method that provides valuable information for the diagnosis of various diseases. However, ECG has insufficient sensitivity (55%) and specificity (70%) to serve as a screening tool for detecting PH.¹

In daily clinical practice, we have frequently observed drastic changes in the ECG findings of patients with PAH whose hemodynamics and survival markedly improved after treatment with PAH-targeted drugs (Fig. 1).^{2–4} However, the clinical usefulness of the changes in ECG parameters in patients with PAH with marked improvement in hemodynamics and survival has not been intensively investigated. In this study, we aimed to evaluate changes in ECG parameters and identify ECG parameters that correlate with prognosis in patients with PAH.

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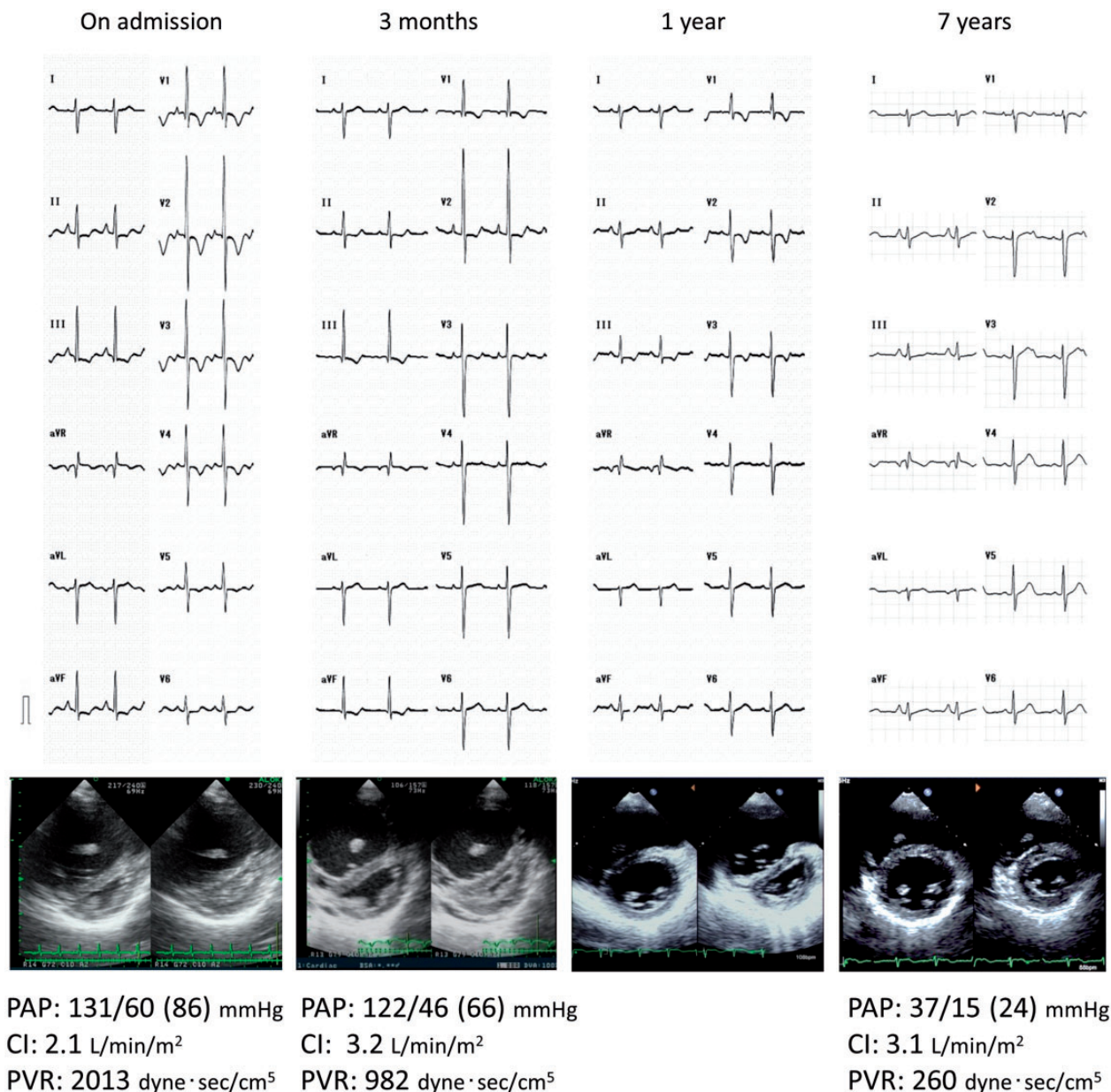


Fig. 1. Change of electrocardiogram parameters in a patient with idiopathic PAH. A representative electrocardiogram (upper panels) recorded before and after introduction of epoprostenol in a patient with idiopathic PAH. Three months after epoprostenol treatment, R wave amplitude in lead VI decreased by 5 mm (16 mm to 11 mm). Echocardiographic images (lower panels) show enlargement of the right ventricle and flattening of the intraventricular septum on admission, which improved with treatment.

Methods

Patient selection

Consecutive patients with PAH who were treated at the National Hospital Organization Okayama Medical Center between May 2003 and November 2011 were enrolled in this study. Patients with idiopathic/heritable PAH and associated PAH (connective tissue disease, congenital heart disease, and portopulmonary hypertension) were included. PH was defined as mean pulmonary artery pressure (mPAP) ≥ 25 mmHg with a pulmonary artery wedge

pressure < 15 mmHg, as determined by RHC.¹ Treatment decisions were comprehensively made by cardiologists based on patients' disease severity and response to treatments, without using any specific treatment algorithm. Baseline demographic and clinical information were collected, including age, sex, World Health Organization (WHO) functional class (FC), 6-min walking distance (6MWD), plasma brain natriuretic peptide (BNP) level, RHC data, ECG parameters, and treatments received. Clinical parameters were evaluated at each patient's initial visit to our hospital and repeatedly after treatment initiation.

Survival rates from initial treatment were also evaluated. The follow-up period for monitoring patient survival ended on 30 June 2016. Disease-related deaths and lung transplantation were counted as events. This study complies with the Declaration of Helsinki. All data were retrospectively collected from chart reviews after approval by the Institutional Review Board of the National Hospital Organization Okayama Medical Center (H24-RINKEN-47).

Standard 12-lead ECG was performed with the patient in the supine position by certified technicians blinded to clinical and hemodynamic data (paper speed = 25 mm/s; sensitivity of 1 mV = 10 mm). The presence of complete right bundle branch block⁵ and right ventricular strain⁶ were determined. Heart rate, QRS axis⁷, QRS wave amplitudes (in leads V1, V6, and I), and ventricular activation time⁸ were measured. Detailed definitions of ECG findings are shown in Table 1.

Statistical analysis

Continuous data were expressed as mean ± standard deviation and categorical data were expressed as count and proportion. Differences between continuous variables were tested using the Student t-test, and differences between categorical variables were tested by the chi-squared or Fisher's exact test. Kaplan–Meier survival curves were used to analyze event rates for disease-related death and lung transplantation. Cox proportional hazards regression modeling was used to identify predictors of survival. Receiver operating characteristic (ROC) analysis was used to determine the cut-off values for selected variables. All analyses were performed with IBM SPSS Statistics 20 software (IBM, Armonk, NY, USA). Statistical significance was defined as $P < 0.05$.

Results

A total of 112 consecutive patients with PAH were enrolled in this study. Among them, we selected patients who

received escalation of treatment after referral. Nineteen patients were being treated using epoprostenol upon referral to our hospital and were excluded from the analysis. Nine patients whose medication regimen with oral PAH-targeted drugs was unchanged after referral were also excluded. One patient was excluded due to missing follow-up ECG data and the remaining 83 patients were studied for further analysis. Approximately half the patients were diagnosed with idiopathic/heritable PAH, followed by patients with connective tissue disease-PAH (Table 2). Most patients were in WHO-FC III or IV. BNP levels and 6MWD suggested impaired exercise capacity. Hemodynamic data demonstrated severe status at baseline with mPAP ~50 mmHg and PVR ~1000 dyne-s/cm⁵. All patients had sinus rhythm. There were four patients with complete right bundle branch block included in the present study. ECG findings at baseline included right axis deviation, high R wave amplitude in V1, and deep S wave amplitude in lead I, which indicate right ventricular hypertrophy and right ventricular expansion. Right ventricular strain in precordial leads was noted.

The patients' clinical features before and three months after treatment at our hospital were also summarized in Table 2. WHO-FC and BNP levels improved. Since 6MWD and RHC were not routinely performed at three months, data for these factors could not be compared. Among ECG parameters, QRS axis, R wave amplitude in lead V1, S wave amplitude in leads I, R/S ratio in V6, ventricular activation time, and right ventricular strain in V2–4 significantly improved.

Two patients underwent lung transplantation and 11 died of PAH-related causes during follow-up. Causes of disease-related deaths were heart failure in five patients, respiratory failure in three patients, and alveolar hemorrhage, multi-organ failure, and renal failure in one patient each. The event-free time of patients was 8.1 ± 3.7 years (95% confidence interval [CI] = 3.2–13.2). We further investigated predictors of survival in patients using a Cox proportional hazards model (Table 3) that included age, sex, WHO-FC, BNP, and change of ECG parameters as variables. Among the variables examined, ΔR wave amplitude in lead V1 is the only parameter which was significantly associated with disease-related deaths in univariate analysis. The absolute values of R wave amplitude in lead V1 at baseline and at follow-up were not related to the prognosis.

We calculated the optimal cut-off value for ΔR wave amplitude in lead V1 to predict survival of patients with PAH using ROC analysis. Analyses revealed that reduction of R wave amplitude in lead V1 ($\Delta V1R$) ≥ 1 mm (0.1 mV) had a sensitivity of 77% and specificity of 63% for predicting survival (area under the curve [AUC] = 0.72; 95% CI = 0.54–0.90). The event-free time of patients with $\Delta V1R \geq 1$ mm was 8.2 ± 3.1 years (95% CI = 2.6–13.2) and significantly better than that of patients with $\Delta V1R < 1$ mm (7.0 ± 4.5 years [95% CI = 3.3–11.0 years]) (log-rank test, $P = 0.017$) (Fig. 2).

Table 1. Definitions of ECG findings.

ECG findings	Diagnostic criteria
CRBBB ⁵	<ul style="list-style-type: none"> • Broad QRS > 120 ms • RSR' pattern in V1–3 • Wide, slurred S wave in the lateral leads (I, aVL, V5–6)
QRS axis ⁷	<ul style="list-style-type: none"> • Direction of the mean QRS vector in the frontal plane
VAT ⁸	<ul style="list-style-type: none"> • Onset of intrinsicoid deflection in V1
Strain ⁶	<ul style="list-style-type: none"> • Down sloping convex ST segment with an inverted asymmetrical T-wave opposite to the QRS axis

CRBBB, complete right bundle branch block; VAT, ventricular activation time.

Table 2. Patient clinical characteristics at baseline and changes of parameters after treatment.

	Before (N = 83)	After 3 months (N = 83)	P value
Age (years)	47.4 ± 14.9		
Male (n (%))	18 (22)		
Etiology (n (%))			
I/HPAH	37 (45)		
CTD-PAH	28 (33)		
CHD-PAH	19 (11)		
PoPH	19 (11)		
WHO-FC, median	III	III	
n (I/II/III/IV)	0/10/53/20	1/42/35/5	<0.001
6MWD (m)	241 ± 174		
BNP (pg/mL)	276 ± 373	119 ± 267	<0.001
Cardiac catheterization data			
mPAP (mmHg)	49.5 ± 19.2		
RAP (mmHg)	7.7 ± 4.7		
CI (L/min/m ²)	3.5 ± 6.6		
PVR (dyne·s/cm ⁵)	961 ± 643		
PAH-specific drug (n (%))			
None	0	0	1.000
ERA	23 (28)	63 (76)	<0.001
PDE5 inhibitor	18 (22)	53 (65)	<0.001
Oral PGI ₂ analogue	25 (30)	21 (25)	0.556
IV epoprostenol	0	45 (54)	<0.001
Dose of epoprostenol (ng/kg/min)	0	25.3 ± 26.1	<0.001
Combination therapy	17 (20)	43 (52)	<0.001
Electrocardiography			
CRBBB (n (%))	4 (5)	4 (5)	1.000
Heart rate (beats/min)	74.2 ± 16.9	77.8 ± 17.7	0.061
QRS axis (°)	92.1 ± 54.1	78.1 ± 52.7	0.001
R amplitude in V1 (mm)	8.5 ± 6.9	5.9 ± 6.0	<0.001
S amplitude in I (mm)	4.9 ± 3.7	3.8 ± 3.4	<0.001
S amplitude in V6 (mm)	5.5 ± 4.6	5.3 ± 5.1	0.642
R/S in V6	2.9 ± 3.8	4.4 ± 4.7	0.007
VAT (ms)	31.4 ± 15.3	35.9 ± 18.9	0.011
Strain in V2 (n (%))	43 (52)	25 (30)	0.001
Strain in V3 (n (%))	37 (45)	21 (25)	0.001
Strain in V4 (n (%))	28 (34)	21 (25)	0.003
Strain in V5 (n (%))	11 (13)	5 (6)	0.065
Strain in V6 (n (%))	1 (1)	1 (1)	1.000
Strain in I (n (%))	0	0	
Strain in II (n (%))	15 (18)	10 (12)	0.302
Strain in aVL (n (%))	0	1 (1)	1.000
Strain in aVF (n (%))	17 (20)	12 (14)	0.267

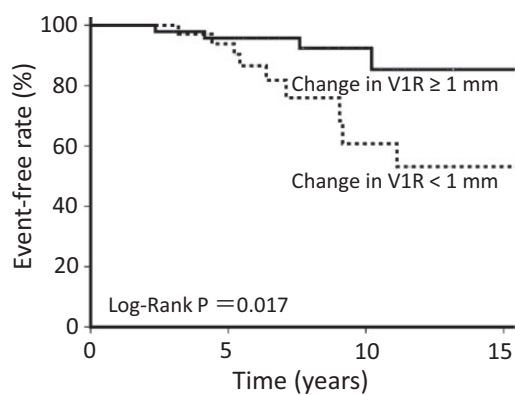
Results are expressed as mean ± SD or n (%) unless otherwise stated.

I/HPAH, idiopathic/heritable pulmonary arterial hypertension; CTD-PAH, pulmonary arterial hypertension associated with connective tissue diseases; CHD-PAH, pulmonary arterial hypertension associated with congenital heart diseases; PoPH, portopulmonary hypertension; WHO-FC, World Health Organization functional class; 6MWD, 6-min walk distance; BNP, brain natriuretic peptide; mPAP, mean pulmonary arterial pressure; RAP, right atrial pressure; CI, cardiac index; PVR, pulmonary vascular resistance; ERA, endothelin receptor antagonist; PDE5, phosphodiesterase type 5; PGI₂, prostaglandin I₂; IV, intravenous; CRBBB, complete right bundle branch block; VAT, ventricular activation time; Strain in V2, existence of Strain T wave in lead V2.

Table 3. Predictors of survival of patients.

Predictor	Univariate		
	HR	95% CI	P value
ΔWHO-FC	0.833	0.561–1.328	0.367
ΔBNP	0.999	0.999–1.000	0.132
ΔHeart rate	0.998	0.982–1.015	0.852
ΔQRS axis	1.003	0.997–1.009	0.322
ΔR in VI	0.948	0.902–0.997	0.037
ΔS in I	1.023	0.891–1.174	0.747
ΔS in V6	0.969	0.919–1.023	0.260
ΔR/S in V6	1.027	0.988–1.068	0.558
ΔVAT	0.968	0.950–1.087	0.639
ΔStrain in V2	1.174	0.703–1.961	0.539
ΔStrain in V3	0.745	0.421–1.318	0.312
ΔStrain in V4	1.329	0.740–2.387	0.340
ΔStrain in V5	0.753	0.374–1.518	0.428
ΔStrain in V6	0.688	0.186–2.548	0.575
ΔStrain in II	0.829	0.446–1.543	0.554
ΔStrain in aVL	0	0	1.000
ΔStrain in aVF	0.873	0.472–1.614	0.665
ΔHeart rate	0.998	0.982–1.015	0.852
R in VI (baseline)	0.976	0.938–1.014	0.216
R in VI (after 3 months)	1.004	0.900–1.004	0.068
CRBBB	1.453	0.443–4.759	0.537

See Table 2 for abbreviations. HR, hazard ratio; ΔWHO-FC, change of WHO functional class before and after treatment; ΔR in VI, change of R wave amplitude in lead VI before and after treatment; Δ Strain in V2, change of existence of strain T wave in lead V2 before and after treatment.



No. at risk				
Change in V1R ≥ 1 mm	49	42	14	1
Change in V1R < 1 mm	34	28	8	2

Fig. 2. Kaplan–Meier analyses of event-free rate of patients. Patients with a change of R wave amplitude in lead VI ≥ 1 mm at three months after treatment showed significantly better survival than those with a change of R wave amplitude in lead VI < 1 mm (log-rank test, $P=0.017$).

Discussion

We treated severely ill patients with idiopathic/heritable PAH and reported significant improvement in hemodynamics and survival.^{2,3} We commonly observed changes in ECG parameters after successful treatment leading to reduced PAP (Fig. 1). In the present study, we focused on those patients who received intensive treatment with PAH-targeted drugs and evaluated the ECG changes after treatment escalation. Reliable and feasible evaluation tools are necessary to confirm whether patient status improved after the initiation or escalation of treatment. RHC, the gold standard for evaluating hemodynamic parameters, cannot realistically be performed frequently in patients with PAH. Many investigations endeavored to find alternative markers for treatment. While the 6MWD had been considered as powerful biomarker in PAH, it is now considered inadequate for predicting patients' long-term survival.⁹ Many investigations have also explored the use of echocardiography as an alternative evaluation method, but this method is time-consuming and is technique-dependent. Furthermore, the reliability of echocardiographic data has been questioned.¹⁰ In contrast, ECG is easy to perform, non-invasive, available at any hospital, can be performed by physicians who are not cardiologists, and carries a low associated cost. For these reasons, ECG may be an attractive modality for monitoring patients.

Electrocardiographic examination in patients with PH characteristically shows evidence of right ventricular hypertrophy and right atrial enlargement, i.e. large P wave in lead II, right axis deviation, and tall R waves and ST depression in the right-sided chest leads.^{11,12} Another report revealed that 87% of patients met electrocardiographic criteria for right ventricular hypertrophy and 79% demonstrated right axis deviation.¹³ ECG may provide suggestive or supportive evidence of PH, but ECG alone is not sufficiently sensitive for excluding the presence of PH even in high-risk populations with connective tissue diseases¹⁴ or in patients with severe hemodynamic abnormalities.¹⁵ Only a few of the recommended ECG criteria for predicting right ventricular hypertrophy and dilation proved to be useful in patients under treatment.¹⁶ In our patients, ECG findings at the initial visit included high R wave amplitude in V1 and deep S wave amplitude in lead I, which are consistent with previous studies.^{17,18} Furthermore, right axis deviation and right ventricular strain pattern in precordial leads were noted. These parameters were previously reported to have important roles in practicing PAH. Right axis deviation is the only parameter which is important for determining the probability of PH in patients with systemic sclerosis.¹⁹ Right ventricular strain pattern was reported to differentially diagnose precapillary PH from post-capillary PH.²⁰

ECG parameters are reportedly linked to the hemodynamic state of PAH^{21,22} and ECG changes demonstrate a relationship with changes in hemodynamic state and configurations.²³ However, there are limited data on the association between ECG changes and treatment response in PAH. P wave amplitude in lead II or presence of a P wave

amplitude in lead II of <0.175 mV in combination with a T axis of $>25^\circ$ were reportedly useful for monitoring treatment response.^{24,25} Another study comparing ECG characteristics at initial diagnosis and close to the time of death revealed that heart rate, PR interval, QRS duration, R/S ratio in lead V1, and QTc duration significantly increased from the initial to final ECG.²⁶ However, there are no investigations exploring the characteristic changes in ECG parameters after successful treatment with PAH.

This study revealed the potential value of ECG parameters for the prediction of survival in patients with PAH. Specifically, reduction of R wave amplitude in lead V1 by ≥ 1 mm after three months of treatment was related to better survival. In a previous report by Bossone et al., increased P wave amplitude or presence of qR in lead V1 at baseline were identified as predictors of decreased survival in 51 patients with idiopathic PAH.²⁷ The discrepancy of data may be attributed to the difference in disease entity. Furthermore, they evaluated baseline ECG data only. This study focused on the change of ECG parameters to reflect the improvement of patient status, which can be changed by recently advanced PAH treatment.

This study has several limitations. This is a retrospective, single-center study with a relatively small sample size. We cannot exclude selection bias due to the nature of the study design. Furthermore, because the purpose of the present study was to find ECG parameters in following patients with PAH, most of the well-known prognostic parameters other than ECG parameters (6MWD, hemodynamic parameters, echocardiography, and cardiopulmonary exercise test) were not investigated in the current study and whether ECG parameters have more power in predicting survival or not has not been determined. Moreover, right ventricular structural changes over time have not been assessed. Therefore, the pathomechanisms underlying observed ECG changes remain unclear.

In conclusion, this study aimed to find an ECG parameter to reflect patients' improvement with treatment and revealed the potential value of ECG parameters for the prediction of survival in patients with PAH. Specifically, reduction of R wave amplitude in lead V1 by ≥ 1 mm after three months of treatment was related to better survival. Careful observation of ECG parameters and their changes may lead to better recognition of patient status and response to treatment. Because ECG is non-invasive and can be performed repeatedly after the initiation of treatment, ECG parameters may be useful biomarkers in treating PAH.

Conflict of interest

The author(s) declare the following potential conflicts of interest: AO has received lecture fees from Actelion Pharmaceuticals Japan Ltd., GlaxoSmithKline KK, Nippon Shinyaku Co. Ltd., and Pfizer Japan Inc. HM has received lecture fees from Actelion Pharmaceuticals Japan Ltd., AOP Orphan Pharmaceuticals AG, Bayer Yakuhin Ltd., GlaxoSmithKline KK, Nippon Shinyaku Co. Ltd., and Pfizer Japan Inc.

Funding

This work was partly supported by the Practical Research Project for Rare/Intractable Diseases from Japan Agency for Medical Research and Development (no. 27280401).

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