Changes in serum calcitonin concentrations and incidence of adjudicated medullary thyroid carcinoma in the EXenatide Study of Cardiovascular Event Lowering (EXSCEL)

B. Katona1, M.A. Bethel2, R. Patel1, V.P. Thompson3, S.M. Gustavson1, P. Ohman1, N. Iqbal1, J.B. Buse4, A.F. Hernandez3, R.R. Holman2, for the EXSCEL Study Group;
1AstraZeneca, Gaithersburg, USA, 2Diabetes Trials Unit, Oxford, UK, 3Duke Clinical Research Institute, Durham, USA, 4University of North Carolina School of Medicine, Chapel Hill, USA.

Background and aims: Serum calcitonin concentration is used as a tumour marker for neoplasia of the thyroid C-cells, including medullary thyroid carcinoma (MTC), which has been associated with glucagon-like peptide-1 (GLP-1) receptor activation in pre-clinical studies. EXSCEL was a multinational, randomised, double-blinded, pragmatic cardiovascular outcomes trial evaluating exenatide, a once-weekly GLP-1 receptor agonist, versus placebo on the background of usual care in type 2 diabetes. We report changes in serum calcitonin concentrations in exenatide- and placebo-treated participants and incidence of MTC in EXSCEL over a median 3.2-year follow-up period.

Materials and methods: Participants (n=14752) in EXSCEL were randomised 1:1 to exenatide 2mg once-weekly or placebo. Serum calcitonin concentration was measured in participants at baseline (ineligible for trial if >40ng/L) and annually throughout follow-up (trial medication discontinued if ≥50ng/L). A repeated measures mixed model analysis was performed, including serum calcitonin concentrations only from participants with a baseline and at least one post-baseline value. Median serum calcitonin concentration for treatment groups was calculated at baseline and at yearly intervals thereafter. Thyroid malignancies, including MTC, were collected prospectively throughout the trial and adjudicated using pre-specified criteria by an independent committee, blinded to treatment assignment.

Results: In the intention-to-treat population at baseline, 52 (30 exenatide, 22 placebo) participants had a serum calcitonin concentration >40ng/L, and during follow-up 23 participants (15 exenatide, 8 placebo) had a serum calcitonin concentration ≥50ng/L (excluding those with serum calcitonin concentration >40ng/L at baseline). Median (IQR) baseline serum calcitonin concentration was 1.7ng/L (1.7, 4.3) in the exenatide group and 1.7 ng/L (1.7, 4.2) in the placebo group. Serum calcitonin concentrations were unchanged over 36 months in both groups, with a median (IQR) change from baseline of 0.0 (-0.4, 0.0) in the exenatide group and 0.0 (-0.5, 0.0) in the placebo group. Confirmed MTC occurred in 3 participants (2 exenatide, 1 placebo), all of whom had elevated serum calcitonin concentrations at baseline (413, 422 and 655ng/L).

Conclusion: Treatment with exenatide 2mg once-weekly did not result in an increase in serum calcitonin concentrations, with no evidence of a difference in serum calcitonin concentrations between exenatide- and placebo-treated participants over a median 3.2-year follow-up period. All 3 confirmed cases of MTC in EXSCEL occurred in participants who had an elevated serum calcitonin at baseline, prior to administration of trial medication.

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