Brief Reports

Factors Contributing to the Clinical Effectiveness of the DPP-4 Inhibitor Sitagliptin in Patients With Type 2 Diabetes

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ABSTRACT

Purpose: Treatment with dipeptidyl peptidase 4 (DPP-4) inhibitors may have responders or nonresponders. However, agreement on the effects of patient background and/or contributory factors that have a negative effect on the efficacy of DPP-4 inhibitors is lacking. The aim of the present study was to investigate the effect of resistance factors on the clinical efficacy of sitagliptin (SITA) for patients with type 2 diabetes.

Methods: We performed a retrospective study based on the medical records of patients who were treated with SITA alone (SITA-A; $n = 16$), a combination of a sulfonylurea (SU) without a change in dose and add-on SITA (SU + SITA; $n = 29$), SITA alone after the discontinuation of premedication with antidiabetic agents (SITA-AD; $n = 18$), or a combination of an SU with a dose reduction and SITA (L-SU + SITA; $n = 17$). Multivariate logistic regression analysis was employed to estimate the influence of resistance factors on hemoglobin (Hb) A_{1c} lowering by SITA treatment for 3 months.

Findings: The HbA_{1c} levels were significantly lower after 3-month treatment with SITA-A (6.3% [0.2%]), SU + SITA (7.1% [0.2%]), and L-SU + SITA (6.6% [0.2%]), but not with SITA-AD (6.3% [0.2%]), than baseline levels before treatment. Multivariate logistic regression analysis established that a decreased efficacy of SITA was markedly related to baseline HbA_{1c} levels of $\geq$7.5% and dyslipidemia.

Implications: These results suggest that checking for the presence or absence of resistance factors, including elevated HbA_{1c} levels and dyslipidemia, may contribute to the appropriate usage of SITA.

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Key words: DPP-4 inhibitors, sitagliptin, sulfonylureas, type 2 diabetes mellitus.

INTRODUCTION

Dipeptidyl peptidase 4 (DPP-4) inhibitors are a new generation of oral antidiabetic agents for type 2 diabetes patients. DPP-4 inhibitors promote insulin secretion and suppress glucagon release via increased activity of incretin hormones, including glucagon-like peptide 1 and gastric inhibitory polypeptide, secreted from the intestines.[1,2] The characteristic effect of DPP-4 inhibitors involves the acceleration of insulin secretion after meals in a blood glucose–dependent manner, causing a reduction in the risks for hypoglycemia, iatrogenic hyperinsulinemia, and/or weight gain.[3,4] Furthermore, DPP-4 inhibitors have been reported to have pleiotropic and beneficial effects on pancreatic β-cell and α-cell turnover in neonatal rats and in mice with streptozotocin-induced diabetes,[5,6] suggesting the prevention of development of type 2 diabetes.

The DPP-4 inhibitors, including sitagliptin (SITA), vildagliptin, linagliptin, alogliptin, teneligliptin, axagliptin, anagliptin, and trelagliptin, have been used in type 2 diabetes treatment in Japan. It has been reported that the hemoglobin (Hb) A_{1c}–lowering effect of DPP-4 inhibitors in Asian patients with type 2 diabetes is greater than

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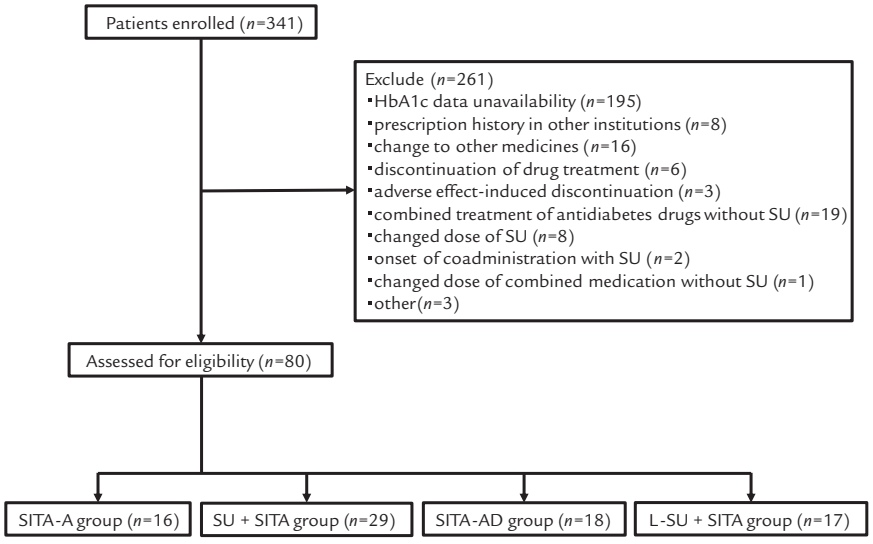

Figure 1. CONSORT diagram. HbA_{1c} = hemoglobin A_{1c}; L-SU = sulfonylurea at a lowered dose; SITA-A = sitagliptin alone; SITA-AD = sitagliptin alone after the discontinuation of antidiabetic agents; SU = sulfonylurea.

in other ethnic groups.[7] The clinical efficacy of SITA (50 mg/d or 24 weeks) in Japanese patients with type 2 diabetes, who predominantly have impaired insulin secretion and reduced β-cell function, has been reported to be closely related to higher baseline HbA_1c, lower body mass index, and a shorter diabetes duration, suggesting that there may be responders and nonresponders to treatment with DPP-4 inhibitors.[8–10] However, there is currently no agreement about the details of patient background and/or contributing factors that may have a negative effect on the efficacy of DPP-4 inhibitors.

Therefore, we retrospectively investigated whether there are contributing factors to the clinical effectiveness of SITA in patients with type 2 diabetes, and we examined the proper usage of this DPP-4 inhibitor.

PATIENTS AND METHODS

Patients

This retrospective, observational study was conducted at Ehime University Hospital (Shitsukawa, Japan) using data from patients' medical records. A total of 341 patients newly treated with SITA between March 1, 2010, and February 29, 2012, were screened. Subsequently, 261 were excluded owing to a lack of HbA_{1c} data (n = 195), prescription history located in other institutions (n = 8), change to other medicines (n = 16), discontinuation of drug treatment (n = 6), discontinuation due to adverse events (n = 3), combined treatment with antidiabetic medications without a sulfonylurea (SU) (n = 19), changed dose of an SU (n = 8), initiation of coadministration with an SU (n = 2), changed dose of combined medication without an SU (n = 1), or "other" reasons (n = 3) (Figure 1).

To evaluate the effect of the administration method on HbA_{1c} lowering after SITA treatment, the 80 remaining patients were assigned to 1 of 4 groups: (1) treatment with SITA monotherapy without antidiabetic medication history (SITA-A; n = 16); (2) combination treatment with an SU without a change in dose and add-on SITA (SU + SITA; n = 29); (3) discontinuation of pretreatment with antidiabetic medications, and newly started SITA monotherapy (SITA-AD; n = 18); and (4) combined treatment with an SU at a decreased dose and add-on SITA (L-SU + SITA; n = 17). The presence of a prescription for an antidyslipidemic or antihypertensive medication at baseline was used for identifying dyslipidemia or hypertension, respectively, at baseline.

A further analysis was carried out to assess the effects of potential contributing factors on the clinical effectiveness of SITA in the 80 patients, who