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LY2605541—A Preferential Hepato-Specific Insulin Analogue

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COMMENTARY

The first generation of basal insulin analogs, insulin glargine and detemir, are characterized by a more predictable day-to-day insulin absorption rate, a flatter time/action profile, and a longer duration than the older, intermediate-acting NPH insulin (1). The duration of insulin glargine is longer than insulin detemir (1). The second-generation basal insulin analog insulin degludec has an even longer half-life of about 25 h, a very flat profile of action with a duration exceeding 42 h, and a reduced risk of nocturnal hypoglycemia in both type 1 and type 2 diabetic patients compared with insulin glargine (2). Yet, there is still room for further refinements of the basal insulin analogues. Insulin treatment commonly results in weight gain; thus, an insulin analog associated with no weight gain or weight loss will be a great therapeutic advance. The peripheral administration of insulin does not replicate the two- to threefold higher portal versus systemic circulating insulin levels, causing an imbalance between hepatic and peripheral metabolic actions. Therefore, an insulin analog with hepatic specificity could be of interest.

In this issue, Moore et al. (3) report on the effect of the novel basal insulin LY2605541 on hepatic and nonhepatic glucose uptake in their elegant dog model. During peripheral intravenous infusion of LY2605541, a switch from hepatic glucose output to uptake was reported, and nonhepatic glucose uptake increased less than in control experiments with human insulin, indicating that LY2605541 possesses preferential hepatic effects, thereby mimicking endogenously secreted insulin (3).

The active component of LY2605541 is insulin lispro, a short-acting insulin analog, which is covalently coupled to a single 20-kilodalton polyethylene glycol (PEG) moiety via an urethane bound to lysine B28 (Fig. 1) (4,5). This results in a large hydrodynamic radius of the analog, delaying the absorption rate of insulin lispro by slowing diffusion rate and reducing renal filtration. The PEGylation of insulin lispro also prolongs its half-life by increasing stability against proteolysis. The increase in molecular size appears to alter the tissue distribution of this insulin (4,5). Hypothetically, the hepatic sinusoidal endothelium with its wide fenestration may allow greater transport of LY2605541 to the liver than to muscles and fat, ensuring a preferential hepatic action.

Efficacy and safety of LY2605541 has been tested in two phase II studies (6,7). In a randomized 12-week open-label study in type 2 diabetic patients, once-daily basal insulin LY2605541 and insulin glargine were both administered in the morning (6). At 12 weeks, fasting blood glucose was similar in the two groups, as was HbA_{1c}. Intra- and interday blood glucose variability was reduced with LY2605541, which also induced a weight loss of −0.6 kg, compared with a weight gain of 0.3 kg in the insulin glargine group. The incidence of total and nocturnal hypoglycemia did not differ between the two groups, although LY2605541-treated patients had a 48% reduction in nocturnal hypoglycemia after adjusting for run-in period of hypoglycemia. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and triglycerides increased in the LY2605541 group and were higher than during insulin glargine treatment. The number of patients developing detectable antibodies against LY2605541 or insulin glargine did not differ between the groups (6). At week 12, mean insulin dose/kg was 1.5-fold greater with LY2605541 than with insulin glargine treatment (6).

In another open-label crossover study, type 1 diabetic patients received once-daily LY2605541 or insulin glargine plus mealtime insulin for 8 weeks, followed by crossover treatment for 8 weeks (7). Mean daily glucose control evaluated from self-monitored blood glucose profiles (−0.55 mmol/L), fasting blood glucose

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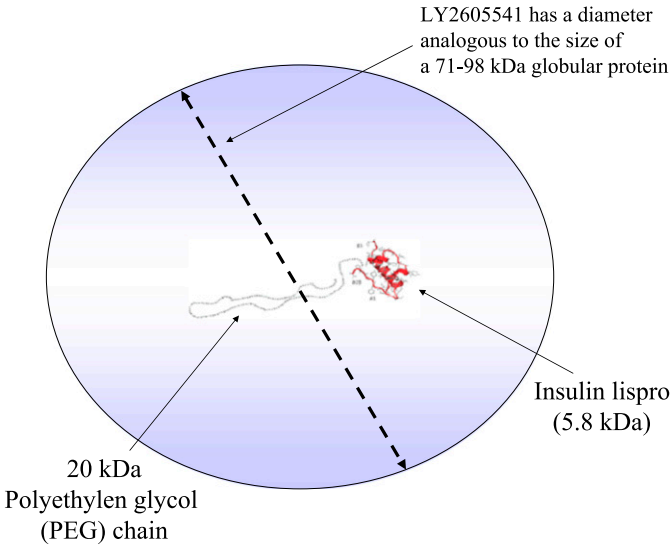

Figure 1—Insulin lispro is a 5.8-kilodalton (kDa) peptide hormone. PEG is a neutral linear, which is conjugated to insulin lispro to give rise to the basal analog LY2605541. It is able to bind three molecules of water, allowing it to become highly hydrated, thereby increasing the hydrodynamic size of the molecule, which delays the absorption and reduces renal filtration resulting in protracted half-life of LY2605541 (5). The PEGylation also protects against proteolytic degradation. PEGylation is novel in the context of insulin, but is a well-established strategy to improve the therapeutic properties of proteins.

variability, and HbA_{1c} (−0.18%) were reduced with LY2605541 compared with insulin glargine. Mealtime insulin dose decreased with LY2605541 and increased with insulin glargine, resulting in a 24% lower dose in LY2605541-treated patients. Mean weight decreased during LY2605541 treatment (−1.2 kg) and increased (0.7 kg) with insulin glargine. Total hypoglycemia rates were higher and the risk of nocturnal hypoglycemia was lower with LY2605541 (25%), while severe hypoglycemia did not differ between the two treatments. LY2605541 treatment resulted in more gastrointestinal-related events, and ALT and AST increased during treatment with LY2605541. The lipid profile differs significantly after 8 weeks with higher triglycerides and LDL and lower HDL with LY2605541 compared with insulin glargine (7).

Details on the pharmacokinetics and pharmacodynamics properties of LY2605541 are mostly available in abstract forms. LY2605541 has a T_{max} after 18–42 h and a T½ of 24–45 h compared with 10–12 and 12–15 h for insulin glargine (8). The T½ increased from about 35 h in patients with normal kidney function to about 46 h in patients with end-stage renal disease (9). The intra-subject coefficient of variability was <18% with LY2605541 and <32% for insulin glargine, as detected by euglycemic clamp studies (8). Therefore, LY2605541 seems to be suitable for daily dosing with low intra-subject variability and a longer duration than insulin glargine. In a 14-day clamp study with once-daily administration, steady-state concentrations were obtained after 7–10 days, with an almost peakless glucose infusion, a peak-to-trough ratio of <1.5, and with an approximately 8.4-fold higher concentration at day 14 compared with day 1 (10). LY2605541 exhibits a flatter glucodynamic profile than insulin glargine (11).

The reason for the increase in liver enzymes with LY2605541in the clinical trials is unknown. Increased fat deposition in the liver has been suggested. Another explanation could be that PEGylation has adverse effect on the liver. The background for the higher triglyceride and LDL levels and lower HDL concentration during LY2605541 has so far been unexplored.

The binding affinity of LY2605541 to the insulin receptor is 17 times less than insulin lispro (about 6%), and the affinity for insulin-like growth factor 1 receptor is more than 32 times less than insulin lispro, which may indicate lesser mitogenic potential (12). The reduced binding capacity of LY2605541 to the receptor may also in part explain that the molar quantities required to achieve half-maximal response are greater with LY2605541 than lispro. Other possibilities could be increased nonreceptor-mediated clearance or less bioavailability after administration subcutaneously. The fate of PEG insulin LY2605541 after receptor binding is unknown.

LY2605541 blunts hepatic glucose production (3). How this influences the counter-regulatory response to hypoglycemia is of potential interest. The primary mechanism responsible for the acute recovery rate after hypoglycemia is an increase in hepatic glucose production induced by adrenaline and glucagon in type 2 diabetic patients, counteracting the inhibitory effect of insulin (13). In the later phase of counter-regulation, a diminished peripheral insulin action of LY2605541 may

promote lipolysis with increased delivery of free fatty acid and glycerol to the liver promoting glyconeogenesis (14), which in combination with less peripheral glucose utilization could improve counter-regulation (3).

The weight-sparing effect is probably a result of the hepato-selectivity of LY2605541 leading to less lipogenesis and increased lipid oxidation compared with insulin glargine.

LY2605541 is currently in phase III development and results of clinical trials of longer duration in relation to hepatic fat content, risk of hypoglycemia, weight regulation, lipoprotein subclass distribution and concentration, and other cardiovascular disease risk factors in comparison with not only insulin glargine but also insulin degludec are of fundamental interest. Further clinical data will reveal whether a basal insulin analog with preferential liver specific action results in therapeutic advantages.

Duality of Interest. During the last three years, S.M. has served as a consultant or advisor to Novartis Pharma, Novo Nordisk, Merck Sharp & Dohme, Sanofi, AstraZeneca, Johnson & Johnson, Roche, MannKind, Boehringer Ingelheim, Zeeland, Eli Lilly, Intarcia Therapeutics, and Bristol-Myers Squibb. S.M. has also received fees for speaking from Novo Nordisk, Merck Sharp & Dohme, AstraZeneca, Johnson & Johnson, Roche, Schering-Plough, Sanofi, Novartis Pharma, Eli Lilly, Bristol-Myers Squibb, and Boehringer Ingelheim. No other potential conflicts of interest relevant to this article were reported.

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