Original Article

Initiation of Insulin Aspart to Indian Subjects on OADs show Significant Improvement in Glycaemic Outcomes: The A_1chieve® Observational Study

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Abstract

The prevalence of diabetes is increasing worldwide and India stands second next only to china. The management of diabetes in real life settings needs to be evaluated for deriving better management practices. A_1chieve® observational study evaluated the use of modern insulin in real life settings. This was a 24-week, international, prospective, multicenter, non-interventional, observational study of people with type 2 diabetes. India recruited with 20,554 subjects and a total of 1815 patients were enrolled to receive insulin aspart as bolus insulin therapy of whom 1450(79.9%) were insulin naïve and 365(20.1%) were insulin users. At the end of 24 weeks, only one SAE was reported in this study and overall hypoglycemia events per patient year decreased from 2.49(348 episodes) to 0.17 (20 episodes). There were no major hypoglycemic episodes reported in either insulin naïve or insulin treated subjects. There was a significant improvement in the HbA_{1c} values from the baseline in both insulin naïve and insulin users. The mean HbA_{1c} value was reduced from 9.5 to 7.4($p<0.001$) for insulin naïve subjects and from 9.2 to 7.7($p<0.001$) in insulin experienced subjects. Fasting plasma glucose values decreased by 70 mg/dL and 50 mg/dL in insulin naïve and insulin experienced, respectively and the difference from baseline was statistically significant ($P<0.001$). The post prandial glucose value was also significantly ($p<0.001$) reduced by 105 mg/dL for insulin naïve subjects and 55 mg/dL for insulin experienced subjects. The composite end point was achieved by 46.6% of insulin naïve and 38.1% of insulin-experienced subjects. The study concluded with good HbA_{1c} reduction along with lower incidence of hypoglycemia and better health related quality of life outcomes in both in insulin naïve and insulin experienced subjects who used insulin aspart as bolus insulin treatment.

Introduction

The prevalence of diabetes in India at present is more than sixty million and is estimated to reach a mammoth hundred million by the year 2030.[1] This is in line with the ICMR-INDIAB study which estimated the prevalence of 62 million with 77 million pre-diabetic subjects in the country.[2] With the prevalence increasing managing diabetes optimally is a big challenge especially in India where people have adopted a sedentary lifestyle along with western food habits. In real life settings, choosing the right medication, which adapts to person needs and demands, like modern insulin, can help in effective management with a minimal risk of hypoglycemia.[3] In this A_1chieve® observational study the advantages of modern insulin was evaluated in real life settings.

Methods

Study design and patient description

This was a 24-week, international, prospective, multicentre, non-interventional, observational study of people with T2D who had begun using basal insulin detemir (Levemir, Novo Nordisk, Denmark), bolus insulin aspart (NovoRapid, Novo Nordisk) and biphasic insulin aspart 30 (NovoMix 30, Novo Nordisk), alone or in combination, to evaluate their clinical safety and effectiveness in routine clinical use . The study recruited 66,726 subjects from 28 countries across four continents (Asia, Africa, South America, and Europe) and India has contributed with 20,554 subjects, which was almost 1/3 of the total study population. According to their previous treatment status the subjects belonged to the following groups: No therapy 1314 (6%), oral glucose lowering drugs 15509 (76%) and insulin ± oral glucose lowering drugs 3731(18%). These patients were prescribed using basal insulin detemir (Levemir, Novo Nordisk, Denmark), bolus insulin aspart (NovoRapid, Novo Nordisk) and biphasic insulin aspart 30 (NovoMix 30, NovoNordisk), alone or in combination, to evaluate their clinical safety and effectiveness in routine clinical practice in India. Based on the subjects needs the treating physician prescribed the above mentioned insulin therapies to manage diabetes. There was no study-defined procedures and the studyreflected routine clinical practice in India. Here we present results of subjects who were prescribed NovoRapid with/without oral glucose lowering drugs. A total of 1815 patients were enrolled to receive this treatment of whom 1450(79.9%) were insulin naïve and 365(20.1%) were insulin users. Ethics committee approval was obtained and signed informed consent from all participants was collected before start of the study. Participants were free to withdraw at will at any time and analysis was done up to this point of withdrawal. Data was collected from physician notes and patient's recall and was captures in standard case report form.

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Primary and secondary outcomes

The primary objective of this study was to evaluate the clinical safety of the insulin analogues by the incidence of serious adverse drug reactions (SADRs). Major hypoglycaemic episodes which were considered related to the study insulin between baseline and final visit was analyzed under this section. Major hypoglycaemic events were defined as events with symptoms consistent with hypoglycaemia for which the person was unable to self-treat and accompanied by plasma glucose <3.1 mmol/L or 56 mg/ dL, or reversal of symptoms after either food intake or glucagon or intravenous glucose administration. The secondary safety assessments were the change in number of hypoglycaemic episodes, nocturnal hypoglycaemic, adverse drug reactions (ADRs) events 24 weeks from baseline. Nocturnal hypoglycaemia was defined as a symptomatic event consistent with hypoglycaemia that occurred during sleep between bedtime after the evening insulin injection and before getting up in the morning. Minor hypoglycaemia was any event, with or without symptoms of hypoglycaemia, with a plasma glucose reading below 3.1 mmol/L or 56 mg/dL, that the participant was able

Table 1 : Baseline characteristics of Indian cohort

	Total	No therapy	OGLD alone	Insulin ± OGLD
N	20554	1314	15509	3731
Percent of total	-	6.4	75.4	18.2
Sex M/F (%)	62.8/37.2	56.9/43.1	62.7/37.3	65.5/34.5
Age (years)	51.8 (10.1)	54.6 (12.6)	50.8 (9.5)	55.3 (10.5)
Weight (kg)	68.9 (10.5)	63.4 (8.4)	69.1 (10.2)	69.9 (12.1)
BMI (kg/m2)	26.3 (3.7)	28.4 (4.9)	26.1 (3.4)	26.5 (4.3)
Diabetes duration (yr)	6.3 (4.6)	2.2 (4.8)	5.7 (3.8)	9.9 (5.5)
HbA_{1c} (%)	9.3 (1.4)	9.3 (1.3)	9.3 (1.3)	9.2 (1.5)

Table 2: Hypoglycemia

Visit/Change	All [Patients, n (%); events, n (events/patient year)]	Insulin naïve [Patients, n (%); events, n (events/patient year)]	Insulin experienced [Patients, n (%); events, n (events/patient year)]
Baseline	1815	1450	365
Overall hypoglycaemia	170 (9.4) 348 (2.49)	96 (6.6) 175 (1.57)	74 (20.3) 173 (6.16)
Nocturnal hypoglycaemia	100 (5.5) 126 (0.90)	59 (4.1) 70 (0.63)	41 (11.2) 56 (1.99)
Major hypoglycaemia	36 (2.0) 51 (0.37)	15 (1.0) 16 (0.14)	21 (5.8) 35 (1.25)
Minor hypoglycaemia	161 (8.9) 297 (2.13)	93 (6.4) 159 (1.43)	68 (18.6) 138 (4.92)
Week 24	1520	1218	302
Overall hypoglycaemia	15 (1.0) 20 (0.17)	4 (0.3) 5 (0.05)	11 (3.6) 15 (0.65)
Nocturnal hypoglycaemia	5 (0.3) 5 (0.04)	1 (0.08) 1 (0.01)	4 (1.3) 4 (0.17)
Major hypoglycaemia	0 (0.00) 0 (0.000)	0 (0.00) 0 (0.000)	0 (0.00) 0 (0.000)
Minor hypoglycaemia	15 (1.0) 20 (0.17)	4 (0.3) 5 (0.05)	11 (3.6) 15 (0.65)

to self treat.

The efficacy parameters were analyzed by assessing the changes in HbA_{1c}, fasting plasma glucose (FPG), postprandial plasma glucose (PPG), body weight, along with quality of life between baseline and 24 weeks. Health-related quality of life (HRQoL) was measured using the EQ-5D questionnaire at baseline and after 24 weeks of therapy with insulin analogues. This questionnaire is a descriptive system of HRQoL states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression). This EQ-5D VAS score ranged from 0 (worst imaginable health) to 100 (best imaginable health).

Statistical analysis

For hypoglycaemia change from baseline, the percentage of people reporting at least one event was analyzed using Fisher's exact test. Change from baseline HbA_{1c}, FPG, PPG, blood lipids and EQ-5D VAS score was analyzed using paired t-test.

All data were analyzed by Novo Nordisk using SAS (Version 9.1.3).

Results

The participant's baseline characteristics for the entire Indian cohort stratified by pre-study therapy (insulin-naive or insulin users) are given in Table 1.

Out of this subject population 1815 subjects were prescribed NovoRapid with or without oral glucose-lowering drugs. The clinical safety outcomes were measured by incidences of serious adverse drug reactions (SADR) and hypoglycaemic events. Only one SAE was reported in this study population, with no relation to the drug Number of hypoglycemia was analyzed for major, minor, nocturnal events and was compared with baseline values at the end of 24 weeks of treatment. The rates of hypoglycemia were lower at 24 weeks compared to baseline in both insulin naïve and insulin experienced subjects. Overall hypoglycemia events per patient year decreased from 2.49(348 episodes) to 0.17 (20 episodes) and there were no major hypoglycemic episodes reported in either insulin naïve or insulin treated subjects at the end of the 24 weeks on insulin analogues (Table 2).

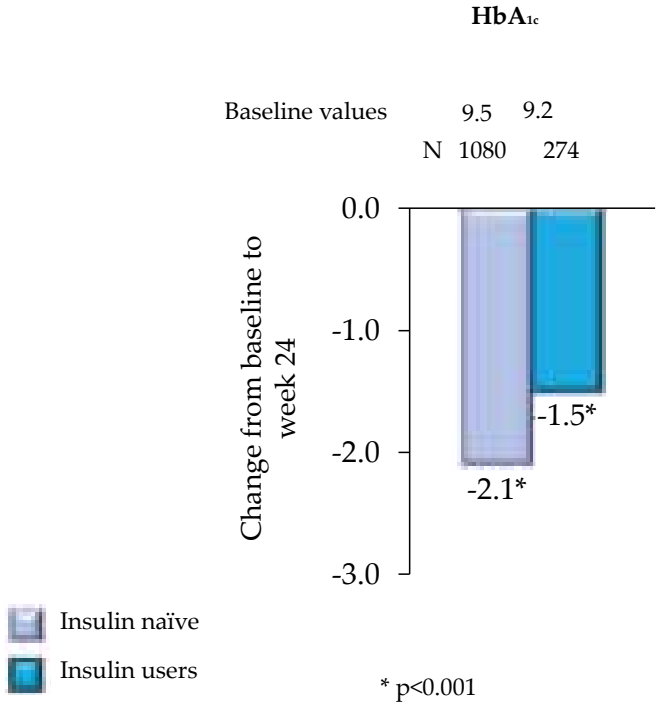

Fig. 1 : HbA_{1c} values measured after 24 weeks treatment

The efficacy parameters were evaluated for HbA_{1c}, FPG, PPG and the difference from baseline to 24 weeks was calculated. There was a significant improvement in the HbA_{1c} values from the baseline in both insulin naïve and insulin users. The mean HbA_{1c} value was reduced from 9.5 to 7.4($p<0.001$) for insulin naïve subjects and from 9.2 to 7.7($p<0.001$) in insulin experienced subjects (Figure 1) The ADA recommended target of HbA_{1c} <7% was achieved by 25.3% of the insulin naïve subjects and 19.5% of the insulin experienced subjects at the end of 24 weeks which at baseline was achieved only by 2.4% and 2.7%, respectively. Fasting plasma glucose values decreased by 70 mg/dL and 50 mg/dL in insulin naïve and insulin experienced, respectively and the difference from baseline was statistically significant ($P<0.001$) (Figure 2). The post prandial glucose value was also significantly ($p<0.001$) reduced by 105 mg/dL for insulin naïve subjects and 55 mg/dL for insulin experienced subjects (Figure 2). The composite endpoint was defined as at least 1% reduction in HbA_{1c} (i.e. change from baseline in $HbA_{1c} \leq -1\%$), no increase in body weight (i.e. change from baseline in body weight ≤ 0kg) and no hypoglycaemia reported in the past 4 weeks. In this study, 46.6% of insulin naïve and 38.1% of insulin-experienced subjects achieved the composite end point, respectively.

Health-related quality of life (HRQoL) was analyzed based on the EQ-5D questionnaire given at baseline and after 24 weeks of treatment. It consisted of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Quality of life with respect to mobility improved significantly($p<0.0001$) in 85.2% of all subjects at the end of the 24 weeks compared to only 32.4% of subjects at baseline. 70.8% of all subjects reported not having any problem in self-care which improved significantly(0.0001) from 33.5% at the start of

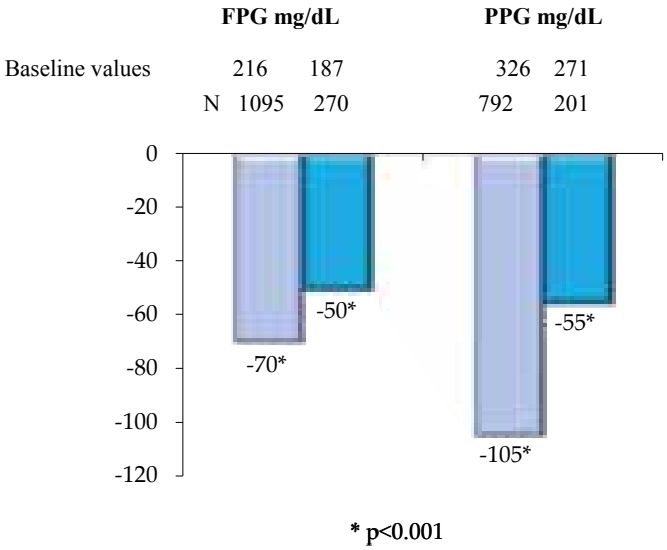

Fig. 2 : FPG and PPG values measured at the end of 24 weeks

the study. (73.3%) at the end of study using insulin analogues said to have no problems with performing their usual activities compared to only 32.4% at the start of study(0.0001). Only 31.5% had no pain or discomfort at the start of the study compared to 75.9% after using NovoRapid (insulin aspart) for 24 weeks (p<0.0001). In terms of mental health status it was found that 78.9% did not suffer from any anxiety or depression after using NovoRapid (insulin aspart) compared to only 32.6% at the start of the study(p<0.0001).

Discussion

India has a diverse and heterogeneous population along with an increasing diabetes prevalence which stands to 61.3 million next only to China[1]. The estimated diabetic population in India by the year 2030 will be 101 million and there is an increased need to manage diabetes optimally and prevent future complications. With available multiple treatment options like OADs, GLP-1 analogues and insulin, treatment of diabetes should aim to optimize glycemic control and minimize the side effects and suitably adapt to the daily needs of the patients. The A_1chieve® observational study aimed to evaluate the safety and efficacy of modern insulins in a diverse, heterogeneous population in a real life setting. However, the scale of the study provides scope for broader investigation into current practice and effective treatment strategies in India.

Glycemic control is evaluated through HbA_{1c} which is widely recognized as the gold-standard marker in diabetes management.[4] Contribution of FPG and PPG to HbA_{1c} is complex and may vary depending on previous 2-3 months of glycaemic control.[5] PPG contributes approximately 70% of the total glycaemic burden at HbA_{1c} levels < 7.3%, decreasing to around 30% at an HbA_{1c} level > 10.2%.[5] In contrast, the contribution of FPG increases with increasing HbA_{1c} levels, suggesting that PPG may be a better indicator of tighter HbA_{1c} control.[5]

Asians tend to develop the disease at a younger age and have higher PPG compared to the Caucasians population.[6,7] Venn and coworkers demonstrated a difference in glycaemic responses to a glucose load and to a commonly consumed breakfast cereal in the communities.[7] Similarly, Valensi et al. have shown that PPG is higher among Indians at the time of initiation of insulin therapy as compared to other populations.[8] The A_1chieve® study evaluated the safety and efficacy of insulin analogues on an Indian population The safety of insulin aspart (NovoRapid) was demonstrated with no major hypoglycemia during this 24 week study. The advantage of using modern insulin, insulin aspart (NovoRapid) was clearly demonstrated with a significant reduction of HbA_{1c} (p<0.001) in both insulin naïve and insulin experienced subjects and about 25% of insulin naïve patients and 19.5% previous insulin experienced subjects achieved ADA recommended <7% within the study duration of 24 weeks. There was also a significant (p<0.001) reduction in fasting and post prandial glucose values FPG decreased by 70mg/dL and PPG by 105mg/dL in insulin naïve patients. Insulin experienced subjects also had significant (p<0.001) reductions with FPG by 50mg/dL and PPG by 55mg/dL within 24 weeks of the study period. The study outcome with good HbA_{1c} reduction along with less incidence of hypoglycemia reflected to better health related quality of life outcomes both in insulin naïve and insulin experienced subjects. Patients reported better mobility, better self-care and had better management of usual day-to-day activities with less anxiety and discomfort compared to pre-treatment QOL assessment.

Conclusion

Insulin analogues have been designed to enhance desired molecular properties without altering immunogenicity.[3] Insulin analogues are designed to provide clinicians the opportunity to more closely emulate normal insulin physiology and to select different insulin regimens depending on patient preferences and lifestyle.[3] This will thereby makes insulin treatment less restrictive to different circumstances.[3] Rapid acting insulin analogues with faster onset of action have improved postprandial glycaemic control.[3] The fast acting modern insulin, insulin aspart (NovoRapid) has shown good outcomes in this A_1chieve® observational study. Insulin aspart (NovoRapid) demonstrated significant improvement in glycemic outcomes with less hypoglycemia. The quality of life also improved in this real life setting thereby suggesting better roles of modern insulin in treating diabetes in India.

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