Letter

Diabetes Metab J 2015;39:444-445
http://dx.doi.org/10.4093/dmj.2015.39.5.444
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)

Ye An Kim

Department of Internal Medicine, Seoul National University Hospital Healthcare System Gangnam Center, Seoul, Korea

Dipeptidyl peptidase-4 (DPP-4) inhibitor is one of the widely used diabetic medications these days. In clinical practice, some patients respond more effectively to this drug and show better glycemic improvement. Several studies [1-4] analyzed the predictors of response to DPP-4 inhibitors, however the results were somewhat inconsistent. The discrepancy might be due to the different definition of efficacy predictors and heterogeneity of study population.

In this article entitled "Predictive factors for efficacy of dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes mellitus," Yagi et al. [5] evaluated the predictive factors for the efficacy of DPP-4 inhibitors based on the change of glycosylated hemoglobin (HbA1c) after 12 months of treatment. They described the predictors to be a decrease in HbA1c level after 3 months of treatment, a high baseline HbA1c level, a low baseline body mass index, and no history of coronary artery disease (CAD). This article is interesting, especially in that the long-term effects of DPP-4 inhibitors on glycemic control could be predicted by the short term response, which might make it easier to identify the good responders to DPP-4 inhibitors. Although there are some clinical significances, some points need to be clarified.

First, the criteria for DPP-4 inhibitor add-on therapy needs to be clarified better in this study. The study patients aged 68.3±35.8 years old, and baseline HbA1c were 7.5%±1.3%. Initially, 36.6% of patients already had HbA1c <7% when DPP-4 inhibitors are added on. Considering that the patients were relatively old with mild elevated HbA1c level, the reason for additional DPP-4 inhibitors might be helpful to understand and validate the efficacy of DPP-4 inhibitors. In addition, a majority of patients have already been treated with other anti-diabetic drugs. Forty-four percent of patients used α-glucosidase inhibitors, 32.5% for sulfonylurea, and 15.2% for biguanides. In these patients, the reason for additional DPP-4 inhibitor instead of the dose increment of baseline drugs could be informative.

Second, combination therapy of other anti-diabetic drugs might affect glucose metabolism and exert confounding effects. A previous study has reported that combination treatment of alogliptin and voglibose increased plasma active glucagon-like peptide-1 (GLP-1) levels and pancreatic insulin content synergistically in db/db mice [6]. Another study showed that a combination of miglitol and sitagliptin effectively attenuate postprandial hyperglycemia with various patterns of insulin, glucagon, and GLP-1 release, suggesting that individual hormone-related glycemic responses to the DPP-4 inhibitors and α-glucosidase inhibitor are complex and multifactorial [7]. Synergistic effect of sulfonylurea and DPP-4 inhibitor has been suggested, because some patients showed dramatic glycemic improvement after this combination therapy [8]. Sulfonylurea added to DPP-4 inhibitor might potentiate insulin secretion by activating exchange protein activated by cyclic AMP 2 (Epac2) [9]. There are substantial synergistic or

Corresponding author: Ye An Kim
Department of Internal Medicine, Seoul National University Hospital Healthcare System Gangnam Center, 152 Teheran-ro, Gangnam-gu, Seoul 06236, Korea
E-mail: yeanin@gmail.com

heterogenous responses to combination therapy of DPP-4 inhibitor with other anti-diabetic drugs. Analyzing the patients with similar baseline anti-diabetic drugs could be more appropriate to evaluate the predictive factors for the efficacy of DPP-4 inhibitors.

Third, duration of diabetes is one of the substantial predictors for the response to DPP-4 inhibitors. Several studies have shown that shorter duration of diabetes is associated with greater reduction in HbA1c after DPP-4 inhibitor add-on [1-3]. Further information including duration of diabetes could support the interesting findings in this study. In addition, incidence rate of CAD increases with longer duration of diabetes [10]. As shown in this study, absence of CAD itself could be one of the predictors of DPP-4 inhibitor response, otherwise, shorter duration of diabetes might be the unrevealed connection link of good response for DPP-4 inhibitors.

Lastly, the authors evaluated the predictive factors based on the change of HbA1c after 12 months of treatment. Baseline HbA1c, however, is an important factor that affects the change of glycemic control [4]. In this study, as baseline HbA1c was high, the change of HbA1c would also appear to be more significant. Identifying the predictive factors with reference to the baseline HbA1c could be more interesting if individual responses to DPP-4 inhibitors were considered. Based on the results of this study, short-term follow-up studies with a large patient population are warranted to investigate the predictors of DPP-4 inhibitor response.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. 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.
2. Lim S, An JH, Shin H, Khang AR, Lee Y, Ahn HY, Yoon JW, Kang SM, Choi SH, Cho YM, Park KS, Jang HC. Factors predicting therapeutic efficacy of combination treatment with sitagliptin and metformin in type 2 diabetic patients: the COSMETIC study. Clin Endocrinol (Oxf) 2012;77:215-23.
3. Kim WJ, Park CY, Jeong EH, Seo JY, Seol JS, Park SE, Rhee EJ, Lee WY, Oh KW, Park SW, Kim SW. Retrospective analysis on the efficacy, safety and treatment failure group of sitagliptin for mean 10-month duration. Diabetes Metab J 2011;35:290-7.
4. Esposito K, Chiodini P, Maiorino MI, Capuano A, Cozzolino D, Petrizzo M, Bellastella G, Giugliano D. A nomogram to estimate the HbA1c response to different DPP-4 inhibitors in type 2 diabetes: a systematic review and meta-analysis of 98 trials with 24 163 patients. BMJ Open 2015;5:e005892.
5. 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.
6. Moritoh Y, Takeuchi K, Hazama M. Combination treatment with alogliptin and voglibose increases active GLP-1 circulation, prevents the development of diabetes and preserves pancreatic beta-cells in prediabetic db/db mice. Diabetes Obes Metab 2010;12:224-33.
7. Kishimoto M, Noda M. A pilot study of the efficacy of miglitol and sitagliptin for type 2 diabetes with a continuous glucose monitoring system and incretin-related markers. Cardiovasc Diabetol 2011;10:115.
8. Hirao K, Maeda H, Shirabe S, Yamamoto R, Hirao T, Hirao S, Yamauchi M, Arai K. Combination therapy with a dipeptidyl peptidase-4 inhibitor, sulfonylurea, and metformin markedly improves HbA1c levels in Japanese patients with type 2 diabetes mellitus. Jpn Clin Med 2012;3:1-7.
9. Zhang CL, Katoh M, Shibasaki T, Minami K, Sunaga Y, Takahashi H, Yokoi N, Iwasaki M, Miki T, Seino S. The cAMP sensor Epac2 is a direct target of antidiabetic sulfonylurea drugs. Science 2009;325:607-10.
10. Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. JAMA Intern Med 2014;174:251-8.