ABCD nationwide audits of new diabetes therapies

Dr Bob Ryder, ABCD Autumn Meeting
Royal College of Physicians
November 7, 2014
ABCD nationwide exenatide and liraglutide audits

• Real-life data
  – >13000 patients from
  – >150 centres
  – >500 contributors

• There have been (by 2014)
  – 10 published papers
  – 23 abstracts
  – 13 oral presentations

http://www.diabetologists-abcd.org.uk/GLP1_Audits/PresentationsPostersAbstractsExenatide.htm
http://www.diabetologists-abcd.org.uk/GLP1_Audits/PresentationsPostersAbstractsLiraglutide.htm
The ABCD nationwide exendite audit contributors

The following are those we know about.

**ABCD nationwide exendite audit project steering group:** Ryder JE, Walton C, Rowsell S, Adamson K, Dove D, Thozhukat S


**ABCD nationwide exendite audit readership:**


Acknowledgement

The ABCD nationwide exendite audit is an independent audit supported by an unrestricted grant from Eli Lilly Ltd.
The following are those whom we know about.
Dr Bob Ryder
ABCD Clinical Lead

Dr Piya Sen Gupta
ABCD Research Fellow

Dr Ken Thong
ABCD Research Fellow

Dr Chris Walton
ABCD Chairman 20011-2014

ABCD Nationwide Exenatide and Liraglutide Audits
ABCD GLP1-RA audits v clinical trials

The patients treated with GLP1-RAs in real clinical practice are much heavier and with much poorer glycaemic control than in clinical trials of these agents.

Nevertheless the agents have proven to be very effective.

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Difference in HbA1c and weight responses – exenatide v liraglutide audits

- Patients appear to achieve greater HbA1c reduction but lesser weight reduction in the liraglutide audit as compared with the exenatide audit.
- However, there was much less insulin and TZD discontinuation in the liraglutide audit.
- Contributors may have learnt from the previous use of exenatide (2007-2009) to avoid over-reduction of diabetes treatment when initiating liraglutide (2009-2011).

Reality versus NICE guidelines

- Exenatide and liraglutide used outside NICE guidelines in substantial numbers of patients
- Proven effective in outside NICE guidelines
- In particular used with insulin (40% in the nationwide liraglutide audit) with good effect in many patients
- The NICE 6 month weight loss (≥ 3% initial body weight) and HbA1c fall (≥ 1%) criteria are too restrictive by not taking into account the diversity of patients and their responses which can be much more one criterion than the other

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**GLP-1 receptor agonists in type 2 diabetes - NICE guidelines versus clinical practice**

KEN Y THONG, PIYA S GUPTA, MELISSA L CULL, KAREN A ADAMSON, DAVID S DOVE, SUSANNAH V ROWLES, STEPHANIE TARPEY, CATRIONA DUNCAN, JOHN CHALMERS, ROY HARPER, PAULA MCDONALD, URSULA BRENNAN, CHRIS WALTIN, ROBERT EJ RYDER

**Abstract**

Injectable glucagon-like peptide-1 receptor agonists (GLP-1ra) have the distinct advantage of promoting weight loss as well as lowering glucose in type 2 diabetes. Treatment with a GLP-1ra is costly, thereby necessitating a restriction on widespread use, thus in the UK the National Institute for Health and Care Excellence (NICE) has published guidance on the use of these drugs.

In the UK the Association of British Clinical Diabetologists (ABCD) conducted two nationwide audits on the use of exenatide twice daily and liraglutide once daily and noticed that deviations from NICE guidelines were common. Herein data have been used from both audits (following a combined total of 12,655 type 2 diabetes patients) to evaluate these treatment decisions, critically appraise the NICE guidelines and formulate recommendations for the use of GLP-1ra.

**Key words:** Exenatide, liraglutide, GLP-1 receptor agonist, obesity insulin, thiazolidinedione, type 2 diabetes

**Introduction**

In November 2006 exenatide (twice daily; Byetta®) was the first GLP-1ra to be approved in Europe for the treatment of type 2 diabetes. It was introduced in 2007, and the next agent in the class, liraglutide (once daily, Victoza®), was introduced in 2010. GLP-1ra mimic the actions of the natural gut hormone GLP-1, which enhances insulin secretion, reduces glucagon secretion, slows gastric emptying and suppresses appetite. In addition to their glucose-lowering action, GLP-1ra promote weight reduction - unlike sulphonylureas, TZDs and insulins which cause weight gain. The weight loss aspect of GLP-1ra is particularly appealing in the treatment of type 2 diabetes since many patients are overweight or obese.

**NICE guidelines on the use of exenatide and liraglutide**

NICE aims to provide evidence-based guidance to optimise healthcare and promote effective use of resources in the UK. The NICE guidelines for exenatide and liraglutide are similar both in terms of patient selection and defining a therapeutic response to justify continuing treatment (Table 1). These NICE guidelines are influenced by the cost of GLP-1ra treatment, which is much higher than other oral anti-diabetes therapies. Costs of GLP-1ra are typically higher than other third line diabetes therapies such as TZDs or basal insulin (Table 2). A cost-based analysis favours exenatide over liraglutide, which costs less and is more effective when used in combination with metformin.

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Off licence use with insulin

- Off licence exenatide with insulin safe and effective in real clinical practice
- Reduction in insulin dose frequently occurred
- Weight fell
- 1 in 6 patients came off insulin
An important safety issue uncovered

- Some clinicians attempted to stop insulin when starting exenatide in order to stay within guidelines
- This led to harm to the patient in some instances
- For example there are 11 reported cases of ketosis or diabetic ketoacidosis - 7 of these occurred to patients who stopped insulin at the time of exenatide initiation
- Analysis of audit data allowed us to recommend that when starting a GLP1-RA in an insulin-treated patient not to stop the insulin but rather to tail the insulin off during treatment if response to treatment allowed
Pancreatitis

• Alarm raised (BMJ and Channel 4 Dispatches TV programme) in 2013 that incretin therapies might cause pancreatic damage

• We have been able to contribute by publishing data suggesting that in the ABCD audits there is no evidence of such a side effect:
Rates of acute pancreatitis in people with type 2 diabetes

- Not on GLP-1 based therapy: between 5 and 56 per 10,000 person years
- ABCD nationwide exenatide audit: 12 per 10,000 person year
- ABCD nationwide liraglutide audit: 10.8 per 10,000 person years

[Link: http://www.diabetologists-abcd.org.uk/GLP1_Audits/pancreatitis_incidence_exenatide_audit.pdf]
Rates of acute pancreatitis in people with type 2 diabetes

- Rates of acute pancreatitis in the ABCD exenatide and liraglutide audits are at the low end of the rates expected for people with type 2 diabetes in general.

AND

- 75% of the cases of acute pancreatitis in the ABCD exenatide and liraglutide audits had other causes for acute pancreatitis, in particular gall bladder disease
Otherwise unexplained pancreatitis – is it likely to be due to the GLP-1RA?

- ...it is worth remembering that many cases of acute pancreatitis are “idiopathic” ....
- ....hence exenatide or liraglutide may not be the actual cause even if no other cause is found
GLP1-RAs in professional drivers

- Many patients with a professional drivers licence who would lose their jobs if they went onto insulin, have been able to avoid insulin, and maintain similar glycaemic outcomes and keep their jobs by using exenatide or liraglutide.
Liraglutide in renal impairment

• Liraglutide was safe and effective among patients with moderate renal impairment, which has been an exclusion for use.

Safety and efficacy of liraglutide 1.2mg in patients with mild and moderate renal impairment: the ABCD nationwide liraglutide audit

KY Thong1
MRC, PhD Research Fellow, ABCD nationwide audit, London, Consultant Physician and Endocrinologist, Royal Berkshire Hospital, Reading, UK

C Walton2
NHS, Consultant Physician (Diabetes), Hull Royal Infirmary, Hull, UK

REJ Rydal3
RIA, NCF Clinical Lead, ABCD nationwide audit, Consultant Physician (Diabetes), City Hospital, Birmingham, UK

On behalf of the Association of British Clinical Diabetologists (ABCD)/National liraglutide audit contributors4

1Diabetes, City Hospital, Birmingham, UK;
2Diabetes, Hull Royal Infirmary, Hull, UK;
3Audit contributors listed in appendix 1 (available online at www.practicaldiabetes.com).

Abstract
Liraglutide is not predominantly eliminated by renal excretion. We assessed its safety and efficacy among patients with mild and moderate renal impairment. Patients from a nationwide audit of liraglutide (1.2mg) use were divided according to pre-treatment renal function calculated by the Cockcroft-Gault formula. Adverse events, liraglutide discontinuation and changes in HbA1c, weight, systolic blood pressure and serum creatinine were compared between groups of different pre-treatment renal function.

As compared with patients with normal renal function (n=1446), patients with mild renal impairment (n=298) and moderate renal impairment (n=57) were equally likely to report gastrointestinal side effects (adjusted OR 1.11 [95% CI 0.80–1.54] and 0.67 [95% CI 0.33–1.48]), respectively, but more frequently stopped liraglutide due to gastrointestinal side effects (adjusted OR 2.32 [95% CI 1.45–3.74] and 2.37 [95% CI 0.97–5.81]), respectively. Minor hypoglycaemia and acute renal failure were uncommonly reported and were not more frequent among patients with renal impairment. Patients remaining on treatment in all three groups achieved significant HbA1c and weight reduction at six months between -1.1% (95% CI -1.5 to -0.7) and -3.6 to -3.8 (%), respectively. No effect of renal function was associated with the degree of HbA1c and weight reduction. Liraglutide treatment was associated with a small reduction in serum creatinine among patients with renal impairment.

We concluded that liraglutide was safe, efficacious but more frequently discontinued among patients with mild renal impairment. More data are required to establish its safety among patients with moderate or more significant renal impairment. Copyright © 2013 John Wiley & Sons, Practical Diabetes 2013; 30(2): 71–76.

Key words
Liraglutide, GLP-1, diabetics, renal impairment.

Introduction
Liraglutide, an injectable glucagon-like peptide-1 receptor agonist (GLP-1RA), acts by mimicking the endogenous gut hormone GLP-1. The physiological actions of GLP-1 in the body include decreasing glucagon secretion, increasing insulin secretion and slowing gastric emptying. GLP-1 levels are reduced when diabetes ensues, and liraglutide can reverse this process, thereby increasing insulin secretion in patients with renal impairment, as well as reducing glucaeogenic hormones and enhancing glucose disposal. The effects of liraglutide on renal function are still inconclusive. Thong et al. Practical Diabetes 2013; 30(2): 71–76
Diabetes and NAFLD – impact on ALT

- Liraglutide can reduce ALT when it is elevated – ALT being an index of fat in the liver ....
Liraglutide with different insulin regimes

- Liraglutide was effective with all the common insulin regimes - i.e. with:
  - Basal
  - Basal bolus
  - Biphasic
Effectiveness in South Asians

GLP1-RAs may be less effective at improving glycaemic control amongst non-insulin treated South Asians
Liraglutide – predicting treatment response

- Long duration of diabetes and insulin use both predict reduced response with insulin use being the strongest predictor.

Thong et al. Diabetes 2012; 61 (Suppl. 1): 1038P
Switching to liraglutide from BD exenatide or from DPP4 inhibitor

- Improvements in HbA1c and weight are seen when switching from exenatide and DPP4 inhibitors to liraglutide

Ryder and Gough. Presentation at IDF Scientific Update Satellite Meeting, Dubai, December 6 2011
Safety

- In some patients the nausea, vomiting or diarrhoea was so severe that they developed transient acute kidney injury
- There have been no other new safety issues uncovered
Advert

• I hope you agree we have learned a lot from these audits
• *All of you* please join the current ABCD audits!
Please join the current ABCD audits on N3

• Dapagliflozin
• Exenatide QW
What is N3 and why a presence for ABCD?

- N3 is the national broadband network for the NHS, connecting all NHS locations.
- The important thing from ABCD’s point of view is that it is the official secure place for storing patient data of NHS patients and therefore the most appropriate and secure place for holding our nationwide audit data in the future.

SLGT2 inhibitors – a chance to learn in the same way about a new class

- Dapagliflozin
- Exenatide QW

[Insert diagram showing the mechanism of action of SLGT2 inhibitors]

http://www.diabetologists-abcd.org.uk/n3/Dapagliflozin_Audit.htm
Audit tools are very similar – consider doing both at the same time?

- Dapagliflozin
- Exenatide QW

http://www.diabetologists-abcd.org.uk/n3/n3_Audits_Register_Both.htm
Please join the current ABCD audits

- The current tools have “sophisticated output”
- Makes it very easy for you (or your SpR, or DSN, or medical student ...) to analyse your local data
# Dapagliflozin Nationwide Audit

## Export Data
- **Basic Output**
- **Sophisticated Output**

Export on a [ ] monthly basis. (Leave blank not to group)

## Dapagliflozin Followup Questionnaire

### Surgery
- Has this patient had bariatric surgery?
  - [ ] Yes
  - [ ] No

### Current Medical Status
- Patient still taking dapagliflozin?
  - [ ] Yes
  - [ ] Temporarily stopped, to restart
  - [ ] Permanently stopped

### Test Results
- **Date of Visit**
  - [ ] Date of Visit

- **Blood Pressure**
  - [ ] SBP
  - [ ] DBP
  - [ ] Date of Measure

- **Current Weight**
  - [ ] Weight
  - [ ] Date of Measure
  - [ ] BMI

- Were the following blood tests taken on the same day as each other?
  - [ ] Yes
  - [ ] No

- **HbA1c**
  - [ ] percentage value
  - [ ] mmol/mol
  - [ ] Date of Measure

- **Lipids**
  - [ ] Triglyceride Value
  - [ ] HDL Value
  - [ ] Total Cholesterol
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Today - November 7, 2014
Launch of the ABCD nationwide degludec audit

- Even if you have only a couple of patients
- If everyone contributes their couple of patients
- We must aim to get every degludec patient in the UK in the audit

http://www.diabetologists-abcd.org.uk/Degludec/Degludec_Audit.htm
Variability in glucose-lowering effect over 24 hours at steady state

Area under the GIR curve (time interval, hours)

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Exenatide QW
Worldwide Audit

Login

Username
Password
Login

Click here to reset your password

The ABCD worldwide exenatide QW audit is an independent audit supported by an unrestricted grant from Astra Zeneca.

Created by Harvey Walsh Ltd under the direction of the Association of British Clinical Diabetologists.
Please join the current ABCD audits

• Dapagliflozin
• Exenatide QW
• Degludec

Do it now - volunteer - email Bob Ryder

bob.ryder@nhs.net

or

abcd.audits@diabetologists.org.uk