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Original Article

Effectiveness of Second-Line Agents in the Treatment of Uncomplicated Type 2 Diabetes Mellitus: An Observational Tertiary-Care Based Study

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ABSTRACT

Background: The rational prescribing of second-line drugs in type 2 diabetes mellitus (DM) require clear guidelines. There is no sufficient empirical evidence to support the use of one second-line agent over the other and when to initiate second-line drug is still under discrepancy. **Objectives:** To analyze the utilization pattern and effectiveness of second-line agents in uncomplicated type 2 DM. **Methodology:** 240 uncomplicated type 2 DM patients who were ≥ 18 years receiving either metformin/sulfonylurea or metformin+sulfonylurea was divided into four add-on treatment group 1, 2, 3, 4; that were added pioglitazone, dipeptidyl peptidase-4(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. Effectiveness was based on the reduction in glycosylated hemoglobin (HbA_{1C}), fasting plasma glucose (FPG) and postprandial blood glucose (PPBG) values over 3 and 6 months was done using repeated measures analysis of variance (ANOVA). **Results:** The mean difference for reduction in HbA_{1C} (%) values at 3rd and 6th month with respect to baseline values was 1.32±0.72 and 2.11±0.97; 1.19±0.27 and 1.81±0.53; 1.16±0.41 and 1.66±0.63; 0.97±0.16 and 1.46±0.47 for pioglitazone, DPP-4 inhibitor, voglibose, insulin respectively. The mean difference in FPG and PPBG levels at the 6th month from baseline was 75±31.06 and 115.3±40.32; 77.91±37.95 and 117±41.27; 85.87±21.75 and 118.75±55.86; 91.38±31.8 and 132.03±56.24 for pioglitazone, DPP-4 inhibitors, voglibose and insulin respectively. Reduction in HbA_{1C}, FPG, and PPBG was statistically significant within each group at each time interval with p-value < 0.001. **Conclusion:** All the add-on groups exhibited a significant reduction in HbA_{1C}, FPG, and PPBG over 3 and 6 months. DPP-4 inhibitors exhibited least hypoglycemic episodes. DPP-4 inhibitors are trending and marginally more effective second-line OHA in uncomplicated type 2 DM.

Key words: Anti-diabetic drugs, FPG, HbA_{1C}, PPBG, Second-line agents.

Key message: The present study gives information on the effectiveness of second-line agents when used in combination with metformin or sulfonylurea or both in type-2 DM during clinical practice. This study gives a real-world evidence on the glycemic index achieved with second-line add-on drugs having good efficacy and tolerability over a period of 6-months.

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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] Moreover, diabetes exerts a significant financial burden on the individuals, healthcare system, and the society due to chronicity of the nature of the disease.[3] The cornerstone of management of diabetes is primarily the glucose-lowering therapies.[4] Therefore, the healthcare professional organizations have laid guidelines for the stringent metabolic targets as the principle for diabetes management.[5-6] Presently, there are eleven different classes of hypoglycemic agents along with numerous insulin preparations available as a treatment option for type 2 diabetes.[7]

The confirmatory diagnosis of type 2 diabetes consists of HbA_{1C} ≥ 6.5% along with fasting plasma glucose (FPG) ≥ 126 mg/dL and postprandial blood glucose (PPBG) ≥ 200 mg/dL. If HbA_{1C} is ≥ 7.5% at the time of diagnosis, it is advised to initiate pharmacological treatment with the oral hypoglycemic agent, i.e. metformin.[8-9] Whereas, insulin is started at first for the symptomatic patients presenting with markedly elevated HbA_{1C} and later can be switched to metformin.[10] When to initiate second-line agents is still under discrepancy and there is no clear guideline in this regard. Nevertheless, it is stated that if the target HbA_{1C} is not achieved over a span of 3 months of treatment initiation; it is advised to add a second oral hypoglycemic agent or a glucagon-like peptide 1 (GLP-1) receptor agonists or a basal insulin.[11]

Metformin remains as the first line agent for type 2 diabetes management.[12] There is no consensus to support the use of one second-line agent over the other.[13] Due to the emergence of safety concerns with regards 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.[14-15]

Dual or triple combination therapy having complementary mechanisms of action is not only essential but also logical and necessary to achieve glycemic targets.[16] Henceforth, in view of the limited Indian data, the present study was designed and aimed to investigate: (a) the utilization pattern of second-line agents; (b) analyze the indications for their initiation, and (c) the outcome analysis of combination therapies.

MATERIALS AND METHODS

This study was designed as a descriptive retrospective study, conducted in 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 group 1, 2, 3, 4 were added pioglitazone, dipeptidyl peptidase-4(DPP-4) inhibitor, α-Glucosidase 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 01 July 2012 to 01 July 2015.

Sample size: Calculated statistically using SPSS software version 16.0. 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: Medical records department, Kasturba Hospital, Manipal.

Study duration: 18 months.

Inclusion criteria

- Age ≥ 18 years and either sex.
- Uncomplicated type 2 DM as per 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.

Exclusion criteria

- 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
- Duration of initial antidiabetic treatment before the initiation of second-line add-on agents and previously prescribed OHAs.
- HbA_{1C} (%), FPG (mg/dL), PPBG (mg/dL) at baseline, 3 and 6 months respectively after the initiation of second-line agents.

Statistical Analysis

SPSS software version 16.0 was used for data analysis. The descriptive statistics i.e., mean ± standard deviation, median, interquartile range, number, and percentage were used to describe the data. The repeated measures analysis of variance (ANOVA) was used to analyze the primary parameters at three-time intervals i.e., at baseline, 3rd month, and 6th month for respective groups. The p-value < 0.05 was considered as statistically significant.

RESULTS

The study population 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 21-87 years. The demographic details of the study population have been described in [Table 1]. Metformin was the most commonly prescribed first-line antihyperglycemic agent followed by glimepiride and glibenclamide. The average dose of previous anti-diabetic medications was: glibenclamide 6.18 mg/day, glipizide 9.8 mg/day, gliclazide 97.33 mg/day, glimepiride 6.16 mg/day, and metformin 1267 mg/day.

The number of patients utilizing the second-line add-on agents was 54, 68, 52, and 66 in pioglitazone, DPP-4 inhibitor, voglibose, and insulin group respectively. The pattern of antidiabetic drug use amongst the study population with duration of diabetes has been depicted in [Figure 1]. The pattern of various combination therapies has been summarized in [Figure 2]. The average dose of second-line add-on agents used daily was pioglitazone 17.88 mg, sitagliptin 52.70 mg, vildagliptin 50 mg, voglibose 0.29 mg respectively. Insulin was used at a mean dose of 24.86, 15.11 and 16.23 units/day in the morning, afternoon and night respectively. The baseline characteristics of the study population have been described in [Table 2]. The mean HbA_{1C} observed was 9.99% with standard deviation (SD) of 2.43%. The mean FPG and PPBG of the subjects was 218±78.20 mg/dL and 305.64±106.14 mg/dL respectively.

Table 1: Demographic details of study population.

Parameters	Group 1	Group 2	Group 3	Group 4
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)
Occupation (n)				
Service	14	22	18	10
Business	8	7	3	6
Retired	4	5	3	10
Student	0	1	0	1
Laborer	2	1	0	0
Agriculturist	7	7	5	12
Unemployed	19	25	23	27
Smokers n (%)	16 (29.62)	18 (26.47)	8 (15.38)	10 (15.15)
Alcoholics n (%)	16 (29.62)	20 (29.41)	7 (13.46)	14 (21.21)
Drug Therapy n (%)				
Glibenclamide	7 (22.6)	4 (12.9)	6 (19.4)	14 (45.2)
Glipizide	1 (6.7)	5 (33.3)	3 (20)	6 (40)
Gliclazide	3 (42.9)	1 (14.3)	0 (0)	3 (42.9)
Glimepiride	21 (22.3)	35 (37.2)	17 (18.1)	21 (22.3)
Metformin	52 (24.1)	63 (29.2)	51 (23.6)	50 (23.1)

n = number of patients

Group 1: Pioglitazone; Group 2: DPP-4 inhibitors (sitagliptin/vildagliptin); Group 3: α-Glucosidase inhibitor (voglibose); Group 4: Insulin #sitagliptin = 37; vildagliptin = 31

*Pre-mixed insulin (30% regular/70% NPH) = 60; rapid acting insulin = 6.

The most common reason to initiate add-on therapy was uncontrolled type 2 diabetes measured as the high glycemic index in all respective groups. Though, the other leading causes were morbid obesity and dyslipidemia; infections and poor compliance with oral hypoglycemic agents lead to the initiation of insulin therapy as shown in [Figure 3].

The mean difference for reduction in HbA_{1C} (%) values at 3 and 6 months with respect to baseline values was 1.32±0.72 and 2.11±0.97 for pioglitazone; 1.19±0.27 and 1.81±0.53 for DPP-4 inhibitor; 1.16±0.41 and 1.66±0.63 for voglibose; 0.97±0.16 and 1.46±0.47 for insulin respectively. The reduction in HbA_{1C} was found statistically significant within each group at each time interval with p-value < 0.001 as depicted in [Figure 4]. The mean difference for glycosylated hemoglobin at 3 months was: group 1: 1.32±0.72; group 2: 1.19±0.27; group 3: 1.16±0.41; group 4: 0.97±0.16. The mean difference for glycosylated hemoglobin at 6 months was: group 1: 2.11±0.97; group 2: 1.81±0.53; group 3: 1.66±0.63; group 4: 1.46±0.47. The mean reduction in FPG and PPBG for respective groups

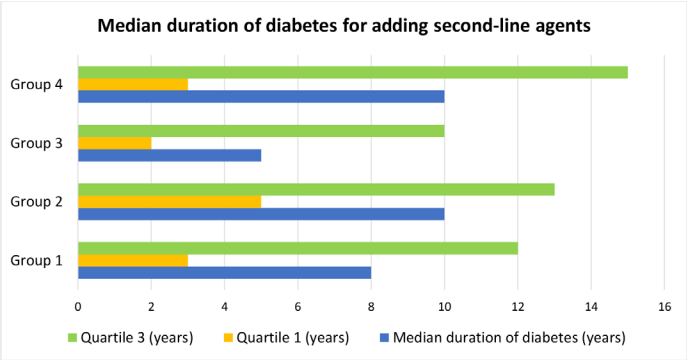

Figure 1: Median duration of type 2 diabetes mellitus for adding second-line anti-diabetic drugs.

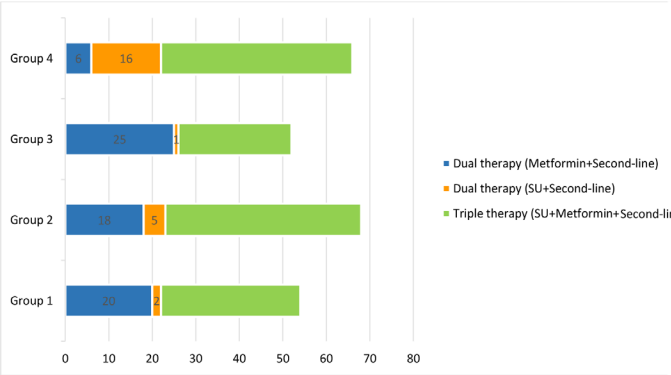

Figure 2: Pattern of antidiabetic drug prescriptions in different groups.

Table 2: Baseline Characteristics of the patients.

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
HbA_{1C} (%)	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 (mm Hg)	121.96±10.66	126.85±11.49	121.35±17.45	130.12±14.47
DBP (mm Hg)	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).

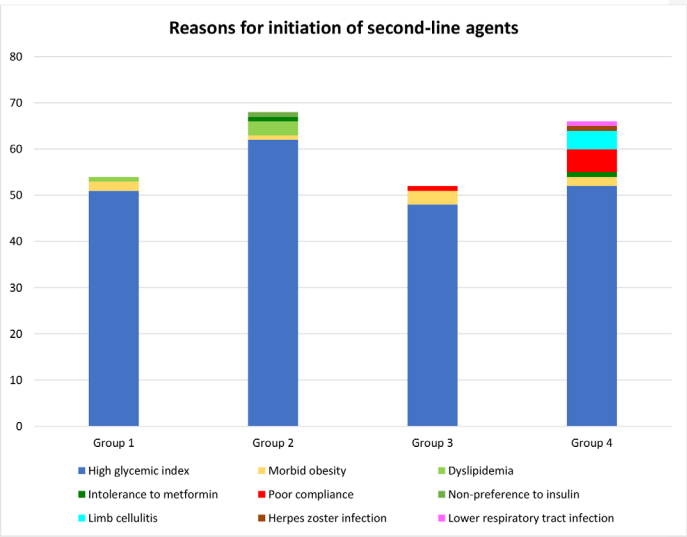

Figure 3: Enumeration of reasons for initiation of second-line agents in various antidiabetic treatment groups.

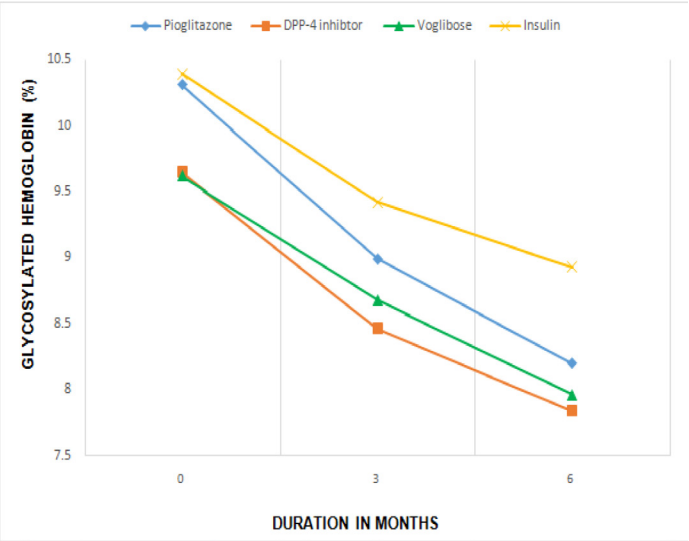

Figure 4: Reduction in HbA_{1C} levels in the different group of second-line agents.

Table 3: Change in FPG levels after the initiation of second-line agents.

Add-on drug therapy	FPG value at baseline (mg/dL)	FPG value at 3 months (mg/dL)	FPG value at 6 months (mg/dL)	Mean diff. at 3 months (mg/dL)	Mean diff. at 6 months (mg/dL)
Group 1 (Pioglitazone)	210±86.02	150±63.19	135±54.96	60±22.83*	75±31.06*
Group 2 (DPP-4 inhibitor)	211±74.43	148.85±48.61	133.09±36.48	62.15±25.82*	77.91±37.95*
Group 3 (Voglibose)	217.75±64.72	154.67±55.11	131.88±42.97	63.08±9.61*	85.87±21.75*
Group 4 (Insulin)	231.55±84.69	172.24±70.05	140.17±52.89	59.31±14.64*	91.38±31.8*

*p-value < 0.001.

Table 4: Change in PPBG values in the different groups of second line agents.

Add-on drug therapy	PPBG value at baseline (mg/dL)	PPBG value at 3 months (mg/dL)	PPBG value at 6 months (mg/dL)	Mean diff. at 3 months (mg/dL)	Mean diff. at 6 months (mg/dL)
Group 1 (Pioglitazone)	298.93±101.05	217.26±76.95	183.63±60.73	81.67±24.1*	115.3±40.32*
Group 2 (DPP-4 inhibitor)	293.81±94.58	212.53±68.73	176.81±53.31	81.28±25.85*	117±41.27*
Group 3 (Voglibose)	304.96±105.97	220.98±83.53	186.21±50.11	83.98±22.44*	118.75±55.86*
Group 4 (Insulin)	323.86±120.63	232.79±83.99	191.83±64.39	91.07±36.64*	132.03±56.24*

*p-value < 0.001.

has been summarized in [Table 3, 4] and was statistically significant (p-value < 0.001) within each group at 3 and 6 months respectively.

DISCUSSION

The present study aimed at investigating the utilization pattern of second-line agents as well as analyzing the outcome of treatment in terms of effectiveness of various second-line agents added for the first time to previously prescribed metformin or sulfonylureas or a combination of both. From 2003-2012 in the USA, the scenario of antidiabetic drug utilization had shown that 44.9% prescriptions had metformin monotherapy, pioglitazone prescription rates were nearly constant and rosiglitazone usage drastically declined. At the same time, newer approved drugs such as DPP-4 inhibitors were on a steady rise occupying 22% share.[17] From 2008-2013 in Taiwan, DPP-4 inhibitors were the most prescribed agent for adjunctive therapy.[18] In our findings from the year 2014, prescription of DPP-4 inhibitor had an increased share of 28.3%. The upsurge in the trend towards DPP-4 inhibitor can be attributed to simple dosing regimen, oral administration, lesser adverse effects, better tolerability, insignificant hypoglycemic episodes, negligible weight alterations, and a desirable glycemic target achievement.[19] The pioglitazone usage was reported more between 2012-2014 in the study undertaken and contributed to 22.5% prescriptions among second-line agents. The usage of pre-mixed insulin (30% regular/70% NPH) was reported as 27.5% compared to a study conducted in Shimoga district of Karnataka (28.57%).[20] The voglibose prescriptions were 21.7% that is commensurable to a Taiwan study focusing on α-glucosidase inhibitors usage (19.21%).[21] Metformin was the most commonly prescribed first-line antihyperglycemic agent followed by glimepiride and glibenclamide. Among sulfonylureas the least prescribed one was gliclazide.

The median duration of diabetes was observed as 8 and 10 years respectively for adding pioglitazone and DPP-4 inhibitor. Hanefeld *et al.* showed the mean duration of diabetes to add pioglitazone as 7 years.[22] The research studies have reported the mean duration of diabetes as 6.8 to 7.3 years for adding DPP-4 inhibitors. 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. It was identified that the maximum number of patients i.e. 28 were prescribed voglibose as the most common second-line agent in those having received antihyperglycemic treatment for past 5 years. Insulin was the most prevalent second-line agent to be added to those receiving first-line drugs for past 10-20 years; while Riddle *et al.* study had 9.3 years for initiating NPH insulin.[23] It depicts that the early stage of diabetes can be well managed by dual or triple oral hypoglycemic agent combination; while on the other hand, the elevated blood glucose levels seen in advanced diabetic stage require intensive insulin therapy.

In general, the glycemic control deteriorates in the first 3-5 years and HbA_{1C} levels increase at an average rate of 0.2-0.3% per year. Usually, the intensive monotherapy fails within 6 years of the initiation of antidiabetic agents. Even the patients who respond well to the monotherapy subsequently fail at a rate of ≥ 5% per year. Therefore, for the second-line agents to be effective, they should work either as insulin sensitizer e.g. pioglitazone or improve insulin resistance e.g. voglibose, sitagliptin, vildagliptin. Eventually, insulin therapy is commenced if drugs acting via either mechanism fail to produce effective results in terms of reducing or maintaining the HbA_{1C} levels.[24]

In the pioglitazone treatment group, the mean difference in HbA_{1C} at 3rd and 6th month with respect to baseline was 1.32±0.72 and 2.11±0.97 respectively which was significant with p-value < 0.001 at each time interval; a greater decline in HbA_{1C} at 6th month. Usually, TZDs cause a decline in HbA_{1C} by 1-1.5% within 12 weeks which matched our finding; while 1.88% mean decline in HbA_{1C} at 3rd month was observed by Al-Azzam *et al.*[25] A systematic review covering pioglitazone combination studies

over 12-26 weeks revealed a decrease in HbA_{1C} up to 2.6% though the results among different studies varied from 0.34-1.57%.[26] The FPG in pioglitazone add-on group exhibited a mean decrease of 60 and 75 mg/dL at 3rd and 6th month respectively from the baseline which was significant ($p < 0.001$) at both the time intervals. Previously conducted 12-week and 16-week pioglitazone add-on studies demonstrated a decline of 38 mg/dL and 20.5 mg/dL respectively in FPG.[27]

The present study observed a mean decline of 1.19±0.27 and 1.81±0.53 in HbA_{1C} at 3rd and 6th month respectively in the DPP-4 inhibitor group. Similar findings were observed by Raz *et al*. and Goldstein *et al*. – a decline of 1% and 1.40-1.90% in HbA_{1C} over 18 and 24 weeks respectively.[28-29] Our study included patients with HbA_{1C} >10% contrary to other studies where HbA_{1C} ranging from 7.5-8.5% were undertaken; a greater decline might be due to this variation. The voglibose add-on treatment group in the present study identified a mean decline of 1.16±0.41 and 1.66±0.63 in HbA_{1C} at 3rd and 6th month respectively from the initial values. A study by Jindal *et al*. in North Indian population gives supporting evidence; an average decrease in HbA_{1C} of 1.17% and 1.96% at 3rd and 6th month.[30] In present voglibose treatment group a mean reduction of 83.98 and 118.75 mg/dL in PPBG at 3 and 6 months respectively which was statistically significant.

Limitations

The retrospective nature of study design and a smaller sample size were the limitations of this study. Analysis of the trend of second-line agents' prescription over 3-years was not feasible owing to small sample size, restrained study timeframe, and limited resources. A larger sample size could have provided sufficient data to compare the efficacy between the groups at respective time intervals. The parameters were recorded with a window period of ±15-20 days at 3rd and 6th month. Sub-group analysis based on the number of glucose-lowering drugs utilized [dual therapy (metformin/sulfonylurea+ second-line agent versus triple therapy (metformin+ sulfonylurea+ second-line agent)] was not carried out.

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. There was a gradual shift in trend towards prescribing DPP-4 inhibitors over the recent years. Our study focused on the effectiveness of second-line agents in combination with metformin or sulfonylurea or both. Pioglitazone add-on group had the greatest decline in HbA_{1C} at 3rd and 6th month followed by DPP-4 inhibitor group. All the four add-on groups exhibited a significant reduction in FPG and PPBG when used as dual or triple combination therapy over 3 and 6 months. DPP-4 inhibitor add-on group was found to be safe in terms of least hypoglycemic episodes. Therefore, it can be inferred that DPP-4 inhibitors are modestly effective second-line anti-diabetic agent in uncomplicated type 2 diabetes.

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ABBREVIATIONS

ANOVA: Analysis of Variance; **DM:** Diabetes Mellitus; **DPP-4:** Dipeptidyl Peptidase-4; **FPG:** Fasting Plasma Glucose; **GLP-1:** Glucagon-like Peptide-1; **HbA_{1C}:** Glycosylated Hemoglobin; **IEC:** Institutional Ethics Committee; **OHA:** Oral Hypoglycemic Agents; **PPBG:** Postprandial Blood Glucose; **SD:** Standard Deviation; **SU:** Sulfonylurea; **TZDs:** Thiazolidinediones; **WHO:** World Health Organization.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUMMARY

The study focused on the real-world evidence regarding the indications for initiating second-line agents in uncomplicated type 2 diabetes mellitus and their effectiveness over a period ranging from 3-6 months. The high glycemic index was the primary reason for initiating second-line agents with DPP-4 inhibitors being relatively more prescribed antidiabetic medication in the recent years compared to other second-line agents. The median duration of type 2 diabetes prior to second-line agent initiation ranged form 5-10 years. All the four add-on groups showed significant reduction in FPG and PPBG when used as dual or triple combination regimen over 3-6 month period. DPP-4 inhibitors and pioglitazone demonstrated maximum decline in glycosylated hemoglobin over 6 month treatment duration; though there was an increased trend in DPP-4 inhibitors prescription.

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