COMMENT ON KAZDA ET AL.

Evaluation of Efficacy and Safety of the Glucagon Receptor Antagonist LY2409021 in Patients With Type 2 Diabetes: 12- and 24-Week Phase 2 Studies. Diabetes Care 2016;39:1241–1249

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We would like to congratulate Kazda et al. (1) for reporting the first phase 2 study of the glucagon receptor antagonist LY2409021 as a novel therapy for type 2 diabetes. This study provides further proof of efficacy of glucagon antagonism as a treatment for type 2 diabetes with acceptable adverse effects at a dose of 30 mg. However, we would like the authors to clarify certain points in the phase 2a study, which would help readers better interpret the study.

We are intrigued about how the authors arrived at the ratio of 1.5:2.1:1:1 for unequal allocation to the different intervention groups (60 mg, 30 mg, 10 mg, and placebo). We would also like the authors to further elaborate on the type of randomization and method used to generate the random allocation sequence for the study. The enlisted eligibility criteria mention a fasting triglyceride level of >400 mg/dL as an exclusion, but the reasons for this are not clear. In fact, previous animal studies have actually reported a decrease in triglyceride levels as a consequence of glucagon receptor antagonism (2). Moreover, no significant change in triglyceride concentration was noted in the phase 1 study of this molecule by the same authors (3). Hence we are curious to understand the grounds for this exclusion.

The study by Kazda et al. also suffers from a very high drop-out rate, especially in the 10-mg arm (35.3%). The authors used weekly change in HbA_{1c} as a secondary outcome measure. It is well known that HbA_{1c} levels change gradually over a 3-month period after any intervention for blood glucose control, with the maximum change in the first month of treatment. Therefore the clinical implication of a weekly change in HbA_{1c} is difficult to comprehend. The efficacy of the treatment is reported to be dose dependent, but the least squares mean change in HbA_{1c} from baseline was highest in the 10-mg group and lower in the 30- and 60-mg groups, which is unexplained.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

References

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