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GLIPTINS: SAME NEW DRUGS, NON-INFERIORITY OR NO SUPERIORITY

Dick B. S. Brashier*[1], Dr. Prashant Mishra[2], Htet Wai Moe[3], Kedar G. Bandekar[4], Neha Akhoon[5]

[1]Professor, Department of Pharmacology, Armed Forces Medical College, Pune– 411 040, Maharashtra, India.
[2]Classified Specialist (Pharmacology), Armed Forces Medical Services, New Delhi – 110001.
[3,4,5]Resident, Department of Pharmacology, Armed Forces Medical College, Pune– 411 040, Maharashtra, India.

***Corresponding Author: Dr. Prashant Mishra**
Classified Specialist (Pharmacology), Armed Forces Medical Services, New Delhi – 110001.

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ABSTRACT

Gliptins are a relatively new class of antidiabetic drugs that inhibits dipeptidyl peptidase-4 (DPP-4). They have revolutionized the treatment of type 2 diabetes mellitus as they changed the ways that diabetes and its management has been perceived by clinicians.[1] Gliptins modulate the physiological mechanism which is already in human body and increase the effect of incretin hormones, peptides which are normally released from the endocrine cells in small intestinal mucosa in response to food.

KEYWORDS: The drawback for clinical usefulness of incretin is that they are rapidly degraded.

INTRODUCTION

Gliptins are a relatively new class of antidiabetic drugs that inhibits dipeptidyl peptidase-4 (DPP-4). They have revolutionized the treatment of type 2 diabetes mellitus as they changed the ways that diabetes and its management has been perceived by clinicians.[1] Gliptins modulate the physiological mechanism which is already in human body and increase the effect of incretin hormones, peptides which are normally released from the endocrine cells in small intestinal mucosa in response to food. It enhances food-induced insulin secretion and modulates glucagon lowering in fed state.[2] In human body, there are two main incretin hormones, GLP-1 and GLP-2 which are physiologically important. They stimulate insulin secretion and augment insulin stores by upregulating insulin gene expression and all the steps in biosynthesis of insulin. In in vitro studies, the incretin showed β-cells trophic effects and GLP-1 showed suppression of glucagon secretion and inhibition of gastric emptying and appetite.[3]

The drawback for clinical usefulness of incretin is that they are rapidly degraded and their duration of action being limited by the enzyme dipeptidyl peptidase-4 (DPP-4). Therefore, the development of DPP-4 resistant GLP-1 analogues or DPP-4 inhibitors was thought to have clinical effectiveness. Gliptins inhibits the DPP-4 enzymes and increases the level of incretin hormones GLP-1 and GLP-2.[4]

History of Approval of Gliptins

The first gliptin approved was sitagliptin and it was approved in 2006. It was approved to be used alone or combination therapy with metformin or peroxisome proliferator-activated receptor gamma (PPAR) agonist. It was tested in a total of 2,719 patients with type 2 diabetes. It is the first DPP-4 inhibitor globally available now.[5] In 2007, the second gliptin, vildagliptin was approved by European Union and other countries but USFDA approval is still pending as USFDA demands additional data of clinical study for safety and efficacy.[6] Saxagliptin, approved in 2009, was approved to be used in people with type 2 diabetes who are resistant to insulin or do not produce enough insulin to maintain normal blood sugar levels. It was approved based on the results of eight clinical trials.[7] Another gliptins approved later were linagliptin, teneligliptin, gemigliptin, anagliptin, alogliptin, evogliptin, omarigliptin and trelagliptin.

Important Features of Each Gliptin

Each gliptin has its own important clinical features.

Sitagliptin

Sitagliptin was the first drug in the class of DPP-4 inhibitors which is orally effective to enhance the ability of the body to lower blood glucose when it is elevated. From the results of clinical studies, there was no association with weight gain and hypoglycemia. The study results for complications from these studies are comparable to placebo. The side effects commonly found with sitagliptin were runny nose, headache, sore throat, diarrhea and joint pain.[8]

Vildagliptin
Vildagliptin was the second drug in the class of DPP-4 inhibitors. From the studies, Vildagliptin showed effectiveness as it extend the action of insulin by delaying the degradation of GLP-1 and suppress the release of glucagon. Long term treatment with Vildagliptin was tolerated in clinical studies. It is also not associated with weight gain which is beneficial for patients with type 2 diabetes.[9]

Saxagliptin
Saxagliptin was approved in 2009 for use as monotherapy or in combination with other drugs for type 2 diabetes. It was also not associated with weight gain and hypoglycemia but it increased the risk of hospitalization for heart failure by about 27%. It was found out in the clinical studies that combination therapy with metformin was more effective than saxagliptin monotherapy. Good benefit with saxagliptin was that it did not increase the rate of ischemic events of heart.[10]

Linagliptin
Linagliptin approved in 2011 was a more potent inhibitor of DPP-4 than the drugs of the same class. In clinical studies, the most common complication was severe joint pain associated with use of linagliptin.[11]

Teneligliptin
Teneligliptin was approved in Japan, Korean and India. In clinical studies, teneligliptin showed favorable results in glycemic control in type 2 diabetic patients showing insufficient results of glycemic control treated with combination of exercise, control of diet and thiazolidine or sulfonylurea. As the metabolites of this drug were found out to be eliminated through renal and hepatic excretion, dosage adjustment is not required in patients with renal impairment.[12]

Gemigliptin
Gemigliptin was approved by Korean FDA in 2012. It was the first new anti-diabetic drug in history of Korean pharmaceutical industry. In clinical studies, it was effective for use in type 2 diabetes patient as monotherapy or combination therapy with metformin. Dose adjustment is not required in patients with renal or hepatic impairment. The incidence of adverse drug reaction was similar to those of placebo.[13]

Anagliptin
Anagliptin was approved in Japan since 2012. In clinical studies, it was also effective and safe for both monotherapy and combination therapy. The side effects were similar to other drugs of the same class. Few reports from clinical studies showed that Anagliptin might prevent atherosclerotic disease and diabetic microangiopathy but further investigation is necessary to clarify these effects.[14]

Alogliptin
Alogliptin was approved in US and Europe since 2013. Like other DPP-4 inhibitors, alogliptin was found out in clinical studies to cause little or no weight gain and little risk of hypoglycemia. It can be used as both monotherapy and combination therapy with metformin. USFDA added a warning of risk of heart failure with use of alogliptin in 2016.[15]

Evogliptin
Evogliptin is another drug from the class of DPP-4 inhibitor developed and approved in South Korea in 2015. In clinical studies, it showed effectiveness as monotherapy and combination therapy with metformin.[16] It was generally well tolerated and adverse events were dizziness and headache, urticarial, abdominal discomfort, mild insomnia and sleep disorder.[17]

Omarigliptin
Omarilgliptin was approved in Japan at 2015. It is a potent drug effective as oral, once-weekly DPP-4 inhibitor for treatment of type 2 diabetes. Therefore it is an important option for patients who prefer once-weekly dosing. In clinical studies, it was generally well tolerated.[18]

Trelagliptin
Trelagliptin was also approved in Japan at 2015. Trelagliptin is a potent DPP-4 inhibitor as it is effective to be used as once-weekly dosing. In clinical studies, it was effective for patients with type 2 diabetes who are not achieving the expected glycemic control with metformin.[19]

Is One Gliptin Superior to Another?
There are varieties of gliptin available now for the treatment of type 2 diabetes. Obviously it should be questioned that "Is one gliptin really superior to another?" As the drugs are not often compared with each other in the same class, evidence to answer the questions whether benefits of one drug exceed others in the class cannot be fully expected.[20] The gliptins share the same mechanism of action by inhibiting DPP-4. But there are some differences in pharmacokinetic and pharmacodynamic properties between gliptins.[21] Amongst gliptins, saxagliptin is the only DPP-4 inhibitor with active metabolite. Therefore, there may be possibly higher chance of drug-drug interactions with saxagliptin.[22] Linagliptin is primarily excreted through hepatobiliary route when sitagliptin, vildaglipitn, saxagliptin and alogliptin are excreted through kidneys. The gliptins excreted via kidneys might need dosage adjustment according to glomerular filtration rate.[23]

Another important and clinically significant difference between gliptins is duration of DPP-4 inhibition after oral administration. Duration of inhibiting DPP-4 by once daily dose of sitagliptin 100 mg issimilar to that of vildagliptin 50 mg twice daily and remarkably greater

than that of once daily dose of saxagliptin 5 mg or vildagliptin 50 mg. Omarigliptin and trelagliptin, which are the latest approved gliptins in Japan, can be given as a once-weekly dosing which favors the compliance of patients.[24]Regarding glucose-lowering efficacy, gliptins showed similar efficacy and safety both in monotherapy and combination therapy. In various clinical studies, gliptins showed practically similar glycemic control regarding HbA1c reduction. Regarding safety profiles of gliptins, all the DPP-4 inhibitors showed good tolerability profile with no severe hypoglycemia and no weight gain.[25]

Do we need so many gliptins?

As the modern chemotherapy where drug discovery and development process of screening thousands of molecules for various disease conditions has been developed, there has also been criticized for many molecules were developed with identical chemical structure and similar pharmacological profile. At present time, the only practical differences between different gliptins are dosing frequency and ability to be used in different patient populations. These differences are scant to distinguish which gliptin is better in efficacy as antidiabetic agent and safety. It is very difficult to distinguish one gliptin from each other in terms of their therapeutic utilization. Many new gliptins were developed with the only proof of non-inferiority profile. This condition indicates that research and development of the same drugs with noninferiority or no superiority spend resources on drugs for the disease conditions for which the treatment options have already existed. This can also be assumed as negligence for the conditions of other important public health conditions and we do not need more gliptins with non-inferiority profiles in this same class.

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