Divergent Hypoglycemic Effects of Hepatic-Directed Prandial Insulin: A Six-Month Phase 2b Study in Type 1 Diabetes

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https://doi.org/10.2337/dc19-0152

OBJECTIVE

Hepatic-directed vesicle insulin (HDV) uses a hepatocyte-targeting moiety passively attaching free insulin, improving subcutaneous insulin's hepatic biodistribution. We assessed HDV-insulin lispro (HDV-L) versus insulin lispro (LIS) in type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

Insulin Liver Effect (ISLE-1) was a 26-week, phase 2b, multicenter, randomized, double-blind, noninferiority trial.

RESULTS

Among 176 randomized participants (HDV-L $n = 118$, LIS $n = 58$), the difference in change from baseline A1C was 0.09% (95% CI −0.18% to 0.35%), confirming noninferiority (prespecified margin ≤0.4%). Overall, there were no statistically significant differences between treatments for hypoglycemia or insulin dosing. However, baseline A1C modified the treatment group effect (interaction $P < 0.001$) on clinically apparent hypoglycemia designated by treatment-blinded investigators as severe. Thus, at higher baseline A1C, there was less hypoglycemia and lower insulin dosing with similar A1C outcomes during HDV-L versus LIS, whereas greater risk of hypoglycemia despite similar A1C outcomes and insulin doses were observed with lower baseline A1C. Among poorly controlled participants (A1C ≥8.5%), incidence rates of severe hypoglycemia in the HDV-L and LIS arms were 69 and 97 events/100 person-years, respectively ($P = 0.03$), whereas with A1C <8.5%, respective rates were 191 and 21 events/100 person-years ($P = 0.001$). Similar A1C-dependent trends in hypoglycemia were seen with continuous glucose monitoring. Among poorly controlled participants, bolus insulin doses at end point were ∼25% lower with HDV-L ($P = 0.02$), despite similar A1C outcomes; in better-controlled participants, insulin doses and A1Cs were stable over time in both subgroups. No safety signals were identified.

CONCLUSIONS

Hepatic biodistribution of HDV-L appears to potentiate insulin effect in T1D, with divergent clinical outcomes in hypoglycemia dependent on baseline A1C.

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Received 22 January 2019 and accepted 21 August 2019

Clinical trial reg. no. NCT02794155, clinicaltrials.gov

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc19-0152/-/DC1.

A recent study concluded that "it is impossible to normalize the glucose distribution between the liver and muscle when regular insulin is administered peripherally" (1). Hepatic-directed vesicle insulin (HDV), a novel insulin delivery system (2–4) using biotin-phosphatidylethanolamine in a phospholipid matrix, targets insulin to the liver, providing more normal insulin biodistribution by mimicking portal vein delivery. The flat dose-response of HDV for hepatic glucose balance along with oral glucose tolerance results in preclinical studies (5) support low-dose, fixed-combination treatment.

Subcutaneous (SC) HDV-human regular insulin reduces postprandial glucose excursions compared with SC human regular insulin (2,3). We report here a 6-month randomized, double-blind, noninferiority study of HDV-insulin lispro (HDV-L) compared with insulin lispro (LIS) in conjunction with basal insulin.

RESEARCH DESIGN AND METHODS

Design and Participants

Insulin Liver Effect-1 (ISLE-1) was a 26-week, phase 2b, multicenter (21 North American sites), randomized, double-blind trial in type 1 diabetes (T1D) treated with multiple daily injections of insulin. The primary objective was A1C noninferiority (HDV-L vs. LIS). The protocol was approved by independent ethics boards and compliant with the Declaration of Helsinki (6).

Main inclusion criteria were as follows: age ≥18 years, T1D for ≥12 months, A1C ≥7.0 (≥53 mmol/mol) to ≤10.5% (≤91 mmol/mol), and treatment with basal insulins glargine or detemir. Main exclusion criteria were as follows: total insulin dose ≥1.5 IU/kg/day, NPH insulin as basal, and recurrent severe hypoglycemia or impaired awareness of hypoglycemia. Informed consent was obtained.

Procedures

To augment a safety database, participants were randomized 2:1 (HDV-L:LIS) by remote administration, stratified by A1C (<8.5% [<69 mmol/mol], 8.5 to ≤9.5% [69 to ≤80 mmol/mol], and >9.5% [>80 mmol/mol]). HDV-L was 1% HDV-bound LIS and 99% unbound LIS formulated by mixing 0.8 mL HDV into 10 mL commercial LIS. The comparator was LIS similarly diluted with water. Informed of ~10% dilution, participants used an intensive supervised insulin treatment algorithm.

Hypoglycemia, entered into case report forms (CRFs) on the basis of diaries and glucose records, was subjectively judged by treatment-blinded investigators as mild, moderate, severe, or life-threatening. Masked continuous glucose monitoring (CGM) (Dexcom G4) was used for 5–7 days at baseline and weeks 13 and 26. A1C, lipids, and liver enzymes were measured approximately monthly. Paired baseline/end point liver fat MRIs were performed in a subset.

Statistical Analysis

The modified intention-to-treat (mITT) population included randomized participants receiving at least one dose of study treatment with at least one postrandomization efficacy end point (regardless of actual treatment). Multiple imputation methods were used to account for missing data. Safety analyses included all randomized participants. A sample size of 150, assuming an A1C SD of 0.8% and A1C treatment difference of ≤0.4%, provided 99.9% power for noninferiority (prespecified 0.4% margin). A1C change was analyzed using ANCOVA within the mITT cohort at each visit. Prespecified subgroup analyses included baseline A1C <8% (<64 mmol/mol), 8% to <9% (64 to <75 mmol/mol), and ≥9% (≥75 mmol/mol). To increase power, we compressed analyses into two groups, splitting the middle group without excluding any participants. This divided the overall cohort approximately in half and corresponded to one of the randomization stratification cut points. Direct likelihood models were used for A1C treatment comparisons, percent time <54 mg/dL, bolus insulin, and basal insulin within the two subgroups.

Poisson regression models adjusting for site as random effect compared severe and moderate hypoglycemia rates within A1C groups, testing for baseline A1C by treatment group interaction. Event number per participant was truncated at 15, accounting for extreme outliers.

RESULTS

Participants were randomly assigned to HDV-L (n = 118) or LIS (n = 58) treatment; 141 participants completed the study (HDV-L n = 98, LIS n = 43) (Supplementary Fig. 1). Male patients comprised 62 and 72% of HDV-L and LIS participants, respectively. Mean baseline age was 46.7 ± 14.4 years (HDV-L) and 44.1 ± 15.7 years (LIS). Mean ± SD baseline A1C was 8.12 ± 0.79% (HDV-L) and 8.22 ± 0.90% (LIS). BMI was 27.3 ± 3.96 kg/m^2 for HDV-L and 27.5 ± 4.02 kg/m^2 for LIS at baseline.

Overall Results

Mean change in A1C from baseline to week 26 was −0.09% with HDV-L and −0.16% with LIS (estimated treatment difference [ETD] HDV-L to LIS 0.09% [95% CI –0.18 to 0.35]) for the mITT population, confirming HDV-L noninferiority (Fig. 1*A*). There were no statistically significant treatment effects from week 0 to week 26 for basal, bolus, or total insulin doses (Fig. 1*B*). At week 26, mean ± SD basal doses were 0.36 ± 0.20 U/kg/day for HDV-L and 0.43 ± 0.23 U/kg/day for LIS, bolus doses were 0.33 ± 0.17 U/kg/day for HDV-L and 0.38 ± 0.21 U/kg/day for LIS, and total doses were 0.66 ± 0.25 U/kg/day for HDV-L and 0.76 ± 0.35 U/kg/day for LIS.

No statistically significant between-group differences were observed in measures of hypoglycemia across the mITT population. Median percent time <54 mg/dL by CGM during week 26 was 1.6% (interquartile range 0.2–4.1%) for HDV-L and 1.5% (interquartile range 0.1–4.5%) for LIS (Fig. 1*C*). Mean ± SD percent of self-monitoring of blood glucose values <54 mg/dL were 3.67 ± 2.89% for HDV-L and 3.70 ± 3.76% for LIS. Severe hypoglycemia events were recorded 80 times by 118 participants during HDV-L treatment and 14 times by 58 participants during LIS treatment.

Subgroup Analysis

The prespecified plan to assess subgroups on the basis of A1C was important because baseline A1C was shown to modify treatment group effect on severe hypoglycemia incidence (P for interaction < 0.001). As discussed above, further analyses were based on subgroups (A1C ≥8.5% vs. <8.5%), showing less hypoglycemia in HDV-L compared with LIS participants with lesser control but higher risk in HDV-L participants with greater control. A similar but not statistically significant interaction for moderate hypoglycemia was seen (P = 0.12).

Participants with A1C ≥8.5% showed comparable A1C reductions (~0.5%) for both treatments at week 26 (Fig. 1*D*), although HDV-L participants used ~25% less bolus insulin than LIS participants

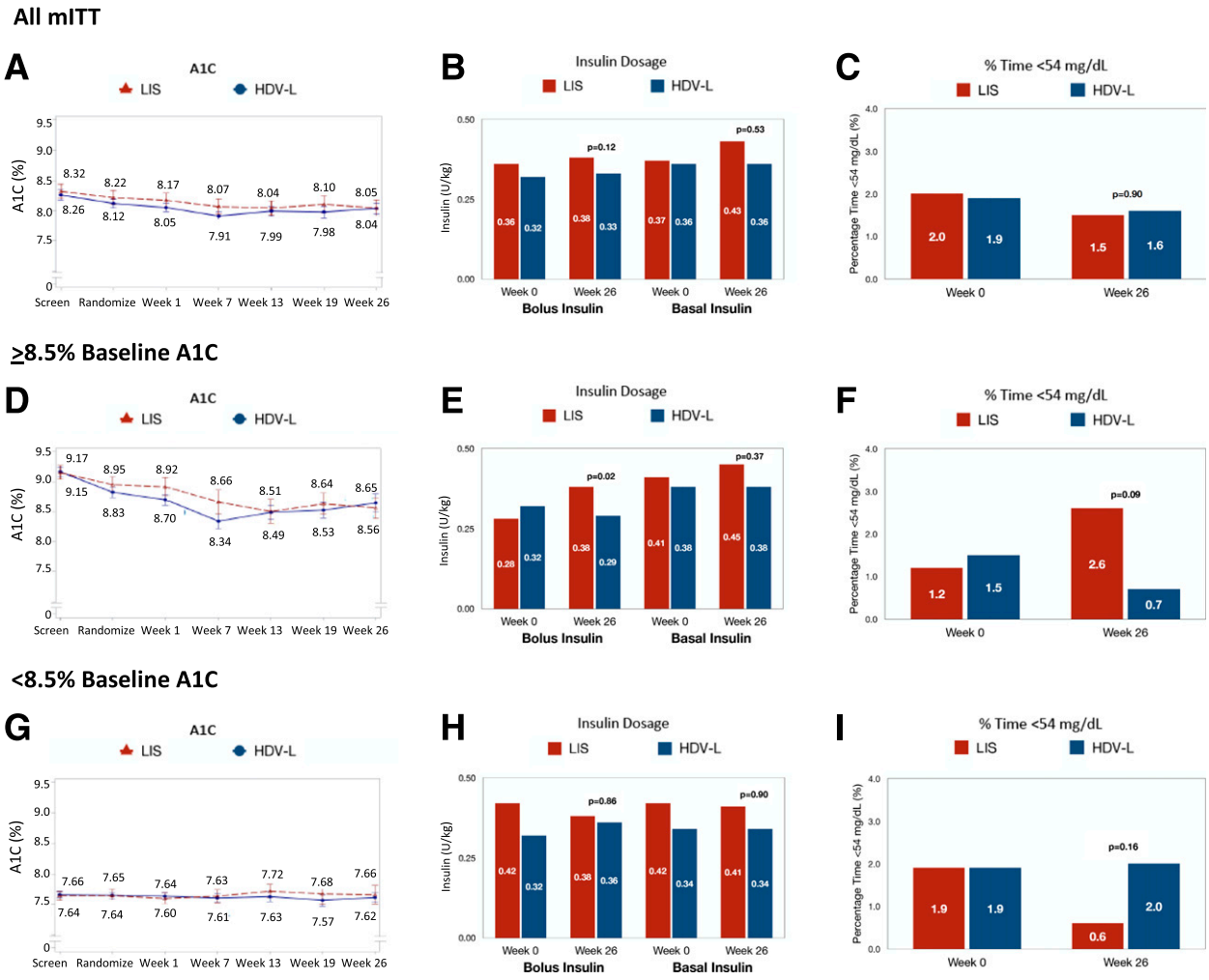

Figure 1—Changes in A1C, insulin dosage, and hypoglycemia between LIS and HDV-L by all mITT (*A–C*), baseline A1C ≥8.5% (*D–F*), and baseline A1C <8.5% (*G–I*).

(Fig. 1*E*) and recorded less percent time <54 mg/dL at week 26 (Fig. 1*F*). CRF-reported rates of severe hypoglycemia were lower for HDV-L versus LIS (69 vs. 97 events/100 person-years, $P = 0.03$). However, this difference was based on small numbers of participants (HDV-L $n = 8$, LIS $n = 2$). CRF-reported rates of moderate hypoglycemia in the A1C ≥8.5% subgroup were similar (1,151 vs. 1,087 events/100 person-years, respectively, $P = 0.47$).

Participants with baseline A1C <8.5% showed little A1C change over time (Fig. 1*G*) without difference in bolus/basal insulin dosage at end point for either treatment (Fig. 1*H*). With baseline A1C <8.5%, LIS participants showed a decrease in median percent time <54 mg/dL (<3.0 mmol/mol); HDV-L participants showed no change (Fig. 1*I*). Median percent time <70 mg/dL (<3.9 mmol/mol) (HDV-L vs. LIS) was 6.2 vs. 3.6% ($P = 0.39$). CRF-reported incidence of severe hypoglycemia was higher with HDV-L than with LIS (191 [$n = 7$] vs. 21 [$n = 1$] events/100 person-years, respectively, $P = 0.001$), and moderate hypoglycemia was higher with HDV-L than with LIS (1,206 vs. 534 events/100 person-years, $P = 0.05$).

Safety

Total cholesterol reduced with HDV-L versus LIS [−0.17 vs. 0.19 mmol/L, ETD HDV-L to LIS −0.31 mmol/L [95% CI –0.55 to −0.08 mmol/L], $P = 0.01$). No significant between-group differences (HDV-L vs. LIS) were observed in LDL cholesterol (−0.17 vs. 0.09 mmol/L, ETD −0.18 mmol/L, $P = 0.11$) or triglycerides (−0.019 vs. 0.073 mmol/L, ETD −0.13 mmol/L, $P = 0.70$). HDV-L versus LIS treatment was associated with a small effect on HDL cholesterol (−0.083 vs. 0.044 mmol/L, ETD −0.093 mmol/L, $P = 0.03$).

Liver function test changes from baseline to week 25 (HDV-L vs. LIS) were as follows: ALT 45 ± 135 nkat/L (range −316, 867 nkat/L) vs. 63 ± 138 nkat/L (range −500, 316 nkat/L), AST 33 ± 192 nkat/L (range −450, 1,333 nkat/L) vs. 55 ± 125 nkat/L (range −283, 400 nkat/L), total bilirubin, 0.086 ± 4.5 μmol/L (range −10.3, 20.5 μmol/L) vs. 0.00 ± 2.9 μmol/L (range −8.6, 5.1 μmol/L), and γ-glutamyl transferase 1.6 ± 136 nkat/L (range −417, 567 nkat/L) vs. 52 ± 165 nkat/L (range −167, 783 nkat/L).

Among 21 participants with MRIs (HDV-L $n = 14$, LIS $n = 7$), 4 had measurable baseline liver fat, and 1 (treated with HDV-L) showed a measurable liver fat increase (3.1% baseline, 11.4% end point) with a modest rise in triglycerides

(1.29 mmol/L baseline, 2.8 mmol/L week 25) but without evidence of hepatic dysfunction. No treatment-related serious adverse events were reported.

CONCLUSIONS

This first-ever, to our knowledge, 6-month study of a liver-targeted rapid-acting insulin formulation in T1D demonstrated HDV-L (vs. LIS) to be noninferior by change in A1C, with significant total cholesterol reduction, no treatment-related severe adverse events, and no between-group difference in liver function tests. Given the putative mechanism of HDV-L to provide more physiologic insulin distribution, the divergent hypoglycemia risk results in the A1C subgroups of this study are not surprising. By delivering a portion of the SC dose directly to the liver, ~30–60% of oral carbohydrate is expected to be sequestered as hepatic glycogen (1), reducing peripheral glucose exposure and demanding reduced peripheral insulin exposure.

Although poorly controlled HDV-L and LIS participants experienced similar A1C reductions (~0.5%), the groups experienced relevant differences in both insulin dosing and hypoglycemia. Poorly controlled HDV-L participants did not meaningfully alter HDV-L doses over time (whereas LIS doses increased by ~25%) and yet appeared to experience lower hypoglycemia risk as demonstrated by less percent time <54 mg/dL and a lower CRF-reported severe hypoglycemia. We hypothesize that better-controlled HDV-L participants were unable to recognize a functional increase in insulin potency, resulting in increased percent time spent <54 mg/dL and significantly increased CRF-reported hypoglycemia, despite no change in insulin dosing or difference in A1C. The divergent hypoglycemia risk findings and differing insulin dose adjustments observed in poorly versus better-controlled subgroups are unified by the hypothesis that HDV's alteration of biodistribution of SC insulin, which better includes the liver, increases the functional potency of insulin across A1C subgroups.

Despite limitations of a nonstandard definition of severe hypoglycemia, a relatively small control group, a limited CGM database, and (by chance) disparity in baseline insulin doses in the better-controlled subgroup, results support HDV-L as being noninferior to LIS for A1C outcomes and suggest that HDV-L may be associated with less hypoglycemia in poorly controlled patients. Additional studies are needed to optimize insulin dosing with bolus HDV-L, especially for A1C <8.5%.

Acknowledgments. Dr. Allison Goldfine (Joslin Diabetes Center, Boston, MA) initially served as lead investigator and was involved in protocol development and implementation. Manuscript development was supported by Chris Parkin (CGParkin Communications, Inc., Henderson, NV).

Duality of Interest. The study and editorial assistance were funded by Diasome Pharmaceuticals, Inc. D.K. reports that he is a consultant for Abbott, Ascensia, EOFlow, Intarcia, Know, Lifecare, Novo Nordisk, and Voluntis and has received research funding from Diasome Pharmaceuticals, Inc.; Lexicon; and Novo Nordisk. B.B. reports stock ownership in Aseko; the receipt of consulting fees from Adocia, Intarcia, Janssen, Medtronic, MannKind, Novo Nordisk, and Sanofi and speakers' bureau fees from AstraZeneca, Lilly/Boehringer Ingelheim, Janssen, Medtronic, MannKind, Novo Nordisk and Sanofi; and research funding from Diasome Pharmaceuticals, Inc. N.C. reports research funding from Diasome Pharmaceuticals, Inc. M.P. and D.B.M. are consultants to and option holders in Diasome Pharmaceuticals, Inc. W.B.G. is a consultant to and shareholder in Diasome Pharmaceuticals, Inc.

Author Contributions. D.K. and B.B. were involved with data acquisition, data review, and manuscript revisions. N.C. performed multiple statistical analyses and was involved in manuscript revisions. M.P. and W.B.G. were involved with protocol design, data analyses, and manuscript revisions. D.B.M. was involved in study implementation oversight, data analyses, and manuscript authorship. D.B.M. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Prior Presentation. Parts of this article were presented as an oral presentation at the 79th Scientific Sessions of the American Diabetes Association, San Francisco, CA, 7–11 June 2019.

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