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Commentary

Commentary on cardiovascular safety of DPP4Is: Focus on Alogliptin

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ABSTRACT

DPP-4 inhibitors are present in the market for almost more than a decade. In Management of T2DM, DPP-4 inhibitors are established therapy option. The precise guidance for the pre- and post-approval and also CV safety of the newer antidiabetic agents was released by the USFDA in 2008. A neutral effect of Pooled safety analyses, as well as retrospective meta-analyses of clinical trials, have consistently demonstrated that DPP-4 inhibitors are not associated with any increase in cardiovascular adverse events, and have even pointed towards a risk reduction. The combination therapy of Alogliptin with other agents like metformin and pioglitazone have been shown to provide better and superior efficacy as compared to individual monotherapy. The hypoglycemic risk is less with Alogliptin. Alogliptin has been shown to be associated with less risk of hepatotoxicity, weight gain, and acute pancreatitis. Alogliptin does not worsen outcomes in patients with a history of heart failure (HF), neither does it increase rate of new hospitalization for heart failure (HF), as per the data from EXAMINE trial.

1. Introduction

DPP-4 inhibitors are present in the market for almost more than a decade. In the management of type 2 diabetes mellitus (T2DM), DPP-4 inhibitors are established therapy option. Clinical experience with DPP4I has shown them to be very effective, both when used in monotherapy as well as in combination with other anti-diabetic drugs.

Sitagliptin, was the first approved DPP-4 inhibitor for the management of type 2 diabetes mellitus (T2DM). There are several other DPP4Is like Alogliptin, Linagliptin, Saxagliptin, Vildagliptin available globally, and few restricted in some geographic areas are Anagliptin, Gemigliptin, and Teneligliptin. DPP-4 inhibitors essentially lower hemoglobin A1c (HbA1C) by 0.5% to 1% and found to be effective and well tolerated.[1]

1.1. Alogliptin

Alogliptin is an oral hypoglycemic agent which belong to Dipeptidyl peptidase-4 inhibitor (DPP4I) and is highly selective. Alogliptin as a monotherapy as well as in combination with other antidiabetic agents has been extensively studied as per the phase II & III data in patients with type 2 diabetes mellitus (T2DM). Alogliptin is a well tolerated DPP-4 inhibitor, associated with lower risk of hypoglycemia, weight gain, hepatotoxicity and acute pancreatitis. The dosage of Alogliptin needs to be adjusted in patients with hepatic and/or renal impairment.[2]

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1.2. Worldwide approval status[2]

The USFDA and EMA have approved DPP-4 inhibitor Alogliptin (Nesina, Vipidia) for the management of type 2 diabetes mellitus. Alogliptin fixed dose combination available in the international market include Alogliptin & metformin (Kazano, Vipdomet) and Alogliptin & pioglitazone (Oseni, Incresync). Recently Alogliptin (Aloja) & Alogliptin/metformin (Aloja M) also approved in India by Indian regulatory body DCGI in 2014.

1.3. Cardiovascular safety of DPP4Is

The placebo-controlled trials of various DPP-4 inhibitors namely, SAVOR-TIMI: Saxagliptin, TECOS: Sitagliptin, CARMELINA: Linagliptin, and EXAMINE Alogliptin and of active comparator CAROLINA: linagliptin vs active comparator [glimepiride]); were undertaken through large prospective outcome studies of prolonged duration for evaluating cardiovascular safety in high-risk populations. No large cardiovascular outcome trial are available for DPP-4 inhibitors namely Vildagliptin & Teneligliptin, as they are not marketed in US.[3]

A meta-analysis by Patil et al. (2012) involving 18 randomized trials (n = 8544) where patients were randomized to DPP-4 inhibitors (n = 4998) and other antidiabetic medications such as sulfonylurea metformin, and/or placebo (n = 3546) revealed that DPP-4 inhibitors were not only linked with lower risk of developing CV event [risk ratio (RR) 0.48, 95% confidence interval (CI) 0.31–0.75, P < 0.001] but also have reduced risk of causing nonfatal MI or acute coronary syndrome (ACS) (RR 0.40, 95% CI 0.18–0.88, P < 0.02) compared to placebo or other oral hypoglycemic agents.[4]

In meta-analysis and a systematic review to evaluate the CV safety of gliptins (DPP4Is), 50 trials enrolling 55,141 contributors were included with mean follow-up of 45.3 weeks. DPP-4 inhibitors (Gliptins) compared with all comparators (placebo and active) showed no difference in all-cause mortality and CV mortality but signalled toward increase in heart failure outcome (RR = 1.16, 95% CI 1.01–1.33, P = 0.04).[5]

1.4. Cardiovascular safety of Alogliptin

In December 2007, the original New Drug Application (NDA) of Alogliptin was submitted by Takeda San Diego. There is a criteria laid down as a Guidance For Industry : Diabetes Mellitus-Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes Mellitus (T2DM), in December 2008. The USFDA, in June 2009 requested for conducting additional cardiovascular safety trial as per the criteria. On the basis of interim data from Examination of cardiovascular outcomes with Alogliptin versus standard of care in patients with T2DM and acute coronary syndrome (EXAMINE) trial which had begun in October 2009, Alogliptin (Nesina) and fixed dose combinations with pioglitazone (Oseni), and metformin (Kazano) were approved on January 25, 2013.[6,7]

2. Examine Trial

Throughout the clinical development program of Alogliptin, no inequality in cardiovascular events (CV) was seen among 4168 patients with type 2 diabetes mellitus who received Alogliptin, 691 patients who received placebo, and 1169 patients who received active comparators.[8] Given the low cardiovascular-risk profile of the patient population and the low event rate, the cardiovascular safety in patients at high cardiovascular risk could not be assessed.

Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial was conducted to determine whether Alogliptin is non-inferior to placebo with respect to major cardiovascular events (MACE) in patients with type 2 diabetes mellitus who are at very high cardiovascular risk — those with recent acute coronary syndromes.

The Non-inferiority of Alogliptin versus placebo was confirmed based on the similar rates of death from nonfatal myocardial infarction, cardiovascular causes, and nonfatal stroke, in type 2 diabetes mellitus (T2DM) patients with a recent episode of acute coronary syndrome (ACS).[9]

2.1. Examine trial: A post-hoc analysis of Alogliptin for heart failure outcome

Alogliptin treated [433 (16·0%)] patients had similar exploratory extended MACE endpoint with placebo 441 (16·5%) treated patients, with a hazard ratio [HR] 0·98, 95% CI 0·86–1.12.

Alogliptin was non- inferior to placebo in lowering the risk of the composite primary endpoint of CV death, MI or stroke (11·3% vs 11·8%, HR 0·96, upper boundary of the one-sided 95% CI 1.16.

Alogliptin had no effect on composite events of CV death and HHF in the post hoc analysis (HR 1·00, 95% CI 0·82–1·21) and results did not differ by baseline BNP concentration. Concentrations of NT-pro-BNP decreased significantly from baseline to 6 months in the Alogliptin group (median value at baseline 423 pg/mL [IQR 156–1103] vs 220 pg/mL (IQR 89-551) at 6 months, p<0·001). Similar changes were observed in the placebo group (399 pg/mL (IQR 149-982) vs 213 pg/mL (IQR 88-564), p<0·001). The difference in change between treatment groups was not significant (p=0·077).

There was no difference in the rates of cardiovascular outcomes, including hospital admission for heart failure (HF), in Alogliptin versus placebo. The raised concentration of NT-pro brain natriuretic peptide, history of heart failure, or both did not affect the cardiovascular outcome. Both groups had similar use of diuretics (both thiazide and

Table 1: Examine trial

Study Design	Number of Patients	Result
A multicenter, prospective, phase III, double-blind, Non-inferiority based randomized controlled trial conducted in T2DM patients with an acute coronary syndrome (i.e, myocardial infarction (MI) or hospitalization for unstable angina), the cardiovascular outcomes of Alogliptin (6.25-25 mg/d) versus placebo was evaluated. The mean follow-up period was approximately 4.75 years. Non-inferiority trial with a pre-specified non-inferiority margin of 1.3 for the hazard ratio (HR) for the primary end points of a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.	5380 patients (18.8% i.e 400 Patients from India across 33 centers) Types of patients: Type 2 diabetes and either an acute myocardial infarction or unstable angina requiring hospitalization within the previous 15 to 90 days to receive Alogliptin or placebo in addition to existing anti-hyperglycemic and cardiovascular drug therapy	A primary end-point event occurred in 305 patients allocated to Alogliptin (11.3%) and in 316 patients assigned to placebo (11.8%) (HR, 0.96; upper boundary of the one-sided repeated confidence interval, 1.16; P<0.001 for non-inferiority). Glycated hemoglobin (HbA1c) levels were significantly lower with Alogliptin than with placebo (mean difference, −0.36 percentage points; P<0.001).

loop). At the end of 6 months of therapy, both groups showed similar reduction in NT-pro brain natriuretic peptide concentration. Alogliptin was not associated with volume expansion in the high-risk T2DM patients with acute CV event.[10]

3. Conclusion

DPP-4 inhibitors are first line anti-diabetic agent in patients in whom metformin cannot be used. In patients with diabetes who are unable to achieve HbA1c targets with metformin monotherapy, DPP-4 inhibitors can be used as an add-on therapy. They are used as a third agent in patient already on combination therapy with metformin plus a sulfonylurea, a thiazolidinedione or insulin, who are not able to achieve HbA1c targets despite combination therapy.[2]

In India and US, Alogliptin is approved as a monotherapy in patients who are inadequately controlled on diet and exercise. Alogliptin as a monotherapy has been shown to improve the glycemic control in patients with type 2 diabetes. The tolerability and efficacy of Alogliptin was also demonstrated in both Asian and Caucasian patients.

Randomized controlled trials demonstrated, improved glycemic control with Alogliptin as a monotherapy, in combination with metformin, sulfonylurea, voglibose, pioglitazone, or insulin, or as add on agent in patients on metformin and pioglitazone combination. Alogliptin was well tolerated, weight neutral, and associated with lower risk of hypoglycemia.[2]

Alogliptin, Saxagliptin and Sitagliptin were not associated with increased risk of mortality versus placebo as per the data based on the Examine (approximately 5400 patients with recent acute coronary syndrome; median follow-up 1.5 years), SAVOR-TIMI (16,500 patients with pre-existing cardiovascular disease (CVD) or multiple risk factors; mean follow- up period of 2.1 years) and TECOS (14, 600 patients with established cardiovascular disease (CVD) ; mean follow-up of 3.0 years) trials in relation to the primary composite cardiovascular outcome [CV death, non-fatal MI, non-fatal stroke, and in EXAMINE, hospitalization for unstable angina] (HR of 0.96, 1.00 and 0.98, respectively). There was however no reduction in cardiovascular risk.[3]

The post hoc data of Examine trial, showed no significant difference in hospitalization for heart failure rates, in Alogliptin versus placebo, despite small numerical imbalance (hazard ratio 1.19; 95% CI, 0.90–1.58). There was no worsened outcomes in patients with history of heart failure. Also, Alogliptin was not associated with any increase in new hospital admissions for heart failure.[3]

The ADA EASD 2022 consensus in T2D report, recommend DPP4I for more modest glucose-lowering efficacy, neutral effect on weight, better tolerability with minimal risk of hypoglycaemia. The consensus report also specifies on the CV safety of Alogliptin demonstrated from the CVOT (Examine study).[11]

In Asian patients, Alogliptin reported a higher efficacy and good tolerability, as compared to non-Asian patients with diabetes mellitus.[12] Alogliptin is found to be effective and well tolerated DPP4I with proven cardiovascular safety.

4. Source of Funding

None.

5. Conflict of Interest

Dr Abhijit Trailokya, Dr. Santosh Kale and Dr Amar Shirsat are associated with Indoco Remedies Mumbai.

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