INCRETIN THERAPEUTICS IN DIABETES: 1902 TO PRESENT

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ABSTRACT

The existence of incretins was first hypothesised in 1902 and a putative therapeutic role was postulated 30 years later. However, the development of incretin therapeutics was arrested until the birth of molecular biology in the middle of the last century, which enabled the fascinating medicinal effects of these molecules to be unravelled. This review provides an update on how incretins have revolutionised the treatment of type 2 diabetes.

Key Words: Incretin; Exenatide; Liraglutide; Diabetes Mellitus; GLP-1

INTRODUCTION

The prevalence of type 2 diabetes is increasing in an epidemic fashion. The World Health Organisation (WHO) estimates more than 180 million people have diabetes worldwide and this number is likely to double by 2030. The WHO projects that diabetes deaths will increase by more than 50% in the next ten years unless urgent action is taken. Inevitably, diabetes and its complications will emerge as one of the major threats to future public health resources with huge economic and social costs.

The latest treatment recommendations in diabetes suggest a target HbA1C of ≤7%, which has been shown in the Diabetes Control and Complications trial (DCCT) and UK Prospective Diabetes Study (UKPDS) cohorts to reduce the risk of micro- and macro-vascular disease. However, despite the availability of many anti-diabetic agents, approximately 60% of patients with diabetes do not achieve target HbA1C levels. Clearly, additional therapeutic options are needed, preferably ones that will further improve glycaemic control, reduce weight and overcome other clinical shortcomings of available agents such as hypoglycaemia. Surprisingly, a class of compounds termed ‘incretins’ first discussed in 1902, well before insulin and oral hypoglycaemic
agents were discovered, fulfils these criteria. So why did they not come into therapeutic use until 2005?

THE HISTORY OF INCRETINS

In 1902, Bayliss and Starling proposed that intestinal mucosa contains a hormone, which stimulates the exocrine secretion of the pancreas ("Secretin").(7) However, oral administration of extracts of intestinal mucosa failed to help several patients with type 1 diabetes.

In 1932 La Barre proposed the name ‘incretin’ for a hormone extracted from the upper gut mucosa, which caused hypoglycaemia and proposed a possible therapeutic role in diabetes.(8)

In 1939–1940, based on their studies, Leow et al. concluded the existence of incretins was “questionable.” (9) No further research in this area was performed for about thirty years until 1970. However, as molecular biology advanced this hypothesis was re-visited with the subsequent development of a therapeutic strategy that would revolutionise the treatment of type 2 diabetes and this is further discussed below

THE INCRETIN SYSTEM

Incretins are a group of hormones released into the bloodstream from gastrointestinal ‘L’ and ‘K’ cells, in response to a nutrient load.(10) They cause a post-prandial increase in insulin secretion, even before blood glucose levels become elevated but act in a glucose dependent manner thereby limiting the risk of hypoglycaemia.(10) Incretins have other benefits on glucose metabolism. They slow the rate of absorption of nutrients into the blood stream by reducing gastric emptying; they reduce satiety, which aids weight loss; and they inhibit glucagon release.(10) The two molecules that are recognised to have incretin effects are Glucagon-Like Polypeptide-1 (GLP-1) and Gastric Inhibitory Peptide (GIP).(10)

In newly diagnosed type 2 diabetes with relatively good glycaemic control (HbA1c ~ 6.9%), both GIP and GLP-1 secretion in response to glucose and mixed meal challenges are the same or even increased when compared with healthy subjects.(11) Exogenous GLP-1 administration is able to increase insulin secretion to normal levels and to lower plasma glucose effectively.(12) In contrast, exogenous GIP, even at supraphysiological doses, has markedly reduced insulinotropic actions with little or no glucose-lowering effects.(12) Therefore, therapeutic strategies for type 2 diabetes mellitus are focussed on the use of GLP-1 analogues and not GIP.

The major drawback of GLP-1 as a treatment for type 2 diabetes is its short half-life of ~2 minutes.(13) GLP-1 is rapidly degraded by Dipetidyl Peptidase-4 (DPP-4). With such a short half-life, bolus subcutaneous
injections of GLP-1 result only in a transient effect on insulin secretion and plasma glucose levels.(14)

It is likely the research on incretins from 1902-1940 failed to identify a suitable therapeutic agent for diabetes due to the use of endogenous incretins from human tissue, which are prone to DPP-4 degradation and have a very short half-life that negates any potential insulinotropic effect. Advances in molecular biology enabled the development of synthetic incretins resistant to DPP-4 degradation. Furthermore, as incretins require, at least, some functioning β-cells, they only have insulinotropic effects in type 2 diabetes; in the unsuccessful studies in 1902-1940 they were used in type 1 diabetes.

Based on this, the potential of using GLP-1-based therapy for treating type 2 diabetes mellitus was realised by the development of GLP-1 mimetics, which are resistant to DPP-4 activity, therefore having a longer half-life relative to endogenous GLP-1.

The two GLP-1 mimetics in clinical use are Exenatide and Liraglutide. Exenatide, the first in this new class of drugs, was introduced in the United States in 2005 and in Europe in 2007. Liraglutide was licensed in Europe in July 2009 and in the United States and Japan in January 2010.

**EXENATIDE**

Exenatide is licensed as an adjunctive therapy in patients with type 2 diabetes who are taking metformin and / or a sulphonylurea but have not achieved adequate glycaemic control.(15) Exenatide shares 53% amino acid homology to human GLP-1 and binds directly to GLP-1 receptors.(16) It is administered as a twice daily subcutaneous injection.

The clinical effects of exenatide treatment have been investigated in six published, randomized controlled trials with a total of 2,731 patients. These clinical studies have demonstrated that Exenatide improves glycaemic control and reduces body weight in patients with type 2 diabetes. The pivotal studies were the 30-week duration AMIGO (AC2993 diabetes Management for Improving Glucose Outcomes) trials, which are summarised in Table 1 below.

The most common side-effects associated with Exenatide include nausea, vomiting, and diarrhoea, which are dose-dependent and more common during drug initiation but subside over time.(15)

The risk of hypoglycaemia is increased in patients on exenatide who are also taking a sulphonylurea.(18) In contrast, the risk of hypoglycaemia is not increased when Exenatide is combined with metformin or a thiazolidinedione.(20)

Cases of acute pancreatitis have been reported with Exenatide but recent estimates indicate an incidence of 0.33-0.44 per 1000 adults per year.(21,22) Furthermore, the pancreatitis risk may be increased in patients with type 2 diabetes compared to non-diabetic patients, suggesting the risk is related to the underlying disease state, rather than being a complication of exenatide.
therapy. If pancreatitis is suspected then Exenatide treatment should be stopped.

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<tbody>
<tr>
<td>AMIGO-1</td>
<td>17 336</td>
<td>Metformin</td>
<td>0.4% reduction</td>
<td>0.8% reduction</td>
<td>0.1% increase (p&lt;.002 vs. Placebo for both exenatide groups)</td>
</tr>
<tr>
<td>AMIGO-2</td>
<td>18 377</td>
<td>Sulphonylurea</td>
<td>0.5% reduction</td>
<td>0.9% reduction</td>
<td>0.1% increase (p&lt;.001 vs. Placebo for both exenatide groups)</td>
</tr>
<tr>
<td>AMIGO-3</td>
<td>19 733</td>
<td>Metformin and Sulphonylurea</td>
<td>0.6% reduction</td>
<td>0.8% reduction</td>
<td>0.2% increase (p&lt;.001 vs. Placebo for both exenatide groups)</td>
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Table 1: Summary of the AMIGO trials.(17,18,19)

Recently the FDA (Food and Drug Administration) issued a safety warning on Exenatide associating it with the development of renal failure.(23) This warning was based on 78 post-marketing cases. In light of this the FDA revised the drug label for Exenatide due to the occurrence of serious potential consequences of altered kidney function.

LIRAGLUTIDE

Liraglutide is an acylated analogue of human GLP-1 and shares 97% sequence homology to native GLP-1.(24) It is highly protein bound, which causes decreased susceptibility to metabolism by DPP-4. The half-life of Liraglutide is approximately 13 hours, which makes it suitable for once-daily subcutaneous administration.(25)
Liraglutide has recently received FDA approval. It has enabled many patients to achieve HbA1c targets whilst inducing weight loss, reducing systolic blood pressure and improving β-cell function. The clinical effects of Liraglutide have been investigated in the LEAD (Liraglutide Effect and Action in Diabetes) series of phase III studies, which included over 4,000 patients with type 2 diabetes. A summary of these trials is presented in Table 2.

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of participants</th>
<th>Liraglutide + [drug]</th>
<th>Comparator Group</th>
<th>Effect of Liraglutide on HbA1C</th>
<th>Effect of Comparator Group on HbA1C</th>
</tr>
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<tr>
<td>LEAD-1</td>
<td>1041 Glimepiride</td>
<td>Rosiglitazone or placebo</td>
<td>1.1% reduction</td>
<td>0.4% reduction</td>
<td></td>
</tr>
<tr>
<td>LEAD-2</td>
<td>1091 Metformin</td>
<td>Glimepiride or placebo</td>
<td>1.0% reduction</td>
<td>0.7% reduction</td>
<td></td>
</tr>
<tr>
<td>LEAD-3</td>
<td>746 None</td>
<td>Glimepiride</td>
<td>1.1% reduction</td>
<td>0.5% reduction</td>
<td></td>
</tr>
<tr>
<td>LEAD-4</td>
<td>533 Metformin + Rosiglitazone</td>
<td>Placebo</td>
<td>1.5% reduction</td>
<td>0.5% reduction</td>
<td></td>
</tr>
<tr>
<td>LEAD-5</td>
<td>533 Metformin + Glimepiride</td>
<td>Insulin Glargine or placebo</td>
<td>1.3% reduction</td>
<td>1.1% reduction</td>
<td></td>
</tr>
<tr>
<td>LEAD-6</td>
<td>464 Metformin +/- Glimepiride</td>
<td>Exenatide</td>
<td>1.1% reduction</td>
<td>0.8% reduction</td>
<td></td>
</tr>
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Table 2: Summary of the LEAD trials (26-31).

In general, Liraglutide appears well tolerated, although an increased incidence of mild nausea has been consistently described.

Liraglutide has been associated with thyroid hyperplasia and medullary thyroid carcinoma and this has led to a ‘black-box’ warning. Liraglutide stimulates the same receptor in pancreatic β-cells that is also found in the C-cells of thyroid tissue, which is where the insidious medullary thyroid cancer forms. However, rodent C-cell tumours induced by Liraglutide are caused by a non-genotoxic, specific receptor-mediated mechanism, to which rodents are particularly
sensitive whereas humans are not.(32) To date there is no evidence of a causal relationship between Liraglutide and human C-cell medullary thyroid cancer.

Phase 1 trials of an oral agent of Liraglutide are due to start this year.

OTHER LONG ACTING GLP-1 MIMETICS

Other GLP-1 mimetics are currently in clinical trials and include: AVE0010, Albiglutide, Taspoglutide, and once-weekly Exenatide (Exenatide QW).(33-36) All are currently unlicensed.

AVE0010, was found in a phase IIb trial of 542 patients to be well tolerated and significantly improved glycaemic control versus placebo in type 2 diabetes patients inadequately controlled with metformin alone. The once daily regimen demonstrated a clear dose response with a similar HbA1c reduction to twice daily regimen. AVE0010 was also found to be associated with weight loss.

Albiglutide is a novel dipeptidyl peptidase-4-resistant glucagon-like peptide-1 dimer fused to human albumin.(34) In clinical trials Albiglutide improved fasting plasma glucose and postprandial glucose with a favourable safety profile in subjects with type 2 diabetes. Albiglutide's long half-life may allow for once-weekly or less frequent dosing.

A recent randomised, double-blinded, placebo-controlled study of 129 patients, found that Taspoglutide, a human once-weekly glucagon-like peptide-1 analog, was safe and well tolerated.(35) The proportion of patients achieving HbA1c <7% after 8 weeks of treatment was between 53-72% compared to 19% for placebo.

A once-weekly formulation of exenatide, Exenatide QW, has been shown in clinical trials to achieve better glycaemic control compared to twice-daily Exenatide with a lower incidence of adverse-effects.(36) Clinical trials have demonstrated beneficial cardiovascular effects by reducing systolic blood pressure and hyperlipidaemia. There is evidence to suggest that Exenatide QW preserves \( \beta \)-cell mass and function. It may also have a disease-modifying effect in Non-Alcoholic Fatty Liver Disease (NAFLD). Exenatide QW has been shown to reduce weight. (36) Whether exenatide QW could be investigated as an anti-obesity treatment in patients without type 2 diabetes warrants further research.

DPP4 INHIBITORS

The therapeutic potential of native GLP-1 is limited by its short physiologic half-life, owing to its rapid inactivation by the enzyme dipeptidyl peptidase 4 (DPP4) and to renal clearance. As such, several selective inhibitors of DPP-4 are being developed for the treatment of type 2 diabetes.
These orally administered agents can increase circulating levels of endogenous GLP-1 and GIP counteracting hyperglycaemia.

Licensed DPP4 inhibitors include Sitagliptin, Vildagliptin and more recently, Saxagliptin. In clinical trials, DPP4 inhibitors have been associated with a 0.4-0.7% HbA1c reduction over a 12 month period.(37)

Over 12,500 patients have taken part in 25 studies investigating Sitagliptin and Vildagliptin. Most studies lasted 24 weeks; the longest trials evaluated 52 weeks of treatment. So far, no study has reported on patient-oriented parameters like mortality, diabetic complications, costs of treatment and health-related quality of life. Comparison with other already established oral hypoglycaemic agents did not reveal advantages of DPP-4 inhibition. No definite conclusions could be drawn from published data on sitagliptin and vildagliptin effects on markers of β-cell function. Weight gain was not observed after sitagliptin and vildagliptin therapy. Overall, sitagliptin and vildagliptin seem well tolerated and no severe hypoglycaemia has been reported. However, all-cause infections increased significantly after sitagliptin treatment but did not reach statistical significance following vildagliptin therapy. This may be related to the role of DPP4 in lymphocyte function. DPP-4 is associated with lymphocyte signalling and there is a lack of data on the benefit-risk ratio of DPP-4 inhibition, which specifically analyses the potential adverse effects on parameters of immune function. Furthermore, there is also a lack of long-term data on cardiovascular outcomes and safety associated with DPP4 inhibitors.(38)

Other DPP4 inhibitors, which are currently in phase 3 clinical trials, include Linagliptin, Dutaglaptin, Gemiglipitin, and Alogliptin.

Whilst GLP-1 mimetics have an evidence basis, which demonstrates larger reductions in HbA1c and disease modifying effects on the adverse cardiovascular profile associated with type 2 diabetes, such data has not yet been matched with the DPP4 inhibitors, which are unable to demonstrate non-inferiority. It seems the downside of subcutaneous injectable administration of GLP-1 mimetics is not enough to justify the preferential route or oral administration associated with DDP4 inhibition.

CONCLUSION

The advent of Exenatide and Liraglutide has changed the face of managing type 2 diabetes. Incretins lower HbA1c, facilitate weight loss, reduce systolic blood pressure and improve the lipaemic index of patients with type 2 diabetes. The avoidance of hypoglycaemia by preserving the feedback loop independent of insulin has placed incretin mimetics firmly on the treatment ladder for type 2 diabetes. Newer once-weekly agents, which are currently in phase III trials, afford the advantage of improving patient satisfaction and compliance whilst achieving target HbA1c levels.
Novel roles for incretins as disease modifying agents in NAFLD and anti-obesity agents warrant further research. The use of incretins in type 1 diabetes to reduce insulin requirements is currently being investigated.

However, as incretins are new agents, long-term prospective data on their efficacy and safety is lacking.

What is clear is incretins deserve a firm place in the physicians’ armoury in the battle against the epidemic that is type 2 diabetes.

REFERENCES


