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REVIEW

A review of newer treatment approaches for type-2 diabetes: Focusing safety and efficacy of incretin based therapy

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Abstract Diabetes resulting from both genetic and lifestyle factors causes high insulin deficiency or its resistance. As hyperglycemia and decreased insulin secretion and/or its sensitivity appear to be the primary defects associated with diabetes, available treatments focus on reducing those defects. A novel approach of treatment is to target the incretin mimetic hormones, which are secreted by intestinal cells in response to food intake, provoking glucose-dependent insulin secretion from the pancreas. Efficacy and safety studies of dipetidyl peptidase inhibitors (DPP-IV), sitagliptin, vildagliptin and linagliptin provide similar improvements in HbA1c levels when compared with metformin, sulfonylureas or glitazones without contributing to weight gain and hypoglycemia. Caution is required when choosing the gliptin in people with renal or hepatic impairment and with a risk of pancreatitis. The glucagon like peptide (GLP-1) analogues Exenatide and Liraglutide also have positive impact on glycemic control especially when used as a combination therapy. Another upcoming approach is using sodium-glucose co transporter two inhibitors in kidney, by exploring pathophysiology of renal glucose re absorption in the proximal tubule.

Introduction

Even though diabetes is not a new born disease with a history since 1552 its prevalence is increasing day by day. As in other diseases newer drugs are getting added up and some become outdated or withdrawn. Even the most commonly used oral hypoglycemic agent (OHA) metformin is found to be ineffective in the long-term therapy for many patients. Sulfonylureas are used in case of patients who are not responding to metformin. But they can put patients at an increased risk of hypoglycemia, weight gain, heart attacks and strokes. Glitazones are also associated with cardiovascular risks. To avoid such pitfalls and to improve glycemic control with minimum side effects new therapeutic approaches are developed. Dipeptidyl peptidase (DPP)-4 inhibitors, which enhance postprandial levels of the incretin hormones glucagon like peptide (GLP)-1

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and glucose-dependent insulinotropic polypeptide (GIP), are newer therapeutic options with minimal side effects (Dicker, 2011).

The revised consensus algorithm accounts for the introduction of incretin-based therapies into clinical practice. The algorithm was authored in 2009 by the American Diabetes Association and European Association for the Study of Diabetes for the initiation and adjustment of therapy in Type 2 diabetes. The incretin hormones are gut borne and have clinically meaningful effects on glucose homeostasis, particularly in the postprandial period. So according to the algorithm their use can be emphasized in cases of hypoglycemia and increased body weight. Also 66% of the β-cell response during post prandial period is due to the incretin effect. The foundation of incretin-based therapies is to target this newly recognized feature of diabetes pathophysiology, resulting in sustained and powerful glycemic control and body weight control (Stonehouse et al., 2012; McIntosh et al., 2005).

The incretins are peptide hormones released into the circulation, in response to luminal nutrients, minutes after a meal. In humans, the major incretins are glucagon-like peptide-1 (GLP-1) secreted by the L cells in the ileum and colon and glucose-dependent insulinotropic polypeptide (GIP) secreted by the K cells in the duodenum. Hormonal effects on multiple organs are found to be exhibited by both GLP-1 and GIP and stimulate insulin secretion in a glucose-dependent manner along with appetite suppression and delayed gastric emptying. As a result of these combined effects, significant contribution has been made for the control of postprandial glucose resulting in a better glycemic control with relatively low risk of hypoglycemia. (Prins, 2008) The incretins are predominant gut borne mediators of insulin release, and GLP-1 deals with glucagon suppression. GLP-1 represents a clinically better therapeutic option over GIP as its insulinotropic effects are preserved in type 2 DM while GIP activity is impaired (Fujioka, 2007). However both incretins are rapidly inactivated in vivo by the enzyme DPP-IV. Two approaches considered to enhance the incretin effect in type 2 diabetes are to either administer GLP-1 receptor agonists that are resistant to cleavage by DPP4 or to inhibit DPP4 enzyme activity. These pharmacological approaches thereby effectively increase the half-life and circulating levels of the incretins (Prins, 2008).

Incretin-analogue based therapies

Glucagon-like peptide 1 (GLP-1) analogues are the foundation of incretin-based therapies and the main advantage is that they can be used as monotherapy, or in combination with other diabetic medications along with diet and exercise in adults with type 2 DM (Chiniwala and Jabbour, 2011) Emerging evidence suggests minimum risk of hypoglycemia with incretin-based treatments except in combination with insulin secretagogues. They also exhibit beneficial effects on cardiovascular and hepatic health, the central nervous system, inflammation and sleep (Stonehouse et al., 2012) The administration of incretin analogues resistant to cleavage by DPP4 was really appreciable. Two drugs exenatide and liraglutide are clinically used now, given as subcutaneous injection. Formulation developments are on going to check whether long-acting once-weekly injections are possible. Exendin, the clinical formulation of exenatide is a potent activator of the GLP-1 receptor with almost 50% homology to GLP-1, while liraglutide maintains normal activity at the GLP-1 receptor. Both are resistant to cleavage by DPP4 and have a long circulating half-life (Prins, 2008).

Dipeptidyl-peptidase IV inhibitors

Dipeptidyl-peptidase (DPP) IV is a ubiquitous enzyme that is responsible for the inactivation of both incretin hormones GLP-1 and GIP. DPP IV inhibitors are FDA approved oral medications in type 2 diabetes, which inhibit dipeptidyl peptidase-4 thereby increase circulating concentrations of incretin hormones and provide glycemic control with improved islet cell function (Pratley and Salsali, 2007) and by this mechanism of action they allow GLP1 to stay in the body for longer time which improves control of glucose as well as reduce appetite. They help the pancreas to secrete insulin in glucose dependent manner in post-prandial period and thereby reducing dramatic episodes of blood sugar spikes (Stonehouse et al., 2012) Also they are well tolerated, carry a low risk of hypoglycemia and weight gain (Stonehouse et al., 2012; Pratley and Salsali, 2007).

Another new approach is the use of sodium glucose co transporter-2 inhibitors which are in the phase III studies for the treatment of type 2 diabetes. Several specific SGLT2 inhibitors currently under development include dapagliflozin, canagliflozin, empagliflozin, ipragliflozin and tofogliflozin. They work independently and inhibit glucose re-absorption from the glomerular filtrate. Reduced renal threshold for glucose, glycosuria and net calorie loss are the results. Trials regarding long-term outcomes are ongoing (Isaji, 2007; Grempler et al., 2012).

In the present article, we discuss the attributes of new treatment strategies of diabetes and an attempt has been made to compare and elaborate various aspects of incretin based therapies including their efficacy and adverse reactions focused on GLP1 agonists and commonly used gliptins-vildagliptin, Sitagliptin and linagliptin.

Comparison of various efficacy studies of Sitagliptin, Vildagliptin and Linagliptin

A large number of clinical studies and extensive clinical experience demonstrate that gliptins provide unique therapeutic benefits that make them ideal for treatment of type 2 diabetes. They are available in combination pills with Metformin. All these medicines have been shown to significantly reduce HbA1c when used as monotherapy and in combination with other traditional agents. But they are comparatively more expensive. Several studies were designed and done to compare these drugs with other OHAs to clarify their efficacy in relation to traditional agents. Various meta analysis were done to study the safety issues also. They are found to be associated with minimum side effects like headache, nausea as well as mild skin reactions.