National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Safety profile of second-line agents as add-on to oral monotherapy or dual therapy in uncomplicated type 2 diabetes in South Indian population

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Received: February 28, 2018; **Accepted:** April 02, 2018

ABSTRACT

Background: Nowadays, there is an abundance of many therapeutic options available for the management of type 2 diabetes mellitus (DM). Hence, shifting the trend toward personalized treatment that focuses on the differences among different classes of pharmacological agents with regard to the mechanism of action, efficacy, and most important - the safety. Most of the clinical guidelines reconcile the risk-benefit ratio of the individual therapies. Moreover, there is limited evidence comparing the efficacy and safety of second-line drugs in combination therapies. It becomes crucial to rationalize the combination therapies with respect to attainment of glycemic targets, reduction in the short- and long-term complications and providing a better quality of life. In clinical practice, optimal treatment of type 2 DM must take into account the various comorbidities and adverse drug reactions (ADRs). **Aims and Objective:** The aims of the study were to assess the ADRs associated with second-line antidiabetic drugs when used as add-on agent in uncomplicated type 2 DM. **Materials and Methods:** Patients aged ≥18 years of age, diagnosed as uncomplicated type 2 DM who were previously receiving at least one oral antidiabetic drug (metformin or sulfonylurea) or dual-combination therapy (metformin+sulfonylurea) and for the first-time initiated on a second-line add-on agent, i.e., pioglitazone or dipeptidyl peptidase-4 (DPP-4) inhibitor (sitagliptin/vildagliptin) or α-glucosidase inhibitor (voglibose) or insulin (pre-mixed insulin [30% regular/70% NPH]) were included in the study. The ADRs associated with second-line agents were assessed based on hypoglycemic events, weight changes, frequency of ADRs, liver and renal function tests, and medical events reported. **Results:** A total of 240 patients (mean age 56.79 ± 11.73 years) were prescribed one of four different class of hypoglycemic agents. Overall, the median weight gain of 1.5 kg was observed in the insulin group, with no change of median weight in DPP-4 inhibitor group; while pioglitazone and voglibose group demonstrated a median weight loss of 1 and 0.5 kg, respectively, at the end of 6 months. The maximum number of hypoglycemic episodes was reported in insulin treatment group, i.e., 33; while least with DPP-4 inhibitor, i.e., 12. Out of 274 ADRs, the most common were gastrointestinal adverse effects, i.e., 30.66% and least were the dermatological ADRs (5.11%). **Conclusion:** Henceforth, DPP-4 inhibitor add-on group was found to be safest in terms of least hypoglycemic episodes and side effects when used as add-on therapy.

KEY WORDS: Hypoglycemic episode, Dipeptidyl Peptidase-4 Inhibitor, Adverse Drug Reactions, Voglibose, Pioglitazone

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2018.8.0208302042018	

INTRODUCTION

Diabetes is one of the leading cause of mortality and morbidity throughout the globe.[1] In the recent years, the prevalence of type 2 diabetes has been on the rise in India with an average prevalence of 9.1% observed in 2013.[2] Nowadays, there is an abundance of many therapeutic options available for

the management of type 2 diabetes mellitus (DM). Hence, shifting the trend toward personalized treatment that focuses on the differences among different classes of pharmacological agents with regard to the mechanism of action, efficacy, and most important - the safety. Due to a wide plethora of hypoglycemic agents, the biggest challenge is to make the best therapeutic decision.[3] The use of oral hypoglycemic agents has varied in the past two decades, though metformin remains as the first-line agent for diabetes management.[4] Therefore, the treatment algorithm begins with metformin and later progresses to dual and triple combination therapy consisting of oral and injectable antidiabetic drugs.[5]

Presently, there are 11 different classes of hypoglycemic agents (biguanides, sulfonylureas, thiazolidinediones (TZD), α-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists, amylin mimetics, meglitinides, dopamine-2 agonists, and bile acid sequestrants) along with numerous insulin preparations available as a treatment option for type 2 DM. However, the remaining question which is still unanswered is how to choose the most appropriate hypoglycemic agent in a particular individual? Most of the clinical guidelines reconcile the risk-benefit ratio of the individual therapies. Moreover, there is limited evidence comparing the efficacy and safety of second-line drugs in combination therapies. Although, the efficacy of an antidiabetic drug is given primary importance in order to achieve a desired glycemic index; at the same time, one cannot neglect the safety profile. At the same time, one cannot neglect the safety profile.

Over the previous decade, the most commonly prescribed dual combination therapy was metformin plus sulfonylurea. Soon it was taken over by metformin plus TZD dual therapy. However, due to the emergence of safety concerns with regard to stroke, heart failure, myocardial infarction, bladder cancer, and bone fractures; a decline was seen in the utilization pattern of rosiglitazone and pioglitazone after 2006 and 2011, respectively.[6-8] Thereafter, from 2011 onward a rise in the prescription rates was observed with newer oral hypoglycemic agents such as DPP4 inhibitors such as sitagliptin, and vildagliptin, and α-glucosidase inhibitors such as voglibose in combination with metformin.[6]

Only 50% newly diagnosed cases respond to monotherapy while the rest 50% require combination therapy. It becomes crucial to rationalize the combination therapies with respect to attainment of glycemic targets, reduction in the short- and long-term complications and providing a better quality of life.[9] In clinical practice, optimal treatment of type 2 DM must take into account the various comorbidities and adverse drug reactions (ADRs).[5] There are very few studies providing data on the safety profile comparison between the second-line agents used as adjunctive therapy to metformin or sulfonylurea or metformin + sulfonylurea. However, a handful of previously conducted studies provide data on the glycemic control by the individual antidiabetic drug class based on fasting plasma glucose and postprandial blood glucose for a short duration, i.e., 3 or 6 weeks. None of the earlier conducted prospective observational studies, with respect to Indian subcontinent, have taken into account regarding the effects of second-line agents on the renal and hepatic functions or on the occurrence/progression of diabetic complications in type 2 DM patients. Henceforth, in view of the limited Indian data on the safety profile of second-line drugs as a combination therapy - the present study was aimed to assess the ADRs associated with second-line antidiabetic drugs when used as add-on agent in uncomplicated type 2 DM.

MATERIALS AND METHODS

This study was designed as a descriptive retrospective study, conducted in the Department of Pharmacology and Internal Medicine, Kasturba Medical College, Manipal, from January 2015 to July 2016. The Institutional Ethics Committee (IEC) approval was obtained before initiating the study (letter no. IEC: 538/2014). Four add-on treatment Groups 1-4 were pioglitazone, DPP-4 inhibitor, voglibose, and insulin (pre-mixed insulin [30% regular/70% NPH]), respectively, and received the second-line agents for a duration of 6 months or longer.

Study Sample

Uncomplicated type 2 DM for the first-time initiated on second-line add-on agent during July 1, 2012–July 1, 2015.

Sample Size

Considering a reduction of 0.2% in HbA_{1C} and 80% power of the study; a sample size of 60 in each group was derived. Henceforth, a sample size of 240 was taken for studying four different drug groups.

Source of Data

The study was conducted at Medical Records Department, Kasturba Hospital, Manipal.

Study Duration

The study duration was 18 months.

Inclusion criteria

The following criteria were included in this study:

- Age ≥18 years.
- Uncomplicated type 2 DM as per the WHO criteria.
- Previously receiving at least one oral antidiabetic drug (metformin or sulfonylurea) or dual-combination therapy (metformin + sulfonylurea) and for the first-time initiated on a second-line add-on agent, i.e., pioglitazone or DPP-4 inhibitor (sitagliptin/vildagliptin) or α-glucosidase

inhibitor (voglibose) or insulin (pre-mixed insulin [30% regular/70% NPH]).

Exclusion criteria

The following criteria were excluded from the study:
- Type 1 DM
- Gestational DM
- Diabetic ketoacidosis
- Hyperosmolar hyperglycemic nonketotic coma
- Diabetic microvascular and macrovascular complications
- Clinically significant renal and liver disease.

Following details were collected for subjects fulfilling inclusion criteria:
- Demographic data and baseline characteristics
- Median duration of type 2 DM for the initiation of second-line agents
- Comorbid medical conditions
- Concomitant medications
- Number of hypoglycemic events
- Weight changes
- Frequency of ADRs reported
- Analysis of liver and renal function tests in the study population
- Medical events after initiation of second-line agents.

Statistical Analysis

SPSS software version 16.0 was used for data analysis. The descriptive statistics, i.e., number, percentage, mean ± standard deviation, median, and interquartile range were used to describe the data. $P < 0.05$ was considered as statistically significant.

RESULTS

The study population of 240 diagnosed as uncomplicated type 2 DM consisted of 135 males (56.3%) and 105 females (43.8%). The mean age of the subjects was 56.79 ± 11.73 years, ranging from 21 to 87 years. The subjects were prescribed one of four different classes of hypoglycemic agents as an add-on agent to the existing antidiabetic treatment for a duration of 6 months or more. The DPP-4 inhibitor group had sitagliptin (n = 37) and vildagliptin (n = 31) while the insulin group had pre-mixed insulin (30% regular/70% NPH) (n = 60) and rapid-acting insulin (n = 6) as add-on drugs Table 1. The average dose of second-line drugs has been summarized in Table 2. The baseline characteristics of the sample population have been described in Table 3.

The most common comorbid medical conditions were hypertension and dyslipidemia as depicted in Table 4. The list of concomitant medications has been summarized in Table 5. The weight changes in the study population over 3 and 6 months are summarized as median with Q1 and Q3 since the study population demonstrated extremely varying values. Overall, the median weight gain of 1.5 kg was observed in the insulin group, with no change of median weight in DPP-4 inhibitor group. Both the pioglitazone and voglibose group demonstrated a median loss of 1 and 0.5 kg, respectively, at the end of 6 months [Table 6]. Overall, the second-line add-on agents were found to be associated with lesser frequency of hypoglycemic episodes. Most of the patients experienced less than two episodes. The maximum number of hypoglycemic episodes was reported in insulin treatment group, i.e., 33 and pioglitazone add-on group, i.e., 26. DPP-4 inhibitor group observed the least number of hypoglycemic episodes, i.e., 12 [Figure 1]. Therefore, sitagliptin and vildagliptin were found to be safe with low risk of hypoglycemic episodes.

Out of 240 patients enrolled, a total of 274 ADRs were recorded. The most common were gastrointestinal adverse effects, i.e., 30.66% followed by musculoskeletal adverse effects, i.e., 26.28%. Dermatological ADRs were the least to be reported, i.e., 5.11% [Figures 2 and 3]. The analysis of the liver and kidney function tests was performed by recording

Table 1: Different groups of add-on agents

Parameters	Group 1	Group 2	Group 3	Group 4
Add-on agent	Pioglitazone	DPP-4 inhibitor (sitagliptin/vildagliptin)	α-Glucosidase inhibitor (voglibose)	Insulin
Number of patients (*n*)	54	68	52	66
Mean age (years)	54±11	57±12	56±10	59±13
Sex				
Male *n* (%)	31 (57.41)	37 (54.41)	29 (55.77)	38 (57.57)
Female *n* (%)	23 (42.59)	31 (45.59)	23 (44.23)	28 (42.43)
Median duration of diabetes (years)*	8 (3, 12)	10 (5, 13)	5 (2, 10)	10 (3, 15)
Prior antidiabetic drug therapy				
Dual therapy (metformin+second-line)	20	18	25	6
Dual therapy (SU+second-line)	2	5	1	16
Triple therapy (SU+metformin+second-line)	32	45	26	44

*Values expressed as median (Q1, Q3)

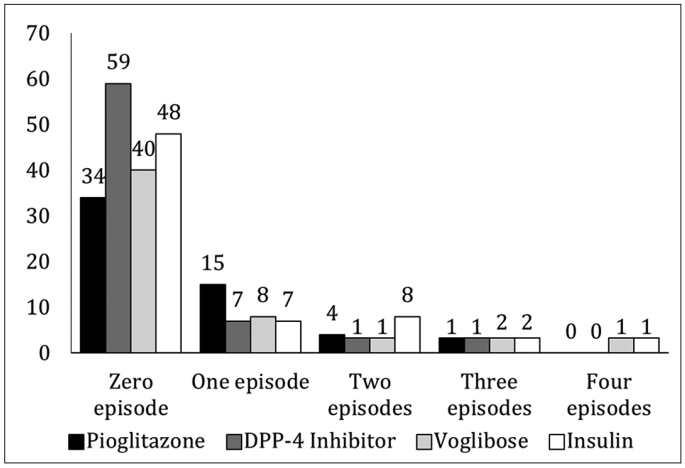

Figure 1: Number of patients experiencing hypoglycemic episodes in the different study groups

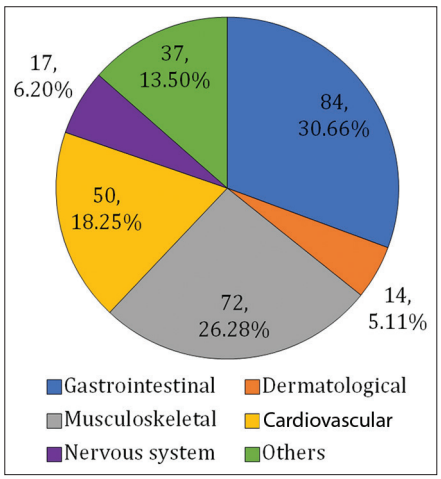

Figure 2: Types of adverse drug reactions

Table 2: Average dose of second-line agents administered

Drug therapy	Mean dose (per day)
Pioglitazone	17.88 mg
Sitagliptin	52.70 mg
Vildagliptin	50.00 mg
Voglibose	0.29 mg
Insulin	
Morning	24.86 U
Afternoon	15.11 U
Evening	16.23 U

the changes in the liver enzymes, serum urea, and serum creatinine at 6 and 12 months after the initiation of second-line agents (baseline values within the normal range) [Tables 7 and 8]. The other medical complications were reported in 11 patients which were not related to administration of second-line agents. These events were mainly reported in the insulin add-on group and included portal hypertension, cellulitis, fatty liver, left ventricular hypertrophy, ischemic heart disease, bronchitis, and sensorineural hearing loss. While only one patient in the voglibose treatment group was diagnosed with acute gastroenteritis.

DISCUSSION

The present study aimed at investigating the safety profile of second-line agents added for the first time to previously prescribed metformin or sulfonylureas or a combination of both. The mean age in years among different treatment groups was 54 ± 11, 57 ± 12, 56 ± 10, and 59 ± 13 in pioglitazone, DPP-4 inhibitor, voglibose, and insulin group, respectively. Median weight gain of 1.5 kg was observed in the insulin group, while no change in median weight was reported in DPP-4 inhibitor group. Both the pioglitazone and voglibose group demonstrated a median loss of 1 and 0.5 kg, respectively, at the end of 6 months. The insulin treatment group had maximum hypoglycemic episodes, while least were reported in DPP-4 inhibitor group. Gastrointestinal ADRs were the most frequent adverse drug reaction reported among the treatment groups. Renal function tests among various add-on groups were recorded. Two patients among voglibose add-on group reported slightly raised liver enzymes. However, around 11 patients in insulin add-on group had elevated liver enzymes. There was no serious deterioration in renal functions in any treatment group.

Our findings indicated a slight skewness toward male patients (56.3%). The previously conducted studies also exhibited a slight male predominance.[10,11] Metformin was the most commonly prescribed first-line antihyperglycemic agent followed by glimepiride and glibenclamide. Our study recognized that both metformin and sulfonylureas were received by 61% patients before the initiation of second-line agents. The present study suggested a varying time interval among the different groups for supplementing metformin or sulfonylureas with second-line agents. The median duration of diabetes was observed as 8 and 10 years, respectively, for adding pioglitazone and DPP-4 inhibitor which was similar to the earlier study. The research studies have reported the mean duration of diabetes as 6.8–7.3 years for adding DPP-4 inhibitors.[12,13] Our study identified the median duration of diabetes on a higher side in the Group 2 probably due to increased availability and upsurge in popularity of DPP-4 inhibitors in India after 2011. Among voglibose group, 28 patients had median age of 5 years.

A median weight loss of 1 kg at 3 and 6 months, respectively, from the baseline values in the pioglitazone add-on group; though weight gain was noted in a few patients. Usually, the use of TZDs is associated with weight gain due to water and fluid retention. Einhorn *et al.* observed a weight gain of 0.95 kg when pioglitazone + metformin combination was used.[13] A meta-analysis was done by McIntosh *et al.*, demonstrated a gain of 2.3 kg weight.[14] The decrease in weight as observed in our study could be accounted to the recommendation of

Table 3: Baseline characteristics of the study population

Parameters	Group 1 (pioglitazone)	Group 2 (DPP-4 inhibitor)	Group 3 (voglibose)	Group 4 (insulin)
Weight (kg)	67.17±14.23	66.34±10.93	65.25±13.45	66.68±15.10
HbA1C (%)	10.31±2.87	9.65±1.94	9.62±2.40	10.39±2.48
FPG (mg/dL)	210.19±86.02	211.26±74.43	217.75±64.72	231.55±84.69
PPBG (mg/dL)	298.93±101.05	293.81±94.58	304.96±105.97	323.86±120.63
ESR (mm/hr)*	20 (12, 42)	20 (12, 51)	29 (15, 48)	30 (19, 51)
SBP (mmHg)	121.96±10.66	126.85±11.49	121.35±17.45	130.12±14.47
DBP (mmHg)	79.11±6.59	81.32±6.44	79.00±6.07	82.97±8.09
Pulse (beats/min)	88.61±6.00	78.74±4.93	74.85±6.88	81.73±8.76
Hb (g/dL)	12.43±1.84	12.40±1.57	12.64±1.90	12.49±1.96

*Values expressed as median (Q1, Q3). FPG: Fasting plasma glucose, PPBG: Postprandial blood glucose

Table 4: Frequencies of comorbid medical conditions

Comorbidity	Group 1, *n* (%)	Group 2, *n* (%)	Group 3, *n* (%)	Group 4, *n* (%)
Hypertension	22 (40.74)	41 (60.30)	22 (42.31)	39 (59.09)
Dyslipidemia	9 (16.67)	16 (23.53)	5 (9.62)	16 (24.24)
Asthma/COPD	0 (0)	1 (1.47)	1 (1.92)	3 (4.55)
Hypothyroidism	0 (0)	0 (0)	1 (1.92)	1 (1.51)
Osteoarthritis	0 (0)	0 (0)	0 (0)	1 (1.51)

Table 5: Prescription pattern of concomitant medications

Drug	Group 1	Group 2	Group 3	Group 4
β-blocker				
Atenolol	1	1	2	8
Propranolol	0	0	0	1
Metoprolol	5	6	1	1
Carvedilol	0	0	1	0
Nebivolol	0	1	0	1
Angiotensin-converting enzyme inhibitor/angiotensin receptor blocker				
Losartan	2	2	0	2
Telmisartan	4	13	5	15
Ramipril	2	0	0	1
Calcium channel blocker				
Amlodipine	8	18	12	10
Hypolipidemic agents				
Rosuvastatin	0	4	2	6
Atorvastatin	9	12	3	9
Fenofibrate	0	0	0	1
Others				
Levothyroxine	0	0	1	1
Beclomethasone+salbutamol	0	1	1	3
Diclofenac	0	0	0	1

fixed calorie as a part of routine care. There was no change in median weight in DPP-4 inhibitor add-on group. However, Reasner *et al.* observed a mean decrease of 1.5 kg with sitagliptin + metformin combination.[15] A 52-week study also observed a marginal weight loss of 0.2 kg.[16] A review has also concluded weight neutrality of vildagliptin on the basis of various clinical studies and randomized trials.[17]

The voglibose add-on treatment group demonstrated a median weight decline of 0.5 kg at 6th month, while no change was

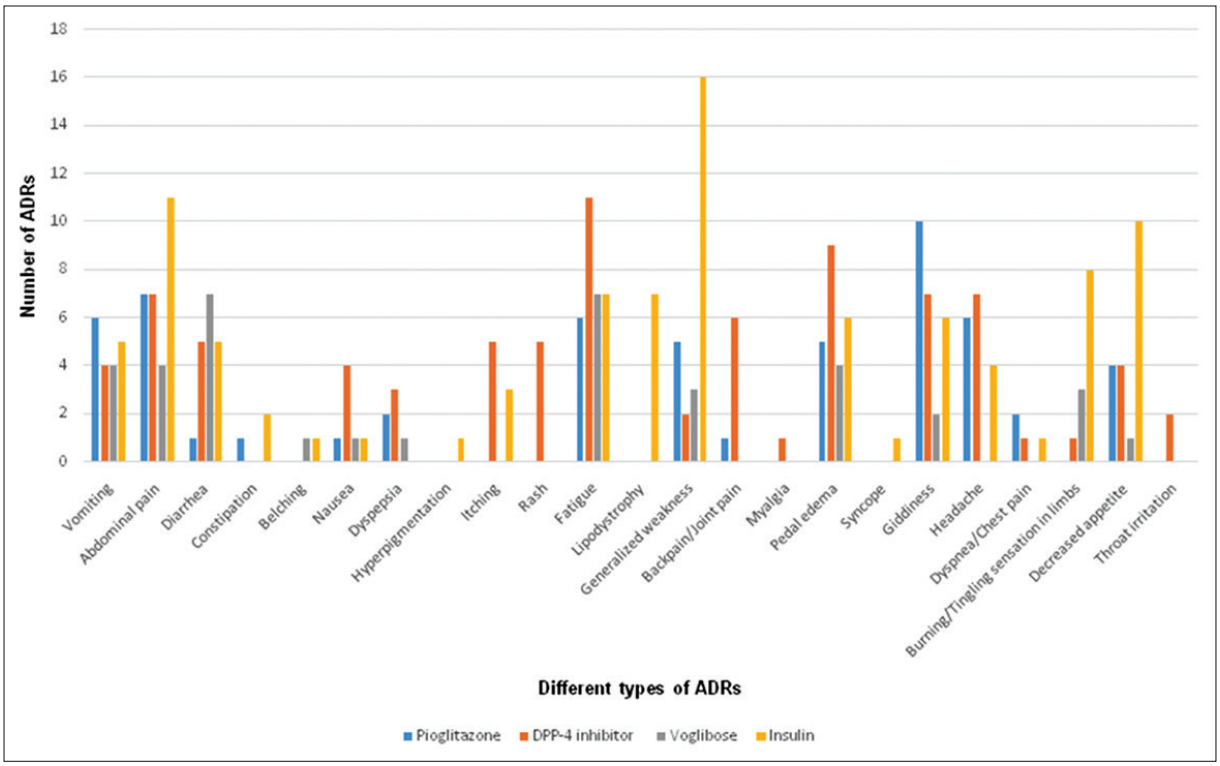

Figure 3: Frequencies of the reported adverse drug reactions

Table 6: Change in weight over 6 months duration

Drug therapy	Weight at baseline (kg)*	Weight at 3 months (kg)*	Weight at 6 months (kg)*
Group 1 (pioglitazone)	66 (60, 72)	65 (58, 73)	65 (59, 74)
Group 2 (DPP-4 inhibitor)	66 (60, 74)	66 (60, 72.5)	66 (60, 72.5)
Group 3 (voglibose)	63.5 (55, 74)	63.5 (55, 73)	63 (54.5, 73)
Group 4 (insulin)	62 (60, 72)	62 (59, 72)	63.5 (59, 74)

*Expressed as median (Q1, Q3)

Table 7: Grading of severity of liver enzymes

Severity of grading*	ALT		AST		ALP		Total bilirubin	
	6 months	12 months	6 months	12 months	6 months	12 months	6 months	12 months
Grade 1	8	5	14	13	2	1	1	2
Grade 2	0	0	3	4	0	0	0	1
Grade 3	0	0	0	0	0	0	1	0
Grade 4	0	0	0	0	0	0	0	0

For ALT, AST, and ALP. Grade 1: 1.25–2.5 ULN, Grade 2: 2.5–5 ULN, Grade 3: 5–10 ULN, Grade 4: >10 ULN. For total bilirubin. Grade 1: >1.0–1.5 ULN, Grade 2: >1.5–2.5 ULN, Grade 3: >2.5–5 ULN, Grade 4: >5 ULN. *Severity assessment is in accordance with the acquired immune deficiency syndrome Clinical Trials Group and expressed as multiples of the ULN. Grading: Grade 1 - mild, Grade 2 - moderate, Grade 3 - severe, Grade 4 - life threating, ULN: Upper limit of the normal

observed at 3rd month. Another study observed a weight loss of 0.5 kg with voglibose combination at 12 weeks in Japanese population.[18] A meta-analysis is having a compiled data from 41 clinical studies established insignificant effect on weight due to α-glucosidase inhibitors.[19] The present study exhibited a median weight gain of 1.5 kg in insulin add-on group at 6th month and no change at 3rd month. A review by Yki-Järvinen had assembled results from various studies; which revealed weight gain of 2 kg when pre-mixed insulin (30% regular/70% NPH) is added to metformin or sulfonylurea in insulin naïve diabetic patients.[20] Chow *et al.* had demonstrated a weight gain of 1.6 kg and 2.1 kg at 3rd and 6th month, respectively, by insulin combination with oral hypoglycemic agents.[21]

Overall, the second-line add-on agents were found relatively safe in terms of experiencing hypoglycemic episodes. The subjects developed <2 hypoglycemic episodes over a

Table 8: Patients progressing to Stage 1 and 2 of diabetic kidney disease based on serum creatinine

Drug therapy	Serum creatinine at 6 months		Serum creatinine at 12 months	
	Stage 1	Stage 2	Stage 1	Stage 2
Group 1 (pioglitazone)	54	0	53	1
Group 2 (DPP-4 inhibitor)	61	7	64	4
Group 3 (voglibose)	52	0	52	0
Group 4 (insulin)	57	7	63	1

Stages of diabetic kidney disease. Stage 1: Serum creatinine <1.5 mg/dL, Stage 2: Serum creatinine 1.5–2 mg/dL, Stage 3: Serum creatinine 2.1–5 mg/dL, Stage 4: Serum creatinine 5.1–7.9 mg/dL, Stage 5: Serum creatinine >8 mg/dL. None of the patient demonstrated decrease in the GFR values. Stage 1 - hyperfiltration, Stage 2 - normal/increased GFR, Stage 3 - Normal GFR; Stage 4 - Decreased GFR (12–15 mL/min); Stage 5 - Decreased GFR (<10–15 mL/min)

period of 6 months. Pioglitazone group had the maximum number of patients experiencing hypoglycemia. This might be due to its combination with sulfonylureas. Vlckova *et al.* depicted a 3–4 times the hazard of developing hypoglycemia when pioglitazone is combined with a sulfonylurea.[22] In DPP-4 inhibitor group, only 9 patients experienced more than one hypoglycemic episode. Aschner *et al.* observed that sitagliptin equated with placebo in the occurrence of hypoglycemic episodes.[23] As per a review, there was no significant hypoglycemia reported among DPP-4 inhibitors.[24] Henceforth, sitagliptin and vildagliptin were found to be safest to be added as a second-line agent to previously prescribed metformin or sulfonylurea. Insulin group experienced relatively more number of hypoglycemic episodes than other add-on groups. Bodmer *et al.* concluded a 0.8–2.6% incidence of hypoglycemia in insulin add-on group with metformin and sulfonylurea.[25]

A total of 274 ADRs were reported while assessing the safety profile for the add-on agents. The gastrointestinal (30.66%) ADRs were predominantly reported followed by musculoskeletal (26.28%) ADRs. Dermatological (5.11%) ADRs were the least reported ones. Cardiovascular and gastrointestinal adverse effects were prevalent in the pioglitazone add-on group. The most commonly reported side effects were giddiness, pedal edema, abdominal pain, vomiting, headache, weakness, and fatigue. TZDs have been in spotlight for safety concerns in terms of volume overload and congestive heart failure.

Usually, the overall incidence of pedal edema reported varies from 3% to 20% among patients treated with pioglitazone.[26] Volume expansion is attributed to both vasodilatation and significant sodium retention at renal tubules induced by peroxisome proliferator-activated receptor gamma-mediated insulin sensitization.[27] A meta-analysis had shown pooled odds ratio for TZD-induced edema as 2.26; TZDs use has two-fold higher risk for developing edema in comparison to those not taking TZDs.[27] Another study observed a 12.2% incidence of gastrointestinal side effects with pioglitazone and sulfonylurea combination and 23.4% incidence with metformin and sulfonylurea combination.[28] The increased incidence of gastrointestinal adverse effects can be contributed to the concomitant administration of metformin with pioglitazone in the present study.

DPP-4 inhibitor (sitagliptin/vildagliptin) add-on group experienced most commonly the gastrointestinal side effects such as abdominal pain, diarrhea, nausea, and vomiting. The chief complaints such as fatigue, joint pain, and myalgia followed by dermatological itching and rashes were observed. Two patients suffered throat irritation. There was no serious adverse effect reported in the DPP-4 inhibitor group. The previous study observed a 56.5% overall incidence of adverse effects in sitagliptin add-on group with the maximum number of patients experiencing gastrointestinal side effects (11.9%) such as abdominal pain (2.2%) and diarrhea (2.6%).[29] A meta-analysis reported gastrointestinal adverse events most frequently with DPP-4 inhibitor use and 0.3–1.2% incidence of cardiovascular event.[30] However, no cardiovascular event was observed in the present study.

Ferraninni *et al.* observed the incidence of headache, fatigue, back pain, and diarrhea similar to the present study.[16] A review by Desai *et al.* has discussed in detail regarding sitagliptin-associated allergic reactions based on clinical findings. In the present study, five patients each developed itching and rashes. The reason underlying the pathogenesis of allergic reactions is still unknown; but it is hypothesized that DPP-4 molecule is expressed on certain subsets of CD4 and CD8 T-cells, B-cells, and natural killer cells. Lymphocyte activation leads to upregulation of DPP-4 enzyme; this might modulate the immune function.[31] A pooled data on vildagliptin observed the incidence of cough (3.4%) which was comparable to that seen in the study subjects. Edema was reported in 13.2% patients which could be accounted for the decreased cardiac capacity or renal impairment or concomitant administration of other medications such as calcium channel blockers among the elderly patients.[32]

The voglibose add-on group had mainly gastrointestinal adverse effects (34.6%) followed by fatigue and generalized weakness. A systematic review also depicted gastrointestinal symptoms as most commonly encountered adverse effects due to α-glucosidase inhibitors.[19] Kalra *et al.* have provided evidence from pooled data of Indian population regarding

tolerability of α-glucosidase inhibitors on the physician's five-point scale as very good (37%) and good (51%).[33] An evidence-based review has also emphasized the fact that α-glucosidase inhibitors provide a good glycemic control with mild transient gastrointestinal disorders.[34,35] Dabhi *et al.* have emphasized a central component in experiencing nausea, vomiting, and dizziness after 20–30 min of oral consumption of voglibose.[36] Gastrointestinal and cardiovascular adverse effects were noted in the insulin group. The gastrointestinal symptoms could be attributed to metformin while using the insulin-metformin combination as stated in a meta-analysis.[37]

Safety assessment of liver function tests was performed at 6 and 12 months. In pioglitazone add-on group one patient showed rise in AST and ALP levels. A systematic review by Chilcott *et al.*, yielded that abnormal liver function in pioglitazone-treated patients was almost equivalent to control group in clinical trials.[38] Hussein *et al.* observed reversible liver dysfunction in one patient treated with pioglitazone.[39] In DPP-4 inhibitor group, around four patients had slightly elevated liver enzymes. Analysis of the pooled data from 19 double-blind studies on sitagliptin reported 1.5 and 1 incidence rate per 100 patient-year for increased ALT and AST, respectively, among sitagliptin-treated patients versus 1.4 and 1 incidence rate per 100 patient-year for increased ALT and AST, respectively, in the comparator group.[40] Another compiled data analysis yielded only four patients out of 9334 with deranged liver functions and raised bilirubin levels were reported in 411 patients out of 9508 in the vildagliptin-treated group.[41]

Two patients among voglibose add-on group reported slightly raised liver enzymes. The previous study had observed 1–3% incidence of raised liver enzymes with voglibose.[42] However, around 11 patients in insulin add-on group had elevated liver enzymes. This might be due to the advanced stage of diabetes among those treated with insulin. A review by Bugianesi *et al.* has concluded that insulin resistance is the main pathophysiological hallmark for nonalcoholic fatty liver disease.[43]

Renal function tests among various add-on groups were recorded. There was no serious deterioration in renal functions in any treatment group. Around 7 patients in insulin add-on group had slightly elevated serum creatinine at 6th month, though the GFR was normal. These findings could be due to advanced disease and other medical events. DPP-4 inhibitor add-on group exhibited slight elevation in serum creatinine in 7 patients after 6 months of treatment initiation, and four patients reported raised creatinine values at 12th month. Ligueros-Saylan *et al.* analyzed pooled data for vildagliptin safety and found that most patients enrolled in clinical trials were having mild renal impairment at the onset of trial itself. Nevertheless, they concluded that presence of mild renal impairment did not adversely affect the safety of vildagliptin relative to patients with normal renal function.[44] Based on our findings, an inference could be drawn that none of the add-on agent worsens the renal functions to the extent to raise any concern regarding the drug withdrawal or dose reduction or drug discontinuation. Only Stage 1 and 2 of diabetic kidney disease (hyperfiltration or normal GFR) were reported after initiation of second-line agents. None of the patients exhibited decrease in the GFR values. The limitation of the study was small sample size and short duration of the study period. Temporal association of drug use with ADRs and information with reference to temporary drug dechallenge–rechallenge and dose alteration was not recorded.

CONCLUSION

Type 2 DM is a modern pandemic and requires lifelong treatment. Failure to achieve the glycemic target and rapid progression to complications are the main concerns in the management of diabetes. There are various antidiabetic agents available to lower blood glucose levels. The present study assessed the safety parameters based on the hypoglycemic episodes and ADRs. The insulin treatment group had maximum hypoglycemic episodes, while least was reported in DPP-4 inhibitor group. Overall, gastrointestinal ADRs were the most frequent side effects. Henceforth, DPP-4 inhibitor add-on group was found to be safest in terms of least hypoglycemic episodes and side effects when used in combination with metformin or sulfonylureas or both.

ACKNOWLEDGMENT

The authors would like to thank the Staff of Medical Records Department, Kasturba Hospital, Manipal, for their cooperation.

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How to cite this article: Gill R, Adiga S, Varma M. Safety profile of second-line agents as add-on to oral monotherapy or dual therapy in uncomplicated type 2 diabetes in South Indian population. Natl J Physiol Pharm Pharmacol 2018;8(8):1097-1106.

Source of Support: Nil, **Conflict of Interest:** None declared.