Novel treatments for type 2 diabetes

THE NEED FOR NOVEL THERAPIES

Type 2 diabetes mellitus is a major threat to health with a prevalence increasing in epidemic proportions. The World Health Organization estimates that by 2030, type 2 diabetes will affect over 360 million people worldwide. Inevitably, diabetes and its complications will strain public health resources.

Despite the availability of many anti-diabetic agents, approximately 60% of patients do not achieve the target glycated hemoglobin (HbA1C) level of ≤7%. Reasons for this include: non-compliance; side-effects of treatments; fear of hypoglycaemia; weight-gain; problems with dose titration of anti-diabetic agents; and more stringent HbA1C targets set by healthcare organisations which tend to change. Clearly, additional therapeutic options are needed that will overcome these clinical shortcomings.

INCRETIN THERAPEUTICS

Incretin therapeutics, which are based on mimicking the endogenous effects of glucagon-like peptide 1 (GLP-1), have revolutionised the management of type 2 diabetes since they came into clinical use in 2006.

GLP-1 mimetics have proved popular with both physicians and patients as they offer an additional therapeutic strategy that overcomes many of the pitfalls associated with current therapies: they avoid hypoglycaemia by acting in a glucose-dependent manner; they facilitate weight loss by slowing gastric emptying and reducing satiety; and they inhibit glucagon release. GLP-1 mimetics have proved valuable in bridging the gap between patients with poor diabetic control (HbA1c >8%) who have failed oral hypoglycaemic therapy but are reluctant to start insulin due to the undesirable effects of weight gain and fear of hypoglycaemia.[1]

The two licensed GLP-1 analogues are exenatide and liraglutide, both of which are administered subcutaneously. Exenatide is associated with a sustained 3-year HbA1c reduction of 1%, and 46% of patients achieve a target HbA1c <7%. In comparative studies with metformin, sulphonylureas, and insulin glargine, exenatide has demonstrated superior HbA1c reductions.[2]

In comparative studies, liraglutide has demonstrated superior HbA1c reductions compared to glimepiride, metformin, rosiglitazone, and insulin glargine. In a head-to-head comparative study against exenatide, liraglutide was associated with superior HbA1c reductions of 0.3%.[3]

The popularity of GLP-1 agonists is further enhanced by clinical data, which demonstrate disease modifying effects on the adverse cardiovascular profile associated with type 2 diabetes. Exenatide is associated with ~5kg weight reduction; 12% reduction in serum triglycerides; 5% reduction in serum total cholesterol; 6% reduction in serum low-density lipoprotein cholesterol; 24% increase in cardio-protective serum high-density lipoprotein cholesterol; and improvement in the hepatic steatosis biomarkers (alanine aminotransferase) of 41%.[4] Liraglutide has demonstrated similar findings in addition to achieving a 4% reduction in systolic blood pressure.[3]

The most common side-effects associated with exenatide include nausea, vomiting, and diarrhoea, which are dose-dependent but subside over time. Cases of acute pancreatitis have been reported but estimates indicate an incidence of 0.33–0.44 per 1000 adults per year.[5] Recently the Food and Drug Administration (FDA) issued a safety warning on exenatide associating it with the development of ischaemic renal failure.[6]

In general, liraglutide appears well tolerated with a lower incidence of nausea compared to exenatide. Liraglutide has been associated with thyroid hyperplasia and medullary thyroid carcinoma, which has led to a 'black-box' warning. However, this association seems confined to rodents, and to date there is no evidence of a causal relationship between liraglutide and human C-cell medullary thyroid cancer. Phase I trials of an oral agent of liraglutide are due to start this year.

Other GLP-1 analogues in clinical trial phase include longer acting compounds, which offer the advantage of once-weekly administration. These include: taspoglutide, albiglutide and lixisenatide, also known as AVE0010, and a once-weekly preparation of exenatide.

AMYLIN AGONISTS

Amylin agonists have all the incretin actions except stimulation of insulin secretion. Pramlintide is the only licensed amylin analogue and is associated with HbA1C reductions of 0.5–1.0%. Adverse effects are mainly nausea, which improves with continuing treatment.[7]

DIPEPTIDYL PEPTIDASE IV INHIBITORS

The therapeutic potential of endogenous GLP-1 is limited by its short physiologic half-life, owing to its rapid inactivation by dipeptidyl peptidase IV (DPP-IV). Several selective inhibitors of DPP-IV have been developed and those that are licensed include: sitagliptin, vildagliptin and, more recently, saxagliptin. They achieve a 0.4–0.7% HbA1c reduction over 12 months, and as monotherapy are not associated with hypoglycaemia.[8] Adverse effects include nasopharyngitis and urinary tract infections. To date, 88 cases of pancreatitis associated with sitagliptin therapy have been reported to the FDA.

Other DPP-IV inhibitors, which are currently in phase III clinical trials, include linagliptin, dutogliptin, gemigliptin, and alogliptin.

CENTRAL NEUROTRANSMITTER MODULATORS

Body fat stores and insulin action are controlled by the temporal interaction of circadian neuroendocrine oscillations. Bromocriptine modulates neurotransmitter

action in the brain. Studies using bromocriptine in type 2 diabetes have shown improvements in glycaemic control and glucose tolerance with HbA1c reductions of ~0.56%.[9] Despite receiving FDA approval, bromocriptine is not part of the type 2 diabetes management guidelines from the National Institute for Health and Clinical Excellence.

EXPERIMENTAL AGENTS

The Glimins

Imeglimin, an oxidative phosphorylation inhibitor, is a first in a new class of oral anti-diabetic drugs known as 'the Glimins', which target the three key defects of type 2 diabetes: insufficient insulin production; excessive hepatic gluconeogenesis; and impaired glucose uptake by skeletal muscles. Its efficacy is currently being examined in phase IIa clinical trials.[10]

Renal sodium-dependent glucose co-transporter-2 inhibitors

The glucose reabsorption system in the kidney is mediated by renal sodium-dependent glucose co-transporter 2 (SGLT2) receptors. Most filtered glucose is reabsorbed by the low affinity, high capacity SGLT2 receptors located in the proximal renal tubule. SGLT2 inhibitors enhance urinary glucose excretion, which lowers blood glucose levels independent of insulin with HbA1c reductions of 0.55–0.9%;[11] examples include: remogliflozin, etabonate, sergliflozin, and dapagliflozin.

Fructose 1,6-bisphosphatase inhibitors

Excessive gluconeogenesis is central to the pathophysiology of type 2 diabetes. Recently, the use of selective fructose 1,6-bisphosphatase inhibitors, a rate-controlling enzyme of gluconeogenesis, has been explored.[12] Current data, which illustrate glucose-lowering effects, are limited to rodent studies.

Peroxisome proliferator-activated receptor α/γ ligands

The promise for peroxisome proliferator-activated receptor (PPAR) agonists to reduce cardiovascular risk type 2 diabetes is of continued interest. In the SYNCHRONY trial,[13] aleglitazar was associated with HbA1c reductions of 0.36–1.35% as well as improving adverse high-risk lipid profiles. It is now being advanced into phase III clinical studies. However, there are concerns about PPAR α/γ ligands. Two such agents, muraglitazar and tesaglitazar, were withdrawn after concerns about their association with major cardiovascular events.

MBX-2982

G-protein coupled receptor 119 (GPR119) is a receptor in the gut and pancreas that interacts with bioactive lipids to stimulate glucose-dependent incretin and insulin secretion. MBX-2982, a GPR119 agonist, which has completed three phase I clinical studies, has consistently shown clinically meaningful glucose reductions. It has now entered phase II clinical trials.[14]

THE ROLE OF THE COMMUNITY DIABETES TEAM

With the management of diabetes making the transition from secondary into primary care, coupled with imposing pressures of guidelines to tighten glycaemic control, GPs will soon be leading the way in optimising therapeutic strategies for patients with type 2 diabetes. The next decade is likely to be exciting with the explosive pace at which new, safer, and more effective anti-diabetic treatments are rolling off the clinical phase belt. The role of the community diabetes team in instituting these novel treatments will be essential in improving diabetes care.

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