No Evidence of Increase in Calcitonin Concentrations or Development of C-Cell Malignancy in Response to Liraglutide for Up to 5 Years in the LEADER Trial

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OBJECTIVE

To describe the changes in serum levels of calcitonin in liraglutide- and placebo-treated patients in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) trial over a 3.5–5-year period.

RESEARCH DESIGN AND METHODS

Patients (*n* = 9,340) with type 2 diabetes and high risk for cardiovascular events were randomized 1:1 to liraglutide or placebo. We analyzed calcitonin levels, thyroid and C-cell adverse events, and neoplasms.

RESULTS

At 36 months, patients randomized to liraglutide versus placebo showed no evidence of increase in calcitonin concentrations in male (estimated treatment ratio [ETR] 1.03 [95% CI 1.00, 1.06]; *P* = 0.068) and female (ETR 1.00 [95% CI 0.97, 1.02]; *P* = 0.671) subgroups. There were no episodes of C-cell hyperplasia or medullary thyroid carcinoma in liraglutide-treated patients.

CONCLUSIONS

There was no evidence of a difference in calcitonin concentrations between the liraglutide and placebo groups, and no C-cell malignancies occurred in the liraglutide group.

Serum calcitonin (calcitonin) is used as a tumor marker for neoplasia of the thyroid C-cells, such as medullary thyroid carcinoma (MTC) and C-cell hyperplasia (CCH) (1,2). The progression of CCH to MTC is accompanied by rising calcitonin concentrations (2,3). In healthy individuals, calcitonin concentration is usually <10 ng/L (1), with levels higher in men (<8.4 ng/L) than in women (<5.0 ng/L) (4). A calcitonin concentration >100 ng/L has a high specificity for MTC, whereas lower concentrations have much lower specificity (4). The role of routine calcitonin monitoring for detection of MTC remains ill-defined but may be a more sensitive method in establishing MTC than cytology in patients with thyroid nodules (5).

In rodent studies, but not in nonhuman primate and clinical studies, glucagon-like peptide 1 receptor activation has been associated with CCH, C-cell adenomas, and C-cell carcinomas (6–8). The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) trial (NCT01179048)

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**A complete list of the LEADER committee members and investigators can be found in the Supplementary Data online.*

presented an additional opportunity to evaluate long-term calcitonin changes in patients exposed to liraglutide versus placebo (9). Here, we evaluated the impact of liraglutide versus placebo on calcitonin concentrations and thyroid and C-cell adverse events (AEs) with 3.5–5 years of follow-up.

RESEARCH DESIGN AND METHODS

Trial Design

The design of the LEADER trial has been described previously (10). Patients (n = 9,340) with type 2 diabetes at high risk for cardiovascular events were randomized 1:1 to receive liraglutide 1.8 mg or placebo once daily, in addition to standard of care, and followed for 3.5–5 years. Exclusion criteria included basal calcitonin concentration >100 ng/L and patients with a personal or family history of multiple endocrine neoplasia type 2 or familial MTC (4).

Evaluation

Calcitonin was measured in the fasting state, and the blood samples for the measurement of calcitonin concentration were drawn at screening and annually up to the 60-month visits. An independent external calcitonin-monitoring committee of thyroid experts assessed all calcitonin levels ≥20 ng/L and provided clinical advice to the investigators. Thyroid-related AEs were reported as medical events of special interest. The clinical evaluation of thyroid neoplasms by the independent event adjudication committee was conducted in a blinded manner and was determined by diagnostic testing results, pathology reports, specialist consultations, related imaging reports, and/or biomarkers.

Statistical Analysis

An analysis using a linear model with repeated measures evaluated the treatment effect across visits in relation to change from baseline for log-transformed values of calcitonin for male and female subgroups, respectively. Calcitonin concentrations <2.0 ng/L were set as half the lower limit of quantification (LLOQ) value (1.0 ng/L). Elevated calcitonin concentrations were analyzed with logistic regression to determine the number of patients with concentrations above the upper limit of normal (ULN) (5 ng/L for women and 8.4 ng/L for men) and ≥20 ng/L, ≥50 ng/L, and ≥100 ng/L. A left censoring regression model addressing the values below the LLOQ as a latent variable was performed as a sensitivity analysis.

RESULTS

A total of 9,340 patients were randomized. The mean age was 64.3 years; 64.3% were men. The mean BMI was 32.5 kg/m^2 (Supplementary Table 1). Calcitonin concentrations were not normally distributed, partly because of the substantial number of baseline calcitonin values below the LLOQ (~87 vs. ~28% of women and men, respectively). A similar proportion of patients in both treatment arms had calcitonin values greater than or equal to the ULN at baseline across male (liraglutide 21.5%; placebo 22.0%) and female patients (liraglutide 3.2%; placebo 2.7%).

Minor and comparable (between-treatment) changes were observed in calcitonin concentrations over time. A minor decrease in geometric means was observed in male subjects from 5.9 ng/L at screening to 4.7 and 4.6 ng/L in liraglutide and placebo arms, respectively, at 36 months. At 12 months, a significantly smaller decrease in calcitonin levels (by 5%) was observed in males randomized to liraglutide compared with placebo (estimated treatment ratio [ETR] 1.05 [95% CI 1.02, 1.08]; P = 0.0018). However, no differences between treatments were observed at 24 months. Likewise, at 36 months, the ETR for male patients randomized to liraglutide versus placebo was 1.03 (95% CI 1.00, 1.06; P = 0.068); this corresponded to an insignificantly smaller decrease (by 3%) in male patients randomized to liraglutide. Female subgroups also showed no evidence of differences in mean concentrations between treatments at 36 months (ETR 1.00 [95% CI 0.97, 1.02]; P = 0.671) (Fig. 1).

After adjustments for covariates (age, estimated glomerular filtration rate, smoking status, medical history of thyroid disease, and current use of proton pump inhibitor) at 36 months, patients randomized to liraglutide showed no significant difference in mean calcitonin concentrations versus patients randomized to placebo in male (ETR 1.03 [95% CI 1.00, 1.06]; P = 0.082) and female (ETR 1.00 [95% CI 0.97, 1.02]; P = 0.696) subgroups. Results at 36 months for calcitonin values from the left censoring regression model were in accordance with the linear model with repeated measures.

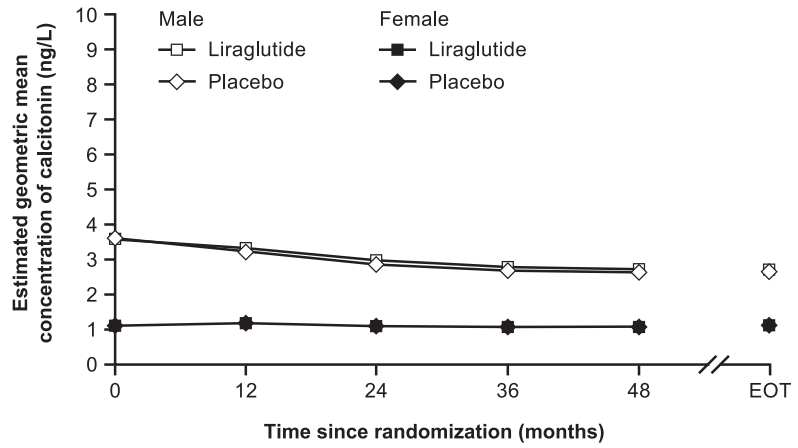
In liraglutide versus placebo groups, a similar proportion of male (24.6 vs. 23.0%) and female (5.4 vs. 4.5%) patients had a post-baseline calcitonin concentration above the ULN. In liraglutide versus placebo groups, a similar proportion of male (4.9 vs. 4.8%) and female (0.3 vs. 0.3%) patients had a post-baseline calcitonin concentration >20 ng/L (Fig. 1 and Supplementary Table 2). Overall, there was no significant influence of treatment on calcitonin concentration, regardless of the patients' baseline renal function, smoking status, use of proton pump inhibitors and/or H2 blockers, or medical history of thyroid disease (Supplementary Fig. 1).

No episodes of MTC were reported in patients in the liraglutide arm, but one event adjudication committee–confirmed event of MTC occurred in one patient in the placebo arm (Supplementary Table 3). Proportions of other thyroid neoplasms were 0.1% in both treatment arms. The incidence of thyroid-related AEs was, likewise, low and similar between groups. The incidences of serious thyroid-related AEs were 0.6 and 0.4% in the liraglutide and placebo arms, respectively (Supplementary Table 4).

CONCLUSIONS

In the LEADER trial, there was no consistent change in calcitonin concentrations over time, no significant difference in calcitonin concentrations between liraglutide and placebo, and no occurrence of C-cell malignancies in the liraglutide arm after randomization. There were no significant differences in mean calcitonin concentrations in patients randomized to liraglutide versus placebo in either sex, similar to a previous pooled analysis of six phase 3 clinical studies in 5,698 patients (8). In contrast, a different study showed that the calcitonin concentrations were statistically higher at weeks 26 and 52 with liraglutide compared with comparators; however, these levels were well within the normal range and, as with our analysis, showed no indication that these differences were of clinical significance (8).

Overall, there was no clear evidence of influence of treatment on calcitonin concentration, regardless of patients' baseline factors, including smoking status, use of proton pump inhibitors and/or H2 blockers, baseline renal status, or medical history of thyroid disease. One case of MTC occurred in the placebo arm, and thyroid-related AEs were both low and comparable between arms. The complete absence of CCH and MTC findings in those patients randomized to liraglutide is in keeping with the low



Liraglutide						
Males (*n*)*	2818	2720	2540	2434	543	2381
Females (*n*)*	1546	1482	1420	1329	255	1297
Placebo						
Males (*n*)*	2768	2659	2469	2311	503	2276
Females (*n*)*	1553	1500	1378	1282	234	1249

Figure 1—Calcitonin concentrations over time. Estimated geometric means were determined using a mixed model of repeated measures on log-transformed values from the full analysis set. *, number of patients with an observed value that contributes to the mixed model of repeated measures. EOT, end of treatment.

incidence of CCH (five cases) and MTC (zero cases) in patients randomized to liraglutide reported in a previous pooled analysis (8). A limitation of this analysis is the lack of a uniform protocol for evaluation of elevated calcitonin concentrations. Strengths include the large population based on a randomized trial and that this is the first analysis investigating the long-term effect of liraglutide on calcitonin concentration, with associated C-cell malignancies.

In this post hoc analysis of results from the LEADER trial, we found no evidence that liraglutide stimulates calcitonin release from human C-cells, or is a potential cause of C-cell proliferation or C-cell pathology in humans.

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Author Contributions. L.H., S.I.S., R.M.T., B.J.v.S., J.D.K., and G.H.D. reviewed and interpreted the data and were involved in drafting and critical revision of the manuscript. S.R. provided the statistical analysis of the data, reviewed and interpreted the data, and was involved in drafting and critical revision of the manuscript. All authors are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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