Factors accounting for variability in weight and HbA1c response to exenatide in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit

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Aims

In December 2008, 18 months after the launch of exenatide in the UK, ABCD launched a project to accelerate understanding of the new agent, through a nationwide audit of its use in real clinical practise. In particular the aims are to examine clinical usage of exenatide in the UK, ascertain whether the experience of clinical usage matches data from phase 3 trials and to inform future practice and guidelines.

Methods

An on-line questionnaire was established in a password protected area of ABCD website for collection of anonymised patient data. A persistent e-mail bombardment of diabetes specialists in the UK was undertaken inviting them to submit clinical data on all their patients treated with exenatide.

Results

The e mail bombardment led to a dramatic response – so that as of February 2009 already we have data promised on 7559 patients, data submitted on 5313 patients, and data available for analysis on 3913 patients (mean (+/- SD) age 54.6 (+/-10.4) years, 2167/3913 (55.4%) male), with all these numbers rising.

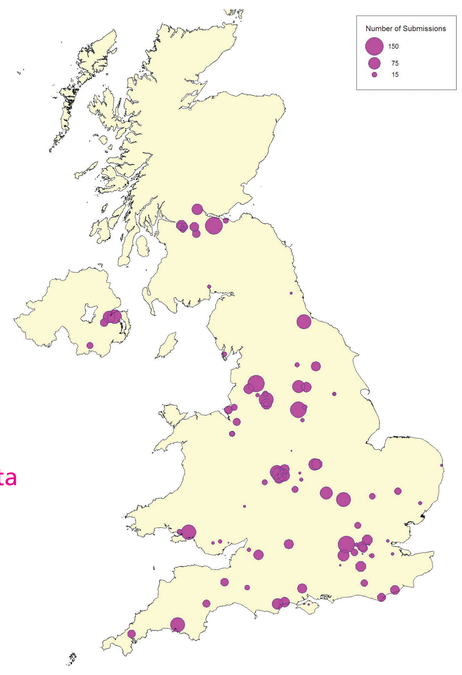

Figure 1.
The sites in the UK contributing data on the preliminary analysis of the 3913 patients who are the subject of this poster.

First analysis of the data so far showed that in response to exenatide mean (+/- SD) HbA1c, weight and body mass index fell as follows: HbA1c by 0.75% from 9.42 (+/- 1.19)% to 8.65 (+/- 1.22)% (p<0.0001), weight by 4.9kg from 114(+/- 23.3) to 109.1(+/- 22.6) kg (p<0.0001), BMI by 1.74 from 39.89 (+/- 7.5) to 38.15 (+/-7.24) kg/m2 (p<0.0001).

The weight and HbA1c response was variable with some patients showing dramatic response (Figures 2a & 3a).

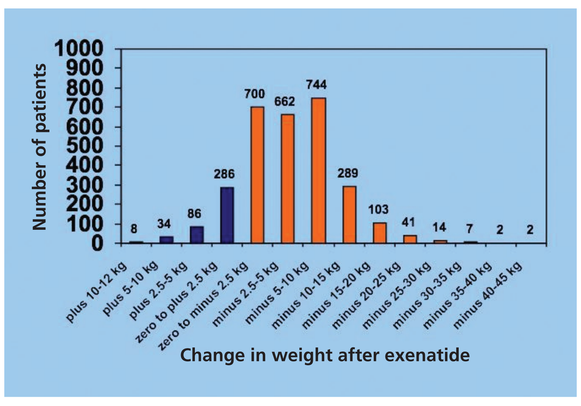

Figure 2a: Difference between last weight after extenatide and weight before exenatide in 2977 patients

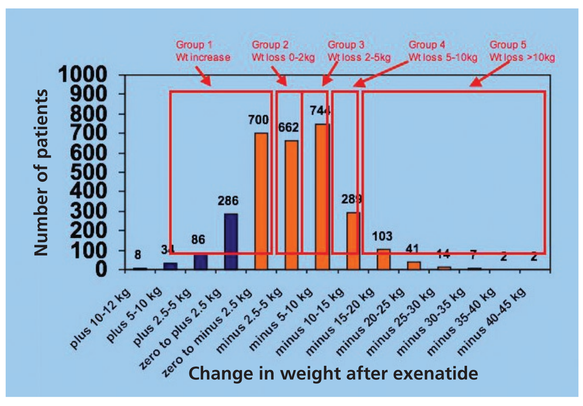

Figure 2b: The patients were divided into 5 groups with regard to weight change

Figure 3a: Difference between last HbA1c after exenatide and HbA1c before exenatide

Figure 3b: The patients were divided into 5 groups with regard to change in HbA1c

To assess factors accounting for variability in response, weight and HbA1c responses were each divided into 5 groupings as shown in figures 2b and 3b. For the 3340 patients shown in figures 2a and 3a, 2230/3340 (66.8%) were not on insulin, 999/3340 (29.9%) were on insulin, with 110/3340 (3.3%) uncertain. These subdivided further into 2073/3340 (62.1%) not on insulin ever, 157/3340 (4.7%) not on insulin at start, but added later, 194/3340 (5.8%) insulin stopped at exenatide start, 101/3340 (3.0%) insulin stopped at exenatide start, but insulin later restarted and 704/3340 (21%) insulin continued at exenatide start.

Analysis of variance was used to compare these different response groups with regard to initial HbA1c, initial weight, initial BMI, duration of diabetes, age, sex, whether on insulin and whether insulin was stopped when exenatide was started. Highly significant differences were found between the groups with regard to many of these parameters.

Weight

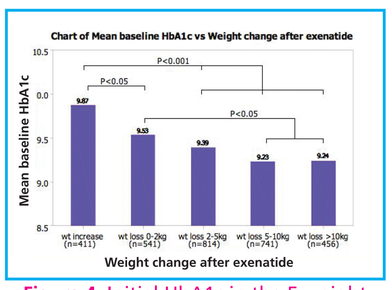

Figure 4: Initial HbA1c in the 5 weight change groupings in 2963 patients

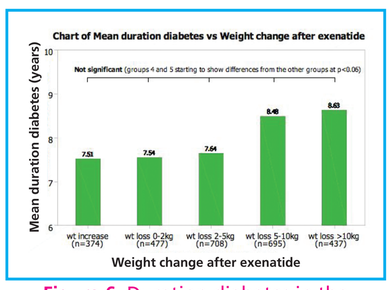

Figure 6: Duration diabetes in the 5 weight change groupings in 2307 patients

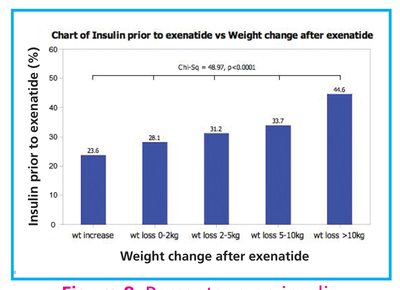

Figure 8: Percentage on insulin pre-exenatide in the 5 weight change groupings in 2897 patients

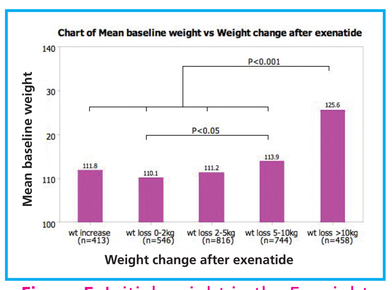

Figure 5: Initial weight in the 5 weight change groupings in 2977 patients

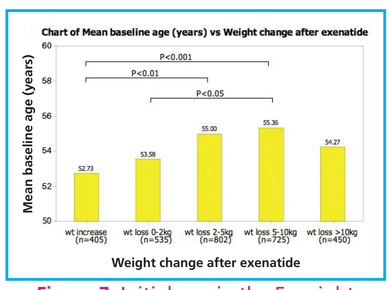

Figure 7: Initial age in the 5 weight change groupings in 2917 patients

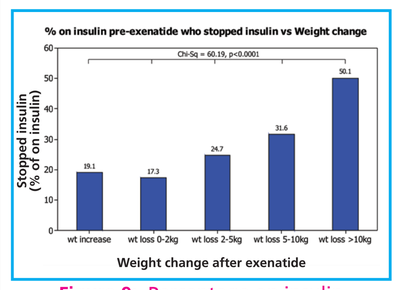

Figure 9: Percentage on insulin pre-exenatide who stopped insulin at exenatide start in the 5 weight change groupings in 934 patients

HbA1c

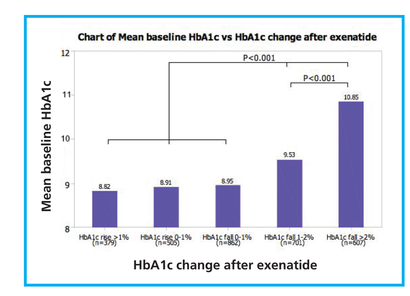

Figure 10: Initial HbA1c in the 5 HbA1c change groupings in 3054 patients

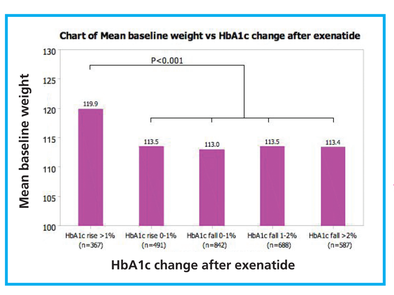

Figure 11: Initial weight in the 5 HbA1c change groupings in 2975 patients

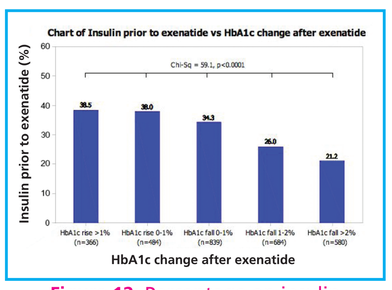

Figure 12: Percentage on insulin pre-exenatide in the 5 HbA1c change groupings in 2953 patients

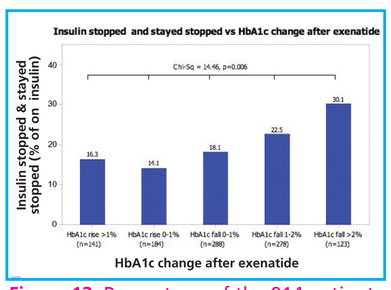

Figure 13: Percentage of the 914 patients on insulin pre-exenatide who stopped insulin and it stayed stopped in the 5 HbA1c change groupings

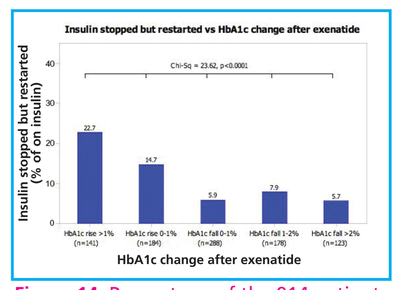

Figure 14: Percentage of the 914 patients on insulin pre-exenatide who stopped insulin but it was restarted in the 5 HbA1c change groupings

These differences can be summarized as follows:

- Those who increase weight, or with lesser degrees of weight loss after exenatide, tend to have higher initial HbA1c, lower initial weight (and BMI – data not shown on poster) and lower age. They are less likely to be on insulin and if on insulin are less likely to have had it stopped.
- Those who lose a large amount of weight after exenatide tend to a lower initial HbA1c, higher initial weight and BMI, slightly longer duration diabetes. They are more likely to have been on insulin and are more likely to have had the insulin stopped.
- Those with the greatest falls in HbA1c after exenatide had higher initial HbA1c.
- Those who experienced the greatest rise in HbA1c after exenatide had a higher initial weight. They were also more likely to be on insulin before being started on exenatide; of those who had their insulin stopped when exenatide was started those with a rise in HbA1c were more likely to have it restarted.

Side effects

Reported side effects included gastrointestinal side effects in 1122/3913 (28.7%) patients, being transient in 773/3913 (19.7%), stopped exenatide temporarily in 67/3913(1.7%), stopped exenatide permanently in 282/3913(7.2%). Headache was reported in 48/3913 (1.23%) and fatigue in 23/3913 (0.6%). Hypoglycaemia rate increased from 104/3913 (2.7%) prior to exenatide to 177/3913(4.5%) after exenatide. 7/3913 (0.18%) cases of pancreatitis were reported. All these cases were followed up and it transpired that 6/7 were mistakes in data entry. There was ***just one case of pancreatitis*** reported but the relationship to exenatide treatment was not clear as the patient had two previous admissions with severe abdominal pain prior to exenatide treatment, admitted to a significant increase in alcohol consumption prior to admission and had extreme hypertriglyceridaemia (triglycerides = 87.8 mmol/L).

Conclusion

These results highlight that

i) Heavier patients with better glycaemic control at initiation of exenatide lose the greatest amounts of weight.

ii) By contrast weight gain was noted in some patients when started on exenatide and these patients had higher initial HbA1c. Also those who put on weight or with lesser degrees of weight loss with exenatide tended to have lower initial weight. This raises the possibility that the weight increase associated with improving glycaemic control in some poorly controlled patients, overrides the weight reducing properties of exenatide in this subgroup of patients.

iii) Strict adherence to the current license for using exenatide in the UK, such that in order to avoid co-treatment of exenatide and insulin, insulin is discontinued when exenatide is started, may lead to worsening of glycaemic control and this worsening of control may be considerable. This is more likely to occur with higher initial weight and lower initial HbA1c – ie in heavy patients whose diabetes is relatively controlled by the insulin whose insulin is stopped when exenatide is started.

ABCD nationwide exenatide audit continues

This poster concerns first analysis of the first 3913 patients with data available for analysis following a deadline for data submission on February 18 2009. Following a further deadline for further data submission of July 20 2009, the audit now has data available for more detailed analysis on approximately 7000 patients; this analysis is ongoing.

ABCD nationwide exenatide audit contributors

The following are those whom we know about who contributed the 3913 patients who are the subject of this poster. The full audit, which is ongoing, has many other contributors who will be listed in future presentations which will include their patients

ABCD nationwide exenatide audit – initial setup, maintenance and nationwide analysis: *Ryder REJ, Walton C, Winocour P, Cull ML, Jose B, Sukumar N, Mills AP, Sands K. Statistical Advisor: Blann A.*

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Acknowledgment

The ABCD nationwide exenatide audit is an independent audit supported by an unrestricted grant from Eli Lilly Ltd