OBSERVATIONS

Cilostazol Attenuates Spontaneous Microaggregation of Platelets in Type 2 Diabetic Patients With Insufficient Platelet Response to Aspirin

Prevention of cardiovascular disease is an important therapeutic goal in patients with type 2 diabetes mellitus (1). Although a low dose of aspirin is recommended for this purpose, some patients were resistant to aspirin (2). We previously reported that spontaneous microaggregation of platelets (SMAPs) formed under no stimulation with exogenous agonists were frequently observed in type 2 diabetic patients (3,4) and a considerable number of patients receiving aspirin still showed SMAP formation (4). The aim of the current study was to investigate whether a switch from aspirin to another antiplatelet drug could improve an insufficient platelet response to aspirin in diabetic patients.

This was an open-label, single-arm, uncontrolled trial of antiplatelet treatment with 200 mg cilostazol daily (a phosphodiesterase III inhibitor) as an alternative to aspirin in 24 Japanese type 2 diabetic patients who persistently showed the inadequate SMAP formation despite treatment with a low dose of aspirin (22 patients with 100 mg aspirin daily and 2 with 81 mg aspirin daily) for at least 1 year. Patients receiving antiplatelet drugs other than aspirin were excluded. Assessments included the changes in SMAP formation as well as platelet expression of active glycoprotein IIb/IIIa and P-selectin at 2 months compared with baseline. These were measured as previously described (4). After ethics committee approval, written informed consent was obtained from all participants.

Twenty-three of 24 patients (65% men; mean age 71 years and mean HbA_{1c} 7.6% [60 mmol/mol]) completed the study. There was no significant difference in clinical parameters comparing the baseline time point with the 2-month time point. As shown in Fig. 1, the degree of SMAP formation was significantly reduced after changing from aspirin to cilostazol (0.32 [interquartile range 0.15–0.48] at baseline, 0.13 [0.00–0.26] at 1 month, and 0.11 [0.00–0.22] at 2 months, $P = 0.001$ by the Friedman test]. This inhibitory effect by cilostazol was observed at 1 month compared with baseline, and this difference persisted at the 2-month time point. At 2 months after the administration of cilostazol, 17 patients (74%) showed a reduction in SMAP formation of >50% compared with baseline. Further, SMAP formation completely disappeared in seven of these patients.

Platelet expression levels of glycoprotein IIb/IIIa (31.7% [interquartile range 14.5–43.3] vs. 12.3% [4.4–17.3], $P < 0.001$) and P-selectin (10.4% [6.0–21.7] vs. 6.6% [2.7–9.7], $P = 0.002$) were also significantly lower at the 2-month time point compared with baseline. Adverse events (headache and palpitations) occurred in two patients, one of whom discontinued the study. No major bleeding events occurred.

This study demonstrated that antiplatelet therapy with cilostazol significantly attenuated SMAP formation and platelet activation in type 2 diabetic patients who had an insufficient platelet response to aspirin. These observations suggest that individualized tailoring of antiplatelet therapy is important for achievement of the desired biologic and clinical effect in diabetic patients. A large-scale, double-blind trial is warranted to confirm these observations.

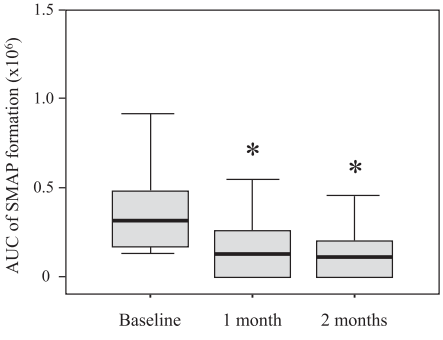

Figure 1—*Box-and-whisker plots of the SMAP formation assessed by area under the curve (AUC) over 5 min in diabetic patients at baseline, at 1 month, and at 2 months after the initiation of cilostazol. In these plots, lines within the boxes represent median values; the* upper *and* lower lines *of the boxes represent the 25th and 75th percentiles, respectively; and the* upper *and* lower bars *outside the boxes represent the 90th and 10th percentiles, respectively. Comparisons between two groups were performed by the Wilcoxon signed rank test with Bonferroni correction* (*$P < 0.017$ *vs. baseline).*

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DOI: 10.2337/dc12-2702

Acknowledgments—This study was supported by the Mitsui Life Social Welfare Foundation and by grants-in-aid for Science Research (C) (grant 24591323).

No potential conflicts of interest relevant to this article were reported.

S.-i.A. designed the study protocol, researched data, and wrote the manuscript. H.M. researched data and contributed to discussion. M.H. and D.K. contributed to discussion. Y.K., S.K., K.I., H.A., S.U., and H.K. researched data. A.K., T.U., and H.M. designed the study protocol, contributed to discussion, and reviewed and edited the manuscript. S.-i.A. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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