Insulin treatment and longer diabetes duration both predict poorer glycaemic response to liraglutide treatment in type 2 diabetes: the Association of British Clinical Diabetologists Nationwide Liraglutide Audit

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Abstract
Background: Liraglutide may be less effective in patients with more advanced type 2 diabetes. This study from the Association of British Clinical Diabetologists Nationwide Liraglutide Audit analysed changes in HbA1c of patients after 26 weeks of treatment with liraglutide 1.2 mg, stratified according to the intensity of their background diabetes therapy, or according to their duration of diabetes.

Methods: Patients using liraglutide as add-on therapy were stratified for receipt to one, two or three oral antidiabetic agents (OADs) or insulin (± OAD), or for diabetes duration of 0–5 years, 6–10 years, or >10 years. Changes in HbA1c were compared across groups after adjusting for baseline HbA1c.

Results: After exclusions to standardise comparisons, 937 patients with background diabetes treatment and 802 patients with recorded diabetes duration were analysed. Least-squares adjusted mean changes in HbA1c (± SEM) were −1.8% ± 0.1 for 135 patients on one OAD, −1.7% ± 0.1 for 284 patients on two OADs,−1.9% ± 0.1 for 94 patients on three OADs (n=94) and −1.0% ± 0.1 for 424 patients receiving insulin. HbA1c changes did not differ significantly between OAD groups, but all OAD groups had greater HbA1c reductions compared with the insulin group (all p<0.00001). Adjusted mean HbA1c changes were −2.0% ± 0.1 for patients with diabetes duration 0–5 years (n=147, p<0.05 vs. longer diabetes durations), −1.6% ± 0.1 for 6–10 years (n=256), and −1.2% ± 0.1 for >10 years (n=399).

Conclusion: The need for insulin and long diabetes duration, but not the number of OADs taken, predicted a smaller treatment response to liraglutide.


Key words: type 2 diabetes, liraglutide, insulin, diabetes duration, oral antidiabetic drug

Introduction
Guidelines for the management of type 2 diabetes place a strong emphasis on the need for personalised antidiabetic treatment. Accordingly, it is important to identify factors which predispose to an optimum treatment response to a given antidiabetic therapy. Liraglutide is a once-daily GLP-1 receptor agonist approved for use alongside diet and exercise in combination with one or more oral antidiabetic agents (OADs) or with basal insulin for the management of type 2 diabetes.

Studies currently reported in abstract form point towards a
diminished glycaemic response to a GLP-1 receptor agonist treatment among patients with more advanced diabetes, based on assessments of the intensity of antidiabetic treatment or the duration of diabetes. We studied the influence of these indices on the therapeutic response to liraglutide in a large cohort of patients who received liraglutide 1.2 mg in the UK.

**Patients and methods**

This study was part of a nationwide audit of the use of liraglutide in the UK carried out on behalf of the Association of British Clinical Diabetologists (ABCD). Participating physicians provided anonymised information on demographic data (age, gender, ethnicity, height, weight), duration of diabetes, cardiometabolic parameters (glycaemia, blood pressure, lipids, alanine aminotransferase and creatinine) and treatments prescribed, before and after treatment with liraglutide. Only effects on HbA1c are discussed here. Data capture was via an online audit tool or paper forms conveying identical information. By 2013, 117 diabetes centres in the UK had participated and submitted baseline data on 6,238 patients treated with liraglutide.

Patients were stratified for receipt of one, two or three OADs or insulin (with or without concomitant treatment with an OAD), or for diabetes duration 0–5 years, 6–10 years, or >10 years. Patients without at least one follow-up data submission (n=1,296) were excluded from the analysis. To standardise comparisons and to represent the effects of liraglutide add-on therapy, we excluded patients who switched from exenatide (n=870), received liraglutide 1.8mg (n=343), stopped an OAD at liraglutide initiation (n=947), or reduced their total daily insulin by >20% at liraglutide initiation (n=451). We also excluded patients with HbA1c <7.0% at baseline (n=102) and patients without relevant HbA1c data (n=1,173). The latest HbA1c data at 26 weeks of liraglutide treatment prior to any rescue treatment and with a minimum of 13 weeks after liraglutide treatment were used in the analysis. Changes in HbA1c according to diabetes treatment or duration were analysed using ANCOVA, after checking that the statistical requirements for valid ANCOVA had been met. Due to incomplete concurrent data on diabetes treatment and diabetes duration, separate analyses were first performed for these parameters as independent variables, without adjustment for one another, and with baseline HbA1c as a covariate (Figures 1 and 2). Combined ANCOVA analyses were subsequently performed among patients with complete data for both diabetes treatment and duration (Figure 3).

This was a purely observational study, and no investigations or treatments other than those required for the routine management of the patients were performed. Accordingly, formal ethical approval of the study was not required.

**Results**

After exclusions, 1,056 patients were analysed (937 patients with background diabetes treatment with 1–3 OADs or insulin, and 802 patients with information on diabetes duration). All diabetes treatment or duration groups achieved mean HbA1c reductions at 26 weeks that were statistically significant compared with baseline (all p<0.01). Mean changes in HbA1c were significantly larger for patients receiving treatment based on one, two or three OADs, compared with patients receiving insulin...
patients on one, two or three OADs. This contrasts with earlier (LEAD)-2 study.10 There, liraglutide was more effective in reducing HbA1c when added to OAD monotherapy as opposed to combinations of OAD,10 a finding supported by subsequent meta-analyses.4,5 The reason for the difference in findings is not known but may be due to methodological differences between clinical trials and an audit. The use of thiazolidinediones in the audit (18.0% of patients on two OADs and 87.2% of patients treated with insulin, relative to patients receiving other therapies, but nevertheless remained clinically significant. Recent clinical studies have shown that combinations of GLP-1 agonists and insulin are a rational treatment choice, as the inclusion of the GLP-1 agonist improves antihyperglycaemic efficacy while limiting the weight gain and hypoglycaemia associated with insulin.17,18 Hence, the efficacy of liraglutide should both be judged across patients with different stages of diabetes, as well as judged at the level of the individual patient against other available therapeutic options at their stage of disease.

**Conclusion**

Our study confirms and extends previous findings that patients with more advanced type 2 diabetes respond less well to liraglutide compared with patients with earlier-stage disease.

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**Conflict of interest** The ABCD Nationwide Liraglutide Audit program has previously received unrestricted grants from Eli Lilly and Novo Nordisk.

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**Key messages**

- The glycaemic response to liraglutide was smaller in magnitude in patients with type 2 diabetes receiving insulin compared with those on oral therapies only.
- Liraglutide was also less effective in patients with longer duration of diabetes.
- Patients on insulin or with long duration of diabetes still achieved a clinically significant therapeutic response with liraglutide treatment.

(Figure 1); no differences were seen comparing patients on one versus two versus three OADs.

Liraglutide was significantly more effective in patients with duration of diabetes of 0–5 years compared with patients with duration of diabetes of 6–10 years or >10 years (Figure 2). Insulin treatment and diabetes duration remained independent predictors of the magnitude of changes in mean HbA1c for patients with data on both antidiabetic treatment and diabetes duration (Figure 3).

**Discussion**

Observational studies provide a different perspective to randomised trials on the therapeutic profiles of antidiabetic treatments and can add important information on their use in routine, "real world" clinical practice.9 We found in clinical practice that the effect of liraglutide on glycaemia was reduced in type 2 diabetes with more advanced disease, as indicated by the need for insulin treatment or a longer duration of diabetes.

Our results showing a diminished treatment response to a GLP-1 agonist among insulin-treated patients are consistent with previous findings of smaller HbA1c reductions in patients with versus without insulin treatment after starting exenatide twice daily. This was in a similar audit to the current study, in a "real world" setting.9 However, we did not find any difference in glycaemic efficacy when comparing the addition of liraglutide to patients on one, two or three OADs. This contrasts with earlier findings from the Liraglutide Effect and Action in Diabetes (LEAD)-2 study.10 There, liraglutide was more effective in reducing HbA1c when added to OAD monotherapy as opposed to combinations of OAD,10 a finding supported by subsequent meta-analyses.4,5 The reason for the difference in findings is not known but may be due to methodological differences between clinical trials and an audit. The use of thiazolidinediones in the audit (18.0% of patients on two OADs and 87.2% of patients

**Figure 3.** Mean HbA1c reductions according to diabetes treatment and diabetes duration in 785 patients with data on both parameters

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Columns show adjusted mean changes analysed by ANCOVA with baseline HbA1c as a covariate. CI: confidence interval; ED: estimated difference; OAD: oral antidiabetic drug(s).
The authors take full responsibility for the content of this article.

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**References**

Appendix 1. ABCD nationwide prospective liraglutide audit contributors

The following are those whom we know about.


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