Response

Diabetes Metab J 2015;39:446-447
http://dx.doi.org/10.4093/dmj.2015.39.5.446
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Predictive Factors for Efficacy of Dipeptidyl Peptidase-4 Inhibitors in Patients with Type 2 Diabetes Mellitus (*Diabetes Metab J* 2015;39:342-7)

Shusuke Yagi[1], Ken-ichi Aihara[2], Masataka Sata[1]

Departments of [1]Cardiovascular Medicine, [2]Hematology, Endocrinology and Metabolism, Institute of Biomedical Sciences, Tokushima University Graduate School, Tokushima, Japan

We appreciate Dr. Ye An Kim's comments on our study entitled "Predictive factors for efficacy of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus," which was published in the *Diabetes and Metabolism Journal* [1].

In this retrospective study, we showed that the predictive factors of dipeptidyl peptidase-4 (DPP-4) inhibitors lowering the glycosylated hemoglobin (HbA1c) level after 12 months in patients with type 2 diabetes mellitus included a decrease in the HbA1c level after 3 months of treatment, high baseline HbA1c level, low baseline body mass index, and the absence of coronary artery disease, suggesting that the most suitable candidates for treatment with DPP-4 inhibitors are diabetics who are not obese and do not have coronary artery disease. In addition, the long-term efficacy of DPP-4 inhibitors can be predicted by decrements of HbA1c after 3 months of treatment.

First, in our study, the physicians evaluated patients from multiple aspects, including physical activity, cognitive function, and stability of cardiovascular disease, considering the risk of hypoglycemia, after which they set the individual treatment goals and prescribed DPP-4 inhibitors. A majority of patients had already been treated with other anti-diabetic drugs, including α-glucosidase inhibitors, sulfonylureas, biguanides, glinides, and thiazolidinediones. DPP-4 inhibitors are associated with a relatively low risk of hypoglycemia and are weight-neutral [2,3], whereas dose increments of the baseline drugs are associated with various side effects, especially for old patients (e.g., diarrhea for α-glucosidase inhibitors, weight gain for sulfonylureas, and thiazolidinediones). Therefore, for these patients, additional DPP-4 inhibitor administration instead of dose increments of the baseline drugs was chosen, expecting further glycemic effects with less side effects.

Second, there may be substantial synergistic or heterogeneous responses to combination therapy with other anti-diabetic drugs [4]. We reanalyzed the data to elucidate this issue. Stepwise multiple regression analysis showed that co-administration of glinides or sulfonylureas, which are insulin secretagogues, with DPP-4 inhibitors affected the magnitude of decrease in the HbA1c level after 12 months; however, co-administration of α-glucosidase inhibitors, biguanides, or thiazolidinediones did not lead to any statistically significant effects, indicating that combination therapy with stimulators of insulin secretion and DPP-4 inhibitors shows more synergistic effects on lowering HbA1c.

Third, a novel finding of this study was that the absence of coronary artery disease itself was one of the predictors of DPP-4 inhibitor efficacy. As several studies have shown, shorter history of diabetes may be a predictor of greater reduction in HbA1c after treatment with DPP-4 inhibitors [5]; however, in our retrospective study, we were unfortunately not able to ob-

Corresponding author: Shusuke Yagi
Department of Cardiovascular Medicine, Institute of Biomedical Sciences, Tokushima University Graduate School, 3-18-15 Kuramoto-cho, Tokushima 770-8503, Japan
E-mail: syagi@tokushima-u.ac.jp

tain reliable data concerning the duration of diabetes. Further prospective studies are needed to clarify the effects of DPP-4 inhibitors and the duration of diabetes.

Lastly, as Dr. Kim pointed out, identifying the predictive factors with reference to the baseline HbA1c could be interesting when considering the individual responses to DPP-4 inhibitors. The baseline HbA1c may be regulated by multiple factors, including lifestyle-related factors and the administered drugs. Due to the small sample size, we were not able to identify the predictive factors with reference to the baseline HbA1c, and further studies are necessary to elucidate such predictive factors.

We appreciate Dr. Kim for the interest in our study and for the valuable comments and suggestions.

CONFLICTS OF INTEREST

M. Sata has received research funding from Takeda, Tanabe-Mitsubishi, Astellas, Daiichi-Sankyo, MSD, Byer Healthcare, and Ono, and lecture fees from Takeda, Boehringer Ingelheim, Byer Healthcare, Mochida, Astellas, Tanabe-Mitsubishi, Novartis, AstraZeneca, MSD, and Shionogi. The Department of Cardio-Diabetes Medicine, Tokushima University Graduate School, is supported in part by unrestricted research grants from Boehringer Ingelheim, Tanabe-Mitsubishi, Kowa, and Actelion. The others declare no conflict of interest.

REFERENCES

1. Yagi S, Aihara K, Akaike M, Fukuda D, Salim HM, Ishida M, Matsuura T, Ise T, Yamaguchi K, Iwase T, Yamada H, Soeki T, Wakatsuki T, Shimabukuro M, Matsumoto T, Sata M. Predictive factors for efficacy of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus. Diabetes Metab J 2015;39:342-7.
2. Paolisso G, Monami M, Marfella R, Rizzo MR, Mannucci E. Dipeptidyl peptidase-4 inhibitors in the elderly: more benefits or risks? Adv Ther 2012;29:218-33.
3. Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev 2008;(2):CD006739.
4. Boland CL, Degeeter M, Nuzum DS, Tzefos M. Evaluating second-line treatment options for type 2 diabetes: focus on secondary effects of GLP-1 agonists and DPP-4 inhibitors. Ann Pharmacother 2013;47:490-505.
5. Nomiyama T, Akehi Y, Takenoshita H, Nagaishi R, Terawaki Y, Nagasako H, Kudo T, Kodera T, Kobayashi K, Urata H, Yanase T; CHAT. Contributing factors related to efficacy of the dipeptidyl peptidase-4 inhibitor sitagliptin in Japanese patients with type 2 diabetes. Diabetes Res Clin Pract 2012;95:e27-8.