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Effectiveness And Side Effects Of Alogliptin In Type 2 Diabetes Mellitus Patients. Article Review

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A B S T R A C T

Diabetes mellitus is defined as a group of metabolic disorders caused by multiple aetiologies, characterized by hyperglycaemia with disorder of carbohydrate, protein and fat metabolism resulted from defects in insulin secretion, insulin action, or both. The clinical diagnosis of diabetes might manifest as polyuria, polydipsia, and unexplained weight loss, and confirmed hyperglycaemia. In type 2 diabetes progressive loss of b-cell insulin secretion often causes insulin resistance. Insulin resistance manifestations include increasing lipolysis and free fatty acid production, increasing hepatic glucose production, and decrease in glucose intake into skeletal muscle. Alogliptin is a new class of oral hypoglycemic agents, highly selective DPP-4 inhibitor which has been approved of FDA. Alogliptin can be used as monotherapy or in combination with other anti diabetic agents such as metformin, sulfonylureas (glyburide), pioglitazone, and insulin. Based on several studies, alogliptin shows low risk of the occurrence of side effects, such as hypoglycemia, edema, weight gain, RA, joint pain and cardiovascular events. The purpose of this review is to update clinical information about the effectiveness and side effects of alogliptin as diabetic therapy in T2DM patients.

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1. Introduction

Diabetes mellitus is a metabolic disease with hyperglycemia as its characteristics, which occurs due to abnormalities in insulin secretion, insulin work, or both. Common clinical manifestations are polyphagia, polydipsia, polyuria, weight loss, and tingling or pickling sensations[1,2].

The WHO Global Report reported that in 2012 higher-than-optimal blood glucose was responsible for an additional 2.2 million deaths as a result of increased risks of cardiovascular and other diseases, for a total of 3.7 million deaths related to blood glucose levels in 2012. Many of these deaths (43%) occur under the age of 70. Globally, the incidence of high blood glucose from the community causes around 7% of deaths among men aged 20-69 and 8% among women aged 20-69[3]. Diabetes Care in 2004 estimated that in 2030 the prevalence of diabetes mellitus in Indonesia will reach 21.3 million people. The Basic Health Research (Riskesdas) results in 2007 found that the proportion of causes of death due to diabetes mellitus in group age 45-54 year in urban areas was greater (14.7%) compared to rural areas rural areas (5.8%)[4].

Type 2 diabetes mellitus (T2DM) was formerly known as non-insulin-dependent or adult-onset diabetes, due to the less effective use of insulin by cells in the body or because insulin resistance occurred. T2DM affects 90-95% of all diabetic sufferers[5]. High prevalence of T2DM is influenced by several such as modifiable factors and unmodified factors. Risk factors that cannot be modified are, for example, gender, age, race/ethnic, family history of diabetes mellitus, childbirth history with baby's weight>4000 grams, and low birth weight (<2500 grams). Whereas the modifiable risk factors are closely related to unhealthy lifestyles, such as overweight, abdominal/central obesity, lack of physical activity, alcohol consumption, hypertension, dyslipidemia, unbalanced diet, history of impaired glucose tolerance, and smoking habit[6,7].

Diabetes mellitus is also called as a "silent killer" because the complications related disease it provokes in all organs of the body. Diseases that will be caused include heart disease, kidney disease, wounds that are difficult to heal and rot/gangrene, strokes and even patients with severe DM undergo amputation of limbs due to decay. This complication occurs in both type 1 and type 2 diabetes mellitus patients. Diabetes complications are classified as microvascular and macrovascular. Microvascular prevalence is much higher than macrovascular[51]. Microvascular complications include neuropathy, nephropathy, and retinopathy, whereas macrovascular complications consist of cardiovascular diseases, stroke, and peripheral arterial disease (PAD)[8].

Diabetic foot ulcer syndrome is defined as the presence of foot ulcers is associated with neuropathy, PAD, and infections which are the main causes of amputation[9].

To reduce its incidence, complications, and also to achieve good metabolic control in patients with type 2 diabetes mellitus, both pharmacological therapy and non-pharmacological therapy in the form of lifestyle improvements should be applied[10].

In general, therapy for diabetes mellitus is not only in reducing glycemic levels in acute situations, but also needs to maintain glycemic levels over time. Therefore it often requires several drugs with different mechanisms of action[11]. Dipeptidyl peptidase-4 (DPP-4) is a responsible serine protease responsible for the metabolism of incretin hormones such as glucagon peptide-1 and insulinotropic polypeptides which depend on glucose and play an important role in regulating glucose homeostasis[12]. In 2015, DPP-4 was developed by Takeda (Trelagliptin) and approved in Japan as an oral treatment in patients with type 2 diabetes mellitus (T2DM), but in the USA and EU research for phase two clinical trial initiated of this drug was not continued, hindered by the amount of costs[13]. Previously in 2013 a new substance of (DPP-4) drugs was approved from the FDA and EU namely Alogliptin.

Alogliptin is the newest (DPP-4) inhibitor, which is indicated as an additional treatment therapy of diet and exercise to improve glycemic control in adults with T2DM[14]. Currently, (DPP-4) inhibitors, (e.g. sitagliptin, vildagliptin, alogliptin, linagliptin, teneligliptin, anagliptin, and saxagliptin) have been approved in Japan and other DPP-4 inhibitors are currently available in the USA and Europe (sitagliptin, saxagliptin, linagliptin and vildagliptin) which are indicated as pharmacological treatments in (T2DM)[15].

2. Discussion

Definition of Type 2 Diabetes Mellitus (T2DM)

Diabetes mellitus (DM) can be characterized as chronic hyperglycemia accompanied by disorder in carbohydrate, lipid and protein metabolisms[16,17]. Chronic hyperglycemia can cause organ damage, especially in eyes, kidneys, nerves, heart and blood vessels[17].

Insulin insensitivity occurs in T2DM. Insulin levels may decrease slightly or in normal range. Because insulin is still produced by pancreatic beta cells, T2DM is considered a non-insulin-dependent diabetes mellitus[18,19].

The 2013 Global Burden of Disease Study generally identified DM as the ninth major cause of decreased life expectancy. (T2DM) and its complications contribute greatly to the level of total disability worldwide[20]. In 2010, it was estimated that DM caused 3.96 million deaths in adults between the ages of 20-79 in one year[21]. In 2017 there were an estimation of 451 million (aged 18-99 years) patients suffered from diabetes and possibly continued to increase continously; it was estimated that by 2045, the number of DM sufferers will reach up to 693 million worldwide. In 2017, around 5 million deaths caused by DM occured in the age range of 20-99 years old worldwide[22].

Pathophysiology of Type 2 Diabetes Mellitus (T2DM)

In general, there are two mechanisms of pathological failure causing (T2DM). The first mechanism is an impaired insulin secretion as a result of pancreatic β cell dysfunction and the second mechanism is insulin action impairment as a result of insulin resistance[23]. The production of abnormal blood glucose levels is caused by a mechanism that is not

optimal between insulin-sensitive tissue (e.g. liver, muscle, adipose tissue) and the occurrence of B cell damage that causes insulin resistance in T2DM[20].

Insulin resistance is a condition in which insulin in the body does not act sufficiently and proportionally to the concentration of blood glucose in the body[24]. In situation where insulin resistance occurs, the β cell mass undergoes changes in increasing insulin supply and body compensation to excessive insulin demand. In addition, insulin resistance and hyperinsulinemia can cause glucose tolerance impairment[25]. Based on the results of an investigation in molecular mechanism of insulin action, insulin resistance can be affected by genetic and environmental factors[26]. Hyperglycemia occurs when insulin secretion is unable to compensate for insulin resistance. Insulin resistance can increase in obese people, which makes obesity is at least one of the risk factors for T2DM[27].

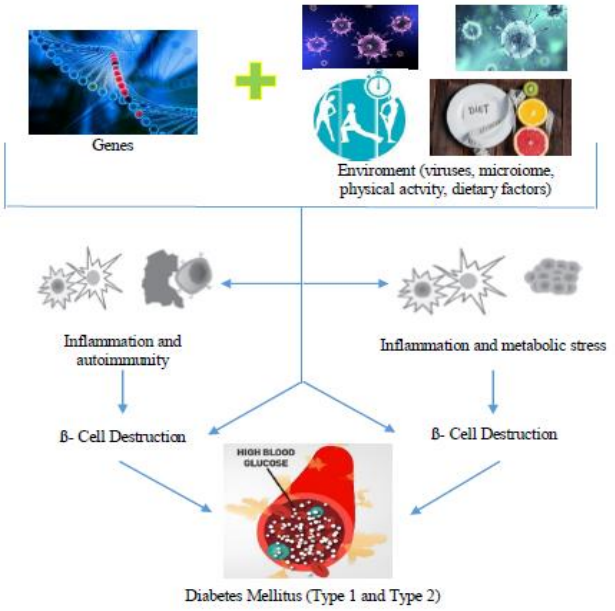

Figure 1. Genetic and environmental risk factors affecting inflammation, autoimmunity, and metabolic stress in DM development [26].

In general, insulin resistance is caused by lacking number of insulin receptors and their catalytic activities, increased Ser/Thr phosphorylation status in insulin receptors and insulin receptor substrate (IRS), increased Tyr phosphatase activity, especially in phosphotyrosine phosphatase 1 B (PTP-1B) which participate in receptor and dephosphorylation of IRS, decreased activity of phosphatidylinositol-3-kinase (PI3K) and Akt kinase, and decreased GLUT-4 expression and function. These changes reduce the process of taking glucose into the muscles and adipose tissue, encouraging the changes in metabolic rates[28,29].

In addition, one of possible mechanisms in the pathophysiology of T2DM is impaired insulin secretion caused by decrease in cellular secretion (individual β cell function level), or decrease in β cell mass (the size and the number of β cells) or in both[30]. Several studies related to β cell mass problems concluded that there is a reduction in the number of β cells in post-mortem pancreatic specimens obtained in necropsy patients with T2DM. The conclusion was made by assessing several parameters such as relative β cell volume, β cell apoptosis frequency, β cells replication, and neogenesis (new island formation from exocrine ducts). The relative volume of β cells was found to be increased in patients who are overweight compared to those who are thin β cell replication, was found to be low in all groups, and neogenesis was found to be temporarily elevated in overweight patients, not different form overweight non-diabetic patients. Meanwhile, the frequency of β cell apoptosis was increased 10 times in patients with normal weight, and 3 times in overweight patients, compared to control group. Therefore the authors concluded that the processes of reduced β cell mass in T2DM is due to increase in β cell apoptosis[31].

The occurrence of hyperinsulinemia in T2DM patients is caused by increasing insulin secretion, decreasing insulin clearance (specifically hepatic insulin extraction), or a combination of these two factors. Seino, S *et al* (2011) showed that the process of insulin secretion increased in moderate obesity at basal condition after 24 hours iv glucose administration. This study also reported that the state of diet was correlated strongly with BMI, whereas insulin clearance in the liver was not different between normal and obesity subjects. Based on the study, it is clear that increasing insulin secretion is the main determinant factor of hyperinsulinemia[32].

Treatment for (T2DM)

Management of DM can be done by applying a healthy lifestyle, medical nutrition therapy, as well as maintaining physical activity. This management can be delivered concurrently with pharmacological interventions such as oral and/or injections anti-hyperglycemia drugs. Oral anti hyperglycemia drugs can be given as a single or combination therapy.

Alogliptin

Alogliptin is a very selective and strong competitive inhibitor of the DPP-433 enzyme system. In glucose, the mechanism of action of DPP-4 is rapidly dividing endogenous incretin hormones, GLP-1 and insulinotropic polypeptide (GIP)[34].

In glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) are incretin hormones responsible for the release of insulin from pancreatic beta cells triggered by glucose level. Those hormones are released in response to food that enters inside the body. GLP-1 also decreases glucagon secretion in the pancreas and results in less liver gluconeogenesis[33]. Within minutes the DPP-4 enzyme will deactivate GLP-1 and GIP. Patients with T2DM will experience a decrease in GLP-1 level and sensitivity to GIP. However, the insulinotropic response to GLP-1 is maintained[34]. Thus, alogliptin as a DPP-4 ihibitor increases the circulation of the active endogenous GLP-1 by preventing inactivation, producing antihyperglycemic effect. When administered at therapeutic

doses, alogliptin diminishes plasma DPP-4 activity by 80% or more, providing a twofold to threefold increase in GLP-1 levels [35].

Alogliptin has the chemical name 2-({6-[(3R) -3-aminopiperidin -1-yl] -3 -methyl-2, 4-dioxo-3, 4 dihydropyrimidin-1 (2H)-yl} methyl) benzonitrile monobenzoate. The chemical structure of alogliptin is shown in Figure 2 with a molecular weight of 461.51 dalton[35].

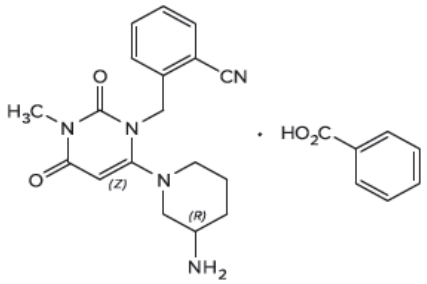

Figure 2. Chemical structure of alogliptin (C18H21N5O2C7H6O2)[35]

Oral alogliptin showed a fast absorption with an average time to reach maximum concentration (Cmax) ranging from 1-2 hours. Food existence in the stomach does not affect the absorption of alogliptin. The half-life (t½) is 21.4 hours, in which supporting once-daily dosing. Approximately 60% of alogliptin is eliminated by renal in an unchanged form and in patients with renal disorders was found an increase in alogliptin (1.7 times in mild renal impairment and 3.8 times in end-stage renal impairment). So, in patients with renal impairment, dose adjustment needs to be made, for moderate renal disorder (Creatinine Clearance/CCR $\geqslant$ 30 to <50 mL/minute) dose reduction should be 12.5 mg once daily and for severe renal disorder (Creatinine Clearance/CCR <30 mL/minute) reduction should be up to 6.25 mg once daily[15,36].

Based on a study conduceted by Betta, R *et al* (2011) and Saisho, Y (2015), 25 mg alogliptin administration to patients with hepatic impairment, did not show any significant increase in serum alogliptin concentration compared to normal patients. Hence, in patients with hepatic impairment, normal dose should be applied [15,33].

Alogliptin Monotherapy

Based on the research to examine the safety, efficacy and tolerability of alogliptin as monotherapy or in combination with other antidiabetic agents, standard mean difference (SMD) showed a significant HbA1c reduction in patients treated with a dose of 12.5 mg alogliptin (SMD = -0.81; 95% CI, -1.11 to -0.51) and in doses of 25 mg alogliptin (SMD = = 0.98; 95% CI = = 1.30 to -0.66) compared to control. Standard mean difference (SMD) is the benchmark in reducing fasting plasma glucose (FPG) level. Based on a study conduceted by Gibbs *et al* (2012) in describe the relationship between DPP-4 inhibition and mean response over time with plots of the relationship between metrics of DPP-4 inhibition (ie, weighted average inhibition [WAI] and time above 80% inhibition). The result of alogliptin (25 mg) was given once daily, time above 80% inhibition is 99 and weighted average inhibition [WAI] is 88 [37,38].

In evaluating the efficacy of alogliptin as monotherapy, a multicentre double-blind study, with a total sample of 329 T2DM patients was conducted[39]. This study was carried out for 26 weeks with alogliptin treatment 12.5 mg once daily (n=133), alogliptin 25 mg once daily (n=131), and placebo (n=65) were assessed. There was a difference in the decreased in HbA1c values in the first week of the study compared to week 26 at each dose of allogliptin (12.5 mg and 25 mg). In the group that accepted 25 mg alogliptin, 128 patients experienced 0.6% reduction in HbA1C level and 44% of those patients even achieved HbA1C level less than 7%. Significant change in FPG was observed at the beginning of week 1 well as at week 4.

Alogliptin in Combination with Metformin

The effectiveness of alogliptin in combination with metformin was evaluated in a 26-week, randomized, double-blind, and placebo-controlled study in 527 T2DM patients[40]. The inclusion criteria in this study were having an initial A1C of 7.0-10.0% and a body mass index ranging from 23 to 45 kg/m2. In addition, patients meeting the inclusion criteria were also required to receive a stable dose of metformin as much as $\geqslant$1500 mg daily for a minimum of 8 weeks. Whereas the exclusion criteria were T2DM patients that had taken additional drugs for the treatment of diabetes within 3 months before screening. Samples that filled the inclusion criteria were then divided into three treatment groups, which consisted of alogliptin 12.5 mg once daily (n=213), alogliptin 25 mg once daily (n=210), and placebo (n=104). It was found that the mean A1C reduction from the start of the study in the two groups of alogliptin was 0.6%, which was statistically significant compared with the placebo group (P<0.001). In addition, most of the samples in the alogliptin group also achieved A1C <7% compared with placebo (P <0.001). In detail mean A1C reduction in 12.5 mg alogliptin plus metformin was 0.6%, 52% patients in the same group achieved A1C $\leqslant$ 7, % and 19 mg/dl reduction in FPG. Meanwhile in the 25 mg alogliptin test group plus metformin the percentage change in A1C was 0.6%, 44% of the patients achieved A1C $\leqslant$ 7, % and 17 mg/dl reduction in FPG. This study concluded that the use of metformin and alogliptin combination can be used in uncontrolled T2DM patients with metformin single therapy.

The efficacy and safety of twice-daily allogliptin combination therapy with fixed dose combination/FDC (alogliptin 12.5 mg plus metformin 500 mg FDC BID) in Asian patients with type 2 diabetes was also studied in a multicentre, randomized and double-blind study for 26 weeks[41]. The inclusion criteria in this study were patients aged 18-75 years with hemoglobin A1c (HbA1c) 7.5% - 10.0% after at least 2 months life style modification such as diet and exercise. Patients that met the inclusion criteria were then randomly classified into four groups: 12.5 mg alogliptin twice daily, metformin 500 mg twice daily, 12.5 mg allogliptin combination group with metformin 500 mg FDC twice daily, and placebo group. The results revealed that the average HbA1c was -0.19% in placebo group, -

0.86% in alogliptin 12.5 mg twice-daily group, -1.04% in metformin 500 mg twice-daily group, -1.53% in the alogliptin 12.5 mg with metformin 500 mg FDC combination twice-daily group. The conclusion of this study is that combination of alogliptin plus FDC metformin twice daily was significantly more effective (P<.0001) in reducing HbA1c than alogliptin or metformin alone and was well tolerated in Asian patients with type 2 diabetes mellitus.

Alogliptin in Combination with Sulfonylurea

The effectiveness of 12.5 mg and 25 mg of alogliptin in combination with sulfonylurea, glyburide was evaluated in one study for 26 weeks involving 500 T2DM patients[42]. The results obtained at week 26 were reduction in HbA1c as much as -0.38% in 12.5 mg dose of alogliptin, -0.52% in 25 mg dose of alogliptin, and 0.01% for placebo (p<0.001). Another study was also conducted to evaluate the efficacy of alogliptin in T2DM patients (18-80 years old) with A1C ranged from 7% -10% receiving sulfonylurea (glyburide) at an (average dose range of =11.2-12.4 mg/day)[42]. The test group was divided into three groups: alogliptin 12.5 mg (n=203), alogliptin 25 mg (n=198), or placebo (n=99) in addition to the group that had received sulfonylurea (glyburide) therapy. At week 26 it was found that A1C reduction was significantly greater in the 12.5 mg and 25 mg alogliptin group compared to placebo P<0.001.

Alogliptin in Combination with Pioglitazone

A randomized double-blind, 12-week placebo-controlled study was conducted to assess the efficacy and safety of alogliptin as an adjunctive therapy for pioglitazone in Japanese adults (over 20 years of age) who were diagnosed with T2DM (n=339)[36]. This study included inclusion criteria in patients who had A1c between 6.9% and 10.4% received pioglitazone therapy (15 or 30 mg/day) and underwent a diet and exercise program for at least 16 weeks. Never received other antihyperglycemic drugs apart from pioglitazone within 16 weeks time. After that, the patients who met the inclusion criteria were classified based on pioglitazone dose to receive additional alogliptin therapy att at dose of 12.5 mg (n=111), 25 mg of alogliptin (n=113), or placebo (n=115). The results obtained were for the endpoint of change in A1c from week 1 to 12, there was a reduction in the mean A1c in each test group; the 12.5 mg alogliptin group was 0.91%, the alogliptin 25 mg group was 0.97%, and the placebo group was 0.19% (p<0,0001 for both comparisons of alogliptin versus the placebo group). Statistically there was an increase in the group of alogliptin added therapy in achieving A1c <6.9% and changes in FPG and PPG.

Investigating study conducted by Aoki, C *et al* (2017) observed the effect of replacement of combination therapy with alogliptin (Alo) or pioglitazone (Pio) into fixed-dose combination therapy of alogliptin and pioglitazone (Alo-Pio FDCT) into hemoglobinA1c (HbA1c), alanine transaminase (ALT), and g-glutamyl transpeptidase (GGT)[43]. T2DM was randomly assigned into two groups i.e patients receving replacement therapy from 15 mg/day pioglitazone into a combination of FDC (alogliptin 25 mg/pioglitazone 15 mg) and patients receiving replacement theraphy changed treatment from single 25 mg/day alogliptin to FDC combination (alogliptin 25 mg/pioglitazone 15 mg). The study was conducted for 16 weeks and reported found that HbA1c and fasting glucose levels increased significantly after receiving alogliptin-pioglitazone FDCT combination therapy (p<0.001) in both groups and also ALT and GGT levels also decreased significantly in both groups. In conclusion, this study showed that the combination of FDCT alogliptin-pioglitazone is effective in reducing HbA1C in T2DM patients compared to single therapy of allogliptin or pioglitazone.

Combination of Alogliptin with Insulin

A 26-week randomized, double-blind, placebo-controlled study with a sample of 395 patients was conducted to assess the efficacy and safety of alogliptin in combination with insulin in T2DM patients who failed controlling blood glucose after receiving treatments of insulin monotherapy or insulin in combination with metformin[44]. Patients were assigned into three groups: 12.5 mg allogliptin group (n=131), 25 mg alogliptin group (n=129), or placebo group (n=130), in addition to insulin therapy with or without metformin. The results showed changes in average HbA1c level as follows: -0.71% in alogliptin group at a dose of 25 mg, -0.63% in alogliptin group at a dose of 12.5 mg; and -0.13% in placebo group. At week 26, changes from baseline in mean HbA1C were significantly greater for alogliptin 12.5 mg (–0.63%) and alogliptin 25 mg (−0.71%) than for placebo (−0.13%) (p < 0.001 for both doses vs placebo). This study concluded that the addition of alogliptin to insulin therapy with or without metformin significantly improved glycemic control in T2DM patients who were uncontrolled by insulin monotherapy or insulin in combination with metformin.

Another study evaluated the efficacy and safety of alogliptin 25 mg in combination with insulin in Japanese T2DM patients who are poorly controlled with insulin and diet or exercise[45]. The study was conducted in a randomized, double-blind, 12-week period with a sample of 179 T2DM patients who took a combination of alogliptin and insulin therapy. The results revealed changes in average HbA1c level i.e -0.96% alogliptin 25 mg group, -0.29% in placebo group, and difference percentage in changes of HbA1c level between groups was at average of -0.66%. Based on recorded data, the proportion of patients who achieved HbA1c <8.0%, <7.0% and <6.0%, was significantly higher in the alogliptin group. The conclusion of this study was that alogliptin 25 mg/day is effective and well received when added to insulin in T2DM patients who are poorly controlled with insulin and diet or exercise in Japan.

Alogliptin Side Effects in Type 2 Diabetes Mellitus (T2DM)

Based on several studies evaluating the incidence of side effects of DPP-4 inhibitors (alogliptin) in type 2 diabetes patients (T2DM), the incidence of hypoglycaemia was reported to be low, either in alogliptin monotherapy or in combination with metformin or with sulfonylurea[44,45].

However, based on a study conduceted by Bosi, E *et al* (2011) in some cases mild to moderate hypoglycemia has been reported (hypoglycemia was experienced by 18 patients (4.5%) in the metformin + 30 mg pioglitazone + 25 mg alogliptin group therapy and 6 patients (1.5%) in the metformin + 45 mg pioglitazone group control). Incident severe hypoglycemia was experienced 2 events (0,5%) in the metformin + 30 mg pioglitazone + 25 mg alogliptin group therapy[14,52]. In most trials comparing a DPP-4 inhibitor with sulfonylureas combined with metformin, the risk for hypoglycaemia was higher in the group treated with a sulfonylurea, the proportion of patients who reported hypoglycaemia was 5% with DPP-4 (N= 588) and 34% with glipizide (N= 594)[53]. Therefore, close monitoring is needed for patients who are at risk of hypoglycemia such as in the elderly, patients with renal disorders, patients who take high-dose sulfonylureas, and patients with autonomic neuropathy[15].

In addition, the side effects reported in the use of alogliptin in T2DM patients were edema and general weight gain associated with combination pioglitazone therapy. An increased incidence of edema was reported when other DPP-4 inhibitors were added to pioglitazone therapy (pioglitazone + 12,5 mg alogliptin percentage peripheral edema n = 0 %, whereas pioglitazone + 25 mg alogliptin percentage peripheral edema n = 2,7 %[36]. In clinical trials, the incidence of pancreatitis was reported to occur in 11 out of 5902 patients (0.2%) who received alogliptin 25 mg daily compared with 5 out of 5,183 patients(<0.1%) who received other DPP-4 groups (e.g. linagliptin, saxagliptin, sitagliptin), the incidence of acute pancreatitis in alogliptin therapy is still under post-marketing supervision[39,46].

A study was conducted by Kathe N et al (2017) to assess the risk of rheumatoid arthritis (RA) side effect DPP-4 inhibitors treatment in diabetic patients compared to second-line antidiabetic therapy[47]. The results of the study showed that DPP-4 inhibitors were not significantly associated with the risk of RA side effects compared to other second-line antidiabetic therapy (OR=1,156, 95% CI 0.936-1,429). However, the US Food and Drug Administration (FDA) warns that (DPP-4) inhibitors such as sitagliptin, saxagliptin, linagliptin, and alogliptin can cause severe joint pain[48].

Complications are more common in T2DM patients, such as heart disease, stroke, and cardiovascular events (CV). In addition, based on the data obtained, it illustrated that alogliptin was not associated with increase in cardiovascular events[14]. A study in cardiovascular outcomes (acute coronary syndrome) in T2DM patients receiving alogliptin (EXAMINE) assigned, T2DM patients with MI or unstable angina who were hospitalized into two groups: alogliptin or placebo. The results showed that there were no differences in the composite primary endpoints such as cardiovascular death, MI, and stroke[49]. EXAMINE study concluded that among patients with T2DM who recently had ACS, the incidence rate of CV adverse events was not increased by alogliptin therapy compared to placebo[39]. Analysis collected from the alogliptin trial in a study of 4,168 patients found that there is no significant increase in cardiovascular events after alogliptin treatment in T2DM patients (hazard ratio, 0.635, 95% CI 0.0-1.41)[15]. Another DPP-4 inhibitor was investigated, in the SAVOR-TIMI research study (Recorded Saxagliptin Assessment of Vascular Results in Patients with Diabetes Mellitus with Thrombolysis in Myocardial Infarction). This study reported that administration of saxagliptin showed an increased risk in HF incidence (HR 1.27 [95% CI 1.07-1,51], p=0.007). In consideration with EXAMINE and SAVOR-TIMI studies the FDA gives warning in the use of DPP-4 inhibitors, especially in patients with a history or suffering from heart and kidney diseases[50].

3. Conclusion

Alogliptin is one of the dipeptidyl peptidase-4 (DPP-4) inhibitors approved by the FDA as an oral antidiabetic drug in T2DM patients. Based on several studies alogliptin can be used as monotherapy or in combination with other antidiabetic therapies in uncontrolled T2DM patients.

In patients with renal impairment, alogliptin dosage needs to be adjusted, for moderate renal disorders it is necessary to reduce the dose down to 12.5 mg daily and for severe renal disorders dosage needs to be reduced down to 6.25 mg daily. While in patients with liver diseases it is not necessary to do a dose adjustment.

Based on several studies, low incidence of side effects was reported in alogliptin therapy. Possible side effects reported by some studies were hypoglycemia, edema, weight gain, RA, joint pain and cardiovascular events. However, more evaluation is still needed to add more data regarding the safety of aloglitpin use in T2DM patients.

4. Referance

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