Original Article

Therapeutic Experience of Saxagliptin as First Add-on after Metformin in Indian Type 2 Diabetes Patients: A Non-interventional, Prospective, Observational Study (ONTARGET-INDIA)

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Abstract

Introduction: Dipeptidyl peptidase 4 (DPP4) inhibitors are widely used in type 2 diabetes mellitus (T2DM) patients but the data available in existing clinical trial programmes on DPP4 inhibitors include limited number of patients from India. Hence, this study attempted to understand usage, efficacy and safety of saxagliptin as first add-on after metformin in Indians with T2DM. **Methodology:** It was a multicenter, prospective, non-interventional and observational study planned to enrol T2DM patients who were inadequately controlled with metformin alone and had been recently (i.e., within past 15 days) prescribed saxagliptin as an add-on to metformin. Type 1 diabetes mellitus, use of glucose lowering drugs apart from metformin or saxagliptin, pregnancy, lactation, and medical condition, which could interfere with safe completion of the study were excluded. **Results:** A total of 1109 participants (658 men and 451 women) with mean ± SD age of 51.17 ± 11.85 years were enrolled from 50 centres throughout India. Significant reduction was observed in mean ± SD change of HbA1c as − 0.86% ± 1.76 from baseline to after 3 months of therapy ($P < 0.0001$). The quality of life assessed by World Health Organization Quality of Life-BREF (WHOQOL-BREF) questionnaire was reported to be "good" or "neither good nor bad" by majority of the participants at baseline and after 3 months of treatment. A total of 15 adverse events (AEs) were reported in the study, however, no serious adverse event (SAE) occurred during the study. All AEs were of mild intensity and did not require any intervention. **Conclusion:** Overall, saxagliptin in combination with metformin was generally well tolerated in Indian T2DM patients and new safety event identified is an increased risk of hospitalisation in heart failure patients. This study is also registered on Clinicaltrials.gov (NCT02588859).

Keywords: DPP4 inhibitors, Saxagliptin, type 2 diabetes mellitus

Introduction

Background

Diabetes is a heterogeneous condition characterised by hyperglycaemia, a result of inadequacies in insulin secretion, insulin resistance/action or combination of both of these factors.[1] Type 2 Diabetes Mellitus (T2DM) is the major cause of diabetes worldwide and accounts for nearly 90%–95% of those with diabetes and in severe cases may lead to death of the patients.[2,3] T2DM patients have a wide range of pathophysiological factors governing the disease like insulin resistance and relative insulin deficiency.[4] Apart from providing useful effects in T2DM patients, the established oral hypoglycaemic agents have various concerns and challenges. Among these, major issues are weight gain, severe and prolonged hypoglycaemia, usage in special

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population (hepatic or renal insufficiency) and multitude of adverse events (AEs).[5,6] To deal with these inconsistencies, dipeptidyl peptidase 4 (DPP4) inhibitors were developed to achieve glycaemic control while reducing the body weight and systolic blood pressure in parallel.[7] The feedback loop comprising insulin-sensitive tissues and beta-cells regulate the normal glucose regulation. If we focus on the action of "incretins", that is, Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) on pancreatic islet, research suggests that GLP-1 primarily influence both alpha and beta cells to augment insulin along with a halt on glucagon secretions.[8,9] This useful action is subdued by dipeptidyl peptidase 4 (DPP4) enzyme within minutes.[10] Hence, research was carried out to develop a new class of drugs with a goal in mind to manage T2DM effectively and to avoid hypoglycaemia associated with other oral antidiabetic agents. This lead to the advent of DPP4 inhibitors, which are efficacious and have very less incidence of hypoglycaemia, resulting in their successful marketing.[11,12] Improvement in glycaemic control with combination of saxagliptin and metformin is established for better tolerance without the incidence of weight gain.[13,14] Moreover, this combination poses improvement in quality-adjusted life-years (QALYs) apart from its effectiveness and cost-effectiveness.[15-17]

Rationale

Metformin is used as first line oral antidiabetic drug in most of the cases.[18] Sulfonylureas (SU) are used as frequent first add-on after metformin inadequacy. SUs are preferred because of good efficacy and faster reduction in glycaemic parameters.[19] However, SU are associated with frequent hypoglycaemic episodes and weight gain which can adversely impact the overall outcome in T2DM.[20] These limitations can be overcome by using candidates from a newer class of incretins, that is, DPP4 inhibitors. Early usage of DPP4 inhibitors has shown to control hyperglycaemia along with favourable effects on overall diabetes.[21,22] There are also some animal studies showing beta cell preservation with incretin-based therapies.[23,24] American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) Diabetes Management Algorithm 2017 suggested DPP4 inhibitors as an alternative for use as first-line monotherapy and in combination therapy (both dual and triple therapies) for better glycaemic control.[25] The DPP4 inhibitors monotherapy has been shown to reduce the glycated haemoglobin (HbA1c) levels by around 1%.[26] Sitagliptin was the first DPP4 inhibitor approved by the United States Food and Drug Administration (US-FDA) in 2006 as monotherapy or in combination with metformin or thiazolidinedione in the treatment of T2DM.[27] Saxagliptin is a modern addition approved by US-FDA in July 2009 to this class as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM.[28]

A review article reported the results of 14 trials published from January 2008 to June 2015. The inclusion criteria for the selection of these 14 studies were "saxagliptin 2.5 and 5 mg/day dosage randomised phase III and IV trials with duration of study ≥24 weeks". These studies involved 7889 participants throughout the world. These multicentre trials were conducted in United States, Australia, Canada, Mexico, Puerto Rico, Taiwan, India, Russian Federation, China, Republic of Korea, Philippines, Brazil, Chile, Argentina, Germany, Hungary, Italy, Poland, Ukraine, Belgium, France, Spain, Turkey, United Kingdom, Peru, South Africa, Israel, Singapore, Finland, Netherlands, Norway, Slovakia, Vietnam, Thailand, and Romania. The results of these studies concluded that saxagliptin significantly improve the glycaemia with low risk of incidence of hypoglycaemia and neutral effects on weight.[29]

Phase III research studies have demonstrated that saxagliptin is efficacious and well tolerated as an add-on therapy in patients with T2DM inadequately controlled with metformin monotherapy.[30,31] Short-term treatment with saxagliptin 5 mg added to metformin XR 1500 mg once daily was generally well tolerated in patients with T2DM who had inadequate glycaemic control with metformin monotherapy. Saxagliptin plus metformin was found to significantly reduce mean weighted glucose, postprandial glucose and fast plasma glucose with lesser adverse effects.[32]

In India, DPP4 inhibitors were introduced in early 2007 but they were not utilised to potential level.[33,34] In modern era, the healthcare professionals aim to provide individualised therapy by focusing on efficacy, financial factors, side effects and several risk factors in patients for better outcome and ease of use.[7] Moreover, the cost-effectiveness of DPP4 inhibitors in combination with metformin as a second line therapy in comparison to metformin + SU for T2DM patients in many parts of world, provide them with edge.[35,36] Aligning to all the above said points and effectiveness, DPP4 inhibitors have potential to be used in Indian settings.

The data available in existing clinical trial programmes on DPP4 inhibitors include limited number of patients from India. Key opinion leaders in diabetic segment of India have identified the need for study on Indian patients to observe the effect of Saxagliptin in real world settings. Hence, this study aimed at achieve following objectives: (a) to understand usage and effect of Saxagliptin as first add-on after metformin in Indian patients and; (b) to assess HbA1c reduction achieved as first add-on after metformin. Other objectives included assessing effect of baseline HbA1c on HbA1c reduction, incidence of hypoglycaemia, AEs during study duration, quality of life and baseline incidence of urinary tract infection and genital tract infection.

Methodology

This was a multicenter, prospective, non-interventional and observational study planned to enrol T2DM patients who were inadequately controlled with metformin alone and had been recently (i.e., within past 15 days) prescribed saxagliptin as an add-on to metformin. Patients taking glucose lowering drugs apart from metformin or saxagliptin, presenting with type 1 diabetes mellitus, pregnant or lactating women, and patients

with medical condition which in the opinion of investigator could interfere with safe completion of the study were excluded. Investigator/designee collected the information as per the study schedule from the study participants. All the potential participants were consecutively screened before enrolment at baseline. Follow-up was planned three months later.

The primary variables in the study were demographic details, disease duration, medical and surgical histories including comorbidities, current medication, saxagliptin discontinuation, switching to other medications and change in HbA1c over the study duration. Other variables included baseline and follow-up HbA1c levels, details of hypoglycaemic episodes experienced by patient in last 1 month before enrolment and during the study, incidence of AEs, changes in WHO Quality of life-BREF questionnaire (WHOQOL-BREF) and urinalysis.

The study was performed in accordance with Ethical principles that are consistent with the declaration of Helsinki, international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use – Good Clinical Practices and the applicable legislation on non-interventional studies. The informed consent was obtained from all participants before inclusion in the study.

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

The disposition of participants in this study is presented in Table 1. There was a total of 1109 participants (658 men and 451 women) enrolled from 50 centers throughout India. Subjects (Mean ± SD age 51.17 ± 11.85 years and body mass index 27.13 ± 4.32 kg/m²) of T2DM with inadequate glycemic control and receiving metformin monotherapy (minimum dose of 500 mg once daily) for at least 3 months, and to whom saxagliptin was prescribed (within last 15 days) in addition to metformin were enrolled in this study [Table 2].

Saxagliptin 5 mg was received by 997 (89.9%) patients and 2.5 mg by 64 (5.77%) participants. Majority of participants, 775 (69.9%) had received 500 mg of metformin followed by 495 (44.63%) of 1000 mg, 53 (4.78%) of 2000 mg, 39 (3.52%) of 850 mg, 38 (3.43%) of 750 mg, and 21 (1.89%) of 1500 mg. The other dosage of metformin, that is, 50, 250 and 2500 mg were received by less than 1.0% of patients. Majority of the participants [971 (99.39%)] continued saxagliptin and only 6 (0.61%) participants discontinued the treatment during 3 months of follow-up. A total of 967 (98.98%) did not switch over to any other oral antidiabetic treatment, while 10 (1.02%) patients switched over to other oral therapy.

The quality of life was assessed by WHOQOL-BREF questionnaire. It assesses the individual's perceptions in the context of their culture and value systems, and their personal goals, standards and concerns and the participants were asked to respond to 26 items, which measured the following broad domains: Physical health, psychological health, social relationships, and environment. The quality of life was reported to be "good" (44.5%-49.8%) or "neither good nor bad" (39.7%-39.2%) by the patients at baseline and after 3 months of treatment, respectively.

Significant reduction was observed in mean ± SD change of HbA1c as − 0.86% ± 1.76 from baseline to after 3 months of events in participants ($P < 0.0001$) [Table 3]. Mild

Table 1: Disposition of patients

	All Enrolled (*n*=1109)
Total no. of subjects completed the study as per protocol, *n* (%)	
Yes	977 (88.10)
No	132 (11.90)
Reason for early withdrawal, *n* (%)	
Death	0 (0.00)
Voluntary discontinuation	27 (2.43)
Subject lost to follow up	74 (6.67)
Investigator thinks continued participation in the study would be detrimental to patient's well being	2 (0.18)
Other	29 (2.61)

n: Total number of subjects, *n*: Total number of subjects available with data, Percentage was calculated using number of enrolled subjects as the denominator

Table 2: Demographic details of patients

	All Enrolled (*n*=1109)
Age (years)	
Mean (SD)	51.17 (11.85)
Median (min, max)	51.00 (18.00, 90.00)
Gender, *n* (%)	
Male	658 (59.33)
Female	451 (40.67)
Height (cm)	
Mean (SD)	163.25 (8.44)
Median (min, max)	163.00 (133.00, 187.00)
Weight (kg)	
Mean (SD)	72.42 (12.48)
Median (min, max)	71.00 (39.00, 129.00)
BMI (kg/m²)	
Mean (SD)	27.13 (4.32)
Median (min, max)	26.60 (17.00, 45.30)

n: Total number of subjects, *n*: Total number of subjects available with data, SD: Standard Deviation, Min: Minimum, Max: Maximum, BMI: Body Mass Index

Table 3: Mean change in HbA1c level from baseline to 3 months after the treatment

	Baseline (*n*=1108)	After 3 months (*n*=976)	Change from baseline	*P**
Mean (SD)	8.48 (1.93)	7.57 (1.64)	-0.86 (1.76)	<0.0001
Min, Max	8.00 (5.10, 15.60)	7.20 (4.40, 16.70)	-0.60 (-8.80, 6.50)	

*Paired *t*-test was used

hypoglycemic events were observed in 26 (2.34%) patients during last month of treatment and 38 (3.89%) patients had hypoglycaemic events since last visit. In this study, proportion of patients who experienced genital tract infection at baseline were low [58 (5.23%)] as compared to those who experienced urinary tract infection [148 (13.35%)].

A total of 15 AEs occurred during the study. These were hypoglycaemia (8), urinary tract infections (3), pyrexia (2) and insomnia and eczema (one each). All these events were of mild intensity and did not require any intervention. No serious adverse event (SAE) occurred during the study. All the AEs were of 15 (100%) mild intensity. Majority of AEs [12 (80.0%)] were not suspected to be related with study drug [Table 4]. Urinary tract and genital tract infection were observed in 148 (13.35%) and 58 (5.23%) patients, respectively, at baseline.

Discussion

This observational, multi-centre, prospective study attempted to assess/understand efficacy and safety of saxagliptin as first add-on after metformin therapy in Indian T2DM patients. The study enrolled persons with T2DM who were prescribed saxagliptin as first add-on after inadequate glycemic control with metformin monotherapy (minimum dose of 500 mg OD). Overall, add-on treatment with saxagliptin to T2DM patients with inadequate glycemic control after metformin monotherapy led to clinically relevant improvements in HbA1c levels with fewer AEs of mild intensity.

Table 4: Evaluation of AE (Safety Set)

	Safety Set (*n*=1109)
Subjects who had AE, *n* (%)*	14 (1.26)
Total no. of Adverse event, *n*	15
Hypoglycaemia	08
Urinary Tract Infection	03
Pyrexia	02
Insomnia	01
Eczema	01
Total no. of SAE, *n* (%)**	0 (0.0)
Severity, *n* (%)**	
Mild	15 (100)
Moderate	0 (0.0)
Severe	0 (0.0)

*Percentage was calculated by using Safety Set as the denominator, **Percentage was calculated by using total number of AEs as the denominator

This study observed significant mean ± SD reduction in HbA1c level (−0.86% ± 1.76) of T2DM patients with add-on treatment of saxagliptin in combination with metformin over a period of 3 months. This data is consistent with earlier report of saxagliptin in combination with metformin which showed additional − 0.52% decrease in HbA1c level in T2DM.[37] Our results corroborate findings from previous studies which document that saxagliptin in combination with metformin leads to reduction of 0.74% in HbA1c level at week 52 from baseline in T2DM patients.[38] Another study reported reduction in HbA1c level by 0.59% from baseline to 24 weeks in T2DM patients in saxagliptin + metformin group.[39] However, a recent study in 60 T2DM patients observed greater mean ± SD decline of HbA1c level by 1.4% ± 0.1 compared to current and previously published literature.[24,37] The differences between our results [Tables 2 and 3] and earlier studies [Table 5] might be influenced by different racial background of study populations, baseline HbA1c levels, BMI, type and dosage of background drugs and prescribed doses of the study drug. Among the DPP4 inhibitors, saxagliptin results in similar HbA1c reductions compared to other DPP4 inhibitors. A systematic review compared the efficacy and safety of sitagliptin 100 mg and saxagliptin 5 mg with placebo and other hypoglycaemic medications. Both drugs (sitagliptin and saxagliptin) reported a greater reduction in HbA1c compared to placebo.[40] In an open label randomised, placebo controlled, five-period crossover study enrolled 22 T2DM patients. The patients received saxagliptin 5 mg q.d., sitagliptin 100 mg q.d., vildagliptin 50 mg q.d., vildagliptin 50 mg b.i.d., or placebo for 5 days. The study published that a greater DPP4 inhibition was achieved with once daily treatment of sitagliptin in comparison to saxagliptin or vildagliptin.[41]

The DDP4 inhibitors reported to have lower incidence of hypoglycaemia and thus better acceptability among diabetic patients. During 3 months of our study, hypoglycaemia was observed in 38/977 (3.89%) patients receiving saxagliptin in combination with metformin. The result is in assertion with a study in which hypoglycaemia occurred in 15 out of 428 (3.5%) T2DM patients being evaluated for 104 weeks.[42] However, a 24 weeks randomised controlled trial reported very less incidence of hypoglycaemic event in 1.4% patients treated with saxagliptin in combination with metformin.[43] In another 24-week study conducted in 207 T2DM patients, the incidence of hypoglycaemia was 6%, 3%, and 2% in saxagliptin, sitagliptin and vildaglitin arm, respectively.[44] An analysis

Table 5: Comparison of variables cited from different articles/studies

Study Author	Year of Publication	No. of Patients	Country	Population	Study Period	Baseline HbA1c Levels	Change in HbA1c Levels	BMI Change	Dosage: *Metformin; Saxagliptin*
Scheen AJ	2010	801	NA	NA	18 weeks	6.5%-10%	-0.52%	NA	1500-3000 mg/day; 5 mg/day
Göke B	2010	858	NA	≥18 years	52 weeks	6.5%-10.0%	-0.74%	NA	≥1500 mg/day; 5 mg/day
Hao Liu	2016	60	China	29-70 years	12 weeks	7.0%-13.0%	-1.4% ± 0.1%	>24 kg/m^2	1000-2000 mg/day; 5 mg/day

of 32 studies demonstrated the event of hypoglycaemia to be similar among sitagliptin, sexagliptin and placebo arms.[41]

Saxagliptin in combination with metformin was well tolerated in this study and no increase in incidence of AEs was observed. Our study observed a low incidence of urinary tract infection in three (0.27%) patients, compared to a previous study that reported much higher incidence of urinary tract infection in 23 (5.7%) T2DM participants treated with saxagliptin and metformin.[38] None of the participant in our study was discontinued as the result of an AE. However, previously published studies reported a discontinuation of 4.2%–4.4% from the study as a result of AEs of combination therapy with saxagliptin.[39,45]

Importantly, the risk of hospitalisation of heart failure patients was reported in T2DM patients treated with saxagliptin in recent years. A study conducted based on the observations from the SAVOR-TIMI 53 trial (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus: Thrombolysis in Myocardial Infarction), included 16,492 patients with T2DM and a history of, or at risk of, cardiovascular events were randomised to saxagliptin or placebo. In all, 8820 patients were randomised to be treated with saxagliptin and 8212 were randomised to be treated with placebo. The average monitored period was 2.1 years. A significant number of patients treated with saxagliptin were hospitalised for heart failure compared to placebo. It was shown that the patients who had a previous incidence of heart failure were at greatest risk of hospitalisation for heart failure. The study published that saxagliptin treatment was associated with an increased risk or hospitalisation for heart failure.[46-48] However, the present study included two patients with a history of congestive heart failure and both patients completed the study without any AE.

Conclusion

Saxagliptin as add on first after metformin is associated with reduction in HbA1c levels as well as to lowers the risk of hypoglycaemia in patients of type 2 diabetes mellitus inadequately controlled by metformin alone. Overall, saxagliptin in combination with metformin was generally well tolerated in this patient population and no new or unexpected safety events were identified.

Clinical Trials Registration

NCT02588859.

Compliance with ethics

Ethical approval and patient consent were received for this study.

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Conflicts of interest

Hardik V and Amit Kumar are employees of AstraZeneca Pharma India Ltd. Other Authors – No conflict of Interest.

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