Update on combination GLP-1 receptor agonist and insulin therapy in the management of type 2 diabetes

Hala Alsafadi, Caroline Atkinson, Vinod Patel

Citation: Alsafadi H, Atkinson C, Patel V (2013) Update on combination GLP-1 receptor agonist and insulin therapy in the management of type 2 diabetes. *Diabesity in Practice* **2**: 148–53

Article points

1. Glucagon-like peptide-1 receptor agonists and insulin combination therapy is a treatment option to consider in some obese people with type 2 diabetes and poor glycaemic control.
2. These individuals can be challenging to treat, and even small benefits in terms of weight loss, improved glycaemic control or a reduction in daily insulin requirements may have significant clinical impact in the long term.
3. The authors argue that current licensing remains restrictive and that further study and national guidance are urgently needed in this area.

Key words

- GLP-1 receptor agonists
- Guidelines
- Insulin

Authors

Hala Alsafadi is a Consultant Diabetologist, Southern Health NHS Foundation Trust; Caroline Atkinson is a Diabetes Specialist Nurse, Southern Health NHS Foundation Trust; and Vinod Patel is Associate Professor (Reader) in Clinical Skills, University of Warwick, and a Consultant in Diabetes and Endocrinology, George Eliot Hospital, Nuneaton.

Type 2 diabetes is a chronic and progressive multifactorial disease characterised by insulin resistance and progressive beta-cell failure. Treatment often must be intensified over time, usually through a combination of agents that address both insulin resistance and beta-cell dysfunction. The use of glucagon-like peptide-1 (GLP-1) receptor agonists as add-on therapy to oral agents in the treatment of type 2 diabetes is now well established in clinical practice within the UK. The authors discuss the evidence on therapeutic regimens involving both a GLP-1 receptor agonist and insulin.

Type 2 diabetes is a chronic and progressive multifactorial disease characterised by insulin resistance and progressive beta-cell failure. Treatment often must be intensified over time, usually through a combination of agents that address both insulin resistance and beta-cell dysfunction (UK Prospective Diabetes Study Group, 1998). Some older therapies are associated with an increased risk of hypoglycaemia and weight gain, which may reduce adherence and lead to greater insulin resistance and worse glycaemic control (Green and Feinglos, 2007). Glucagon-like peptide-1 (GLP-1) receptor agonists bring about a glucose-dependent increase in insulin secretion and, hence, are less likely to cause hypoglycaemia and have more favourable effects on weight than older agents such as sulphonylureas (Shyangdan et al, 2011). The use of GLP-1 receptor agonists as add-on therapy to oral agents in the treatment of type 2 diabetes is now well established in clinical practice within the UK. Since twice-daily exenatide was introduced in 2007, there has been considerable interest in the role of combining a GLP-1 receptor agonist with insulin in obese people with type 2 diabetes, in order to improve glycaemic control with potential secondary benefits on weight.

GLP-1 receptor agonists

GLP-1 is a naturally occurring peptide hormone that is released in the gastrointestinal tract within minutes after eating a meal. It is known to suppress glucagon secretion from pancreatic alpha-cells and stimulate glucose-dependent insulin secretion by pancreatic beta-cells. It also delays gastric emptying and decreases appetite (Holst, 2007). The use of GLP-1 receptor agonist therapy in the treatment of type 2 diabetes has become established in clinical practice within the UK since the launch of the first agent in the class, twice-daily exenatide, in 2007, and subsequently that of liraglutide, once-weekly exenatide and lixisenatide. Trends towards increased use of GLP-1 receptor agonists can be inferred from national prescribing data showing that the cost per item in the "other antidiabetes drug" category, primarily consisting of GLP-1 receptor agonists, has increased substantially (by 144%) since 2007 (Health and Social Care Information Centre [HSCIC], 2011). We believe that the reason for this, beyond efficacy in lowering blood glucose levels, is the potential for beneficial effects on weight and possibly blood pressure, which offer differentiation from a number of other therapeutic modalities in diabetes (Shyangdan

et al, 2011). In our experience, many people with type 2 diabetes who would otherwise have been started on insulin, and who might thus have gained further amounts of weight, have managed to improve their glycaemic control alongside weight loss with GLP-1 receptor agonist treatment. Gastrointestinal side effects, including nausea and vomiting, appear to be the most likely adverse effects seen with GLP-1 receptor agonist treatment (Holst, 2007). In our own experience, these side effects generally occur early on in the treatment, tend to be transient and rarely result in treatment withdrawal.

Controversy still exists regarding the potential regenerative influences of incretin therapy on pancreatic beta-cells versus possible adverse pancreatic proliferative effects. An examination of pancreas tissue from age-matched organ donors with type 2 diabetes treated with incretin-based therapy (n=8) or other therapy (n=12) and controls without diabetes (n=14) recently revealed an approximately 40% increased pancreatic mass in people treated with incretin-based therapy, with both increased exocrine cell proliferation and dysplasia. The pancreas tissue in people treated with incretin-based therapy was deemed notable for alpha-cell hyperplasia and glucagon-expressing microadenomas (in three of eight samples), and a neuroendocrine tumour (Butler et al, 2013). After reviewing the emerging evidence, the European Medicines Agency (2013), the US Food and Drug Administration (2013) and the Medicines and Healthcare products Regulatory Agency (2013) all currently advise that healthcare professionals make no changes to their current practice in relation to these agents. The potential link between these therapies and pancreatitis has been known for several years, and it is reflected in the current prescribing information (Bristol Myers Squibb–AstraZeneca EEIG, 2013a; 2013b; Novo Nordisk, 2013; Sanofi 2013a; 2013b). All individuals should be adequately assessed with regard to their potential risk of pancreatitis; furthermore, they should all be advised about pancreatitis, and informed of how to recognise early symptoms and to seek medical advice should these occur. The SAFEGUARD study is currently underway to further investigate this issue (http://clinicaltrials.gov/ct2/show/NCT01744236 [accessed 20.11.13]).

There are currently four GLP-1 receptor agonists available to use in the UK: exenatide once weekly, exenatide twice daily, liraglutide and lixisenatide once daily. The high cost of these agents relative to older therapies may sometimes limit their general use in the management of type 2 diabetes (Woehl et al, 2008; Waugh et al, 2010). NICE (2009; 2010; 2012) guidance and guidelines recommend adding a GLP-1 receptor agonist as third-line therapy to metformin and sulphonylurea (or in a dual-therapy regimen, under specified circumstances, in the case of agents covered by technology appraisals [NICE, 2010; 2012] subsequent to the 2009 type 2 diabetes guideline update) when HbA_{1c} remains inadequate (at least 58 mmol/mol [7.5%]) and the person has either:

- A BMI ≥35.0 kg/m^2 in those of European descent (with appropriate adjustment for other ethnic groups) and specific psychological or medical problems associated with high body weight.
- A BMI <35.0 kg/m^2 if therapy with insulin would have significant occupational implications or if weight loss would benefit other significant obesity-related comorbidities.

NICE (2009; 2010; 2012) also states that GLP-1 receptor agonist therapy should only be continued if there is evidence of at least 11 mmol/mol (1%) reduction in HbA_{1c} and at least a 3% weight loss of initial body weight at 6 months.

Combination GLP-1 receptor agonist and insulin therapy

The therapy combination of insulin and a GLP-1 receptor agonist may be an attractive option for many people with obesity and poorly controlled type 2 diabetes. Many such individuals, despite insulin treatment, may remain poorly controlled even with escalation of the dose of insulin, while weight continues to increase as a result. There is evidence of improving glycaemic control and potential

Page points

1. There are currently four glucagon-like peptide-1 (GLP-1) receptor agonists available to use in the UK: exenatide once weekly, exenatide twice daily, liraglutide and lixisenatide once daily.
2. The therapy combination of insulin and a GLP-1 receptor agonist may be an attractive option for many people with obesity and poorly controlled type 2 diabetes.

Page points

1. Despite the fact that the current licences are restrictive, there is evidence of significant use of combination therapy in real life.
2. One disadvantage of combining insulin and a glucagon-like peptide-1 receptor agonist is the increase in the total number of injections per day, which may not be preferable for some people with diabetes.

weight loss and no evidence of serious adverse effects when combining insulin and GLP-1 receptor agonist therapy (from an exenatide audit [Thong et al, 2011b]).

The current licensing for combination treatment, which may feel confusing and restricting for many practitioners, can be summarised as follows:

- Exenatide twice daily is now licensed in the UK for add-on therapy to basal insulin, with or without metformin and/or pioglitazone, in adults who have not reached adequate control with these agents (Bristol Myers Squibb–AstraZeneca EEIG, 2013b).
- Exenatide once weekly is not at present licensed for combination with insulin (Bristol Myers Squibb–AstraZeneca EEIG, 2013a).
- Liraglutide is not licensed for add-on therapy to insulin (Novo Nordisk, 2013), but insulin detemir is licensed to be added on to liraglutide (Novo Nordisk, 2012).
- Lixisenatide, the most recently launched GLP-1 receptor agonist, is licensed to be added to basal insulin (Sanofi, 2013a; 2013b).

Despite the fact that the current licenses are restrictive, there is evidence of significant use of combination therapy in real life (Ryder et al, 2011b; Thong et al, 2011b). In clinical practice, there are two main types of prescribing: one is the adding of a GLP-1 receptor agonist to insulin in order to reduce daily insulin requirement and avoid weight gain in individuals with already-known insulin resistance. The other is the addition of insulin to GLP-1 receptor agonists in people with progressive type 2 diabetes who have sub-optimal control owing to the progression of beta-cell dysfunction. It seems likely that the number of individuals in the second category will be on the increase, in line with the rising number of people now established on GLP-1 receptor agonist therapy added onto oral antidiabetes agents (HSCIC, 2011).

One disadvantage of combining insulin and a GLP-1 receptor agonist is the increase in the total number of injections per day, which may not be preferable for some people with diabetes (Thong et al, 2011b). A factor that may also discourage its use is the cost of combination drug treatment. Clearly, this important issue warrants an economic analysis on the cost of GLP-1 receptor agonists as opposed to the strategy of escalating insulin doses, or making no regimen change, in insulin-treated people with type 2 diabetes. Factors that may attenuate the cost of adding GLP-1 receptor agonists in such individuals could include further HbA_{1c} reduction, weight reduction, insulin dose reduction and, possibly, a reduction in multiple health visits for insulin titration.

It is our experience that many diabetologists are reasonably comfortable with using a combination of insulin and GLP-1 receptor agonists off-licence in certain circumstances, as might be the case for the more "challenging" individuals with obesity, severe insulin resistance and poor glycaemic control. We feel that there is an urgent need for national guidelines to provide regulation for the use of combination treatment outside current licences. Local guidelines from Hertfordshire (http://bit.ly/19a4vzm [accessed 20.11.13]) recommend the restricted use of combination treatment in people who have a BMI >35 kg/m^2 and poor glycaemic control (HbA_{1c} >69 mmol/mol [8.5%]) and also advise that:

- Individuals should have seen a dietitian and attempted to lose weight over the previous 6 months.
- They should also "be willing" to switch from an insulin analogue to a human insulin product (unless they are at risk of hypoglycaemia).
- GLP-1 receptor agonists should be stopped at 6 months if the HbA_{1c} has not fallen by at least 5 mmol/mol (0.5%) and there is no weight loss or change in insulin dose.
- Continuation criteria at 12 months include:
  - improvement in HbA_{1c} of **at least** 11 mmol/mol *and* weight reduction of **at least** 3%; *or*,
  - improvement in HbA_{1c} of **at least** 11 mmol/mol *and* insulin dose reduction of **at least** 50%; *or*,
  - improvement in HbA_{1c} of **at least** 5 mmol/mol *and* weight reduction of **at least** 10%.

- GLP-1 receptor agonists should be withdrawn beyond 12 months if the HbA_{1c}, weight or insulin dose deteriorates to a point where the individual would not have met the 12-month continuation criteria.

Evidence from ABCD audits: real-life experience

The Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit was performed in 2008. Data were collected from 126 UK centres over 1 year on 4857 individuals. Just under 40% of these individuals were taking combination insulin and exenatide (Thong et al, 2011b). The people analysed in the audit, on average, were obese (mean BMI, 40.0 kg/m^2), had poor glycaemic control (mean HbA_{1c}, 79.8 mmol/mol [9.45%]) and had been diagnosed with diabetes for a relatively long time (mean duration of diabetes, 11 years). As such, they were generally reflective of what we consider to be the most challenging group of individuals encountered in the diabetes clinic.

Exenatide was added to insulin in 1257 people. Among these individuals for whom data were available, HbA_{1c} was reduced by 5.6 mmol/mol (0.51%) after a mean (range) of 26 (7–164) weeks (Thong et al, 2011b). There was no significant weight reduction, but insulin dose was significantly reduced, by a mean of 42 units/day (Ryder et al, 2010). Exenatide initiation was also associated with discontinuation of glitazones and sulphonylureas in some people on these treatments, and 16.6% of people for whom exenatide was added to insulin were later able to come off insulin (Thong et al, 2011b).

Among the people on combination treatment, 28.4% reported gastro-intestinal side effects. There was a slight increase in hypoglycaemia in people receiving combination treatment compared with those not receiving insulin (8.9% versus 6.1%; $P<0.001$), and this was mainly driven by hypoglycaemia from background insulin therapy. There was no evidence of other safety concerns (Thong et al, 2011b).

There were 11 reported cases of ketosis or diabetic ketoacidosis in the audit and seven of these occurred in people whose physician stopped insulin at exenatide initiation in an attempt to stay within the licensing restriction. (We feel that the ketosis or diabetic ketoacidosis was probably due to people stopping or not increasing insulin treatment in a setting where they are becoming almost totally insulin dependent, as the natural history of type 2 progresses in these specific individuals.) Therefore, the ABCD has recommended not to stop the insulin but rather to add exenatide to the insulin, with appropriate dose adjustment depending on the case concerned, but with the aim of weaning off the insulin in appropriate individuals instead (Thong et al, 2011a).

Treatment satisfaction was also examined in a subgroup of the audit: 58% of responders reported positive satisfaction outcomes, compared with 74% in the non-insulin group (Thong et al, 2011b).

Early reports from the ABCD nationwide liraglutide audit are showing similar results. Forty per cent of individuals were on insulin at the time of liraglutide initiation, and 37% continued insulin with only 3% stopping it (Ryder et al, 2011a).

Clinical trial evidence

Numerous observational studies have evaluated the combination of GLP-1 receptor agonists and insulin in the management of type 2 diabetes, but, to date, there have been few randomised clinical trials (Tzefos and Olin, 2010).

Exenatide

A randomised controlled trial with 261 participants compared the addition of exenatide twice daily to insulin glargine plus metformin and/or pioglitazone over 30 weeks versus the addition of placebo. Participants had a mean BMI of 33 kg/m^2, a mean HbA_{1c} of 68 mmol/mol (8.4%) and a mean diabetes duration of 12 years. Treatment with exenatide twice daily as an add-on therapy resulted in a mean 7.5 mmol/mol (0.69%) reduction in HbA_{1c}; there was also a mean weight loss of 1.8 kg in the exenatide twice daily group (compared with a mean increase of 1.0 kg in the placebo group; $P<0.001$ for between-group difference). Insulin dose was

"Numerous observational studies have evaluated the combination of glucagon-like peptide-1 receptor agonists and insulin in the management of type 2 diabetes, but, to date, there have been few randomised clinical trials."

Page points

1. It is clear from both the Association of British Clinical Diabetologists audits and the randomised trials discussed that only a minority of individuals would meet NICE criteria for continuing glucagon-like peptide-1 receptor agonist treatment beyond 6 months.
2. This raises questions about the appropriateness of NICE targets for this challenging subgroup of people with diabetes.

titrated in both groups, but the increase in the exenatide group was lower (13 units/day versus 20 units/day; P=0.03). Gastrointestinal side effects were more frequent in the exenatide twice daily group (e.g. nausea, 41% versus 8%), but there was no increase in hypoglycaemia or in serious adverse effects (Buse et al, 2011).

Subgroup analysis of the study found that participants with the longest duration of diabetes (over 15 years) had the greatest benefit in HbA_{1c} reduction and weight loss. Severely obese people, with a BMI >36 kg/m^2, had less reduction in HbA_{1c} compared with those who had a BMI of <30 kg/m^2 or 30–36 kg/m^2 (Rosenstock et al, 2012).

Liraglutide

A 26-week, randomised, open-label trial of 323 people looked at the addition of insulin detemir to liraglutide and metformin (versus not adding insulin). At baseline, participants had a mean HbA_{1c} of 60 mmol/mol (7.6%), a mean BMI of approximately 33 kg/m^2 and a mean diabetes duration of a little under 9 years. The addition of insulin reduced HbA_{1c} by 5.5 mmol/mol (0.5%), while there was an HbA_{1c} increase of 0.2 mmol/mol (0.02%) in the control group (P<0.0001 for difference). Weight loss with the addition of insulin detemir was less than in the control group (–1.6 kg versus –0.95 kg; P=0.03 for difference); however, this was on the background of a mean 3.5 kg weight loss during the run-in period. Treatment was generally well tolerated. For instance, diarrhoea was reported as an adverse event in 11.7% of the group receiving insulin detemir and 6.9% of the group not receiving the insulin, while the respective figures for nausea were 3.7% and 5.7%. There was a slight increase in mild hypoglycaemia; a small number of serious adverse effects were reported (in 5.5% of the group receiving insulin detemir and 3.8% of the other group; DeVries et al, 2012).

Based on a preliminary report of this study, among other research, the European Medicines Association approved the use of insulin detemir as add-on therapy to liraglutide but did not support the use of liraglutide as add-on therapy to insulin (European Medicine Agency, 2011).

Lixisenatide

In the GetGoal-L-Asia randomised placebo-controlled trial, lixisenatide 20 µg once daily or placebo was added to insulin glargine, insulin detemir or NPH insulin over 24 weeks in 311 Asian people with type 2 diabetes. At baseline, participants had a mean age of 58.4 years, a mean BMI of 25.3 kg/m^2, a mean diabetes duration of 13.9 years and a mean HbA_{1c} of 69 mmol/mol (8.5%). The participants who received add-on lixisenatide had a drop in HbA_{1c}, relative to the placebo group, of 9.6 mmol/mol (0.88%; least-squares mean difference; P<0.0001), but without significant weight loss differences. Nausea and vomiting were reported in 39.6% and 18.2% of participants, respectively, who received lixisenatide, compared with 4.5% and 1.9% taking placebo. Symptomatic hypoglycaemia was more frequent with lixisenatide than placebo (42.9% versus 23.6%), but was similar between groups (32.6 and 28.3%, respectively) in those not receiving sulphonylureas. There were no reports of severe hypoglycaemia (Seino et al, 2012).

A comment on NICE targets

It is clear from both the ABCD audits and the randomised trials discussed that only a minority of individuals would meet NICE criteria for continuing GLP-1 receptor agonist treatment beyond 6 months, as described earlier. In the exenatide audit (Thong et al, 2011b), for instance, only 34.2% of people on combination therapy achieved an HbA_{1c} reduction greater than 11 mmol/mol (1%). Also of note here is the study by Rosenstock et al (2012), which found that participants with a BMI >36 kg/m^2 had a lesser reduction in HbA_{1c} compared with those who had a BMI of <30 kg/m^2 or 30–36 kg/m^2, when exenatide was added to insulin glargine. These observations raise questions about the appropriateness of NICE targets for this challenging subgroup of people with diabetes.

Conclusion

GLP-1 receptor agonists and insulin combination therapy is a logical option to consider in obese people with type 2 diabetes

and poor glycaemic control. These subgroups of individuals are challenging to treat, with few alternative options. Even small benefits in terms of weight loss, improved glycaemic control or a reduction in daily insulin requirements may have significant clinical impact on individuals in the long term. Current licensing remains restrictive, and further study and national guidance are urgently needed in this area. As part of this, the costs of combination therapy and NHS budgetary constraints, something which is beyond the scope of this article, would need to be considered. ■

Bristol Myers Squibb–AstraZeneca EEIG (2013a) *BYDUREON 2 mg powder and solvent for prolonged-release suspension for injection*. Available at: http://medicines.org.uk/emc/medicine/24665 (accessed 20.11.13)

Bristol Myers Squibb–AstraZeneca EEIG (2013b) *Byetta 5 micrograms solution for injection, prefilled pen. Byetta 10 micrograms solution for injection, prefilled pen*. Available at: http://medicines.org.uk/emc/medicine/19257 (accessed 20.11.13)

Buse JB, Bergenstal RM, Glass LC et al (2011) Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* **154**: 103–12

Butler AE, Campbell-Thompson M, Gurlo T et al (2013) Marked expansion of exocrine and endocrine pancreas with incretin therapy in humans with increased exocrine pancreas dysplasia and the potential for glucagon-producing neuroendocrine tumors. *Diabetes* **62**: 2595–62

DeVries JH, Bain SC, Rodbard HW et al (2012) Sequential intensification of metformin treatment in type 2 diabetes with liraglutide followed by randomized addition of basal insulin prompted by A1C targets. *Diabetes Care* **35**: 1446–54

European Medicines Agency (2011) *Victoza: EPAR Assessment Report – Variation*. EMA, London. Available at: http://bit.ly/1bJAHGO (accessed 20.11.13)

European Medicines Agency (2013) *European Medicines Agency investigates findings on pancreatic risks with GLP-1-based therapies for type-2 diabetes*. EMA, London. Available at: http://bit.ly/14szWS4 (accessed 20.11.13)

Green J, Feinglos M (2007) Update on type 2 diabetes mellitus: understanding changes in the diabetes treatment paradigm. *Int J Clin Pract Suppl* (154): 3–11

Health and Social Care Information Centre (2011) *Prescribing for diabetes in England – 2005–2006 to 2010–2011*. HSCIC, Leeds. Available at: http://www.hscic.gov.uk/catalogue/PUB01493 (accessed 20.11.13)

Holst JJ (2007) The physiology of glucagon-like peptide 1. *Physiol Rev* **87**: 1409–39

Medicines and Healthcare products Regulatory Agency (2013) *MHRA statement on GLP-1 medicines used to treat diabetes*. MHRA, London. Available at: http://www.mhra.gov.uk/NewsCentre/CON286853 (accessed 20.11.13)

NICE (2009) *Type 2 Diabetes – newer agents (partial update of CG66) (CG87)*. NICE, London. Available at: http://www.nice.org.uk/cg87 (accessed 20.11.13)

NICE (2010) *Diabetes (type 2) – liraglutide* (TA203). NICE, London. Available at: http://www.nice.org.uk/ta203 (accessed 20.11.13)

NICE (2012) *Diabetes (type 2) – exenatide (prolonged release)* (TA248). NICE, London. Available at: http://www.nice.org.uk/ta248 (accessed 20.11.13)

Novo Nordisk (2012) *Levemir Cartridge 100 U/ml – Penfill, Levemir Pre-filled Pen 100 U/ml – FlexPen and InnoLet*. Available at: http://medicines.org.uk/emc/medicine/14584 (accessed 20.11.13)

Novo Nordisk (2013) *Victoza 6 mg/ml solution for injection in pre-filled pen*. Available at: http://medicines.org.uk/emc/medicine/21986 (accessed 20.11.13)

Rosenstock J, Shenouda SK, Bergenstal RM et al (2012) Baseline factors associated with glycemic control and weight loss when exenatide twice daily is added to optimized insulin glargine in patients with type 2 diabetes. *Diabetes Care* **35**: 955–8

Ryder RE, Thong KY, Cull ML et al (2010). The Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit. *Practical Diabetes International* **27**: 352–357b

Ryder B, Thong K, Walton C, Winocour P (2011a) *GLP-1 agonists in Combination with Insulin in the Treatment of Type 2 Diabetes* (letter). Association of British Clinical Diabetologists, Malmesbury. Available at: http://bit.ly/IFtu1j (accessed 20.11.13)

Ryder RE, Thong KY, Cull ML et al (2011b) The Association of British Clinical Diabetologists (ABCD) nationwide exenatide and liraglutide audits. *Diabetologia* **54**(Suppl 1): S326

Sanofi (2013a) *Lyxumia 10 micrograms solution for injection*. Available at: http://medicines.org.uk/emc/medicine/27405 (accessed 20.11.13)

Sanofi (2013b) *Lyxumia 20 micrograms solution for injection*. Available at: http://medicines.org.uk/emc/medicine/27406 (accessed 20.11.13)

Seino Y, Min KW, Niemoeller E et al (2012) Randomized, double-blind, placebo-controlled trial of the once-daily GLP-1 receptor agonist lixisenatide in Asian patients with type 2 diabetes insufficiently controlled on basal insulin with or without a sulfonylurea (GetGoal-L-Asia). *Diabetes Obes Metab* **14**: 910–7

Shyangdan DS, Royle P, Clar C et al (2011) Glucagon-like peptide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev* (10): CD006423

Thong KY, Jose B, Blann AD et al (2011a) Response at 3 months to insulin dose decisions made at exenatide initiation in the Association of British Clinical Diabetologists (ABCD) nationwide exenatide audit. *Diabetes Res Clin Pract* **93**: e87–91

Thong KY, Jose B, Sukumar N et al (2011b) Safety, efficacy and tolerability of exenatide in combination with insulin in the Association of British Clinical Diabetologists nationwide exenatide audit. *Diabetes Obes Metab* **13**: 703–10

Thong KY, Walton C, Ryder RE et al (2012) ABCD nationwide Liraglutide audit contributors. Insulin necessity is better than diabetes duration in predicting liraglutide treatment response: The Association of British Clinical Diabetologists (ABCD) Nationwide Liraglutide Audit. *Diabetes* **61**(Suppl 1): 1038P

Tzefos M, Olin JL (2010) Glucagon-like peptide-1 analog and insulin combination therapy in the management of adults with type 2 diabetes mellitus. *Ann Pharmacother* **44**: 1294–300

UK Prospective Diabetes Study Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* **352**: 837–53

US Food and Drug Administration (2013) *FDA Drug Safety Communication: FDA investigating reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas from incretin mimetic drugs for type 2 diabetes*. FDA, Silver Spring, MD, USA. Available at: http://1.usa.gov/1fG9eIH (accessed 20.11.13)

Waugh N, Cummins E, Royle P (2010) Newer agents for blood glucose control in type 2 diabetes: systematic review and economic evaluation. *Health Technol Assess* **14**: 1–248

Woehl A, Evans M, Tetlow AP, McEwan P (2008) Evaluation of the cost effectiveness of exenatide versus insulin glargine in patients with sub-optimally controlled type 2 diabetes in the United Kingdom. *Cardiovasc Diabetol* **7**: 24

"Glucagon-like peptide-1 receptor agonists and insulin combination therapy is a logical option to consider in obese people with type 2 diabetes and poor glycaemic control."