Audit of clinical practice in the use of incretin mimetic agents for the management of patients with type 2 diabetes

Balraj Dhesi 1  
MB ChB (Hons), Foundation Year Trainee

Hiren Chauhan 1  
MB ChB (Hons), Foundation Year Trainee

Ansu Basu 1,2  
MD, FRCP, FRCP, Consultant Physician and Endocrinologist Clinical Director

1 Department of Diabetes, Endocrinology and Lipid Metabolism, City Hospital, Birmingham, UK  
2 The University of Birmingham, Edgbaston, Birmingham, UK

Correspondence to:  
Ansu Basu, Department of Diabetes, Endocrinology and Lipid Metabolism, City Hospital, Dudley Road, Birmingham B18 7QH, UK; email: Ansu.Basu@nhs.net

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Abstract  
The objective of this audit was to compare treatment outcomes in patients on dipeptidyl peptidase (DPP)-4 inhibitors and glucagon-like peptide-1 receptor (GLP-1R) agonists within a hospital clinic setting, and to identify factors that might influence their response to treatment.  
We undertook a retrospective audit of 118 consecutive patients who received either a DPP-4 inhibitor or a GLP-1R agonist as add-on to existing oral hypoglycaemic agent therapy. Primary clinical outcomes compared were change in HbA1c and weight. The clinical characteristics of patients who responded with both weight loss and improvement in HbA1c were compared to those who did not.

The results showed that more patients (73.6%) were on a GLP-1R agonist; 57% of patients on a GLP-1R agonist lost weight and had improved HbA1c compared to 40% of patients on a DPP-4 inhibitor. The mean reduction in HbA1c was 8.4mmol/mol with a mean weight loss of 2.6kg. There were good correlations between the initial HbA1c and decline in HbA1c in both treatment groups. In all, 68.3% of patients on additional insulin treatment improved HbA1c while 46.3% improved in terms of both weight and HbA1c. Patients not on insulin responded better to treatment (OR 1.96; p=0.047) with these agents.

It was concluded that good metabolic control can be achieved if these agents are used judiciously. The DPP-4 inhibitors improve HbA1c but are weight neutral, while the GLP-1R agonists cause both weight loss and improvements in HbA1c. The addition of insulin under specialist supervision can be beneficial. Copyright © 2013 John Wiley & Sons.

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Key words  
incretin mimetics; GLP-1; DPP-4

Introduction  
The gut peptides glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) have different roles in glucose homeostasis. GLP-1 has a stimulatory effect on pancreatic beta cells increasing insulin secretion, and an inhibitory effect on alpha cells reducing glucagon secretion. GIP has no effect on alpha cells and its action is primarily as an insulin secretagogue.  
Circulating levels of GLP-1 and GIP exert their insulinotropic effects by their actions on the GLP-1 and GIP receptors respectively. The incretin effect, i.e. the enhanced insulin secretion following an oral glucose load compared to when glucose is adminis-
tered intravenously, is completely accounted for by GLP-1 and GIP together. GLP-1 is a more potent secretagogue than GIP in type 2 diabetes. However, the levels of GLP-1 are decreased in individuals with type 2 diabetes, and therefore the incretin effect is blunted in these patients. The available incretin mimetic drugs, which include the GLP-1 receptor (GLP-1R) agonists and the dipeptidyl peptidase (DPP)-4 inhibitors, utilise novel pathways to control both fasting and post-prandial blood glucose. The DPP-4 inhibitors act by preventing the degradation of endogenous GLP-1 and GIP. The GLP-1R agonists act directly on the GLP-1 receptor, an effect that is independent of levels of endogenous GLP-1 and therefore may be expected to exhibit different level of efficacy.  
The National Institute for Health and Clinical Excellence (NICE) has provided guidance on the use of these agents. Recent national audits have demonstrated that their use can be extended beyond that recommended by NICE with favourable clinical outcomes. It becomes apparent from clinical practice that there are two opposing cohorts of patients – those who
respond by both a reduction in body weight and improvement in glycaemic control, and those who do neither. An improvement in the understanding of these opposing groups might help clinicians identify patients who are more likely to respond to treatment.

**Patients and methods**

This cross-sectional audit was carried out on 118 consecutive patients who either received a DPP-4 inhibitor (vildaglaptin, sitagliptin) or a GLP-1R agonist (exenatide, liraglutide). The number of patients on an individual drug within the class was too small for any meaningful subgroup analyses. Further, the purpose of the audit was to compare the efficacy of each class rather than individual agents within the class as this information is readily available from clinical trials and meta-analyses.

Eight patients had received treatment with both a DPP-4 inhibitor and a GLP-1R agonist during the course of their diabetes care. If included, their data would confound any comparative analyses between the two agents, and were therefore excluded from further analyses.

All patients were reviewed in the same clinic providing uniformity in clinical practice. DPP-4 inhibitors are used in the diabetes clinic as add-on to existing oral hypoglycaemic agents such as metformin, sulphonylureas and glitazones for improving glycaemic control and avoiding unnecessary weight gain. In a small number of cases they are continued after the patient has commenced insulin therapy for their anti-glucagon effect. GLP-1R agonists are used primarily in obese (body mass index >30kg/m²) patients with poor glycaemic control as add-on to oral hypoglycaemic agents or in conjunction with insulin. The rationale for use in conjunction with insulin is that they might check the weight gain that is so customary in continuing insulin therapy.

The clinical information was retrieved from case notes and hospital database systems. Dual therapy is defined as the use of an incretin mimetic agent as a second-line drug when the first agent was not insulin.

### Statistical analyses

Data were recorded in a customised database (MS Access, Microsoft Corp.) and statistical analyses were undertaken using PASW version 18 (IBM Corp. formerly SPSS). Frequency data are presented as n (%). Continuous variables are presented as mean (± standard deviation). A scatter plot was used to identify two separate subgroups of patients on exenatide and liraglutide – ‘responders’ with weight and HbA1c reduction and ‘non-responders’ with worsening of both weight and HbA1c. The groups were then analysed using stepwise binary logistic regression with results being presented as odds ratio (OR). Student’s t-test was used to compare mean values between two groups. All p-values are two-sided and a value of 0.05 was considered to indicate statistical significance. HbA1c has been expressed in both DCCT and IFCC units.

**Results**

There were 110 patients in the audit. Eighty-one (73.6%) patients were on either exenatide or liraglutide and the remaining 29 (26.4%) were on sitagliptin or vildaglaptin. Dual therapy was used in 26 (23.6%) patients and triple therapy in 33 (30%). Incretin mimetic agents were used as a fourth agent in 12 (10.9%) patients and in 44 (40%) patients the drugs were used in combination with insulin. Two patients were on monotherapy. The demographic characteristics were essentially similar between the two groups, though patients on GLP-1R agonists had a significantly longer duration of diabetes (Table 1).

The mean reduction in weight from baseline for the entire cohort was 2.61kg (95% CI -1.49 to -3.74; t[109] = -4.6; 2-tailed p=0.0001) and the improvement in HbA1c was 8.4mmol/mol (95% CI -4.48 to -12.24; t[108] = -4.27; 2-tailed p<0.0001). Correcting for missing paired data (n=4 for DPP-4; n=2 for GLP-1R), 18/25 (72%) patients on DPP-4 inhibitor and 53/79 (67%) patients on GLP-1R agonist demonstrated at least an improvement in

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**Table 1. Study participants’ baseline characteristics**

<table>
<thead>
<tr>
<th>Age* (years): mean (SD)</th>
<th>GLP-1R agonist (n=81)</th>
<th>DPP-4 inhibitor (n=29)</th>
<th>Entire cohort (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>57.5 (±10.7)</td>
<td>60.6 (±17.0)</td>
<td>58.3 (±12.7)</td>
</tr>
<tr>
<td>Gender (males): n (%)</td>
<td>45 (55.6)</td>
<td>15 (51.7)</td>
<td>60 (54.5)</td>
</tr>
<tr>
<td>Diabetes duration**: (years): mean (SD)</td>
<td>15.3 (±7.4)</td>
<td>10.1 (±6.5)</td>
<td>13.9 (±7.5)</td>
</tr>
<tr>
<td>Duration of therapy**: (months): mean (SD)</td>
<td>18.6 (±9.1)</td>
<td>18.4 (±12.1)</td>
<td>18.5 (±9.9)</td>
</tr>
<tr>
<td>Ethnicity: n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>39 (48.1)</td>
<td>16 (55.2)</td>
<td>55 (50.0)</td>
</tr>
<tr>
<td>African-Caribbean</td>
<td>14 (17.3)</td>
<td>3 (10.3)</td>
<td>17 (15.5)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>28 (34.6)</td>
<td>10 (34.5)</td>
<td>38 (34.5)</td>
</tr>
</tbody>
</table>

*There were no significant differences between the two groups. **The difference was statistically significant, p<0.001.
HbA1c. There were 104 patients where paired data for weight and HbA1c change were available. Within the relatively small group on DPP-4 inhibitors, 10/25 (40%) patients lost weight and improved their HbA1c; the corresponding figure for those on a GLP-1R agonist was 45/79 (57%). When analysed separately, there was a statistically significant reduction in HbA1c with treatment among patients in both groups; weight reduction, however, was only observed among patients receiving a GLP-1R agonist (Table 2). We observed strong correlations between the initial HbA1c and subsequent decline in HbA1c in both groups (Pearson’s r = -0.48 p<0.0001 for GLP-1R agonist; Pearson’s r = -0.90 p<0.0001 for DPP-4 inhibitor), but no statistically significant correlations were observed between initial weight and subsequent weight change (Pearson’s r = -0.21 p=0.06 for GLP-1R agonist; Pearson’s r = -0.26 p=0.18 for DPP-4 inhibitor).

Thirty-seven (45.7%) patients on a GLP-1R agonist and seven (24.1%) patients on a DPP-4 inhibitor were also receiving insulin. In 42/44 patients the GLP-1R agonist/DPP-4 inhibitor was started after the patient had been on insulin; they had continued on insulin at the time of this audit. When the patients on insulin were analysed as a subgroup, 68.3% were found to have improved their HbA1c, while 46.3% were found to have improved both weight and HbA1c.

We compared individuals who lost weight and improved glycaemic control (responders) with those who did neither (non-responders). Univariate analyses identified initial weight (p=0.05) and initial HbA1c (p=0.03) as the two variables that were significantly different between the groups. However, when the variables – age of the patient, duration of diabetes, duration of incretin therapy, type of incretin therapy used, whether on insulin, initial HbA1c, and initial weight – were analysed together using binary logistic regression, the only variable that was found to predict a response to treatment was the use of insulin. Patients who do not respond to treatment with incretin mimetic agents appear to be mostly those on insulin (OR 1.96; p=0.047).

**Discussion**

Most oral hypoglycaemic agents used in the treatment of type 2 diabetes have been associated with weight gain in clinical studies. Additionally, it has been shown that these agents do not alter the natural history of type 2 diabetes which inevitably leads to insulin dependency at a variable time since diagnosis. Drugs that are anti-apoptotic to beta cells are likely to prolong the time to insulin dependency. Incretin mimetic agents are anti-apoptotic to beta cells and may also induce ductal neogenesis.

The Association of British Clinical Diabetologists’ nationwide audits did not include patients on DPP-4 inhibitors. These audits were multi-centre and therefore variability in clinical practice at different centres may have had a confounding influence on the outcome. Our audit results reflect clinical practice in a hospital clinic setting and hence strict inclusion and exclusion criteria, as is customary in clinical trials, were not practicable. More patients in the audit were on GLP-1R agonists than a DPP-4 inhibitor; this may be because DPP-4 inhibitors are more likely to be used in primary care on newly-diagnosed patients with type 2 diabetes.

The effects on HbA1c and body weight with the respective agents in this audit were in line with observations from clinical trials. The DPP-4 inhibitors improve HbA1c but have neutral effect on body weight; the GLP-1R agonists cause weight loss and improvement in glycaemic control. DPP-4 inhibitors induce only modest elevations in GLP-1 levels (15–25pmol/L) that are not associated with weight loss or reduced gastric emptying; GLP-1 levels that are sustained and high (60–70pmol/L) are associated with weight loss.

The addition of insulin under specialist supervision was found to be beneficial in more than two-thirds of the patients. Although data are unavailable, in many cases this was associated with a reduction in insulin dose.

Identifying patients’ response to treatment can be best visualised using a scatter plot (Figure 1); the non-responders being in the upper right quadrant and the responders in the lower left. Our finding that non-responders were more likely to be on insulin suggests that their beta-cell function may have declined to the point that insulin was essential to maintain euglycaemia despite the use of incretin-based therapy. DPP-4 inhibitors and GLP-1R agonists mediate their effect primarily by modulating insulin release and would have very limited benefit in the absence of a critical mass of beta cells. They may continue to exert an anti-glucagon effect that would limit glucose output from the liver in the fasting state as has been demonstrated in a recent
Study of type 1 diabetes patients on liraglutide, Vildagliptin, sitagliptin, saxagliptin and liraglutide have now been licensed for use with insulin in type 2 diabetes. The major limitation of this audit is the small sample size and therefore the effect size observed is likely to be different, although the direction of the change remains similar to published clinical trials and audits. The number of patients on DPP-4 inhibitors was small and this is very likely to be the case as these agents are used more often in a primary care setting for the reasons given above. Perhaps a similar audit in primary care may have added value as it would include more patients on these agents.

Conclusion

The audit reaffirms what has been previously known about these agents. Under specialist supervision a hospital clinical setting, the GLP-1R agonists can be safely used with insulin as a significant proportion of patients may benefit with improvement in HbA1c and weight reduction particularly when weight gain is an inevitable side effect of insulin therapy. NICE recommends that those who do not respond to these agents after six months should have their treatment reviewed and this must be borne in mind for reasons given earlier. Failure to identify non-responders early may carry the risk of missing patients who would, before long, require insulin therapy. Perhaps the time has now come for a fresh review of the existing NICE guidance in the light of emerging evidence from multi-centre clinical trials and audits in the UK.

Declaration of interests

There are no conflicts of interest declared.

The project has been approved for publication by the Caldicott Guardian (Medical Director, Sandwell and West Birmingham NHS Trust).

References


Key points

- GLP-1 receptor agonists and DPP-4 inhibitors if used judiciously can improve metabolic control without an adverse effect on weight
- Insulin use with these drugs should not be discouraged, but should always be undertaken under specialist supervision
- A further review of the NICE guidance on GLP-1-related therapy is necessary

Figure 1. Relationship between weight change and change in HbA1c for the study cohort