Effect of Sarpogrelate, a 5-HT<sub>2A</sub> Antagonist, on Platelet Aggregation in Patients with Ischemic Stroke: Clinical-Pharmacological Dose-Response Study

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Key Words
Antiplatelet therapy · Platelet aggregation · Ischemic stroke · Stroke prevention · Sarpogrelate · Serotonin

Abstract

**Background and Purpose:** It is widely accepted that antiplatelet therapy is effective for secondary prevention of atherosclerotic vascular diseases. We performed a double-blind, controlled clinical-pharmacological study to investigate the antiplatelet efficacy of sarpogrelate, a selective 5-hydroxytryptamine (5-HT<sub>2A</sub>) receptor antagonist, in patients with ischemic stroke, using a new assessment system employing combinations of 5-HT and epinephrine as agonists. **Methods:** Forty-seven patients with ischemic stroke were randomly assigned to three groups: 15 patients received 25 mg sarpogrelate (group L), 16 patients received 50 mg (group M), and 15 patients received 100 mg (group H) orally, three times daily for 7 days. The effect was expressed as maximum intensity of platelet aggregation on the last day of medication. Two combinations of agonists, 0.5 μmol/l 5-HT plus 3 μmol/l epinephrine, and 1 μmol/l 5-HT plus 3 μmol/l epinephrine, were used to induce platelet aggregation. **Results:** With both combinations of agonists, sarpogrelate treatment inhibited platelet aggregation dose-dependently (p < 0.025, Wilcoxon rank-sum test). **Conclusion:** Sarpogrelate treatment inhibited platelet aggregation dose-dependently in patients with ischemic stroke, as judged by a new assessment system employing combinations of 5-HT and epinephrine as agonists.

Introduction

Platelet activation plays an important role in the pathogenesis of atherothrombosis [1–5]. Platelets are activated in vivo by various agonists, such as thromboxane A<sub>2</sub>, ADP, and serotonin (5-hydroxytryptamine; 5-HT), and antiplatelet therapy has been developed to block the metabolic or activation pathway related to each of these agonists, with good clinical outcomes in preventing vascular events [6–12]. For instance, aspirin, the first-line antiplatelet agent generally used throughout the world [13], reduces the risk of vascular events by inhibiting the production of thromboxane A<sub>2</sub> [6–10].

Recently, a number of reports have pointed out the importance of 5-HT in the pathogenesis of atherothrombosis [14–17]. 5-HT induces platelet activation, and 5-HT released from intracellular storage sites in activated platelets stimulates smooth muscle cell proliferation with vascular contraction, potentiating thrombus formation and
vessel occlusion [18]. Furthermore, the finding that plasma 5-HT concentration is higher in patients with coronary artery diseases, diabetes mellitus, stroke and other disorders [14, 16, 19, 20] provides another line of clinical evidence that 5-HT is deeply involved in the development of atherothrombosis. It has been postulated that liberation of 5-HT from nerve terminals, as well as from platelets, results in a local increase in 5-HT concentration [16].

All the findings described above suggest that the 5-HT receptor could be a good target for antiplatelet and antithrombotic therapy. Thus, sarpogrelate \[(\pm)-2-(dimethylamino)-1-[[o-(m-methoxyphenethyl) phenoxyl]methyl] ethyl hydrogen succinate hydrochloride\], a selective 5-HT\(_{2A}\) receptor antagonist, has been developed as an inhibitor of platelet aggregation and vasoconstriction induced by 5-HT [18, 21–23]. It has been reported that extracellular release of 5-HT and P-selectin from platelets is associated with platelet aggregation, and these responses were suppressed by sarpogrelate in platelet-rich plasma (PRP) from healthy volunteers [24].

However, 5-HT alone is a mild platelet agonist which only induces shape change and reversible aggregation, and this renders the evaluation of its inhibitors extremely difficult if 5-HT alone is used to activate platelets [25]. Recently, a new method for monitoring the effects of sarpogrelate has been described [26], and here we describe its application to evaluate the relationship between dosage of sarpogrelate and inhibition of platelet aggregation in patients with ischemic stroke.

**Methods**

**Study Design**

This randomized, double-blinded, intergroup comparison trial was conducted at 5 centers and was approved by the ethics review board at each institution in accordance with the Helsinki Declaration. Patients were enrolled between April 2004 and January 2005 after having given their written informed consent.

The primary endpoint was the inhibitory effect on platelet aggregation in patients with ischemic stroke.

Major inclusion criteria included: (1) ischemic stroke except cardioembolic stroke, based on the NINDS-III classification [27], with focal signs lasting >24 h, (2) defined onset of symptoms, and stable condition at the time of enrollment, (3) age >20 years, (4) systolic blood pressure <180 mm Hg and diastolic blood pressure <110 mm Hg, and (5) maximum intensity of platelet aggregation induced by serotonin (1 \(\mu\)mol/l) and epinephrine (3 \(\mu\)mol/l) above 15% on the day prior to the first medication.

Major exclusion criteria included: (1) modified Rankin Scale (mRS) score of 4 or more, (2) previous or planned vascular surgery, (3) history of intracranial hemorrhage, systemic bleeding, or other bleeding tendency or coagulopathy, (4) and serious complications such as cardiac, renal, hepatic, and blood disorders.

A wash-out period prior to study medication was given to patients who had been receiving antiplatelet agents, anticoagulants or fibrinolytic agents that were expected to affect the efficacy assessment, and these antithrombotic treatments were withheld during the study. For ethical reasons, the wash-out periods were set at the minimum required based on the duration of action of each antithrombotic treatment (e.g. aspirin, ticlopidine hydrochloride; 240 h [10 days], cilostazol; 48 h [2 days], sodium ozagrel, sarpogrelate; 24 h [1 day]). Moreover, we did not limit the use of drugs for the management of other risk factors of recurrence of stroke (e.g. antihypertensives, antidiabetics and antihyperlipidemics).

A limitation of this study is that it could not judge the relative efficacy of sarpogrelate to aspirin. At the planning stage of this study, we had confirmed that aspirin does not inhibit 5-HT-mediated platelet aggregation induced by the agonists that we used (data not shown), so that we could not include an aspirin control group.

**Procedures**

**Treatment**

Each patient was randomly allocated to one of three dosages of sarpogrelate, i.e. 25 mg (group L), 75 mg (group M), or 100 mg (group H), given three times daily for 7 days.

**Measurement of Platelet Aggregation**

Fasting blood samples were drawn on day 0, before the start of treatment, and on day 7 after treatment. Samples were drawn at fixed times (08:00 to 11:30 h, 90 min after administration of sarpogrelate). Platelet-rich plasma (PRP) anticoagulated with 0.1 mg/ml argatroban [28] was prepared and the platelet count in samples of PRP was adjusted to 2 \(\times\) 10\(^{11}\)/l.

Platelet aggregation measurements were performed using a platelet aggregation analyzer (PA-20, KOWA, Japan), as previously described [26]. Briefly, aggregation was induced with two dosage combinations of agonists: 0.5 \(\mu\)mol/l 5-HT plus 3 \(\mu\)mol/l epinephrine (low-dose agonist) and 1 \(\mu\)mol/l 5-HT plus 3 \(\mu\)mol/l epinephrine (high-dose agonist). Results were expressed both as maximum intensity of platelet aggregation on the last day of the medication and as post-treatment percentage inhibition of platelet aggregation at baseline ([baseline – post-treatment]/baseline \(\times\) 100 in each subject). Measurements of platelet aggregation are known to vary depending upon various factors, particularly inducers, and also analytical devices and techniques. In the present study, all reagents and devices were used under identical conditions throughout. In addition, analytical techniques were carefully standardized with the aid of a training program and a standard operating procedure. Platelet aggregation was thus determined under strict control.

**Statistical Analysis**

All measurements of platelet aggregation were run in duplicate for each patient at each point. Data are shown as mean \(\pm\) SD, and as box and whiskers plots.
Efficacy was evaluated on the per-protocol-set basis, whereas safety analysis was performed on all randomized patients. For baseline characteristics of enrolled patients, comparisons between treatment groups were made with Fisher’s exact test or the Kruskal-Wallis test for heterogeneity of variance, and the criterion of significance was set at \( p < 0.15 \) (two-tailed). The Jonckheere test was used to test for dose-response relationship, and the Wilcoxon rank-sum test was used to conduct multiple-group comparison, with the criterion of significance set at \( p < 0.025 \) (one-tailed). Statistical comparisons of safety data were made using the chi-square test, with the criterion of significance set at \( p < 0.05 \) (two-tailed).

**Results**

Forty-seven patients were enrolled and randomly assigned to three groups (L, M, and H). Of these patients, 2 were excluded from the efficacy analysis; 1 (group H) withdrew due to recurrent cerebral infarction and the other (group L) took a medication affecting coagulation during the study.

Baseline characteristics of randomized patients who were included in the efficacy analysis are summarized in

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sarpogrelate group L (n = 14)</th>
<th>group M (n = 16)</th>
<th>group H (n = 15)</th>
<th>Statistical probability value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>62 (9)</td>
<td>67 (9)</td>
<td>70 (8)</td>
<td>0.0340 KW</td>
</tr>
<tr>
<td>Men/women</td>
<td>12/2</td>
<td>10/6</td>
<td>9/6</td>
<td>0.2849 Fi</td>
</tr>
<tr>
<td>Mean (SD) body weight, kg</td>
<td>62.1 (9.7)</td>
<td>61.1 (15.6)</td>
<td>58.4 (8.5)</td>
<td>0.5516 KW</td>
</tr>
<tr>
<td>History, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10 (71.4)</td>
<td>10 (62.5)</td>
<td>11 (73.3)</td>
<td>0.8498 Fi</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>6 (42.9)</td>
<td>4 (25.0)</td>
<td>6 (40.0)</td>
<td>0.5391 Fi</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4 (8.6)</td>
<td>4 (25.0)</td>
<td>4 (26.7)</td>
<td>1.0000 Fi</td>
</tr>
<tr>
<td>Prior ischemic stroke (before qualifying event)</td>
<td>1 (7.1)</td>
<td>1 (6.3)</td>
<td>3 (20.0)</td>
<td>0.5002 Fi</td>
</tr>
<tr>
<td>Mean (SD) duration from the onset of ischemic stroke to medication, days</td>
<td>12.9 (3.6)</td>
<td>17.4 (6.8)</td>
<td>19.6 (12.0)</td>
<td>0.0449 KW</td>
</tr>
<tr>
<td>NINDS classification, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>6 (42.9)</td>
<td>9 (56.3)</td>
<td>5 (33.3)</td>
<td>0.4772 Fi</td>
</tr>
<tr>
<td>Lacunar</td>
<td>6 (42.9)</td>
<td>7 (43.8)</td>
<td>9 (60.0)</td>
<td>0.1999 Fi</td>
</tr>
<tr>
<td>Undetermined</td>
<td>2 (14.3)</td>
<td>0 (0.0)</td>
<td>1 (6.7)</td>
<td></td>
</tr>
<tr>
<td>Arterial system involved, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Internal carotid artery</td>
<td>0 (0.0)</td>
<td>2 (12.5)</td>
<td>0 (0.0)</td>
<td>0.3192 Fi</td>
</tr>
<tr>
<td>Verteobasilar artery</td>
<td>4 (28.6)</td>
<td>6 (37.5)</td>
<td>3 (20.0)</td>
<td>0.6008 Fi</td>
</tr>
<tr>
<td>Anterior cerebral artery</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (6.7)</td>
<td>0.6444 Fi</td>
</tr>
<tr>
<td>Middle cerebral artery</td>
<td>10 (71.4)</td>
<td>8 (50.0)</td>
<td>11 (73.3)</td>
<td>0.3386 Fi</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Size of infarct, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small (diameter &lt;1.5 cm)</td>
<td>7 (50.0)</td>
<td>13 (81.3)</td>
<td>10 (66.7)</td>
<td>0.1999 Fi</td>
</tr>
<tr>
<td>Medium</td>
<td>7 (50.0)</td>
<td>3 (18.8)</td>
<td>5 (33.3)</td>
<td>0.0449 KW</td>
</tr>
<tr>
<td>Large (&gt;1/2 of lobe)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>Modified Rankin scale at randomization, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>3 (21.4)</td>
<td>1 (6.3)</td>
<td>0 (0.0)</td>
<td>0.3018 Fi</td>
</tr>
<tr>
<td>1</td>
<td>5 (35.7)</td>
<td>7 (43.8)</td>
<td>10 (66.7)</td>
<td>0.8440 KW</td>
</tr>
<tr>
<td>2</td>
<td>5 (35.7)</td>
<td>4 (25.0)</td>
<td>4 (26.7)</td>
<td>0.2814 KW</td>
</tr>
<tr>
<td>3</td>
<td>1 (7.1)</td>
<td>4 (25.0)</td>
<td>1 (6.7)</td>
<td>0.0999 Fi</td>
</tr>
<tr>
<td>Mean (SD) blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>138.1 (9.4)</td>
<td>137.9 (14.1)</td>
<td>138.7 (12.1)</td>
<td>0.8440 KW</td>
</tr>
<tr>
<td>Diastolic</td>
<td>84.9 (8.8)</td>
<td>79.6 (12.0)</td>
<td>78.8 (9.0)</td>
<td>0.2814 KW</td>
</tr>
<tr>
<td>Abnormal electrocardiogram, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0 (0.0)</td>
<td>4 (25.0)</td>
<td>4 (26.7)</td>
<td>0.0999 Fi</td>
</tr>
<tr>
<td>Mean (SD) maximum platelet aggregation prior to medication (%) induced by 1 μmol/l 5-HT plus 3 μmol/l epinephrine</td>
<td>52.57 (20.72)</td>
<td>47.78 (14.50)</td>
<td>46.60 (18.19)</td>
<td>0.6519 KW</td>
</tr>
</tbody>
</table>

* KW = Kruskal-Wallis test; Fi = Fisher’s exact test.
An adjusted analysis (analysis of variance) was performed with background factors of patients for which heterogeneity of variance ($p < 0.15$) was found among groups (age, time from onset to study medication, abnormal findings on standard ECG) as covariates, and no effect was found on the efficacy results (maximum intensity of platelet aggregation [%]).

Antithrombotic therapy was performed in 34 patients (11 patients in group L, 11 patients in group M, and 12 patients in group H). Specifically, sodium ozagrel was used in 25 patients, sarpogrelate in 6, cilostazol in 2, and ticlopidine hydrochloride in 1 patient, and all of these patients had conformed to the required wash-out periods (sodium ozagrel and sarpogrelate: 24 h; cilostazol: 48 h; ticlopidine hydrochloride: 10 days). The longest drug-free period was 10 days in 1 patient (treated with ticlopidine hydrochloride). The physician in charge of this patient considered it ethically acceptable to suspend the antiplatelet agent because (1) the antiplatelet drug was discontinued 48 days after the onset of ischemic stroke, when this patient was in the chronic stage, with a stable platelet activation status, and (2) antihypertensive and antihyperlipidemic drugs were being used to manage risk factors for recurrence.

**Primary Endpoint**

The results are shown in figure 1. Values of maximum intensities of platelet aggregation induced by low-dose agonist and by high-dose agonist on the last day of medication are shown in figures 1a and b, respectively. The maximum intensities of platelet aggregation were 30.57 ± 17.76 (group L), 28.09 ± 14.96 (group M), and 14.67 ± 6.41 (group H) with low-dose agonist, and 51.36 ± 22.71 (group L), 46.78 ± 15.10 (group M), and 29.67 ± 12.25 (group H) with high-dose agonist. Clear dose-response relationships were observed (low-dose agonist, $p = 0.0006$; high-dose agonist, $p = 0.0020$; Jonckheere test) (fig. 1a, b).

Values of post-treatment percentage inhibition of baseline platelet aggregation induced by low-dose agonist and by high-dose agonist are as follows. The values of percentage inhibition of platelet aggregation were 3.61 ± 35.33 (group L), 12.56 ± 29.97 (group M), and 43.04 ± 26.39 (group H) with low-dose agonist, and $-2.29 ±$
30.94 (group L), −0.50 ± 26.72 (group M), and 30.19 ± 28.79 (group H) with high-dose agonist. Again, clear dose-response relationships were obtained (low-dose agonist, p = 0.0008; high-dose agonist, p = 0.0014; Jonckheere test).

In multiple-group comparisons, significant differences were found between groups L and H, as well as between groups M and H (p < 0.025; Wilcoxon rank-sum test) (fig. 1a, b).

Safety
There were 27 adverse events in 16 patients, and no difference in frequency was apparent among the groups; 7 events in 5 patients in group L, 9 in 5 patients in group M, and 11 in 6 patients in group H. Bleeding complications occurred in 2 patients (group H, day 8 at study completion): specifically, positive urinary occult blood (from 1+ prior to treatment to 2+ after treatment in 1 patient, and from − (minus) prior to treatment to 1+ after treatment in another patient). Both complications of microscopic hematuria disappeared within 1 month without treatment. There were three serious adverse events in 2 patients. These were an episode of cerebral infarction (group H, day 3 during treatment), paroxysmal atrial fibrillation and fever of unidentified cause (group L, day 2), and from − (minus) prior to treatment to 1+ after treatment in another patient). Both complications of microscopic hematuria disappeared within 1 month without treatment. There were three serious adverse events in 2 patients. These were an episode of cerebral infarction (group H, day 3 during treatment), paroxysmal atrial fibrillation and fever of unidentified cause (group L, day 2 after treatment); none of these events were considered to be related to the study medication.

Discussion
Sarpogrelate has been proven effective for the treatment of peripheral artery diseases (PAD) [29], and its clinical potential has been suggested for the treatment of atherosclerotic cardiovascular disease and diabetes mellitus [15, 30, 31]. A double-blind, randomized controlled trial has been conducted to evaluate and compare the efficacy and safety of sarpogrelate with those of aspirin for prevention of recurrence in 1,510 patients with recent ischemic stroke [32]. Sarpogrelate did not meet a pre-defined criterion of noninferiority to aspirin for efficacy against recurrence of cerebral infarction, because the recurrence rates of cerebral infarction were 72 (6.09% per year) with sarpogrelate and 58 (4.86% per year) with aspirin (hazard ratio 1.25 [95% CI 0.89–1.77], p = 0.19). However, the effects on serious vascular events including stroke, acute coronary syndrome, or vascular event-related death were comparable, i.e., 90 (7.61% per year) with sarpogrelate and 85 (7.12% per year) with aspirin (hazard ratio 1.07 [95% CI 0.80–1.44], p = 0.65), and sarpogrelate was better tolerated than aspirin, with significantly fewer bleeding events (11.9% with sarpogrelate and 17.3% with aspirin [p = 0.004]). This favorable feature of a lower rate of bleeding complications may open up a number of therapeutic options for sarpogrelate, e.g. as an alternative to aspirin in aspirin-resistant or aspirin-intolerable patients, or in combination with aspirin.

In order to ensure best efficacy of antiplatelet therapy, it is most desirable to evaluate whether an antiplatelet agent actually inhibits the platelet function of a particular individual ex vivo. This concept has attracted the attention of a number of clinicians, particularly because of the presence of ‘aspirin resistance’ in 10–40% of patients under aspirin therapy [10, 33, 34]; patients with aspirin resistance have higher rates of vascular accidents if not properly treated with other regimens. Analogously, it is desirable to monitor the efficacy of sarpogrelate in order to obtain information as to appropriate dose, compliance and the presence of ‘sarpogrelate resistance’, if it exists. Therefore, we consider it clinically useful to establish methods for evaluation of sarpogrelate as an antiplatelet agent.

To examine the clinical effect of sarpogrelate, a specific antagonist for 5-HT₂ₐ, it is essential to evaluate its effect on platelet aggregation induced by 5-HT. However, since 5-HT alone is a mild platelet agonist which only induces shape change and reversible aggregation, it is difficult to assess the effects of its inhibitors if 5-HT alone is used to activate platelets [25]. 5-HT synergistically amplifies platelet aggregation induced by ADP, collagen, or epinephrine, and thus the effects of 5-HT receptor antagonists have been conventionally evaluated by using the combination of 5-HT with a low concentration of a platelet agonist such as collagen, which by itself does not induce platelet aggregation [22]. However, as platelet responses to low concentrations of agonists differ considerably among individuals, the threshold concentration of the agonist (e.g. collagen) has to be determined separately for each platelet preparation. The whole process is invariably time-consuming, and it also suffers frequent criticism concerning the use of different doses of agonists among individuals for evaluation of the inhibitory effects of a particular agent.

In the present study, we used a new method for assessment of platelet aggregation, based on combined stimulation with 5-HT and epinephrine [26]. Epinephrine is a physiological platelet agonist, which induces platelet aggregation in platelet-rich plasma (PRP) anticoagulated with sodium citrate, a system conventionally and widely used to assess platelet aggregation; sodium citrate is
known to lower Ca$^{2+}$ concentration, thereby inhibiting the coagulation process. However, it is of interest that in the presence of the physiological concentration of Ca$^{2+}$, epinephrine does not induce the formation of platelet aggregates, although it does potentiate platelet responses [35]. The new assessment method takes advantage of this phenomenon that epinephrine alone even at high concentrations does not induce the formation of platelet aggregates at the physiological Ca$^{2+}$ concentration. Argatroban (0.1 mg/ml), a synthetic thrombin inhibitor which is unaffected by Ca$^{2+}$ concentration, was used instead of sodium citrate as an anticoagulant for PRP preparation.

In this system, 5-HT or epinephrine alone did not induce platelet aggregation even at the highest concentration examined (100 μmol/l epinephrine, or 100 μmol/l 5-HT) [26], whereas the use of the combined agonists invariably induced full platelet aggregation, irrespective of individual differences in relevant factors. A preliminary study in healthy volunteers showed that stable platelet aggregation was induced by the combination of 0.5 or 1 μmol/l 5-HT and 3 μmol/l epinephrine [unpubl. data], and thus, we chose these combinations of stimuli as agonists in the present study.

Using the same protocol for the measurement of platelet aggregation in the hands of different technicians in 5 centers, consistent inhibitory effects of sarpogrelate on platelet aggregation in 45 patients with ischemic stroke were observed. These findings demonstrate that the new assessment method can be used to monitor the effect of sarpogrelate under ex vivo conditions in the clinical setting, and that the system permits valid inter-laboratory comparisons of the antiplatelet efficacy of sarpogrelate.

Our results revealed a dose-dependent inhibitory effect of sarpogrelate on platelet aggregation in patients with ischemic stroke; the efficacy of the total dose of sarpogrelate 300 mg/day is significantly superior to that of 150 or 75 mg/day. This dosage is consistent with the recommended dosage of sarpogrelate in clinical practice [29, 32].

In conclusion, we confirmed that sarpogrelate shows a dose-dependent inhibitory effect on platelet aggregation in patients with ischemic stroke, using a new assessment method. This observation may account for the observed clinical benefit of sarpogrelate in patients with cerebrovascular disease, and provides support for sarpogrelate as a therapeutic option in patients with atherosclerotic vascular disease.

Appendix

The following persons and institutions participated in the present study: J. Nakagawara, Nakamura Memorial Hospital, Hokkaido; A. Suzuki, Research Institute for Brain and Blood Vessels Akita, Akita; T. Katsumata, Nippon Medical School Hospital, Tokyo; K. Kashihara, Okayama Kyokuto Hospital, Okayama; K. Fukuyama, Fukuoka Wajiro Hospital, Fukuoka.

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