EXPERIMENTAL AGENTS IN TYPE 2 DIABETES: THE NEXT 20 YEARS

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ABSTRACT

The next two decades are likely to be exciting in the field of diabetes care. Experimental drugs and new therapies are likely to make the lives of diabetes sufferers easier. This review discusses the impact that current experimental agents may have in revolutionising the management of type 2 diabetes.

Keywords:
Type 2 Diabetes; New Therapies; Experimental Agents; Safety; Research

THE NEED FOR NOVEL THERAPIES

Despite the availability of many anti-diabetic agents, 60% of diabetic patients do not achieve the target Hb\(_{\text{AIC}}\) level of \(\leq 7\%\). Reasons for this include: non-compliance; side-effects of treatments; fear of hypoglycaemia; weight-gain; problems with dose titration; and more stringent Hb\(_{\text{AIC}}\) targets by healthcare organisations. Clearly, additional therapeutic options are needed that will overcome these shortcomings. This review critically considers how emerging experimental agents for type 2 diabetes mellitus (T2DM) will surmount these barriers.

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INCRETIN THERAPEUTICS

Incretin therapeutics, which are based on mimicking the endogenous effects of Glucagon-Like Peptide -1 (GLP-1), have revolutionised the management of T2DM since they came into clinical use in 2006. They have proved popular with both physicians and patients as they offer an additional therapeutic strategy that overcomes many downsides of current therapies: hypoglycaemia avoidance; facilitation of 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. There is also emerging evidence to suggest that GLP-1 agonists exhibit β-cell protective functions through anti-apoptotic mechanisms.

The two licensed GLP-1 analogues are exenatide and, more recently, liraglutide. However, the widespread use of these compounds over the last year has identified a series of problems, which has fuelled the development towards novel GLP-1 mimetics with the hope of overcoming these shortcomings. Problems with exenatide include nausea, vomiting, diarrhoea and an increased risk of pancreatitis. Recently the FDA (Food and Drug Administration) issued a safety warning on exenatide associating it with the development of renal failure.1

Liraglutide, despite a strong evidence basis for glycaemic reduction and disease modifying effects on the adverse cardiovascular and metabolic profile associated with T2DM, has also run into problems; it has been associated with thyroid hyperplasia and medullary thyroid carcinoma and this has led to a ‘black-box’ warning.2 It has also been associated with nausea and vomiting, which has limited its tolerability in some patients.

New GLP-1 mimetics, which include Taspoglutide, Albiglutide, and Lixisenatide (AVE0010), are in clinical trial phase and are being designed to overcome these problems.

Taspoglutide has a pharmacokinetic profile suitable for once-weekly subcutaneous administration. Preliminary data from phase III clinical trials suggest taspoglutide is effective when injected once weekly and less effective when injected bi-weekly. The improvement in glycaemic control (~1.1% decrease in HbA1C from a baseline of 7.9 +/- 0.7%) observed with taspoglutide after 8 weeks compares favourably with exenatide and liraglutide. Taspoglutide also significantly reduces three of five diagnostic criteria for metabolic syndrome: glucose, waist circumference, and fasting triglycerides.3 Side-effects include nausea and vomiting. Severe hypoglycaemia was not reported. There is some data to suggest taspoglutide may be associated with perineal fibroma, otitis media, coronary artery occlusion, colonic polyposis and wrist fractures.3
Albiglutide, a new GLP-1 mimetic, has an extended half-life (~5 days), which may allow for weekly or less frequent dosing. It is relatively impermeable to the central nervous system. This may reduce gastrointestinal adverse effects, which are predominantly mediated through GLP-1 induced hypothalamic satiety suppression. Albiglutide improves glycaemic control (0.8 – 0.9% HbA1c reductions) in a dose-dependent manner. In terms of weight reduction, it has failed to demonstrate non-inferiority compared to exenatide. 2.5% of patients on albiglutide develop neutralising antibodies, which may attenuate efficacy. Adverse effects include nausea and vomiting (dose dependent), headache, dizziness, nasopharyngitis, lumbago, influenza, and local skin reactions. There have been no reports of hypoglycaemia or pancreatitis.

Lixisenatide is also a novel GLP-1 agonist. In various in vitro and in vivo models of T2DM, lixisenatide improved glycaemic measures and demonstrated promising pancreatic β-cell-preserving actions. In a phase II clinical trial involving 361 patients with a mean HbA1c of 8.04 +/- 0.9%, between 46.5 – 52.2% of patients randomised to lixisenatide achieved a target HbA1c of <7% compared to placebo. Side effects included nausea which occurred in 20-24% of patients. A low frequency of hypoglycemia was reported. The results of phase III trials are awaited.

A once weekly preparation of exenatide (exenatide QW) is being assessed in clinical trials. So far it is the only non-insulin single treatment to achieve HbA1c levels of <7% in over 75% of treated patients. It has also demonstrated potential cardiovascular benefits through lowering total and low density lipoprotein (LDL) cholesterol concentrations, triglyceride levels, systolic and diastolic blood pressure, and weight loss. However, adverse effects include local injection site reactions and nausea, although this was lower compared to twice-daily exenatide.

The downside of subcutaneous administration of GLP-1 analogs has led to the design of preferentially administered oral GLP-1 mimetics. Phase 1 clinical trials of an oral preparation of liraglutide are due to start this year.

Despite the development of novel incretin mimetics with longer half-life’s, improved compliance, and cardiovascular and metabolic disease-modifying effects, no experimental agent has yet managed to negate the fundamental flaw of nausea and vomiting associated with GLP-1 analogs. The ability to modify these molecules by rendering them impermeable to cerebral penetration may improve gastrointestinal adverse effects but would come at the cost of failing to suppress hypothalamic satiety and thus facilitate weight gain.

The role of incretin therapeutics is expanding beyond their primary purpose of glycaemic reduction. Whether they can be used as a primary treatment modality for obesity in non-diabetic patients warrants further research. GLP-1 analogs have demonstrated disease-modifying effects in non-alcoholic fatty liver disease (NAFLD); whether they can be used primarily for this purpose requires further investigation.
AMYLIN AGONISTS

Amylin agonists have all the incretin actions except stimulation of insulin secretion. Pramlintide, the first member of this new class of drugs, is an analog of the peptide hormone amylin. Amylin is co-secreted with insulin from pancreatic β-cells. It is relatively deficient in patients with T2DM, depending on the severity of β-cell secretory failure, and is essentially absent in patients with type 1 diabetes. Pramlintide improves glycaemic control (HbA1c reduction of 0.5 – 1.0%), reduces postprandial glucose levels and bodyweight. It is well tolerated, with the most frequent treatment-emergent adverse event being nausea, which subsides over time. Pramlintide treatment is also associated with improvements in markers of oxidative stress and cardiovascular risk and improved patient-reported treatment satisfaction. However, despite its widespread use in America, it has proved unpopular in Europe due to patients requiring an additional subcutaneous injection for administration.

DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS

Several selective inhibitors of DPP-4 have been developed and those that are licensed include sitagliptin, vildagliptin, and more recently, saxagliptin. They offer an alternative oral treatment for T2DM, which unlike the sulphonylureas, are not associated with hypoglycaemia or weight gain. They achieve a 0.4-0.7% HbA1c reduction over 12 months. Adverse effects include nasopharyngitis, urinary tract infections and pancreatitis. However, no study on DPP-4 inhibitors has reported on patient-centred parameters such as mortality, diabetic complications, health economics and health-related quality of life. This has focussed the development of novel DDP-4 inhibitors towards overcoming these short-comings. Such agents, which are in clinical trial phase, include linagliptin, dutogliptin and alogliptin.

Linagliptin belongs to a new chemical class of DPP-4 inhibitors, which comprise xanthine-based compounds. It is a potent long-acting inhibitor with high selectivity for DPP-4 versus the related enzymes DPP-8 and DPP-9. It has modest oral availability in humans, but is absorbed rapidly to inhibit plasma DPP-4 activity by > 80% over 24 h at daily doses as low as 5mg in phase II clinical trials. In phase II studies the effects of linagliptin (HbA1c reduction of ~0.69%) were sustained, and evidence of hypoglycemia were observed, even at doses up to 600 mg. The results from ongoing phase III clinical trials are awaited.

Similar data has been found for other new DPP-4 inhibitors. Preliminary data from phase III clinical trials on dutogliptin showed after 12 weeks of treatment HbA1c fell by 0.82%. Alogliptin has shown in clinical trials to be effective at improving HbA1c (0.7 – 0.8% reduction) whilst remaining weight neutral and not inducing hypoglycaemia.
Unlike GLP-1 mimetics, the downside towards DPP-4 inhibition centre on a lack of long-term data on their ability to modify the adverse metabolic and cardiovascular profile associated with T2DM. Comparison with other already established oral hypoglycaemic agents has not convincingly demonstrated non-inferiority. The experimental DPP-4 inhibitors will need to overhaul these pitfalls if they are to change prescribing patterns.

CENTRAL NEUROTRANSMITTER MODULATORS

The FDA (Food and Drug Administration) has recently approved the use of bromocriptine for the treatment of T2DM. Its mechanism of action is unknown although it probably works by inhibiting serotonin turnover in the central nervous system. Bromocriptine reverses many of the metabolic alterations associated with insulin resistance and obesity by resetting the hypothalamic circadian organisation of monoamine neuronal activities. If administered daily during the early hours of the morning, bromocriptine can prevent or even reverse insulin resistance and decrease hepatic gluconeogenesis associated with HbA1c reductions of 0.56%. It has also been shown to reduce triglyceride and free fatty acid levels, body fat stores, and decreasing the need for oral hypoglycaemic agents in obese patients. Side effects are rare and include nausea, vomiting, dizziness and headache. Despite receiving FDA approval, bromocriptine is not part of NICE guidelines on the management of T2DM.

THE GLIMINS

Imeglimin, an oxidative phosphorylation inhibitor, is a first in a new class of oral anti-diabetic drugs, the glimins, targeting the 3 key defects of T2DM: insufficient insulin production; excessive hepatic gluconeogenesis; and impaired glucose uptake by skeletal muscles. It is currently in phase IIa clinical trials and preliminary data demonstrate that it is as effective as metformin at reducing HbA1c with no safety issues.

RENAL SODIUM-DEPENDENT GLUCOSE CO-TRANSPORTER-2 INHIBITORS (SGLT2)

The glucose reabsorption system in the kidney is mediated by sodium-dependent glucose co-transporter 2 receptors (SGLTs). Most filtered glucose is reabsorbed by the low affinity, high capacity, SGLT2 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%. Dapagliflozin, the most studied of these novel compounds, is highly SGLT2 selective. It induces steady rates of glycosuria amounting to ~70 g glucose excreted daily. In clinical studies it has demonstrated significant
HbA1c reductions (0.55 – 0.95%) and weight loss (1.3 – 2.0kg) compared to placebo. There was no change in renal function. Serum uric acid decreased, serum magnesium and phosphate increased at higher doses, and dose-related 24-h urine volume and haematocrit increased, all of small magnitude. Treatment-emergent adverse events were similar across all groups.16 Similar results have been observed with sergliflozin etabonate.17

SGLT2 antagonism offers a promising approach for the treatment of diabetes. They have the potential to be used as monotherapy, as well as in combination with all approved antidiabetic agents. Because their mechanism of action is independent of the severity of β-cell dysfunction or insulin resistance, efficacy should not decline with progressive β-cell failure or in the presence of severe insulin resistance. However, much clinical research remains to be carried out on the long-term effects of glycosuria and other potential effects of this class of drug.

FRUCTOSE 1, 6-BISPHOSPHATASE (FBPASE) INHIBITORS

Excessive gluconeogenesis is central to the pathophysiology of type 2 diabetes. Recently, the use of selective inhibitors of FBPase, a rate-controlling enzyme of gluconeogenesis, has been explored.18 Current data, which illustrates glucose-lowering effects, is limited to rodent studies.

PEROXISOME PROLIFERATOR ACTIVATED RECEPTOR A/Γ LIGANDS (PPAR/Γ)

This group of drugs, which includes rosiglitazone, has attracted much controversy recently. The FDA began investigating rosiglitazone in 2007 after it was reported that it likely caused an increased risk in heart attacks. Following a 2007 study, an FDA advisory panel agreed that rosiglitazone did not cause a statistically significant increase in heart attacks. The FDA voted to keep the drug on the market, however, a few months later the agency added a ‘black-box’ warning about potential heart risks of rosiglitazone. In 2007, a panel of independent researchers reported that rosiglitazone could, in fact, increase patients’ risk of heart attack. However they recommended that it remain on the market. An FDA oversight committee voted to accept that advice and keep it on the market.

Another PPARα/γ ligand, muraglitazar, was withdrawn after data from phase II and III trials showed a 1.47% increase in death from heart-attacks and stroke compared with 0.67% in the placebo group. Tesaglitazar was similarly discontinued due to concerns with cardiovascular risk.

In spite of this, drug development in the field of PPARα/γ ligands continues, especially around a novel compound, aleglitazar. In the SYNCHRONY trial,19 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.
MBX-2982

G-protein coupled receptor 119 (GPR-119) is a receptor in the gut and pancreas that interacts with bioactive lipids to stimulate glucose-dependent incretin secretion and acts directly on the pancreas to stimulate insulin secretion. MBX-2982, a GPR119 agonist, which has completed three phase 1 clinical studies, has consistently shown clinically meaningful glucose reductions and increases in GLP-1 following a mixed meal. It is considered safe, well tolerated and with no serious side effects or dose related toxicity. It is now in phase II clinical trials.

CONCLUSION

Current therapies for T2DM are not without their problems. New therapies are emerging at an alarming rate but very few are able to address the flaws of existing treatments. This doesn’t hold true in the case of experimental agents with novel mechanisms of action although most of these drugs are in early phase clinical trials with much remaining to be discovered. If experimental agents for T2DM are to change prescribing patterns then they need, at the very least, to demonstrate non-inferiority in terms of efficacy to their parent compounds, and superiority with regards to safety and tolerability. The key to unlocking successful diabetes treatments will only be turned correctly if experimental agents can meet these criteria.

REFERENCES

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