Glucagon-like peptide-1 agonists in the treatment of type 2 diabetes

This review discusses the rationale behind escalation of treatment for type 2 diabetes, and argues that after failure of oral medication the next logical treatment is a glucagon-like peptide-1 agonist.

There are many drivers encouraging the pursuit of lower glycaemic targets in type 2 diabetes. The Quality and Outcomes Framework reimburses GPs for attaining a particular level of glycosylated haemoglobin (HbA_{1c}) in a certain proportion of patients. A strong evidence base demonstrates that early aggressive treatment of type 2 diabetes reduces microvascular complications affecting the eyes, kidneys and feet (UK Prospective Diabetes Study (UKPDS) Group, 1998a), but also the macro-vascular complications of myocardial infarction and stroke as well as death for many years thereafter (Holman et al, 2008). Intuitively, a more 'normal' blood glucose would seem sensible and was a target well before there was an evidence base to support it. However, a number of studies have demonstrated that aggressive blood glucose lowering in patients at a later stage of their disease can sometimes be detrimental, and may even increase mortality (Action to Control Cardiovascular Risk in Diabetes Study Group et al, 2008). Thus, clinicians are currently caught in a dilemma, with much more uncertainty than before as to how aggressively type 2 diabetes should be treated and with what medications. This review argues that glucagon-like peptide-1 (GLP-1)-based therapies can provide a solution to this quandary and are the most logical choice after oral treatments for type 2 diabetes.

There is now overwhelming evidence to suggest that, if tolerated and appropriate, metformin should be the first-line treatment for type 2 diabetes, causing a greater reduction in morbidity and mortality than other agents (UK Prospective Diabetes Study (UKPDS) Group, 1998b). Traditionally patients have been given additional oral agents; sulphonylureas, pioglitazone or dipeptidyl peptidase-4 (DPP-4) inhibitors after metformin fails to improve glycaemic control. The main reasons for this are not necessarily evidence or efficacy based, but may be more based on reluctance by doctors and their patients to initiate injections and on costs, or just general treatment inertia. The oral agents tend to be nearer the start of treatment algorithms such as that from the National Institute for Health and Clinical Excellence (2009) and thus this is unlikely to change significantly. One of the current major areas of divergence and disagreement is what to do when combination oral agents fail to control rising glucose levels. The two main options as classes of agent are the GLP-1 agonists and insulin. Plentiful evidence suggests that this is a difficult decision to make, as the average HbA_{1c} at initiation of injectable therapy is well above the level that is considered acceptable, over 9% in a number of studies (Dale et al, 2010).

GLP-1 is a physiological incretin in man (Edwards et al, 1999). Type 2 diabetes is a disease associated with a reduction in the incretin effect (Nauck et al, 1986), this reduction seems to occur side by side with the development of diabetes. Thus, treatment with GLP-1 agonists would seem a logical way to try and reverse that abnormality and normalize blood glucose levels. Indeed, while regular subcutaneous injections of GLP-1 improved glycaemic control somewhat (Todd et al, 1998), continuous GLP-1 in the form of a 24-hour infusion almost normalizes hyperglycaemia in type 2 diabetes (Rachman et al, 1997). In contrast, type 2 diabetes is usually associated with obesity, an insulin resistant state, and at diagnosis and for many years thereafter patients have an excess of insulin, not too little. The logic to insulin being the next treatment at this stage does not appear obvious. What are the main advantages and disadvantages of these agents over one another? Following the very recent 25th anniversary of the discovery of the role of GLP-1 (Kreymann et al, 1987; Mojsov et al, 1987; Orskov et al, 1987) and the 90th anniversary of the discovery of the role of insulin (Banting et al, 1922) it seems pertinent to assess these 'new' agents (exenatide, liraglutide and exenatide long-acting release) against the 'old'.

Table 1 summarizes some of the attributes that might be considered important in selection of an injectable agent, and the effects of the two options.

Reduction in mortality

A reduction in mortality with insulin seems obvious; since its discovery in 1922 surely there is plentiful evidence that it reduces mortality in type 2 diabetes? In fact, the UK Prospective Diabetes Study follow-up data published in 2008 were the first data to demonstrate that insulin reduces mortality (Holman et al, 2008). Insulin did not reduce mortality in the original UK Prospective Diabetes Study data (1998a) and in many other multicentre studies. It would appear that use in certain patients

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is even associated with an increase in mortality (Action to Control Cardiovascular Risk in Diabetes Study Group et al, 2008). The exact reason behind this is unclear, but what is clear is that patient selection is paramount, as is avoidance of hypoglycaemia.

No GLP-1 agonist has been shown to reduce mortality. Nikolaidis et al (2004) demonstrated that GLP-1 improved morbidity and left ventricular ejection fraction in a small study when given intravenously to patients with left ventricular dysfunction post myocardial infarction. Its effects below would be expected to be advantageous, so the available data would tend to indicate positive outcomes, but hard end point data are awaited. A number of cardiovascular end point studies are ongoing with the GLP-1 agonists with some scheduled to finish as early as 2015. All that can probably currently be concluded is that it appears that the GLP-1 agonists are not associated with a significant increase in mortality.

Reduction in morbidity

Insulin definitely reduces morbidity in type 2 diabetes? Well, it was certainly shown that use of a sulphonylurea or insulin reduced microvascular end points in UK Prospective Diabetes Study 33 (1998a) and use of either reduced macrovascular end points in the UK Prospective Diabetes Study follow up (Holman et al, 2008), although whether this was an effect of one or both has never been elucidated. So data are quite scarce demonstrating a beneficial effect of insulin on morbidity in type 2 diabetes.

The data are also scarce for GLP-1 agonists although an exenatide insurance database demonstrated reduced cardiovascular risk, and a meta-analysis by Ratner et al (2011) tended towards a reduced cardiovascular risk. However, the published studies are too small and short to definitively assess an effect in either direction.

Efficacy

Efficacy studies of insulin are difficult to interpret as the titration regimens are variable and the number of insulin regimens is potentially virtually infinite. However, there are now a number of direct comparator studies of insulin against the GLP-1 agonists.

Aggressive titration of a four times a day insulin combination regimen is likely to be more efficacious than a GLP-1 agonist, however, in reality the likely treatment that most patients with type 2 diabetes are initiated on is a basal insulin. Not surprisingly the majority of comparator studies between GLP-1 agonists and insulin are *vs* a basal insulin. The first reported comparative study between glargine and exenatide by Heine et al (2005) showed an identical 1.1% reduction in HbA_{1c} when insulin was titrated to a target fasting plasma glucose of less than 5.6 mmol/litre. The LEAD 5 study compared liraglutide with once daily glargine, liraglutide reduced HbA_{1c} by 1.3% *vs* 1.1% for glargine, a statistically significant reduction (Russell-Jones et al, 2009), although this was with a dose of liraglutide of 1.8 mg, rarely used in clinical practice. Similarly, once-weekly exenatide in the DURATION-3 study was compared with glargine aggressively titrated to a fasting glucose of 4–5.5 mmol/litre, once-weekly exenatide reduced HbA_{1c} by 1.5%, significantly greater than 1.3% with glargine (P=0.017) (Diamant et al, 2010). All three of these studies took place over 6 months, and longer comparative data are required to see whether the effects last.

Table 1. Comparison of glucagon-like peptide-1 agonists and basal insulin

	Glucagon-like peptide-1 agonists	Basal insulin
Reduction in mortality	Not known	Yes, just recently
Reduction in morbidity	Maybe	Yes
Efficacy at improving glycaemic control	Equal or greater, reduce postprandial	Similar or less, little postprandial effect
Frequency of hypoglycaemia	Rare unless combined with agent that can cause	Common
Effect on weight	Reduce	Increase
Effect on blood pressure	May reduce	Little effect
Side effects	Gastrointestinal common	Lipodystrophy, as above
Cost	More expensive	Cheaper, analogs less so
Special cases, e.g. drivers	Recommended in special circumstances	May necessitate job change
Recommendations and guidelines	Second line	First line

There is considerable mounting evidence to suggest that it is not only HbA_{1c} that is important with relation to cardiovascular morbidity. Postprandial glucose seems to be more important than fasting glucose in predicting cardiovascular disease (Bonora and Muggeo, 2001). Exenatide reduces postprandial glucose levels significantly more than glargine with a seven-point daily self-monitored glucose (Heine et al, 2005), again pointing to a cardiovascularly protective effect of the GLP-1 agonists compared to insulin.

Hypoglycaemia

Hypoglycaemia is an important side effect of many treatments for diabetes, with analysts of the ACCORD data putting the excess mortality in the intensive arm at least partly down to an increase in hypoglycaemia (Action to Control Cardiovascular Risk in Diabetes Study Group et al, 2008; Dluhy and McMahon, 2008). There is no question that any insulin regimen causes much more hypoglycaemia than a GLP-1 agonist, and it would appear that GLP-1 agonists in the absence of a sulphonlyurea probably cause minimal or no hypoglycaemia compared with placebo (Dluhy and McMahon, 2008; Russell-Jones et al, 2009; Diamant et al, 2010). Hypoglycaemia, as well as being associated with increased mortality, is the most disliked aspect of diabetes treatment by patients and causes huge lack of compliance and decrease in quality of life in

patients with type 2 diabetes (Green et al, 2012). The reduction in incidence of hypoglycaemia with the GLP-1 agonists compared with insulin is probably a major factor for their increased popularity among prescribers.

Effect on weight

One of the other major benefits to patients of GLP-1 agonists over insulin is the effect on weight. Insulin has long been known to cause weight gain and although the newer analogues may cause less there is no doubt that over time the newer basal insulins increase weight compared to placebo (Heine et al, 2005; Russell-Jones et al, 2009). In comparison there is also no doubt of the weight-reducing effects of the GLP-1 agonists (Heine et al, 2005; Russell-Jones et al, 2009; Diamant et al, 2010) and in some patients the effect can be very powerful. In one study by Bunck et al (2011), looking at an average dose of exenatide 10 μg twice daily *vs* an average dose of glargine of 34 units, exenatide caused 5.7 kg weight loss and glargine 2.1 kg weight gain giving a relative reduction of 7.9 kg. The average expected weight loss with a GLP-1 agonist is of obvious metabolic benefit and no doubt is responsible for much of the increased concordance and improved quality of life associated with these agents.

Effect on blood pressure

Numerous studies including UK Prospective Diabetes Study (UKPDS) Group (1998c) have shown that small reductions in blood pressure reduce mortality as well as micro- and macrovascular disease in type 2 diabetes. It is thus reassuring that the GLP-1 agonists persistently show reduction in blood pressure compared with insulin both in clinical studies and audit of patient data (Russell-Jones et al, 2009; Ryder et al, 2010). The expectation would be that this blood pressure reduction would translate into a long-term beneficial cardiovascular outcome.

Side effects

There have been data to suggest an increased cancer risk with the newer basal insulins, although the balance of evidence seems to be against this (ORIGIN Trial Investigators, 2012). The GLP-1 agonists may increase the risk of pancreatitis although most evidence seems to point to this being an effect of obesity and diabetes rather than the agents (Alves et al, 2012). There is no doubt that the GLP-1 agonists increase gastrointestinal side effects, particularly nausea; presumably this is connected to their mode of action in delaying gastric emptying. This side effect is more common in the older GLP-1 agonists such as exenatide. Although infrequently it causes patients to stop the medication, it does mean that dose titration is sensible. The later GLP-1 agonists liraglutide and exenatide long-acting release cause much less nausea, but still greater than placebo (Heine et al, 2005; Russell-Jones et al, 2009; Diamant et al, 2010). The once weekly exenatide long-acting release can cause build up of material in a subcutaneous nodule that lasts a few weeks, but these nodules are not dangerous and do not seem to be a problem for patients (Diamant et al, 2010).

The main side effects of insulin have been discussed above, namely hypoglycaemia and weight gain. Other less common but still well recognized and potentially harmful side effects include lipodystrophy and insulin oedema (Patrick and Williams, 1993).

Cost

Cost is an increasingly important motivator to prescribing in the NHS – injectable treatments for diabetes are not cheap. The GLP-1 agonists are generally considered expensive compared to insulin, but they do not usually require patients to check their blood sugar levels at home. The price differential depends on how many times patients check their blood sugar and the dose of insulin they are on. For example, for a patient on liraglutide once daily, treatment costs £78.48 for 30 days compared with a patient on 60 units glargine via Solostar daily which cost £49.80 for insulin and £18 for two glucose monitoring sticks a day, making a total of £67.80. If a patient is on 80 units a day or checks his/her glucose four times a day the insulin regimen becomes more expensive (see *British National Formulary*; Joint Formulary Committee, 2013).

Special cases

The Driver and Vehicle Licensing Agency rules for driving are complex and have recently changed, but it is easier to retain or gain a license for any vehicle if on a GLP-1 agonist rather than insulin, given the lower propensity for hypoglycaemia. Potential withdrawal of a license has been a disincentive to many taxi, bus and train drivers as well as heavy goods vehicle drivers to convert to insulin. Likewise many professions in which a hypoglycaemic episode could be particularly dangerous, such as those working at heights, would probably be better candidates for GLP-1 agonists.

Recommendations

Most guidelines suggest earlier treatment intensification than currently occurs, e.g. HbA_{1c} >7.5% on maximum oral medication (National Institute for Health and Clinical Excellence, 2009). Most algorithms and guidelines also advise insulin initiation in preference to GLP-1 agonists. In general most patients may need intensification to an injectable agent about 10 years after diagnosis. The average duration of diabetes for patients in the ACCORD study was 10 years, and the more intensively treated group had a higher mortality than those less intensively treated (Action to Control Cardiovascular Risk in Diabetes Study Group et al, 2008). In the UK Prospective Diabetes Study (1998a), in which patients were recruited at diagnosis, there was a tendency for the opposite. In the intensive arm of ACCORD 22% more patients were on insulin compared with the standard arm, and there was a significant increase in hypoglycae-

mia, weight gain and death in this group. Thus, it would appear that insulin may not be the best next agent at this stage of the disease (Dluhy and McMahon, 2008). It would seem logical that in an overweight or obese population, treatment with a GLP-1 agonist to bring down HbA_{1c} and weight, without hypoglycaemia, is a safer initial therapy than treatment with insulin.

Conclusions

In the author's opinion, in the majority of patients the first injectable therapy after failure of oral medication should be a GLP-1 agonist. Those patients who are not overweight, but are self motivated and are at little risk from hypoglycaemia may benefit from insulin as their first injectable agent, but this group of patients is rare and, looking at the current rising obesity rates and rising life expectancy, likely to become rarer still. **BJHM**

Conflict of interest: Dr CMB Edwards has received speaker honoraria and/or attended advisory boards for all the major pharmaceutical companies producing insulins and glucagon-like peptide-1 agonists.

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KEY POINTS

- There is a choice after oral medications fail in type 2 diabetes.
- There is significant delay in clinicians making that decision.
- There is controversy about whether insulin or glucagon-like peptide-1 agonists should be the next agent.
- Glucagon-like peptide-1 agonists are equally efficacious with reduced hypoglycaemia and reduced weight compared with basal insulin.
- There are few long-term data favouring either option.
- In the majority of obese patients with type 2 diabetes glucagon-like peptide-1 agonists are the more logical choice.
- Patients prefer glucagon-like peptide-1 agonists.