Drugs of the Future 2011, 36(2): 149-158

CCC: 0377-8282/2011
DOI: 10.1358/dof.2011.36.2.1568339

MEETING REPORT

EMERGING TREATMENT OPTIONS FOR TYPE 2 DIABETES

HIGHLIGHTS FROM THE 46TH ANNUAL MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF DIABETES (SEPTEMBER 20-24, 2010, STOCKHOLM, SWEDEN)

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SUMMARY

The 46th Annual Meeting of the European Association for the Study of Diabetes (EASD) took place on September 20-24, 2010, in Stockholm, Sweden. The meeting was devoted to new developments in the understanding, diagnosis and management of type 2 diabetes. This article highlights the present treatment options, new therapeutic possibilities and advances in the management of type 2 diabetes.

INTRODUCTION

The prevalence of type 2 diabetes is increasing rapidly worldwide and is a considerable public health concern. Type 2 diabetes is a progressive disease characterized by declining beta cell function. This, together with insulin resistance, leads to the loss of glycemic control and eventual diabetic complications. Many treatments are effective early on in the course of the disease. These, however, do not remain effective and thus a more aggressive management of the disease and its complications is required. This report provides details on the current research on incretin-based therapies, as well as the development of new drug classes with novel mechanisms of action that may provide additional advantages in the treatment of type 2 diabetes.

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INCRETIN MIMETICS

As individuals progress from normal glucose tolerance to impaired glucose tolerance and type 2 diabetes, stimulated levels of glucagon-like peptide 1 (GLP-1) decline (1, 2). In addition, there is beta cell resistance to the glucose-dependent stimulatory effects of both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) on insulin secretion (3). The contribution of incretin hormones to the insulin response has been estimated to be reduced to about 36% in patients with type 2 diabetes (4, 5). From a therapeutic standpoint, circulating GLP-1 levels can be increased by the administration of a GLP-1 analogue (resistant to dipeptidyl peptidase 4 [DPP IV] degradation) or by administering a DPP IV inhibitor (6-8).

Mechanism of action of incretins

Incretin mimetics are emerging as an important drug class for the treatment of diabetes and possibly obesity. GLP-1 and GIP are produced in the gut and stimulate glucose-dependent endogenous insulin secretion, decrease glucagon secretion, slow gastric motility and emptying, and reduce appetite and food intake (7, 9, 10). Furthermore, native GLP-1 stimulates beta cell proliferation in animal models and inhibits apoptosis in vitro, which may increase beta cell mass and function. In addition to stimulating beta cell proliferation, GLP-1 also enhances the differentiation of new beta cells from progenitor cells in the pancreatic duct epithelium (11-15). However, native GLP-1 or GIP do not constitute viable therapeutic agents due to their short half-life (< 2 min), resulting from rapid degradation by the enzyme DPP IV and fast renal elimination (16, 17).

A study from Japan provided evidence that both GLP-1 and GIP directly suppress the development of macrophage-driven athero-

sclerotic lesions. This is associated with downregulation of essential molecules required for foam cell formation (e.g., acyl-CoA, cholesterol acyltransferase 1 and CD36) (18). Endothelial cell dysfunction is an early abnormality in atherosclerosis and prediabetes and is associated with an increased expression of vascular adhesion molecules. Liraglutide treatment significantly inhibited TNF-α induction of intercellular adhesion molecule ICAM-1 and vascular cell adhesion molecule VCAM-1 proteins, mRNA expression in vitro, and also blocked endothelial cell dysfunction, all in a GLP-1 receptor-dependent manner (19).

While the physiological basis of the antidiabetic properties of GLP-1 analogues is well understood, little is known about the mechanisms underlying the weight loss effect. A study from Denmark demonstrated that GLP-1 analogues increase arcuate cocaine- and amphetamine-regulated transcript protein (CART) mRNA and block weight loss-induced increases in arcuate neuropeptide Y and Agouti-related peptide mRNA levels, which are responsible for the lowering of food intake and body weight (20).

GLP-1 receptor agonists promote beta cell growth, survival and insulin secretion, and enhance proinsulin biosynthesis. Glucose toxicity can affect the survival, proliferation and function of pancreatic islet endothelial cells, leading to the impairment of beta cell function and beta cell loss. Exenatide promotes islet microendothelium survival via the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) and the adenylate cyclase/cAMP/protein kinase A signaling pathway (21). An animal study demonstrated that chronic treatment with taspoglutide has protective effects on beta cell apoptosis, islet inflammation and islet fibrosis (22).

Metabolic effects of incretin mimetics

It is suggested that in order to exert their anabolic action in the bone, GLP-1 and exendin-4 act via specific receptors that are distinct in structure and/or function from the pancreatic GLP-1 receptor. Hypercholesterolemia appears to be related to low levels of bone mineral density. In an animal study, both GLP-1 and exendin-4 corrected hyperlipidemia and normalized deleterious bone metabolism in the obese state (23). Liraglutide reduces appetite and lowers body weight in both humans and rodents. An animal study demonstrated that liraglutide activates the neuronal pathways involved in appetite regulation that extend from the area postrema/nucleus of the solitary tract complex via the lateral parabrachial nucleus and amygdala to the paraventricular nucleus in the hypothalamus (24). A meta-analysis of six clinical trials with liraglutide reported changes in the two indicators of beta cell function –a significant increase from baseline in beta cell function (measured by the homeostatic model for assessment of beta cell function, HOMA-B) and a significant decrease in the proinsulin:insulin ratio (25).

The effects of exenatide and glimepiride on glycemic control and insulin resistance-related parameters were studied in patients with type 2 diabetes treated with metformin. Both drugs improved diabetes control, but only exenatide was beneficial for insulin resistance-related parameters and caused an increase in adiponectin and a reduction in TNF-α, leading to weight loss (26).

Several biological actions are mediated by DPP IV inhibitors, including glucose-dependent insulin secretion and increased pancreatic beta cell mass via the stimulation of cell proliferation and inhibition of apoptosis. In an animal model of diabetes, vildagliptin preserved the pancreatic beta cell function and cell mass by a direct action on the cell kinetics and suppression of the oxidative and/or endoplasmic reticulum stress mechanism (27). Vildagliptin caused an enhanced proliferation of beta cells associated with improved insulin secretion and glucose intolerance, leading to a significant recovery of islet size and beta cell volume density in lean GK rats with type 2 diabetes (28). In another study, both saxagliptin and sitagliptin showed similar improvements in glycemic control and beta cell mass preservation in a high fat-fed, streptozotocin-treated model of pancreatic beta cell degeneration in mice (29).

Type 2 diabetes is characterized by a progressive decline in the number of insulin-producing cells, largely due to increased cellular apoptosis. Free fatty acids are essential energy metabolites in the normal state, but induce beta cell dysfunction and death when their levels are chronically increased. Pancreatic-derived factor (PANDER) is a cytokine that is secreted by pancreatic islet cells. Overexpression of PANDER induces pancreatic beta cell apoptosis and dysfunction. The Akt pathway is activated by GLP-1, thereby counteracting palmitic acid, inducing PANDER expression and rescuing beta cells from palmitic acid-induced apoptosis (30). Another study reported that the GLP-1 analogue exenatide prevented palmitate-mediated apoptosis, at least in part by interfering with the c-Jun *N*-terminal kinase (JNK) activation pathway (31).

Gut L cells secrete GLP-1 upon nutrient intake, which is impaired in patients with type 2 diabetes. A study has demonstrated the autocrine/paracrine manner of protection conferred by metformin against lipoapoptosis and GLP-1-stimulated GLP-1-secreting L cells. Such antidiabetic drugs restore GLP-1 deficiency by enhancing L cell mass and offer a beneficial long-term effect (32). Liraglutide can bind to the GLP-1-specific receptor on the islets of Langerhans beta cells, promote the expression and biosynthesis of the preinsulin gene, and facilitate insulin expression at the genetic level. Liraglutide can also improve insulin resistance by increasing plasma adiponectin levels (33).

The generation of antibodies to therapeutic proteins can potentially affect pharmacokinetics, trigger adverse events and/or diminish clinical response. Liraglutide and exenatide have 97% and 53% homology, respectively, to human GLP-1. The extended LEAD-6 trial reported that liraglutide treatment resulted in a much lower frequency and magnitude of antibody formation than that triggered by exenatide. High titers of exenatide antibodies affected the glycemic response to exenatide, although switching patients from exenatide to liraglutide treatment did not compromise the glycemic response to liraglutide due to persistent exenatide antibodies (34). Another study demonstrated that exenatide antibodies peak during early treatment and decline thereafter, and are not predictive of safety and efficacy. Since these antibodies do not cross-react with the glucoregulatory hormones GLP-1 or glucagon and diminish over time, long-term clinical consequences are unlikely (35).

Considering the marked inhibitory effects of GLP-1 on gastric emptying, it is tempting to speculate that the inhibition of gastric emptying could play a major role in the body weight-lowering effects of both liraglutide and exenatide. A study was designed to test the effects of acute and chronic exposure to liraglutide and exenatide on

gastric emptying, food intake and body weight. The data suggested that the "gastric-inhibitory" GLP-1 receptors in rats are subject to desensitization during the full 24 hours of exposure to liraglutide, whereas the GLP-1 receptors mediating the effects on body weight are not. These data indicated that liraglutide-induced weight loss depends on the regulation of appetite signals in the brain and not on gastric emptying (36).

GLP-1 analogues and receptor agonists

Although GLP-1 analogues are not licensed with insulin, many diabetologists use this combination to treat patients with type 2 diabetes. A double-blind, placebo-controlled study on the administration of exenatide to patients with type 2 diabetes (suboptimally controlled [glycated hemoglobin HbA1c ≥ 7.1% and ≤ 10.5%] with basal insulin glargine therapy and/or oral agents) reported that exenatide improved HbA1c by improving both fasting and postprandial blood glucose, with significant weight loss and no increased risk of hypoglycemia (37). The Association of British Clinical Diabetologists nationwide exenatide audit revealed that the initiation of exenatide in patients with type 2 diabetes who were on insulin therapy was safe and yielded HbA1c and weight reductions. There was further weight loss with the progressive reduction of insulin dose, but this occurred at the expense of worsened HbA1c levels. When insulin was substituted with exenatide, almost half of the patients had worsened glycemic control (38). This study also found that the combination of insulin and exenatide was used by 36.7% of patients, and exenatide allowed some patients to be weaned off insulin. This latter group of patients may experience a considerable improvement in glycemic control and a significant reduction in weight (39).

GLP-1 analogues can be used instead of bedtime insulin therapy in patients with poorly controlled type 2 diabetes, with varying influences on body weight. Besides the effects of GLP-1 on energy intake, it is unclear whether changes in the resting energy expenditure (REE) contribute to these distinct weight courses. A study in patients with poorly controlled type 2 diabetes maintained on maximal oral therapy revealed that REE decreases early on after the introduction of insulin therapy, but is not affected by GLP-1 analogues. These different effects on REE probably contribute to the opposing weight changes resulting from these treatments (40).

The T-emerge 2 trial compared the safety and efficacy of taspoglutide, a once-weekly human GLP-1 analogue, in combination with twice-daily exenatide in patients with type 2 diabetes who were inadequately controlled with metformin and/or thiazolidinedione. Taspoglutide provided superior glycemic control with a similar weight loss and tolerability compared to exenatide at a higher dose (41). Meal tolerance tests were performed in a subset of T-emerge 2 participants. Both taspoglutide and exenatide improved glucose tolerance and reduced glucagon responses to the same extent, but taspoglutide alone significantly improved insulin secretion from baseline (42). The replacement of sulfonylurea by taspoglutide or insulin glargine in combination with previous metformin therapy in patients with type 2 diabetes induced similar improvements in glycemic control in both arms of the study. Additional weight loss, lower hypoglycemia and more gastrointestinal side effects were, however, observed with taspoglutide treatment (43). Taspoglutide provided superior glycemic control and weight loss when compared with sitagliptin in patients with type 2 diabetes inadequately controlled by metformin (44). When taspoglutide was used as monotherapy in drug-naive patients with type 2 diabetes with low baseline HbA1c, it improved glycemic control, reduced body weight and was well tolerated (45).

An open-label, randomized superiority study compared the impact of once-weekly exenatide and insulin glargine on glycemic control and cardiovascular risk factors in patients with type 2 diabetes. Results showed that once-weekly exenatide was associated with superior improvements in HbA1c and body weight. Both treatment groups displayed small but significant changes in the different surrogate markers of cardiovascular risk, with a better improvement in subjects with abnormal baseline values (46). In another open-label study in patients with type 2 diabetes pretreated with metformin, exenatide was found to be noninferior to insulin aspart with regard to glycemic control but superior in the control of hypoglycemia and body weight. In patients pretreated with metformin and sulfonylurea, glycemic control was inferior with exenatide when compared to insulin aspart, which might be due to more advanced disease conditions, leading to decreased beta cell reserve (47).

In the 26-week, double-blind, double-dummy assessment period of the DURATION-2 trial in patients with type 2 diabetes on metformin, treatment with the once-weekly GLP-1 receptor agonist exenatide resulted in greater improvements in glycemic control and weight compared to results obtained with maximum approved doses of sitagliptin and pioglitazone. In the subsequent 26 weeks, switching to once-weekly exenatide from daily sitagliptin or pioglitazone resulted in improved or sustained glycemic control with weight loss (48). Once-weekly exenatide allows the patients to have continuous exenatide exposure, which might be responsible for superior glycemic control and fewer side effects compared to exenatide administered twice daily (49). Another once-weekly GLP-1 analogue, LY-2189265, caused a greater reduction in postprandial glucose excursion, leading to greater improvement in HbA1c in Hispanics compared to non-Hispanic Caucasians with uncontrolled type 2 diabetes (50).

The once-monthly GLP-1 analogue VRS-859 is composed of exenatide and a long hydrophilic tail of natural amino acids, XTEN, which increases its half-life. In an animal study, an s.c. dose of VRS-859 was found to be effective for 1 month in providing sustained glycemic control and significant weight loss, without any adverse effects (51).

The once-daily human GLP-1 analogue liraglutide is now widely used to treat patients with type 2 diabetes. Both liraglutide and glimepiride appear to be more effective when used early on in patients inadequately controlled with oral antidiabetic monotherapy. However, patients treated with liraglutide are more likely to achieve the HbA1c target and also obtain additional benefits on body weight and systolic blood pressure, and experience a lower risk of hypoglycemia (52). A meta-analysis revealed that a majority of the patients on liraglutide therapy showed significant weight loss without experiencing any nausea, vomiting or diarrhea (53). In patients with type 1 diabetes with residual beta cell function, liraglutide improved or did not alter glycemic control, led to a possible reduction in the daily dose of insulin and caused weight loss (54).

Incretin-based therapy with GLP-1 analogues and DPP IV inhibitors is an important therapeutic option to treat patients with type 2 diabetes. A meta-analysis showed that all incretin therapies significantly reduced HbA1c and fasting glucose, but in comparison to DPP IV inhibitors, GLP-1 analogues caused greater reductions in HbA1c, fasting glucose and body weight (55). Similarly, liraglutide resulted in significantly greater reductions in HbA1c in those patients who experienced a weight loss of > 3% when compared with sitagliptin (56). In another study, exenatide demonstrated significantly better clinical effects than sitagliptin on average 24-hour glucose, postprandial glucose, insulinogenic index and glucagon suppression (57). Liraglutide caused greater improvements in glycemic control, weight loss and/or perception of superior efficacy than sitagliptin in patients with type 2 diabetes and thus led to greater treatment satisfaction (58).

In a phase III study, lixisenatide (AVE-0010; a GLP-1 receptor agonist) was administered once daily as monotherapy in patients with type 2 diabetes. The compound was safe, well tolerated and significantly improved glycemic control, with a pronounced postprandial effect (59). Another study revealed that lixisenatide restored insulin release and accelerated glucose disposition following i.v. glucose challenge in patients with type 2 diabetes, confirming this action as the basis of its control of postprandial blood glucose levels (60).

The GLP-1 analogues, thiazolidinediones (TZDs) and metformin regulate blood glucose through unique and potentially complementary mechanisms. Exenatide added to a TZD, with or without metformin, significantly improved beta cell function and glycemic control when compared with placebo (61). The LifeLink™ database retrospectively analyzed the risk of cardiovascular events in patients with type 2 diabetes (treated with exenatide or other glucose-lowering therapies) and found that exenatide treatment was associated with a lower risk of cardiovascular-related events than other classes of glucose-lowering therapies (62).

Cases of acute pancreatitis in patients treated with exenatide have been reported in the literature. A retrospective cohort study using distinct analytic methods and data sets, however, did not find any association with an increased risk of acute pancreatitis in patients who used exenatide compared to other antidiabetic drugs (63). Similarly, liraglutide did not induce pancreatitis in rats or mice receiving the drug for 2 years, or in nonhuman primates treated for 87 weeks (64).

Tolerability and compliance are a concern for patients with type 2 diabetes who receive exenatide over the long term. The delivery of exenatide for up to 12 months as a single administration to patients, thereby avoiding repeated self-injections, has been made possible with ITCA 650, which uses the DUROS technology of s.c. osmotic delivery. A phase II study reported that exenatide treatment with ITCA 650 substantially improved HbA1c and weight and ensured 100% compliance for the long-term treatment of type 2 diabetes. There were further reductions in HbA1c and weight when patients were given higher doses of exenatide using this system (65).

DPP IV inhibitors

The efficacy of sitagliptin has been studied in different trials. Coadministration of sitagliptin and metformin caused reductions in glucose and increases in active GLP-1, and thus had a complementary effect in patients with type 2 diabetes (66). Again, the efficacy of sitagliptin was compared with glimepiride in patients with type 2 diabetes who were on metformin monotherapy. Although similar improvements in HbA1c were reported with both drugs, sitagliptin caused weight loss and a lower risk of hypoglycemia, whereas glimepiride caused weight gain (67). In drug-naive patients with type 2 diabetes, a fixed-dose combination of sitagliptin and metformin produced a significantly greater improvement in glycemic control, a lower incidence of edema and a slightly higher incidence of gastrointestinal side effects when compared with pioglitazone. The sitagliptin/metformin combination resulted in a decrease in body weight, compared with an increase in body weight with pioglitazone (68). Another study compared the efficacy and safety of two treatment regimens comprised of either insulin detemir in combination with sitagliptin or sitagliptin in combination with the patients' prior sulfonylurea regimen, if any. Both groups continued on metformin and other oral drugs. There were larger reductions in HbA1c and fasting plasma glucose levels after once-daily insulin detemir/sitagliptin use compared with sitagliptin ± sulfonylurea use (with metformin therapy in both arms). This was achieved with modest weight reductions and low hypoglycemia in both arms (69). A pilot study evaluated the efficacy of sitagliptin in patients with poorly controlled type 1 diabetes and found that the drug reduced HbA1c, mean blood glucose and total daily insulin dose (70).

Saxagliptin is a selective DPP IV inhibitor approved for the treatment of type 2 diabetes in combination with metformin, a sulfonylurea or a thiazolidinedione. Pooled data from pivotal phase III studies showed that once-daily saxagliptin 5 mg administered over a 24-week period resulted in a significant reduction in HbA1c from baseline across diverse demographic and diabetes subgroups when compared to placebo (71). The same group of investigators also showed that HbA1c reductions were greatest in patients with higher baseline HbA1c values. The proportion of patients who achieved target HbA1c without associated hypoglycemic episodes was highest in those with lower baseline HbA1c (72).

Alogliptin, another highly selective DPP IV inhibitor, was well tolerated by patients with type 2 diabetes and significantly improved glycemic control when used either as monotherapy or in combination with an α-glucosidase inhibitor, pioglitazone, glimepiride or metformin (73). The addition of alogliptin (25 mg/day) to metformin and pioglitazone (30 mg) in patients with uncontrolled type 2 diabetes provided superior glycemic control and improved beta cell function when compared with patients on pioglitazone (titrated from 30 mg to 45 mg) and metformin therapy, with no clinically important differences in safety (74).

CONVENTIONAL ORAL AGENTS

Avandamet® combines fixed doses of metformin and rosiglitazone, which have complementary modes of action. Avandamet ® was compared with metformin in drug-naive patients with type 2 diabetes and HbA1c ranging from ≥ 7.5% to ≤ 10.5%. The rosiglitazone/metformin combination was found to be superior to metformin alone in improving insulin sensitivity in these patients, along with a significant reduction in HbA1c and constant glycemic control over 80 weeks. At week 80, significant intergroup changes were noted in the

overall, total female and post-menopausal female groups with respect to bone mineral density of the lumbar spine, which may be relevant to fracture risk in this population (75). Similarly, combination treatment with repaglinide and metformin provided superior glycemic control when compared to repaglinide monotherapy in drug-naive Chinese subjects with type 2 diabetes (76).

In the PIOcomb study, investigators compared a pioglitazone plus insulin regimen with metformin plus insulin treatment and with triple therapy (pioglitazone, metformin and insulin). The addition of metformin and/or pioglitazone to basal insulin glargine provided stable metabolic control without increasing the risk of hypoglycemia. There was a significant improvement in biomarkers of insulin resistance and cardiometabolic syndrome and a reduction in daily insulin dose in patients who received pioglitazone with insulin (77). The same study also showed that the addition of pioglitazone to insulin glargine improved biomarkers of chronic systemic inflammation and vascular function in patients with type 2 diabetes, which might be responsible for the lower macrovascular mortality previously indicated in the PROactive study (78). The addition of pioglitazone to insulin in patients with type 2 diabetes requiring hemodialysis was well tolerated and was associated with a lower insulin dose and triglyceride levels and improved glycemic control, indicating a potential impact of pioglitazone on long-term disease prognosis in late-stage diabetes (79).

Apoptosis can be induced by an increase in reactive oxygen species (ROS) production in mitochondria, which is responsible for the loss of beta cell mass in diabetes. Gliclazide significantly reduced the cytotoxic effect of hydrogen peroxide by decreasing the generation of ROS, and thus conveyed a protective effect against beta cell loss (80).

In diabetic patients, acarbose showed faster and better improvement of glycemic control and the lipid profile, and a long-term reduction of inflammatory parameters at baseline and after a standardized oral fat load, when compared with placebo (81). Acarbose also improved insulin resistance biomarkers and showed a long-term effect in improving insulin resistance during oral fat load when compared with the control group (82).

NEW THERAPIES FOR TYPE 2 DIABETES

Dapagliflozin is a selective inhibitor of sodium/glucose cotransporter SGLT2 that inhibits renal glucose reabsorption in an insulin-independent manner and has been shown to reduce hyperglycemia and body weight in patients with type 2 diabetes, without a significant risk of hypoglycemia. A double-blind, active-controlled trial compared the efficacy, safety and tolerability of dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who were inadequately controlled with oral antidiabetic drugs, including metformin. Dapagliflozin was found to be noninferior to glipizide in improving HbA1c at 52 weeks and caused significant weight loss and fewer hypoglycemic episodes. Dapagliflozin was well tolerated, with a tendency for more urinary tract and genital infections (83). Similarly, dapagliflozin, when added to glimipiride in patients with type 2 diabetes uncontrolled with sulfonylurea monotherapy, improved HbA1c and reduced weight, and was well tolerated (84).

Patients with poorly controlled type 2 diabetes were randomized to receive either placebo or dapagliflozin in addition to insulin therapy, with/without concomitant oral antidiabetic drugs. Dapagliflozin improved glycemic control without any increase in insulin requirement, and this insulin-sparing effect led to weight loss and reduced the frequency of peripheral edema (85, 86). In another study, dapagliflozin produced a significant improvement in glycemic control and weight loss in patients with type 2 diabetes at various stages of progression, ranging from treatment-naive to those on insulin with or without oral antidiabetic agents (87). Dapagliflozin was also found to be equally effective when administered as monotherapy, either in the morning or in the evening, to treat patients with type 2 diabetes (88).

Canagliflozin, a potent inhibitor of SGLT2, improved HbA1c and beta cell function and reduced body weight in subjects with type 2 diabetes with inadequate glycemic control on background metformin therapy (89). Canagliflozin increased 24-hour urinary glucose excretion, lowered the renal threshold for glucose excretion, reduced body weight in obese healthy subjects and reduced mean plasma glucose in patients with impaired fasting glucose and/or impaired glucose tolerance (90). In patients with type 2 diabetes, canagliflozin showed similar effects, including improved beta cell function, and was well tolerated, without causing hypoglycemia (91, 92). Another potent and highly selective SGLT2 inhibitor, BI-10773, demonstrated a dose-dependent reduction in glycemic control when compared with metformin in patients with type 2 diabetes. This investigational drug caused a reduction in body weight and showed a favorable safety profile (93).

Glucokinase activators are allosteric activators of the glucokinase enzyme that bind to the same region as naturally occurring glucokinase-activating mutations in humans. These activators are being developed as novel potential treatment for patients with type 2 diabetes. Preclinical studies with the glucokinase activator MK-0941 showed robust glucose-lowering effects in both acute and chronic disease (up to 9 months) in association with hypoglycemia in fasted and fed nondiabetic animals. In phase I studies, MK-0941 showed promise as an investigational agent for type 2 diabetes. However, when MK-0941 was evaluated in three randomized, double-blind phase II trials, similar outcomes were not observed. A better understanding of its mechanism of action and its downstream metabolic effects are needed before it is to be considered as a viable treatment (94).

The free fatty acid receptor FFA1 is predominantly expressed by the pancreatic beta cells and is involved in FFA-induced insulin secretion. A study revealed that TAK-875, an FFA1-selective agonist, directly stimulated intracellular calcium in beta cells of both rat and human islets, and thus potentiated glucose-dependent insulin secretion but did not stimulate alpha cells, which can increase glucagon secretion. This agent only stimulated insulin secretion at elevated glucose levels, without affecting the secretion of glucagon, and thus may have the added advantage of establishing a minimal risk of hypoglycemia (95).

In obesity, hyperinsulinemia activates fatty acid biosynthesis and transport pathways, reduces adipose lipolysis and suppresses ketone body synthesis, leading to enhanced triglyceride storage. Treatment with a methionine aminopeptidase MetAP 2 inhibitor reduces body weight and food intake and increases fat oxidation in obese mice, although the exact mechanism of weight loss is not clear. Fumagillin (ZGN-201), a MetAP 2 inhibitor, reversed hyperin-

sulinemia and other obesity-associated metabolic adaptations, and led to rapid weight loss in obese mice (96).

Linagliptin is a potent and highly selective DPP IV inhibitor in late stages of development for the treatment of type 2 diabetes. Linagliptin, when added to sulfonylurea to treat patients with uncontrolled type 2 diabetes, produced significant reductions in HbA1c. Linagliptin was safe and did not cause any significant increase in hypoglycemia (97). Similar observations were noted when linagliptin was used as monotherapy to treat patients with type 2 diabetes for whom metformin therapy was inappropriate (98). Decreases in renal function did not have a major effect on the elimination of linagliptin and so there is no need to adjust the linagliptin dose in patients with type 2 diabetes and renal impairment (99).

Dutogliptin is another novel and potent DPP IV inhibitor currently in phase III development for the treatment of type 2 diabetes. A post hoc analysis of a 12-week, multicenter, randomized, double-blind, placebo-controlled trial demonstrated that dutogliptin caused significant reductions in both HbA1c and fasting plasma glucose in patients with type 2 diabetes not optimally controlled with metformin and/or thiazolidinediones. Patients with diabetes for less than 5 years experienced the greatest absolute decrease in HbA1c and fasting plasma glucose (100).

When gemigliptin (LC15-0444), a DPP IV inhibitor, was used as monotherapy for 12 weeks to treat type 2 diabetes, it significantly improved HbA1c, fasting plasma glucose, postprandial glucose, insulin secretory function, as assessed by HOMA-B and C-peptide, and insulinogenic index. This drug significantly reduced total cholesterol and LDL cholesterol from baseline, did not have any effect on body weight and was well tolerated by patients (101).

The G protein-coupled receptor GPR119 is expressed by pancreatic beta cells and L cells in the gastrointestinal tract in humans. Activation of this receptor in the intestine results in the release of GLP-1. A naturally occurring ligand with high affinity for GPR119 has now been identified, and when used in healthy subjects it induced secretion of GLP-1, which can improve glucose homeostasis through several mechanisms (102).

GFT-505 and GFT-1007, its main active circulating metabolite, activate the peroxisome proliferator-activated receptor subtypes PPARα and PPARδ. GFT-505 potently reduces plasma triglycerides and total cholesterol and increases HDL cholesterol in animal models of dyslipidemia. GFT-505 also prevents the development of atherosclerotic plaques and has insulin-sensitizing properties in mice. In a double-blind, placebo-controlled phase IIa trial conducted in 98 patients with atherogenic dyslipidemia, GFT-505 led to a significant reduction in triglycerides, apolipoprotein C3, apolipoprotein B, fibrinogen and haptoglobin, and increases in HDL cholesterol, apolipoprotein A1 and apolipoprotein A2. In 47 patients with impaired fasting plasma glucose, impaired glucose tolerance and abdominal obesity, GFT-505 led to a significant reduction in fasting plasma glucose, fasting plasma insulin and C-peptide, and thus the HOMA insulin resistance index was significantly reduced. A beneficial effect on plasma lipids was observed, as well as a significant reduction in markers of inflammation, without any change in homocysteine levels. GFT-505 can be used in the future as an effective and safe drug to treat prediabetic patients with impaired fasting glucose and atherogenic dyslipidemia (103).

Most of the current treatments have focused on improving diabetes control with little effect on dyslipidemia, hypertension and obesity. Thiazolidinediones improve insulin sensitivity and diabetes control but are associated with adverse cardiovascular outcomes and weight gain. P-1738 is a novel insulin sensitizer with no PPARα/γ transactivation potential. It improved glycemic and extraglycemic parameters in a model of obesity in mice and showed a favorable weight profile (104).

FFA1 is highly and dominantly expressed in pancreatic beta cells and is activated by medium- to long-chain FFAs to potentiate glucose-stimulated insulin secretion. A novel, oral and selective small-molecule agonist of this receptor, TAK-875, is under development as a once-daily treatment for type 2 diabetes. In an animal study, TAK-875 showed glucose-dependent insulin secretion, leading to a significant improvement in HbA1c, with no effect on body weight or pancreatic insulin content (105).

Imeglimin targets insulin-resistant organs and addresses beta cell failure. By decreasing mitochondrial oxidation, imeglimin inhibits excessive hepatic glucose production and restores peripheral glucose uptake, as well as glucose-dependent insulin secretion. Imeglimin was found to be as effective as metformin in reducing HbA1c and fasting plasma glucose in patients with type 2 diabetes, with no serious or severe adverse events. It can be used as monotherapy or as add-on therapy with other classes of antidiabetic agents (106).

Oxyntomodulin is released from L cells of the small intestine in response to meal ingestion and is believed to exert its biological effects as a dual glucagon receptor and GLP-1 receptor agonist. A new, potent, dual glucagon–GLP-1 receptor agonist, ZP-2929, has a pharmacokinetic profile compatible with once-daily dosing. This compound improved glucose control and the blood lipid profile, and decreased body weight in murine models of insulin resistance and obesity (107).

Colesevelam is indicated for glycemic control and LDL cholesterol lowering in patients with type 2 diabetes and hypercholesterolemia, respectively. Metformin and colesevelam were used together in Hispanic drug-naive patients with type 2 diabetes and results showed significant reductions in LDL cholesterol, non-HDL cholesterol, total cholesterol, triglycerides and HbA1c. There was also significant improvement in apolipoprotein A1 and apolipoprotein B (108).

Animal and human studies have suggested that vitamin D may play a role in modifying the risk of diabetes and that of other autoimmune diseases. The potential mechanism of action of vitamin D on glucose metabolism includes a direct effect on beta cell function and insulin sensitivity. A study showed that vitamin D supplementation in apparently healthy subjects with insufficient 25-hydroxyvitamin D levels improved beta cell function and insulin sensitivity over a short period of time (109). Another study revealed that vitamin D3 supplementation in adults with glucose intolerance attenuated the increase in glycemia that occurs over time, and the combination of calcium carbonate with vitamin D3 improved glycemia more than vitamin D3 or calcium alone (110). Investigators from China suggested that lower 25-hydroxyvitamin D levels are significantly associated with an increased risk of metabolic syndrome independent of parathyroid hormone in the Chinese population (111).

ACKNOWLEDGMENTS

I would like to thank my wife Salma, who supported me, and my daughter Sruti for always keeping me smiling. I would also like to thank my son Prithu, who always has time to help me, even when he is at university.

DISCLOSURES

The author states no conflicts of interest.

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