Project: Is the effect of short versus long acting exenatide to reduce HbA1c moderated by baseline HbA1c?

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Research background

In unselected type 2 patients the DURATION-1 and 5 trials have established that exenatide once a week is more effective than exenatide twice a day in reducing glycated haemoglobin. While exenatide once a week is also more effective in lowering fasting / pre-prandial glucose, exenatide twice a day reduces postprandial glucose much more (presumably, as a result of slowing of gastric emptying). Given that postprandial glycaemia is increasingly the dominant contributor to glycated haemoglobin as the latter normalizes this suggests that exenatide twice a day may be relatively more effective than exenatide once a week in lowering glycated haemoglobin when the latter is only moderately elevated.

Research objectives

1. Primary objective: To determine if baseline HbA1c moderates the effect of once weekly exenatide, relative to twice daily, on the change in HbA1c.
2. Secondary objective: To determine the relationship between the change in HbA1c and post-prandial glycaemic response, under once weekly exenatide compared to twice daily.

Research hypotheses

1. Twice-daily exenatide will be more effective, relative to once-weekly, in reducing HbA1c in subjects with lower baseline HbA1c compared to subjects with higher baseline HbA1c.
2. There will be a relationship between post-prandial glycaemia and the change in HbA1c following treatment with twice daily exenatide.

Data sources

Hypothesis 1 will be analysed by pooling data from the DURATION-1 (ClinicalTrials.gov Identifier: NCT00308139) and DURATION-5 (ClinicalTrials.gov Identifier: NCT00877890) clinical trials. Hypothesis 2 will be analysed using data from the subset of subjects in DURATION-1 who completed the meal tolerance test.

Statistical analysis plan

Analyses will be conducted on the evaluable population, defined as patients who completed the study procedures to at least week 20 (DURATION-5) or week 24 (DURATION-1).

Baseline characteristics of the two cohorts will be presented and compared using t-tests for continuous variables and chi-square tests for categorical variables. Statistical significance will be set at $p<0.05$ and no adjustment for multiple testing will be conducted.

This analysis is exploratory and hypothesis generating in nature, and pre-existing data is not available for robust power calculations. However, our calculations suggest that by pooling data from the two studies we will have >80% power for detecting an interaction between treatment and baseline HbA1c if twice daily exenatide reduces HbA1c by 0.3% more than weekly exenatide amongst subjects with the lowest 25% of baseline HbA1c, compared to weekly exenatide being more effective by 0.9% amongst the remaining 75% of subjects. This pattern of means would be consistent with average HbA1c at final followup of 7.1% for weekly exenatide and 7.7% for twice daily, as reported in in the DURATION-5 ITT population.

Hypothesis 1:

The moderating effect of baseline HbA1c on the effect of exenatide on change in HbA1c will be analysed in an interaction analysis. A general linear model will be used with HbA1c at week 24/26 as the dependent variable. Fixed effects will be included for treatment group, baseline HbA1c, the treatment by baseline HbA1c interaction, concomitant SU use at baseline as a covariate, and study as a stratification factor. Baseline HbA1c will initially be analysed as a continuous variable (%) with any non-linearity in the main or interaction effects modelled via splines or fractional polynomials as appropriate. Depending on the distribution of baseline HbA1c, categorisation will also be considered as secondary analyses.

Hypothesis 2:

The relationship between change in HbA1c from baseline to weeks 14 and 24/26 and the change in postprandial glycaemia to week 14 will be analysed in a linear regression model. Fixed effects will be included for treatment group, study cohort and concomitant SU use at baseline. A differential relationship by treatment group will be assessed by including the interaction between postprandial glycaemia and treatment. Postprandial glycaemia will initially be analysed as a continuous variable (mmol/l) with any non-linearity in the main or interaction effects modelled via splines or fractional polynomials as appropriate. Depending on the distribution of postprandial glycaemia, categorisation will also be considered as secondary analyses.

Strengths of this research are the ability to explore interactions, including non-linearities, by pooling data from two studies to achieve a reasonable sample size. The analysis will provide novel data on a possible moderation of the effect of weekly exenatide and of the relationships between postprandial glycaemia, gastric emptying and response to exenatide treatment. Findings will be exploratory and hypothesis generating. Further confirmatory studies will be planned based on this new information.