Letter

Diabetes Metab J 2019;43:911-912
https://doi.org/10.4093/dmj.2019.0207
pISSN 2233-6079 · eISSN 2233-6087

dmj
DIABETES & METABOLISM JOURNAL

Dipeptidyl Peptidase-4 Inhibitors versus Other Antidiabetic Drugs Added to Metformin Monotherapy in Diabetic Retinopathy Progression: A Real World-Based Cohort Study (*Diabetes Metab J* 2019;43:640-8)

Jun Sung Moon

Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

For over a decade since its launch, dipeptidyl peptidase-4 (DPP-4) inhibitors have shown great glycemic efficacy, and some drugs have proved cardiovascular safety in large prospective clinical trials. DPP-4 inhibitors are attractive in that they can be prescribed for a wide range of patients due to their low risk of side effects, such as low hypoglycemia risk and neutral effect in weight gain in clinical practice [1]. Therefore, the use of DPP-4 inhibitors has increased dramatically and is now widely used as the add-on therapeutic option in patients that are inadequately controlled with metformin in Korea [2].

Based on experimental and preclinical studies, DPP-4 inhibition was expected to play a role in protecting vascular complications beyond glycemic control [3]. However, controversies and concerns still exist regarding the safety of DPP-4 inhibitors, especially in diabetic retinopathy. DPP-4 inhibitors not only increase glucagon-like peptide-1 concentrations but also chemokines such as stromal cell-derived factor 1α (SDF-1α), which is closely related with angiogenesis and neovascularization. In murine models, a DPP-4 inhibitor aggravated diabetic retinopathy by increasing vascular permeability through SDF-1α/C-X-C chemokine receptor type 4 (CXCR4)/Src/vascular endothelial (VE)-cadherin signaling pathway [4].

In this issue, Chung et al. [5] demonstrate the effects of DPP-4 inhibitors as add-on therapy to metformin on the progression of diabetic retinopathy in real-world setting. They compared DPP-4 inhibitors with sulfonylurea or thiazolidinedione using national database, and DPP-4 inhibitors showed greater benefit than sulfonylurea on diabetic retinopathy progression regardless of comorbidities, duration of metformin use, intravitreal injections and calendar index year (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.66 to 0.97). Although the changes were statistically insignificant after adjustment including fasting blood glucose levels in subgroup analysis (HR, 0.89; 95% CI, 0.64 to 1.24; P=0.493), DPP-4 inhibitors did not aggravate diabetic retinopathy progression. These results are consistent with a prior study [6] based on the same database (but different enroll period and design), so DPP-4 inhibitors do not seem to aggravate the progression of diabetic retinopathy. From a clinician's perspective, these evidence supports that the use of DPP-4 inhibitors and does not violate the principle of '*Primum non nocere*'. However, there are some factors to be considered before hasty conclusions are made.

First of all, the lack of critical risk factors, as the authors commented, does not strongly guarantee the safety of DPP-4 inhibitors in this study. Since higher glycosylated hemoglobin and longer duration of diabetes were undeniable risk factors for the progression of retinopathy, careful interpretation is required when comparing safety among drugs. Recent studies

Corresponding author: Jun Sung Moon https://orcid.org/0000-0003-1569-3068
Department of Internal Medicine, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
E-mail: mjs7912@yu.ac.kr

conducted in Korea showed that the average time from diagnosis to first panretinal photocoagulation is over 17 years, and one-third of patients with over 15 years of disease duration were free from diabetic retinopathy [7,8].

Second, the lesson to be learnt from the clinical trials is that the safety of each DPP-4 inhibitors could be different between drugs in the same class [9], so more detailed analysis might be needed to determine the class effect of DPP-4 inhibitors. In addition, there is still no specific antidiabetic agent class showing protective effects against the progression of diabetes. Thus, further long-term and large prospective cohort studies would clarify whether a specific class has protective effects beyond the glucose-lowering effect.

CONFLICTS OF INTEREST

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

REFERENCES

1. Kim MK, Ko SH, Kim BY, Kang ES, Noh J, Kim SK, Park SO, Hur KY, Chon S, Moon MK, Kim NH, Kim SY, Rhee SY, Lee KW, Kim JH, Rhee EJ, Chun S, Yu SH, Kim DJ, Kwon HS, Park KS; Committee of Clinical Practice Guidelines, Korean Diabetes Association. 2019 Clinical practice guidelines for type 2 diabetes mellitus in Korea. Diabetes Metab J 2019;43:398-406.
2. Ko SH, Han K, Lee YH, Noh J, Park CY, Kim DJ, Jung CH, Lee KU, Ko KS; Task Force Team for the Diabetes Fact Sheet of the Korean Diabetes Association. Past and current status of adult type 2 diabetes mellitus management in Korea: a National Health Insurance Service Database Analysis. Diabetes Metab J 2018;42:93-100.
3. Avogaro A, Fadini GP. The effects of dipeptidyl peptidase-4 inhibition on microvascular diabetes complications. Diabetes Care 2014;37:2884-94.
4. Lee CS, Kim YG, Cho HJ, Park J, Jeong H, Lee SE, Lee SP, Kang HJ, Kim HS. Dipeptidyl peptidase-4 inhibitor increases vascular leakage in retina through VE-cadherin phosphorylation. Sci Rep 2016;6:29393.
5. Chung YR, Ha KH, Kim HC, Park SJ, Lee K, Kim DJ. Dipeptidyl peptidase-4 inhibitors versus other antidiabetic drugs added to metformin monotherapy in diabetic retinopathy progression: a real world-based cohort study. Diabetes Metab J 2019;43:640-8.
6. Kim NH, Choi J, Kim NH, Choi KM, Baik SH, Lee J, Kim SG. Dipeptidyl peptidase-4 inhibitor use and risk of diabetic retinopathy: a population-based study. Diabetes Metab 2018;44:361-7.
7. Yun JS, Lim TS, Cha SA, Ahn YB, Song KH, Choi JA, Kwon J, Jee D, Cho YK, Park YM, Ko SH. Clinical course and risk factors of diabetic retinopathy in patients with type 2 diabetes mellitus in Korea. Diabetes Metab J 2016;40:482-93.
8. Park S, Rhee SY, Jeong SJ, Kim K, Chon S, Yu SY, Woo JT. Features of long-standing Korean type 2 diabetes mellitus patients with diabetic retinopathy: a study based on standardized clinical data. Diabetes Metab J 2017;41:393-404.
9. Secrest MH, Udell JA, Filion KB. The cardiovascular safety trials of DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors. Trends Cardiovasc Med 2017;27:194-202.