Reductions in alanine aminotransferase levels with liraglutide treatment are greatest in those with raised baseline levels and are independent of weight loss: real-world outcome data from the ABCD Nationwide Liraglutide Audit

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Abstract

People with type 2 diabetes mellitus experience an increased prevalence of non-alcoholic fatty liver disease (NAFLD) compared with the general population and often with worse outcomes. As part of the ABCD Liraglutide Nationwide Audit Programme, we obtained and analysed data from 2009 to 2018 to assess the impact of liraglutide on alanine aminotransferase (ALT) levels as a marker of liver inflammation (often used in clinical trials as a marker of NAFLD). After excluding those with insufficient or incomplete data, we analysed the results from 1,759 patients treated in the real-world clinical setting. Our results demonstrated an overall significant decrease in median ALT (–1 U/L, 95% CI –1 to –2, p<0.001) compared with baseline, which was more pronounced in patients with elevated ALT based on gender-specific ranges (male: –4 U/L, 95% CI –3 to –6, p<0.001; female: –3 U/L, 95% CI –2 to –4, p<0.001). There was no correlation between weight loss and degree of ALT change (rho=–0.0002, p=0.41). Our data mirror outcomes from large randomised controlled trials and show that the impact of liraglutide on ALT is likely generalisable to real-world practice. Some of our data suggest that there may be a slight increase in ALT in those with normal levels at baseline, although the clinical significance of this is uncertain.

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Introduction

Non-alcoholic fatty liver disease (NAFLD) is known to have an increased prevalence in people with type 2 diabetes, with some estimates ranging from 30% to 70% depending on the source.[1,2] Although no direct causative links have yet been established, it is clear they must share some common pathophysiological processes. There is evidence already that NAFLD changes can herald the onset of diabetes, especially when these changes are progressive.[3,4] Additionally, the presence of type 2 diabetes alongside NAFLD increases the rate of progression to cirrhosis as well as the rate of hepatocellular carcinoma.[5] Despite this, the biggest cause of mortality amongst this cohort is car-

diovascular disease, independent of traditional risk factors including long-term glycaemic control.[6]

Management of this condition is therefore key in improving patient outcomes. Recommendations tend to suggest lifestyle interventions including weight loss as first-line treatment.[7] No drugs are currently licensed for use in the treatment of NAFLD and, until recently, there was a paucity of strong evidence for any pharmacological intervention other than perhaps pioglitazone.[8] In those with diabetes, it is important to recognise the growing need to select medications that may also reduce cardiovascular risk or confer a positive impact on other associated co-morbidities such as NAFLD.

Alanine aminotransferase (ALT) levels are used frequently as a marker of liver inflammation; levels have been shown to correlate with the extent of NAFLD histologically and progression to fibrosis and the test is reportedly specific (85%), even if limited somewhat by sensitivity (45%).[2,9,10]

Glucagon-like peptide 1 (GLP-1) agonists such as liraglutide have been investigated with some promising results. A meta-analysis of individual patient data from the LEAD (Liraglutide Effect and Action in Diabetes) trial demonstrated significant reductions in ALT in the liraglutide treatment group, although these improvements were not found to be significant when adjusted for weight loss.[11] The LEAN trial[12] completed in 2013 and demonstrated the safety and efficacy of liraglutide as a treatment for NAFLD in patients without diabetes, and used histological sampling and imaging alongside ALT as part of the assessment. GLP-1 agonists compare favourably with other oral hypoglycaemic agents. Randomised controlled trial data have shown that liraglutide can achieve greater improvements in liver biochemistry when compared with both metformin and gliclazide,[13,14] as well as sitagliptin.[15] Improvements in liver function are comparable to pioglitazone with the additional benefit of weight loss.15 Other GLP-1 agonists such as exenatide have also been shown to decrease ALT.[16] No head-to-head comparison of different GLP-1 agonists is currently available.

The liraglutide audit was initially launched by ABCD in 2009 to assess the real-world clinical use, outcomes and side effects of liraglutide therapy. To the point of analysis, anonymised data from 5,985 people with type 2 diabetes treated with liraglutide have been collected from 92 centres around the UK.

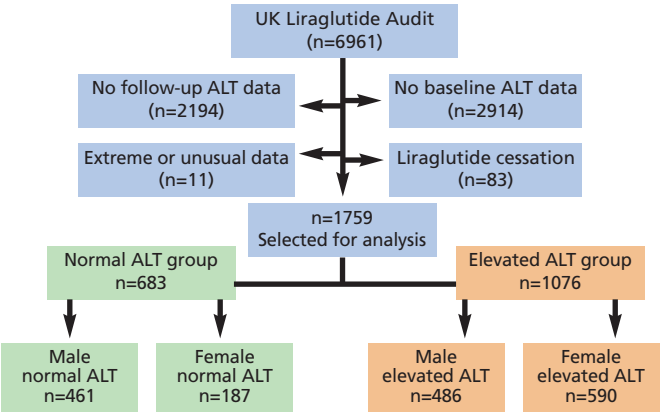
The aim of this analysis of the ABCD liraglutide audit data was to establish if the following hypotheses were held true for a real-world cohort of patients:

1. Liraglutide leads to a reduction in ALT levels
2. Baseline elevated ALT levels predict a better metabolic response to liraglutide therapy in terms of HbA_{1c} and weight
3. Baseline ALT, to be assessed using stratified groups and separately via linear regression, predicts ALT response to liraglutide
4. Reduction in ALT correlates with weight loss

Methods

Data were obtained from the UK ABCD audit of liraglutide use (2009–2018). Inclusion criteria were set such that all patients included had a minimum dataset of a baseline ALT and a repeat measurement 6 weeks to 1 year later to be used as a follow-up. Any patients discontinuing liraglutide prior to the follow-up were excluded from the analysis. Some patients with extreme values or possibly erroneous entries were excluded (n=11; 0.6%). The patients were then stratified on gender-specific reference ranges for ALT into 'normal' or 'elevated' ALT groups (normal ranges: male, ALT <30 U/L; female, ALT ≤19 U/L) as described by Prati *et al*,[17] as laboratory specific reference ranges were not known. This process can be seen in the flowchart in Figure 1.

Figure 1. Flow chart showing sources of patient data and numbers included and excluded as outlined in the methods section



A separate analysis was performed by stratifying the population into normal ALT (based on male reference range, <30 U/L), raised ALT (30–59 U/L) and markedly elevated (twice upper limit of normal, >59 U/L) in order to demonstrate the impact of different baseline levels on the response to ALT.

Statistical analysis

Mean changes in weight, body mass index (BMI) and HbA_{1c} (where data were available) were calculated. Median changes in ALT were used as this parameter followed a skewed/non-parametric distribution. Subsequently, changes in ALT, HbA_{1c} and weight over time were calculated within and between groups using ANOVA and paired t-tests for normally distributed data and Wilcoxon signed rank tests and the Kruskal–Wallis test for skewed data. Spearman's rank correlation coefficients were used to assess the relationship between baseline variables including ALT and metabolic response.

Results

The baseline characteristics of the 1,759 patients extracted from the audit data are shown in Table 1. The population had a mean±SD age of 55.2±11.9 years; 53.7% were male and the median duration of diabetes was 10 (IQR 6–14) years. The majority (76.6%) were Caucasian. The maximum daily doses of liraglutide used, where recorded (n=1,687), were 0.6 mg in 3.4%, 1.2 mg in 81.7% and 1.8 mg in 14.8%.

Table 1 Baseline characteristics of observed population

Characteristic	n=1,759
Age, years ± SD	55.2±11.9
Male, %	53.7
Median diabetes duration, years (IQR)	10 (6-14)
Caucasian, % (where known, n=1636)	76.6
Mean HbA_{1c}, % ± SD	9.2±1.71
mmol/mol ± SD	77.6±18.7
Mean BMI, kg/m² ± SD	34.2±7.6
Mean weight, kg ± SD	102.1±22.5
Median ALT, U/L (IQR)	31 (22-44)
Males	26 (19-37)
Females	31 (23-45
Median ALT at baseline, U/L (IQR)	
Female - Normal ALT	16 (13-18)
Female - Raised ALT	31 (25-43)
Male - Normal ALT	23 (18-26)
Male - Raised ALT	45 (38-57)

ALT, alanine aminotransferase; BMI, body mass index
IQR, interquartile range; SD, standard deviation

Over a median duration of 7.7 months, median ALT change across the entire population was –1 U/L (95% CI –1 to –2, p<0.001). The mean change in BMI was –1.3 kg/m² (95% CI –1.1 to –1.5, p<0.001) and the mean change in weight was –3.5 kg (95% CI –3.1 to –3.8, p<0.001). HbA_{1c} decreased, with a change of –0.8% (95% CI –0.7% to –0.9%, p<0.001) or –8.9 mmol/mol (95% CI –8.0 to –9.8, p<0.001).

In both raised ALT subgroups, statistically significant changes in median ALT were noted of –4 U/L in men (95% CI –3 to –6, p<0.001) and of –3 U/L in women (95% CI –2 to –4, p<0.001). These differences are statistically significant at p<0.001 using the Wilcoxon signed rank test. The median ALT values of each group at baseline and at follow-up are shown in Figure 2, and the median change in ALT values with confidence intervals is displayed in Figure 3.

When stratified into three groups based on baseline ALT (Figure 4), in both raised ALT subgroups there were significant changes in ALT from baseline, most notably in the 'markedly elevated' group with a median change of –17 U/L (95% CI –14 to –23, p<0.001) and in the 'elevated' group of –4 U/L (95% CI –3 to –5, p<0.001).

Using the Kruskal–Wallis test (non-parametric analysis of variance), the differences between groups in both analyses were statistically significant (p<0.0001).

Table 2 shows the Spearman's rank correlation coefficients between ALT at baseline and the pre-defined treatment outcomes of interest. Notably, there is no association between baseline ALT and weight loss or HbA_{1c} reduction; however, elevated ALT at baseline predicted a greater reduction in ALT at follow-up (Spearman's rho=0.117, p<0.0001). The median ALT reduction was 1 U/L across all three doses and no significant difference between doses was found when assessed by the Kruskal–Wallis test (p=0.66).

In addition to the above, there is no correlation between change in weight and change in ALT, which suggests that the ALT improvements achieved by liraglutide are independent of weight loss.

Figure 2. Bar chart showing median alanine aminotransferase levels (ALT) in each group at baseline and follow-up for normal (female ALT ≤19 U/L; male <30 U/L) and raised ALT at baseline in patients commencing liraglutide. Error bars represent interquartile ranges

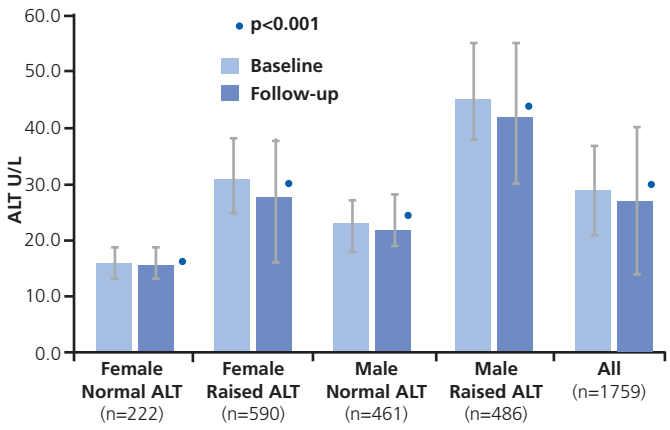


Figure 3. Bar chart demonstrating average (median) change in alanine aminotransferase (ALT) from baseline subdivided by baseline ALT as follows: female, normal ALT (ALT ≤19 IU/L, n=222); female, elevated ALT (ALT >19 IU/L, n=590); male, normal ALT (ALT <30 IU/L, n=461); male, elevated ALT (ALT ≥30 IU/L, n=486) and finally the entire population (n=1,759). Error bars represent 95% confidence intervals. All differences between baseline and follow-up measurements significant to p<0.001 (Wilcoxon signed rank test)

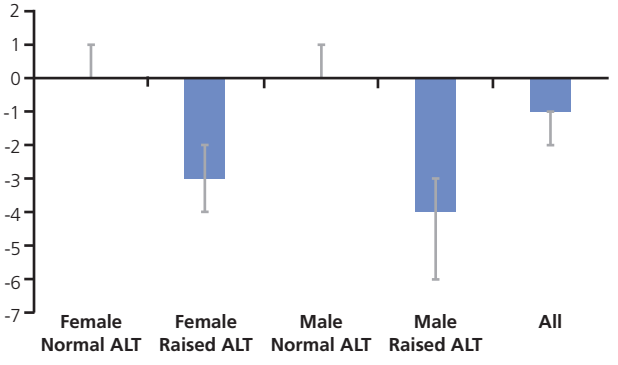


Figure 4. Bar chart showing median alanine aminotransferase levels (ALT) in each group at baseline and follow-up for normal (<30 U/L, n=959), elevated (30–59 U/L, n=638) and markedly elevated (defined as twice upper limit of normal, ALT >59 U/L, n=162) ALT at baseline in patients commencing liraglutide. Error bars represent interquartile ranges

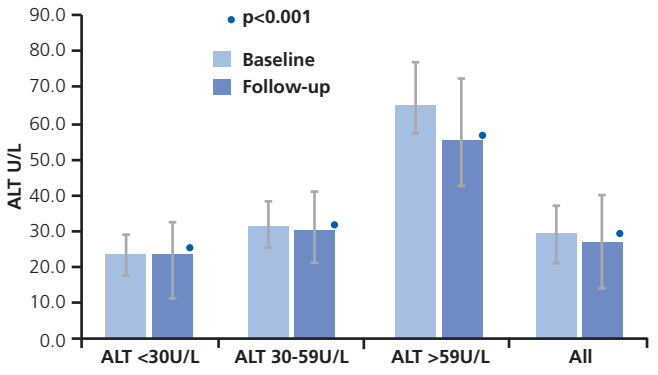


Table 2 Spearman's rank correlation between baseline alanine aminotransferase (ALT) at baseline and metabolic/clinical outcomes in patients receiving liraglutide

Metabolic/clinical parameter	Spearman's rho	P value
Change in weight (n=1,625)	–0.001	0.75
Change in HbA_{1c} (n=1,575)	–0.0003	0.88
Change in ALT (n=1,759)	0.117	<0.0001
Change in weight vs change in ALT	–0.002	0.4

Discussion

Main findings

People in this analysis of the nationwide UK ABCD Liraglutide Audit had established diabetes with a mean duration of over 10 years and suboptimal glycaemic control with raised BMI at baseline. The majority were Caucasian with almost an equal split between male and female patients, so they were generally representative of the UK population.

Over the observation period, liraglutide resulted in statistically significant reductions in HbA_{1c} (0.8%, 8.9 mmol/mol), BMI (1.3 kg/m^2) and ALT (1 U/L) across the whole population. This ALT reduction is relatively minor; however, the reduction in ALT in those with elevated baseline measurements is significantly more pronounced, falling by a median of 4 U/L in males and 3 U/L in females.

Alongside the Spearman's rank correlation analysis, which demonstrates baseline ALT is correlated with change in ALT at follow-up, by stratifying our population into three groups we have demonstrated that patients respond in different ways and to different extents depending on the baseline measurements. The 'elevated' group showed a small significant decrease in ALT and the group with ALT >59 U/L at baseline demonstrated large falls in ALT of 17 U/L. This suggests strongly that those with the worst ALT at baseline are likely to gain the greatest benefit in improving ALT and subsequently liver inflammation.

Baseline ALT levels did not correlate to or predict response of weight, BMI or HbA_{1c} to liraglutide therapy.

In addition to the above, we noted reasons for discontinuing liraglutide were generally related to efficacy, presumably in regard to NICE guidance[18] for continuation which sets goals in terms of HbA1c reduction and weight loss which must be achieved. Only four patients in our cohort of 1,759 discontinued liraglutide due to concerns about deteriorating liver function as assessed by liver enzymes including ALT. None are known to have developed pancreatitis.

Strengths and limitations

These data are real-world data without excluding important groups of patients and therefore are likely to represent more generalisable findings than those encountered in randomised controlled trials. The cohort is representative of the UK population and our analysis was enabled from the audit data due to the regular periodic monitoring of blood tests in UK general practice and secondary care. Although we are using ALT as a marker of potential NAFLD, as we do not have full access to the patient records we are unable to assess the proportion of our patients who held a confirmed diagnosis of NAFLD. Additionally, we have no information on confounding factors such as alcohol consumption, other liver diseases or use of statins.

ALT elevation is suggestive of liver inflammation and a reduction is reassuring. However, this does not necessarily correlate directly to a reduction in the severity of NAFLD, although this is common practice in many studies with a potentially valid basis despite some concerns highlighted in the review by Rinella.[2,9,10] There was also no collection of other potentially useful markers of liver inflammation such as aspartate aminotransferase or platelet count, which may have been used in conjunction with ALT to calculate a Fib4 score (a recognised non-invasive way of assessing for NAFLD).[19] Other more accurate methods of assessing liver fat content or NAFLD severity, beyond the scope of our observational dataset, might include the use of liver transient elastography measurements (eg, FibroScan or equivalent) or magnetic resonance imaging.[20] The gold standard test of liver biopsy would be invasive and its role in any protocol would have to be considered and appropriate.[20] Ultimately, ongoing further assessment of liraglutide, ideally using multiple markers of NALFD, would be useful in further supporting its use in patients both with and without diabetes.

Data from a control population were not available as all the data generated from the ABCD UK Nationwide Liraglutide Audit are from patients receiving this therapy. No assessment of other co-morbidity or factors such as alcohol intake were made as these data were not collected as part of the initial audit.

Interpretation

These real-world data are consistent with the findings of previous research. The closest comparison can be drawn with the

Key messages

- Changes to ALT following commencement of liraglutide are comparable in our real world data to existing clinical trials
- Reductions in ALT from baseline are greatest in those with most raised levels at baseline
- No correlation was found between degree of weight loss and degree of ALT changes suggesting a weight loss independent mechanism may be underlying this

results of the LEAD trial,[11] which demonstrated significant reductions in ALT, albeit from a higher baseline (33.8 U/L in females, 47.3 U/L in males), at an average of 8.2 U/L at 26 weeks. Notably, this was using a 1.8 mg dose of liraglutide which is maximally titrated, while many of the patients in our cohort were included in our final dataset on the lower 0.6 mg or 1.2 mg doses. It could be argued therefore that the slightly larger reduction in ALT observed in the LEAD cohort is the result of higher baseline levels, something which our data have established is a factor. Our data suggest that there is no dose-dependent incremental benefit of liraglutide on decreasing ALT levels.

No correlation whatsoever was demonstrated between amount of weight loss and change in ALT, with a notably insignificant p value. It is unlikely therefore that the improvement in ALT (and subsequently NAFLD) is due to weight loss, and therefore the improvements may be explained by a direct effect of the liraglutide itself. One hypothesis of how liraglutide exerts this action could be a primary action on fatty liver infiltrates and so, by reducing these, it achieves its maximal effects in terms of HbA_{1c} reductions and weight loss. However, had this been the case, we would have expected baseline ALT to predict metabolic response with regard to these parameters, which was not the case in our data, and ALT at baseline did not predict an improved glycaemic response to treatment in this cohort, a phenomenon which had been noted previously.[21]

An alternative explanation is that there may be additional confounding factors which we have not identified due to the limitations of our dataset.

As our data are from the real world, they are likely to be more generalisable to the diabetes clinic and will have included patients with complications and extremes of weight and other parameters as well as possible off-licence usage, such as is often encountered in practice.

Conclusion

Real-world evidence or liver function tests in patients on GLP-1 agonists, such as liraglutide, is limited. Randomised controlled trial data are universally supportive of the role of liraglutide in NAFLD. Our analysis of real-world use of liraglutide provides additional supporting data on the potential impact of liraglutide on ALT as a marker of NAFLD. Although across the entire cohort changes were statistically significant, the clinical significance of such small decreases in ALT is likely to be minimal. However, this large real-world observational cohort has also emphasised that the effect of liraglutide is likely to be greatest in those with the worst baseline liver function; this is comparable to randomised controlled trial data. In these patients, the ALT reductions achieved may well translate into clinical improvements. Elevated baseline ALT levels do not predict weight loss or HbA_{1c} reductions following commencement of liraglutide. Finally, and perhaps most interestingly, our data suggest that liraglutide may have an effect on ALT independent of weight loss; more data on this point are needed.

Conflict of interest REJR: speaker fees and/or consultancy fees and/or educational sponsorships from AstraZeneca, BioQuest, GI Dynamics, Janssen, Novo Nordisk, Sanofi-Aventis and Takeda. AP: has received honoraria from Novo Nordisk for educational discussions

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ABCD nationwide liraglutide audit – initial setup, maintenance and nationwide analysis:
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