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LETTER TO THE EDITOR

Response to insulin degludec and insulin glargine 300 U/mL: Which of these two insulins causes less hypoglycemia?

I appreciate your inquiry[1] about our recent published paper[2].

The population of our study consisted of Japanese type 2 diabetes patients with well-controlled blood glucose without obesity (body mass index 23.1 ± 3.3), and glycated hemoglobin was 6.80 ± 0.35% at baseline. During the study period, glycated hemoglobin and bodyweight did not change significantly. Table 1 shows the concomitant antidiabetic agents, which stayed the same over the study period. In addition, to minimize the influence of these possible confounding factors, the study was carried out in a cross-over manner. In regard to switching the dose, the package insert of Lantus XR in Japan states, "When changing from another basal insulin except insulin glargine 100 U/mL; (a) When changing from a once-daily treatment regimen with another basal insulin, the administration should usually be initiated with the same units as the daily dosage of the intermediate or another long-acting insulin." Switching the dose of Lantus XR is based on this. The same titration algorithm was applied to both groups, and insulin doses were similar throughout the study period (insulin glargine 300 U/mL [Gla300]⇒insulin degludec 100 U/mL [Deg100] group: 5.9 U ⇒ 5.8 U, Deg100⇒Gla300 group: 6.2 U⇒6.4 U). It is unlikely that the titration algorithm affected the frequency of hypoglycemia. After minimizing the impact of concomitant medications and under similar conditions, Gla300 showed less nocturnal hypoglycemia than Deg100. Examination of Deg100 nocturnal hypoglycemia by combined oral medications suggested that metformin combination might be the cause of nocturnal hypoglycemia.

Table 1 | Concomitant antidiabetic agents

	Overall (n = 24)	I-Gla300-Deg (n = 12)	Deg-I-Gla300 (n = 12)	P-value
DPP4 inhibitor (n)	20	10	10	0.5
Metformin (n)	11	7	4	0.313
SGLT2 inhibitor (n)	6	4	2	0.394
Sulfonylurea (n)	1	1	0	0.322
Glinides (n)	16	7	9	0.55
α-GI (n)	14	5	9	0.212

The official approval of the difference of the ratio used the χ^2-test. α-GI, alpha-glucosidase inhibitor; Deg-I-Gla300, •••; DPP4, dipeptidyl peptidase-4; I-Gla300-Deg, •••; SGLT2, sodium–glucose cotransporter 2. The patients were randomly divided into two groups: I-Gla300-Deg and Deg-I Gla300. In the I-Gla300-Deg group, the pretrial Deg was replaced with the same dose of Gla300. At an outpatient visit 1 month later, Gla300 was switched to the same dose of Deg. The Deg-IGla300 group was treated and monitored in the same manner.

Each element of our Japanese-specific study is very different from the studies mentioned in the letter, such as BRIGHT, DELIVER and COMFIRM (i.e., the target patient character, the study design, background therapy etc.). Our study was carried out according to the package insert in Japan. We believe that each study described in the letter was carried out in accordance with the package insert of each country. When comparing Japanese and Caucasian patients, the pathology is different because, for example, the β-cells of Japanese patients secrete less than half of the insulin as the β-cells[3]. As a result, the dosage of insulin is also different, so I believe that the description on the package insert is different between Japan and Europe. Given this, it becomes difficult to discuss the consistency in the comparison with these studies mainly carried out in the USA. Because we did not measure fasting plasma glucose and self-monitored plasma glucose, it might be difficult to compare our study and the BRIGHT study. However, the result of the BRIGHT study is similar to ours. Also, the BRIGHT study used the model for primary analysis and included the baseline efficacy parameter values as covariates[4], which means the possible influence of baseline small numerical differences in glycated hemoglobin were taken in account for their study analysis.

In regard to insulin degludec, we did not evaluate Deg200, because only Deg100 can be used in Japan. Our study results based on the Japanese clinical setting were theoretically consistent with the pharmacokinetic/pharmacodynamic data comparing both Gla300 and Deg100 within the approved dose levels for Japan[5].

I expect that further studies will bring additional insights into the efficacy and safety of these agents.

Thank you so much for your kind suggestion.

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DISCLOSURE

Mizuho Yamabe has received honoraria for lectures from Novo Nordisk and Sanofi.

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