Research Article

Targeted Pharmacovigilance for Dipeptidylpeptidase-4 (DPP-4) inhibitors : A Cross-Sectional Study

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ABSTRACT

The objective of this study was conducted on patients diagnosed with Type-2 Diabetes Mellitus (T2DM) in an outpatient setting with an aim to determine the frequency, severity, causality, predictability, and preventability of adverse drug reactions (ADRs) of Dipeptidylpeptidase-4 (DPP-4) inhibitors. A total of 250 patients receiving DPP-4 inhibitors and attending diabetic clinic over a period of 6 months were included in the study. Demographic profile of the patients and ADRs were recorded in a predesigned Case Record form. ADR severity was assessed by University of Virginia Health System Adverse Drug Reaction Reporting program criteria, causality assessment was done by using a WHO-UMC scale and preventability assessment were assessed and categorized by using Schumock and Thornton criteria. Out of 250 patients, 135 patients reported a total of 164 ADRs. Most common ADRs were Gastro-intestinal system disorders (40.2%), followed by CNS disorders (29.3%), musculoskeletal disorders (9.1%), Genito-urinary disorder (4.3%), metabolic disorders (1.2%), Cardiovascular disorder (0.6%), Skin & subcutaneous tissue disorder (8.5%) and others (6.7%). The maximum frequency of ADRs was seen with Teneligliptin (92.6%) followed by Sitagliptin (4.2%), Vildagliptin (2.4%) and Linaligliptin (0.6%). 130 (79.3%) ADRs were mild, 33 (20.1%) ADRs were moderate and 1 (0.6%) ADR were severe. 137 (83.5%) ADRs were classified as possible and 27 (16.5%) probable on causality assessment. Multiple ADRs were seen in DPP-4 Inhibitor of which majority belonged to teneligliptin. Majority of ADRs belonged to gastrointestinal system, were of mild severity, non-serious and not preventable.

Keywords: Pharmacovigilance, Type-2 Diabetes Mellitus, Adverse dug reaction, DPP-4 Inhibitor (Gliptins).

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INTRODUCTION

Type 2 Diabetes mellitus also called Non-insulin-dependent diabetes mellitus (NIDDM), a most common form of diabetes mellitus is a long-term metabolic disorder that is characterized by high blood sugar, insulin resistance, and relative lack of insulin. The World Health Organization (WHO) considers T2DM as an apparent epidemic which is especially increasing at an alarming rate in developing countries. [1]

Apart from insulin replacement, there are various classes of oral hypoglycaemic agents available for management of diabetes. Dipeptidylpeptidase-4 (DPP-4) inhibitors , called Gliptins are class of oral anti-diabetic agents which selectively inhibits the DPP-4 enzyme that rapidly degrades two major incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulin releasing polypeptide (GIP).Evidence from randomized controlled trials has established that DPP-4 inhibitors reduce levels of glycated hemoglobin (HbA1c), do not affect body weight, pose a low risk of hypoglycemia, and do not increase the risk of cardiovascular events.[2]

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as "any response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function".[3] Adverse drug reactions (ADRs) are considered among the leading causes of morbidity and mortality, causing around 6% of hospital admissions and approximately 6-15% of hospitalized patients experience a serious ADR.[4]

Owing to the fact that the DPP-4 Inhibitor class of drugs have been in the market for last few years only, the data regarding their safety is limited particularly in Indian population. Hence, the present study is planned to actively generate baseline data on the safety profile of currently prescribed Gliptins in diabetic Indian population by actively monitoring for ADRs.

MATERIALS AND METHODS

This cross-sectional study was conducted on patients receiving DPP-4 inhibitors after obtaining approval by the Institutional Ethics Committee. The study was conducted in the department of Pharmacology in collaboration with General Medicine. All the patients diagnosed with Type 2 Diabetes Mellitus between 20-90 years old receiving DPP-4 Inhibitors were included in the study. The patients who

were not willing to give consent were excluded from this study. Data on Adverse drug reaction of DPP-4 Inhibitor in Type 2 Diabetes Mellitus was collected by patient's individually in OPD of General Medicine department and Diabetic Clinic of AIIMS, Rishikesh. The suspected adverse drug reaction data was entered into patient's case record form (CRF). The details regarding the ADR was filled in the Central Drugs Standard Control Organisation (CDSCO) ADR Performa and subsequently uploaded in the WHO-UMC using the Vigiflow software.

Study tools

The severity of all ADRs has been assessed on the basis of the University of Virginia Health System, Adverse Drug Reaction Reporting program criteria comprises of three sections namely "mild": a reaction that does not require treatment or prolongation of the hospital stay; "moderate": a reaction that requires treatment and/or a prolonged hospitalization by at least one day and "severe": a reaction that is potentially life-threatening or that which contributes to the death of the patient, that which is permanently disabling, that which requires intensive medical care (including extended hospitalization). [5]

The causality of ADRs due to suspected medications was assessed using the WHO-UMC scale. The ADRs are categorised according to certain criteria: time relationship to drug intake, any alternative medications taken, response to withdrawal and response on re-introduction of the drug. Depending on these criteria the ADRs are classified as Certain, Probable, Possible and Unlikely. [6]

Preventability of ADRs was assessed using by Schumock and Thornton criteria, [7] which comprises of three sections namely definitely preventable, probably preventable and not preventable.

RESULTS

Table 1 describes the demographic parameter of study participants. 135 patients out of total of 250 patients (54%) included in the study, developed ADRs out of which some patient's complaint of multiple ADRs. Total no. of 164 ADRs were reported by 135 patients. Among 135 patients 72 (53.3%) were males and 63 (46.7%) were females.

Table 1: Demographic profile of the patient

S. No.	Parameter	Group	Total no. Of patients (n=135)	
			N	%
1	Age	21-30 years	2	1.5
		31-40 years	18	13.3
		41-50 years	44	32.6
		51-60 years	45	33.3
		61-70 years	23	17.0
		>70 years	3	2.2
2	Gender	Male	72	53.3
		Female	63	46.7
3	Duration of T2DM	<5 years	46	34.1
		5-10 years	58	43.0
		11-20 years	24	17.8
		>20 years	7	5.2
4	Co-morbid conditions	Hypertension	58	43.0
		Diabetic Peripheral Neuropathy	41	30.4
		Obesity	15	11.1
		Hypothyroidism	4	3.0
		Dyslipidemia	4	3.0
		CAD	5	3.7
5	DPP-4 prescribed	Teneligliptin	123	91.1
		Sitagliptin	7	5.2
		Vildagliptin	4	3.0
		Linaligliptin	1	0.7
6	Concomitant other anti-diabetic drugs	a) OHAs		
		Metformin	129	95.6
		Gliclazide	13	9.6
		Glibenclamide	16	11.9
		Pioglitazone	7	5.2
		Glimepiride	78	57.8
		b) Insulin	7	5.2

Table 2 show the pattern of ADRs categorized according to different system organ class (SOC) involved. A total of 164 ADRs were reported among 135 type 2 diabetic patients. It was seen that the maximum number of ADRs (40.2%) were due to involvement of gastro-intestinal system, followed by CNS disorders (29.3%), musculoskeletal disorders (9.1%), Genito-urinary disorder (4.3%), metabolic disorders (1.2%), Cardiovascular disorder (0.6%), Skin & subcutaneous tissue disorder (8.5%), whereas 6.7% of ADRs could not be classified under any SOC.

Table 2: Distribution pattern of ADRs with DPP-4 Inhibitors according to different system organ class (SOC) involved

SOC involved	ADR	Teneligliptin	Sitagliptin	Vildagliptin	Linagliptin	Total	
						No.	%
GI system disorder	Vomiting	5	-	-	-	66	40.2
	Diarrhoea	7	-	-	-		
	Constipation	7	-	-	-		
	Dyspepsia	3	-	-	-		
	Flatulence	4	-	-	-		
	Gastritis	6	-	-	-		
	Decreased appetite	14	-	1	-		
	Abdominal pain	12	-	-	-		
	Nausea	4	-	-	-		
	Stomach heaviness	2	-	-	-		
	stomatitis	1	-	-	-		
CNS disorder	Headache	9	1	-	-	48	29.3
	Dizziness	13	1	-	-		
	Anxiety	10	-	-	-		
	Numbness in leg	1	1	-	-		
	Insomnia	6	-	-	-		
	Burning sensation in sole	1	-	-	-		
	Drowsiness	3	-	-	-		
	Tingling sensation	1	1	-	-		
Musculoskeletal disorder	Myalgia	2	-	-	-	15	9.1
	Joint pain	4	-	-	-		
	Generalized body pain	2	1	-	-		
	Pain in hand	4	-	1	-		
	Chest pain	1	-	-	-		
Genito-urinary disorder	Burning micturition	1	-	1	-	7	4.3
	Nocturia	1	-	-	-		
	Increased frequency of urination	1	-	-	-		
	UTI	2	1	-	-		
Metabolic disorder	hypoglycemia	2	-	-	-	2	1.2
Cardiovascular disorder	Hypotension	1	-	-	-	1	0.6
Skin & subcutaneous tissue disorder	Swelling	2	-	-	-	14	8.5
	Rash	3	-	-	-		
	Eczema	1	-	-	-		
	Itching	8	-	-	-		
others	Fatigue	2	-	1	-	11	6.7
	Cough	2	-	-	-		
	Weight increased	1	-	-	-		
	Weight loss	1	-	-	-		
	Weakness	1	-	-	1		
	Fever	-	1	-	-		
	Allergic rhinitis	1	-	-	-		
	Total	**152 (92.6)**	**7 (4.2)**	**4 (2.4)**	**1 (0.6)**	**164**	**100**

Seriousness of ADRs was evaluated as per criteria in CDSCO ADR Performa. Out of 164 ADRs reported with various drugs in DPP-4 Inhibitor class, 1 ADR was classified as serious, and remaining 163 ADRs were categorized as non-serious.

Figure 1 shows the severity assessment of ADRs with different drugs of DPP-4 Inhibitor class, according to the University of Virginia Health System Adverse Drug Reaction Reporting program criteria. Out of 152 ADRs reported with Teneligliptin, majority of 120 ADRs were mild (78.9%), and only 1 (0.7%) ADR was categorized as severe. Similarly maximum ADRs reported with Sitagliptin, Vildagliptin and Linaligliptin were also of mild severity.

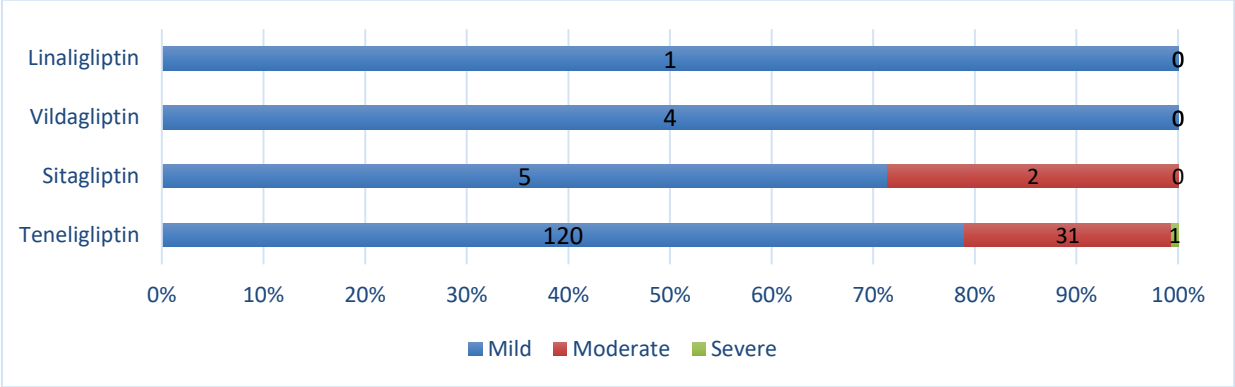

Figure 1: Severity assessment of ADRs with different DPP-4 Inhibitor, according to the University of Virginia Health System Adverse Drug Reaction Reporting program criteria (N=164)

Causality assessment of ADRs

Causality assessment of ADRs was done using WHO-UMC scale which categorises ADRs as "certain", "probable", "possible" and "unlikely". Figure 2 shows that overall, out of 164 ADRs, 27 (16.5%) ADRs were categorized as probable and 137 (83.5%) ADRs were possible. None of the ADRs were categorized as certain or unlikely.

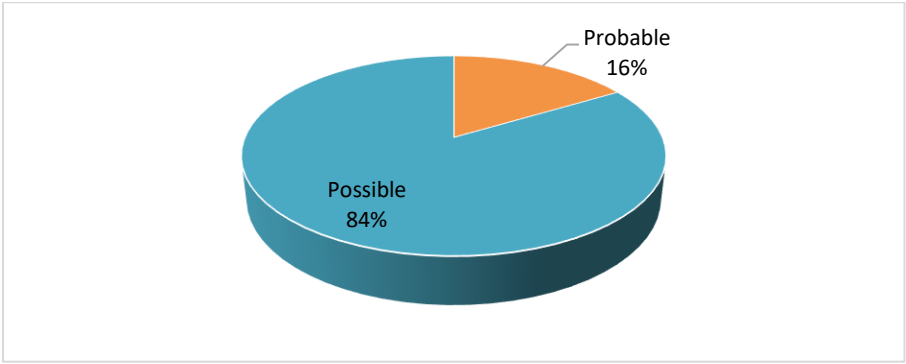

Figure 2: Causality assessment of ADRs using WHO-UMC scale (N=164)

Figure 3 shows the preventability assessment of ADRs with different drugs of DPP-4 Inhibitor class as assessed and categorized using modified Schumock and Thornton criteria. Over all, out of 164 ADRs reported 5 (3.2%) ADRs were categorized as definitely preventable, 94 (57.3%) ADRs were probably preventable and 65 (39.6%) ADRs were not preventable.

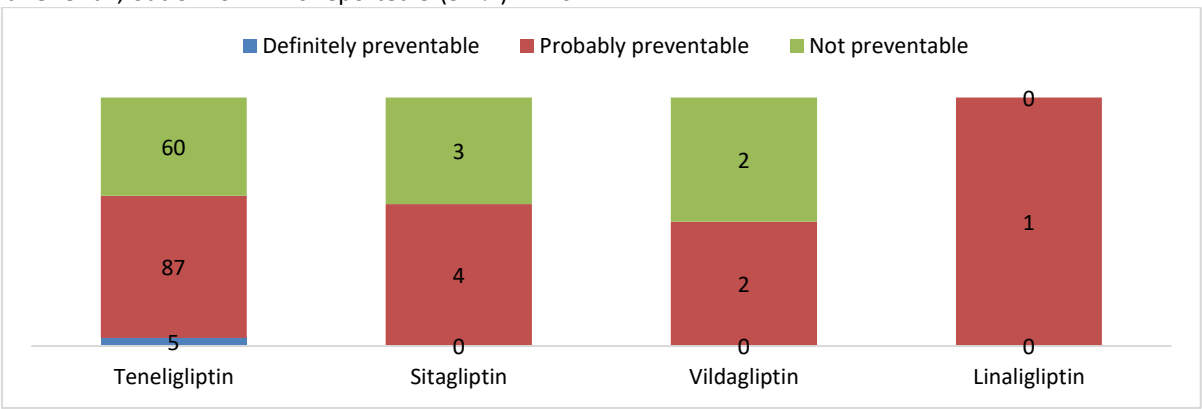

Figure 3: Preventability assessment of ADR as per Schumock and Thornton criteria (N=164)

DISCUSSION

Gliptins have been approved for use in the India since 2007; the data regarding their safety is limited, particularly in Indian population. In this study study assessing ADRs associated with gliptins, patients aged between 41–60 years encountered most of the ADRs, which accounts for 65 % of all cases. This was in contrast to other study where majority of patients reporting ADRs belonged to >60 years.[8] Although one study showed similar higher incidence of ADR in < 60-year age group. [9] The reason for this could be attributed to the fact that higher incidence of diabetes is found in this age group in our study.

In our study , 54% patients receiving gliptins during the six months' study period reported ADRs. This was in contrast to other study where the reported rate of ADR with gliptin therapy was only 17.9%.[10] Although one study reported a higher incidence of ADR of 46% similar to our study, but it included all the antidiabetic medications. [11] The higher rate of adverse drug reporting in our study can be attributed to active pharmacovigilance adopted for reporting of ADR in our study. A study comparing active and spontaneous ADR reporting revealed that the yield of ADR was four times more when active pharmacovigilance was used.[12]

In the current study, 91% of all the reported ADRs were by the patients receiving Teneligliptin. The higher percentage of ADR by tenegliptin can be attributed to the fact that it was most commonly prescribed gliptin in 92% of the study population. The incidence of ADR reported by patient receiving teneligliptin was also higher as compared to previous study. [13]

In our study, Gastrointestinal system (40%) were the most common system organ class affected by adverse reaction followed by Central nervous system (29%) and musculoskeletal system (9%). This was in concurrence with other studies where the most common systems involved was gastrointestinal system, musculoskeletal and central nervous system.[10,13]

Amongst all the gastrointestinal adverse effect decreased appetite and abdominal pain were the most common adverse effect reported due to GI involvement by DPP-IV inhibitors. Most of the ADRs were usually mild severity. In contrast other studies have mainly reported dyspepsia as major adverse effect among gastrointestinal adverse effect. [10,14]

The second most common ADR reported in our study were CNS disorder mainly headache and dizziness. Similar observation was reported in study done on DPP-IV inhibitors which reported slightly elevated risk for nervous system disorders.[15]

In concurrence with this study, other study reported 11 % of ADRs with DPP-IV inhibitors due to involvement of musculoskeletal system. [10] A study done to evaluate musculoskeletal complaints with gliptins reported that musculoskeletal adverse reactions are often associated with gliptins impairing the treatment adherence in patients with type 2 diabetes.[16]

In our study only 1.2% of patients reported hypoglycaemia which was of mild severity. Both the patients received combination of teneligliptin with metformin and didn't require change in medication. These finding of overall lower risk of hypoglycaemia is also confirmed in other studies.[10,15]

On analysing the causal association of the ADRs with WHO-UMC scale, we observed that 16.5% of the reactions were probable, 83.5 % of the reactions were possible. This result was similar to other study where same scale was used to assess causality and 17% were classified as probable and 83 % ADRs possible.[17] Another study classified higher number of ADRs (31%) as probable and fewer (69 %) ADRs as possible using the same scale.[10]

Analysis of the severity of ADRs using University of Virginia Health System Adverse Drug Reaction Reporting program criteria scale showed that majority of ADRs were of mild severity (79.3%), which is in contrast to another study where most ADRs were of moderate severity (51%) . [10] The reason for this could be that majority of the patient in our study were taking medication for long duration and were experiencing less severity.

Assessment of the preventability of ADRs by the Schumock and Thornton Scale showed that 57% of the ADRs were probably preventable, 40% of ADRs were not preventable and 3 % of ADRs were definitely preventable.

In contrast to this, one study reported that 54 % of ADRs were not preventable and 45% of ADRs were probably preventable. ADRs observed in this study like hypoglycaemia, dyspepsia gastritis and burning micturition could have been prevented with proper counselling before the initiation of therapy.

CONCLUSION

This study assessing the pattern of ADRs associated with relatively newer antidiabetic agents like DPP- 4 inhibitors in a tertiary care Centre provides insight of frequency, causality, severity and preventability of reported ADRs. Overall, Gliptins appear to have a good safety profile, but they also have potential to cause ADRs. Gastro-intestinal, CNS and musculoskeletal disorders were most common ADRs. Active pharmacovigilance is better tool for risk identification and management. This study on gliptin helps to elucidate the baseline safety profile of gliptin in tertiary care centre in Uttarakhand.

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