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Dipeptidyl Peptidase-4 (DPP-4) Inhibitors: New Oral Medications for the Treatment of Type 2 Diabetes

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Abstract

Type 2 diabetes (T2D) is a metabolic disorder characterized by hyperglycaemia, insulin resistance at peripheral target tissues, and pancreatic β-cell dysfunction. It is a global health problem with epidemic proportions and a huge economic burden. The dipeptidyl peptidase (DPP-4) inhibitors are a new class of antihyperglycaemic agents that are developed for the treatment of T2D. Many clinical studies have suggested that DPP-4 inhibitors (gliptins) are safe from cardiovascular perspective, and may also possess cardioprotective effect. These are regulators of inflammation and metabolism, and also prevent the proteolytic breakdown. These reduce postprandial glucose with minimal risk of hypoglycaemia and gastrointestinal adverse effects. These increase biologically intact forms of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), both of which enhance glucose-induced insulin secretion from pancreatic β-cells. These medications become popular and are widely used worldwide for their efficacy, safety, weight neutrality, and tolerability. This article reviews basic studies of the DPP-4 inhibitors in briefly for the management of T2D.

Keywords: Type 2 diabetes, oral hypoglycaemic drugs, glucose lowering, DPP-4 inhibitor

1. Introduction

Dipeptidyl peptidase-4 (DPP-4) inhibitors are membrane-bound enzymes that cleave N-terminal dipeptide from their substrates and are recommended as second- and third-line therapy. These belong to the S9b dipeptidyl peptidases family (Gong et al., 2015). These are weight-neutral, well-tolerated, rarely cause hypoglycaemia (FDA, 2015). These are also known as CD26 (cluster of differentiation 26 or T-cell activation antigen CD26), or adenosine deaminase complexing protein 2. These are expressed in almost all organs and tissues of the body, with the highest expression in kidney, small intestine, and placenta (Lambeir et al., 2003). These improve glycemic control, reducing both fasting and postprandial glucose levels to lower HbA1c levels, without weight gain and with an apparently benign adverse event profile (Sethi et al., 2014). But weight gain and/or hypoglycaemia have been observed when DPP-4 is used with Sulfonylureas (Amori et al., 2007).

These work by blocking the action of the enzyme DPP-4 that breaks down hormones called incretins. These help to lower blood glucose in two ways: i) boost the production of insulin in the pancreas and increase insulin secretion and more insulin allows glucose to more efficiently move out of the bloodstream and into the body cells, and ii) decrease the amount of glucose released by the liver and less glucose enters the bloodstream (Deacon et al., 2004). These are oral agents that inhibit the activity of the enzyme DPP-4, and hence prolong the actions of endogenous GLP-1. These are a suitable treatment option for the elderly and occupational drivers (Rai et al., 2019). Six DPP-4 inhibitors available are Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin, Septagliptin,

and Allogliptin (Green et al., 2015).

2. Literature Review

Literature review is a starting section but it is an important item for a researcher (Polit & Hungler, 2013). It is a helpful subject area for the new researchers to advance their research efficiently (Creswell, 2007). Dror Dicker has shown that the different DPP-4 inhibitors are distinctive in their metabolism, their excretion, their recommended dosage, and the daily dosage that is required for effective treatment. But, when compare their efficacy regarding lowering HbA1c levels, safety profile, and patient tolerance these show similar manner (Dicker, 2011).

Manoj Kumar Sethi and his coauthors have investigated that the DPP-4 inhibitors work through preventing the inactivation of the incretin hormones that is glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) through stimulation of insulin secretion and reduction in glucagon secretion with a potential to increase β-cell mass (Sethi et al., 2014). Matilda Florentin and her coworkers have shown that DPP-4 inhibitors have a favorable safety profile, do not cause hypoglycaemia or weight gain and do not require dose titration. These can be administered in patients with chronic kidney disease after dose modification and elderly patients with diabetes (Florentin et al., 2022).

Lihua Duan and his coauthors have summarized the recent advances in direct and indirect regulatory role of DPP-4 in atherosclerosis. They have also shown that ongoing trials assessing the cardiovascular effects of DPP-4 inhibitors and GLP-1R agonists will provide further insights into the cardiovascular actions of DPP4 inhibitors (Duan et al., 2017). Eleni Xourgia and her coworkers have summarized the mechanism of action the advantages and disadvantages of SGLT-2 and DDP-4 inhibitors, their effects on cardiovascular (CV) events, their role in current guidelines for T2D treatment and how they are implemented in daily clinical practice (Xourgia et al., 2017). Devajit Mohajan and Haradhan Kumar Mohajan have studied diabetes mellitus, eating disorders, and various anthropometric indices. They have also studied on insulin and various oral medications for the treatment of T2D. They have stressed that overweight and obesity are the roots of many non-communicable diseases (Mohajan & Mohajan, 2023a-z).

3. Research Methodology

There is no alternative but research to an academician for the development of carrier (Pandey & Pandey, 2015). Methodology is the guideline to perform a good research efficiently (Kothari, 2008). Therefore, research methodology is a working procedure for planning, arranging, designing, and conducting a meaningful and valuable research (Legesse, 2014). To prepare this paper we have used secondary data sources that are related to DPP-4 inhibitors. We have consulted the published and unpublished research papers, books and handbooks of renowned authors. We have also collected valuable information from websites and internets to develop the paper. We start our research through the discussion of historical background of DPP-4 inhibitors. Then we have tried to highlight functions and dose adjustment of DPP-4, and finally we have studied side-effects of DPP-4.

4. Objective of the Study

The central objective of this study DPP-4 inhibitors that are used as oral medications for the treatment of type 2 diabetes. Other minor objectives of the study are as follows:

- to focus on historical background of DPP-4 inhibitors,
- to highlight on functions and dose adjustment of DPP-4, and
- to show the side-effects of DPP-4.

5. Historical Background

DPP-4 inhibitors are discovered in 1967. Since the discovery these have been a popular subject of research (Sebokova et al., 2006). The first inhibitors are characterized in the late 1980s and 1990s. In the 1990s it was discovered that the enzyme DPP-4 inactivates the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (Gutniak et al., 1992). In 2006, Sitagliptin was approved by the Food and Drug Administration for use as monotherapy or in combination with metformin. Vildagliptin was discovered by Novartis in 1998, and in 2008, it was approved in Europe (Peters, 2007). Five of the DPP-4 inhibitors (sitagliptin, vildagliptin, alogliptin, saxagliptin and linagliptin) were approved by regulatory authorities and entered the market between 2006 and 2013 (Rai et al., 2019). In 1994, Cyanopyrrolidines is unveiled with a nitrile function group. Sitagliptin was approved in 2006 as the treatment for T2D. A combined product of Sitagliptin and Glucophage was approved in 2007 (Wiedeman, 2007).

6. Functions and Dose Adjustment of DPP-4

DPP-4 inhibitors play a physiological role in the regulation of the incretin (GLP-1, GIP) hormones. The effectiveness of delayed degradation of substances, such as GLP-1 is based on a phenomenon named the

"incretin effect". These increase prandial insulin level and reduce pancreatic β-cell apoptosis to decrease glucagon level, and regulate growth hormone (Mest & Mentlein, 2005). The DPP-4 inhibitors are suitable for patients with renal impairment with dose adjustments. These lower HbA1c values up to 0.5-0.74% (Bennett et al., 2011; Doucet et al., 2011). These work by inhibiting DPP-4, which is an enzyme that destroys the hormone GLP-1 that aids glucose-dependent insulin production (Bannister & Berlanga, 2016).

DPP-4 inhibitors show non-glycemic favorable effects including reductions in systolic blood pressure, total cholesterol and triglycerides, as well as improvement in β-cell function (Kim et al., 2014). DPP-4 inhibitor drugs are taken as a tablet once daily any time of the day and are being taken at the same time. If a dose is missed, should be taken immediately when remember. If it is close to the time for the next dose, should skip the missed dose and should go back to the normal time. A patient should not take extra doses or two doses at the same time (Davidson, 2009).

Older population should take DPP-4 inhibitors due to their confined effect on blood glucose lowering, neutral effect on caloric intake, less negative effect on muscle, and total body protein mass (Dicker, 2011). Many preclinical and clinical studies have suggested that DPP-4 inhibitors may modulate atherosclerotic disease by reducing plasma lipids, suppressing inflammation, and promoting vascular relaxation (Duan et al., 2017). Incretin-based therapies, such as GLP-1 receptor agonists and DPP-4 inhibitors can help weight reduction, blood pressure reduction, and reduced hypoglycaemia risk in addition to glycemic control (Matthijs et al., 2013).

7. Side-Effects of DPP-4

DPP-4 inhibitors can cause some unexpected side-effects among few patients. These side-effects are gastrointestinal problems, such as nausea, diarrhea, and stomach pain; flu like symptoms, such as headache, runny nose, and sore throat; skin reactions, such as painful skin followed by a red or purple rash, joint pains; and urinary tract infections (Dicker, 2011). These increase risk for infection and headache. These also have the associated increased risk of pancreatitis and should be avoided in patients with high triglycerides. These may cause severe and disabling joint pain among some patients (Scirica et al., 2013). If a patient has any one or more of the following conditions, DPP-4 inhibitors may not be suitable for him/her: the patient is pregnant or breastfeeding, has any significant problems with liver, such as active liver cirrhosis, has renal failure, and has heart failure (Sethi et al., 2014).

8. Conclusions

The goal of antidiabetic treatment is to achieve a complete safety as possible regarding HbA1c, fasting plasma glucose, and postprandial glucose concentration. The DPP-4 inhibitors are new medicines for the treatment of type 2 diabetes. These are supposed to improve metabolic control without causing severe hypoglycaemia. These are orally active, safe, do not frequently cause weight gain, and well-tolerated that can improve glycemic condition both in monotherapy as well as combination therapy. These have a favorable safety outline of kidney impairment and the elderly patients can use it confidently. When the physicians prescribe GPP-4 inhibitors, they should consider important parameters, such as the patient's age, the time from initial diabetes diagnosis, body weight, compliance, and financial means.

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