Review Article

Red carpeting the newer antidiabetics

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ABSTRACT

The rapidly increasing prevalence of diabetes on a global scale beseeches an urgent need for newer and better treatment options. Our better understanding of the pathophysiology of diabetes has enabled a continual churn out of newer antidiabetic agents with varying modes of action. Sodium-Glucose Transport Proteins-2 inhibitors, dipeptidyl peptidase IV inhibitors, glucagon-like peptide analogues, glucokinase activators, dual peroxisome proliferator-activated receptor agonists, monoclonal antibodies, and dopamine-2 receptor agonists either as monotherapy or combination therapy with the existing oral hypoglycemic agents compound our fight against diabetes. A review of the newer drugs targeting various aspects in the management of diabetes is presented.

Key words: Glucokinase activators, newer antidiabetics, Sodium-glucose transport proteins-2 inhibitors

INTRODUCTION

Diabetes mellitus is an entity of considerable morbidity comprising a spectrum of multisystem dysfunctions stemming from the combination of insulin resistance and inadequate insulin secretion. Management of diabetes, akin to a tightrope walk, requires a comprehensive understanding of various factors such as over-all clinical picture, adverse effect profile, the complex of inter-play of drugs, etc. More than two-thirds of people with type 2 diabetes will eventually require more than one oral agent, with or without insulin. There is a perpetually increasing newer range of antidiabetic drugs targeting novel aspects of diabetes which warrant adequate awareness by the treating clinicians. The newer antidiabetic drugs of different classes are discussed below.

Sodium-glucose transport proteins-2 (SGLT2) inhibitors

Sodium-dependent glucose co-transporters (SGLT) are found in the intestinal mucosa of the small intestine and the proximal tubules of the nephrons. Two types of SGLT are of considerable importance in diabetes—SGLT1 and SGLT2 (members of genes SLC5A1 and A2, respectively).[1] Intestines predominantly sport SGLT1 whereas the proximal tubules of the nephrons display both SGLT2 and SGLT1. A sodium-to-glucose co-transport ratio of SGLT1 is 2:1 and that of SGLT2 is 1:1 and while the former contributes 2% to glucose reabsorption, the latter contributes 98%.[2] Hence SGLT2 inhibition enables us to considerably reduce transcellular epithelial glucose reabsorption. SGLT2 inhibition is independent of glucose-dependent insulin secretion by the pancreatic β cells.

Dapagliflozin, the notable molecule in the class of SGLT2 inhibitors, reduces blood glucose levels in an insulin-independent manner by inhibition of SGLT2-mediated reabsorption of glucose in the kidney. Dapagliflozin sported a comparable 52-week glycemic efficacy with glipizide and in addition, unlike the latter, resulted in reduced weight and less hypoglycemia.[3] However, the FDA (Food and Drug Administration) presented an unfavorable review of the drug owing to increased incidence of breast and bladder cancers and hepatotoxicity.[4] Remogliflozin, another SGLT2 inhibitor, is found to be potent and highly selective. In experimental

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models, its prodrug remogliflozin etabonate increased urinary glucose excretion in a dose-dependent manner which in turn inhibited the increase in plasma glucose after glucose loading without stimulating insulin secretion.[5] Sergliflozin etabonate, in a study, showed superiority over gliclazide and showed reductions in glycated hemoglobin and improved glycemic control without resulting in insulin secretion, hypoglycemia, and body weight gain.[6] Canagliflozin and other similar molecules are being evaluated with encouraging results.

The adverse effects of SGLT2 inhibitors may include fatigue, hypoglycemia, increased urine output, increased hematocrit, and mycotic genital or urinary tract infections.

DPP IV inhibitors

Dipeptidyl peptidase IV (DPP IV) inhibitors act primarily by blocking incretin degradation [inhibit the breakdown of glucagon-like peptide (GLP—1) and glucose-dependent insulinotropic peptide (GIP) leading to an increase in plasma concentrations of the same]. This results in stimulation of insulin secretion, reduction in plasma glucose and glucagon levels, and inhibition of gastric emptying. Incretins also govern β-cell differentiation, mitogenesis and survival which is how DPP IV inhibition can preserve β-cell mass and improve their secretory function.[7] Treatment with the DPP IV inhibitors is shown to reduce the risk of myocardial infarction (an effect dependent on the blood glucose levels) probably mediated via the GLP-1 receptor pathway and the protein kinase-A (PKA) signaling pathway.[8]

Sitagliptin, the first DPP IV inhibitor, rises postprandial active GLP-1 concentrations without causing hypoglycemia in normoglycemic healthy male volunteers. In a 24-week study, on 741 patients, once-daily sitagliptin monotherapy improved glycemic control in the fasting and postprandial states, improved measures of β-cell function, and was well tolerated.[9] Another study on 2719 diabetics, lasting from 12 weeks to more than a year, showed that sitagliptin improved blood sugar control when used alone or in diabetes patients not satisfactorily managed with metformin or a peroxisome proliferator-activated receptor (PPAR) agonist.[10] Vildagliptin, apart from DPP IV inhibition, is also known to enhance α-cell responsiveness to both the suppressive effects of hyperglycemia and the stimulatory effects of hypoglycemia. These effects may mediate its efficacy to improve glycemic control as well as its low hypoglycemic potential. In an interim analysis of a large, randomized, double-blind, multicentre study, the addition of vildagliptin to metformin showed comparable efficacy to that of glimepiride after 52 weeks.[11] Saxagliptin, another DPP IV inhibitor, showed efficacy both as monotherapy and in combination. Once-daily saxagliptin monotherapy for 24 weeks demonstrated clinically meaningful reductions in HbA1c and FPG compared to placebo.[12] Even in drug naïve type 2 diabetics, saxagliptin showed beneficial glycemic effects.[13] Linagliptin, a new long-acting xanthine based DPP inhibitor with high selectivity to DPP-4 (vs. the related enzymes DPP-8 and DPP-9), is associated with minimal risk of hypoglycemia. In a study, linagliptin monotherapy produced a significant and sustained improvement in glycemic control (reduced fasting and postprandial glucose, improved proinsulin/insulin ratio, homeostasis model assessment), accompanied by enhanced parameters of β-cell function.[14] A herbal supplement berberine is known for its antihyperglycemic effect with DPP IV inhibition and inhibition of the prodiabetic target human protein tyrosine phosphatase 1B being some of the mechanisms that may explain such effect.[15]

Adverse effects, including nasopharyngitis and upper respiratory infections (probably via immunomodulation),[16] headache, nausea, skin reactions and rarely hypersensitivity reactions, and pancreatitis (probably via ductal proliferation and metaplasia)[17] are reported with DPP IV inhibitors.

GLP-1 analogues

Glucagon-like peptide (GLP-1) analogues are synthesized by small intestinal L cells. They heighten glucose-dependent insulin secretion, reduce glucagon secretion, promote weight loss, slow gastric emptying, decrease appetite, and promote β-cell regeneration. They do not cause hypoglycemia, in the absence of therapies that otherwise cause hypoglycemia. They also seem to play a role in halting the progression of more aggressive lesions from underlying steatosis in Nonalcoholic Fatty Liver Disease (NAFLD).[18]

Exenatide, a GLP-1 analogue and insulin secretagogue with glucoregulatory effects. It is recommended for use as adjunctive therapy to improve glycemic control in patients who are taking metformin, or a combination of metformin and a sulfonylurea, but have not achieved adequate glycemic control. Exenatide augments glucose-dependent insulin secretion by the pancreatic β-cell. In a study, exenatide once weekly brought sustained improvements in glycemic control (HbA1C and FPG) and body weight through 52 weeks of treatment.[19] Weight-related quality of life, health utility, psychological well-being, and diabetes treatment satisfaction are all shown to be better when exenatide is used in combination with metformin.[20] The side effect profile of exenatide includes hypoglycemia (more upon combination therapy with sulfonylureas and thiazolidinediones), nausea, vomiting, diarrhea, heartburn, indigestion, dizziness, headache, and pancreatitis. Development of anti-exenatide antibodies may also be seen.

Lixisenatide, a once-daily injectable GLP-1 receptor agonist, demonstrates efficacy and safety in T2DM both as monotherapy and in combination with metformin.[21] In the GetGoal-1 Phase III trial, a GLP-1 receptor agonist, lixisenatide has significantly reduced HbA1c levels and reduced weight in T2D patients.[22]

Liraglutide, a long acting GLP-1 receptor agonist, has shown evidence that it may benefit patients with inadequate diabetes control despite their use of another antidiabetic therapy. Liraglutide in type 1 diabetics is known to reduce insulin requirement with improved or unaltered glycemic control. In a study liraglutide induced similar glycemic control, reduced body weight, and lowered the occurrence of hypoglycemia compared to glimepiride, both used in combination with metformin.[23] Liraglutide is contraindicated in those with family history of medullary thyroid cancer.[24] Cases of acute pancreatitis have been reported in use of liraglutide use. Albiglutide is a recombinant human serum albumin (HSA)-GLP-1 hybrid protein with half life of about a week and is found to display resistance to DPP IV.[25] It has shown consistent efficacy in type 2 diabetics. Taspoglutide, another analogue, exerts insulinotropic action *in vitro* and *in vivo*, retains the glucoincretin property of human GLP-1, is fully resistant to DPP IV cleavage and has an extended *in vitro* plasma half-life.[26]

Glucokinase activators

Glucokinase (also called hexokinase IV or D) owing to its glucose sensor role in pancreatic β-cells and being the rate-controlling enzyme for hepatic glucose clearance and glycogen synthesis is known to have an exceptionally high impact on glucose homeostasis. Glucokinase activators (GKAs) stimulate insulin biosynthesis and secretion and augment glucose metabolism and related processes in other glucokinase-expressing cells via GKA-mediated increase in the affinity of glucokinase for glucose and its maximal catalytic rate.[27] GKAs mediate their antidiabetic effects via generalized enhancement of β-cell function and through fasting restricted changes in glucose turnover. Piragliatin, a GKA, has shown an acute glucose-lowering action in patients with mild type 2 diabetes.[28] An experimental GKA molecule ZYGK1 showed promising efficacy in controlling both fasting and non-fasting blood glucose.[29] The side effects although rare of GKAs are hypoglycemia, fatty liver, and hyperlipidemia.

Dual PPAR agonists

Inhibition of PPAR α-agonists (Fibrates) lowers plasma triglycerides and VLDL particles and increases HDL cholesterol while PPAR γ-agonists (thiazolidinediones) influence free fatty acid flux and reduce insulin resistance and blood glucose levels. The PPAR α/γ dual agonism addresses both insulin resistance (the inability of tissues to utilize insulin efficiently for the uptake of glucose) and key aspects of the dyslipidemia that contribute to the high risk of cardiovascular disease (CVD) in diabetics. They have documented heightened insulin sensitivity and are known to improve inflammation, vascular function, and vascular remodeling.[30]

Aleglitazar, a new balanced dual PPAR α/γ agonist, reduces hyperglycemia and improves the levels of HbA1C, HDL-C, LDL, and triglycerides with minimal PPAR-related adverse effects.[31,32] In *in vitro* models, aleglitazar strongly decreased the multiple aspects of the inflamed phenotype of human adipocyte/macrophage co-culture system compared to pioglitazone and fenofibrate suggesting its contribution to prevent progression of adipose dysfunction and insulin resistance, and increased cardiovascular risk.[33] Although muraglitazar a similar molecule showed efficacy as an add-on therapy for poorly controlled diabetics, excess incidence of death, major adverse cardiovascular events (MI, stroke, TIA), and heart failure were noted with it and hence withdrawn.[34]

Monoclonal antibodies

To induce immune tolerance via monoclonal antibodies has been tried as a way to prevent and effectively treat diabetes. Otelixizumab, an anti-CD3 monoclonal antibody, is known to stimulate C-peptide levels and reduce insulin requirement in type 1 diabetes.[35] Similarly studies with teplizumab are also reassuring.[36] Other monoclonal antibodies such as anti-CD20,[37] anti-CTGF,[38] anti-IL-1β,[39] have shown promising results and are yet to be approved.

Dopamine-2 receptor agonist

Timed bromocriptine (centrally-acting dopamine D2 receptor agonist) is believed to act on circadian neuronal activities within the hypothalamus to reset abnormally elevated hypothalamic drive for increased plasma glucose, triglyceride, and free fatty acid levels in fasting and postprandial states in insulin-resistant patients. Its use as monotherapy and in combination with other OHAs is shown to reduce HbA1c, plasma triglyceride, and FFA concentrations in type 2 diabetic patients.[40] Side effects include nausea, fatigue, vomiting, headache, dizziness, orthostatic hypotension, and syncope, the latter two upon initiation or dose escalation.

Others

Chromium (Cr) may reduce myocellular lipids and enhance insulin sensitivity in subjects with type 2 diabetes mellitus independent of its effects on weight or hepatic glucose production.[41] Clinical response to Cr is more likely in insulin-resistant type 2 diabetics with elevated fasting glucose and A1C levels. It also has anti-inflammatory activity apparently mediated by elevated blood vitamin C and adiponectin and inhibition of NFκB, Akt, and Glut-2 and increased IRS-1 gene activation.[42] Sodium tungstate is known to preserve the pancreatic β-cell function in diabetics and normalize the activity of sucrase and SGLT1 in the brush-border membrane of enterocytes.[43] A combination of hyperglycemia-independent pathways are postulated to explain its antidiabetic effects.[44] Vanadium is known to mimic most effects of insulin on the main target tissues of the hormone *in vitro* and it is shown to induce a sustained fall in blood glucose levels in insulin-deficient diabetic rats, and improve glucose homeostasis in obese, insulin-resistant diabetic rodents (*in vivo*). It has shown antidiabetic effects in phase II trials[45] although another study

showed no such benefits.[46] Proxyfan, a central histamine H3 receptor ligand, is shown to significantly improve glucose excursion by increasing plasma insulin levels via a glucose-independent mechanism.[47] Aspartame, guargum, and glucomannan have all displayed notable benefits in glycemic control either singly or as combinations.

Experimental research

A new molecule SR 1664 which is a potent binder to the nuclear receptor PPARγ shows that blockage of cyclin-dependent kinase 5 (Cdk5)'s action on PPARγ is a viable therapeutic approach for development of antidiabetic agents. It also demonstrated fewer side effects, such as weight gain or increased plasma volume, compared to rosiglitazone.[48]

Systemic administration of toll-like receptor (TLR) ligands can suppress autoimmune responses (autoimmune diabetes) which reinforces the hypothesis that TLR stimulation can recapitulate the protective effect of infectious agents on autoimmunity.[49] Low-dose cyclosporine and methotrexate in subjects with new onset type 1 diabetes can safely induce remission of disease and decrease the insulin requirement.[50]

A new compound 5,8-diacetyloxy-2,3-dichloro-1,4-naphthoquinone is known to selectively provoke insulin receptor activation by directly binding to the receptor kinase domain to trigger its kinase activity. It sensitizes insulin's action, elevates glucose uptake in adipocytes, and has oral hypoglycemic effects.[51]

β-Sitosterol has shown promising antidiabetic as well as antioxidant effects probably mediated via apoptosis induced by increased FAS levels and caspase 8 activity, phosphorylation of extracellular signal-regulated kinase and mitogen-activated protein kinase, with no cytotoxicity to normal cells.[52] S-Allylcysteine (a natural constituent of fresh garlic) is shown to have significant antihyperglycemic effects along with lowering of tissue glycoprotein components (such as hexose, hexosamine, fucose and sialic acid in plasma, liver and kidneys).[53] In a study cucurmin, (a natural ingredient of turmeric) via its antioxidant and anti-inflammatory effects, enhanced the ability of bone marrow transplantation to regenerate functional pancreatic islets.[54]

CONCLUSION

There is rapid and accelerated progress in the antidiabetics drug-development front that runs parallel to our ever evolving comprehension of the pathophysiology of diabetes. Clinicians need to be abreast of this plethora of newer antidiabetic drugs coming up, their efficacy, adverse effect profile and stand in diabetes management that empowers them to better manage diabetes.

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