



Improvement of Glycemic Control with Addition of Insulin Detemir to Existing Antidiabetic Therapy: A Sub-Group Analysis of A₁chieve[®] Observational Study

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Abstract

Background: The A₁chieve[®] study evaluated safety and effectiveness of insulin analogues in a large and diverse population. This report presents a subgroup analysis of the A₁chieve[®] observational study pertaining to India.

Objective: To assess safety and effectiveness of initiation or intensification of insulin detemir in patients with type 2 diabetes mellitus (T2DM) not achieving adequate glycemic control.

Methods: The A₁chieve[®] study was a prospective, multi-center, open-label, non-interventional study of 24-weeks duration. In this post-hoc analysis, Indian patients with T2DM who did not achieve their glycemic targets, and were started with or switched to insulin detemir, were evaluated at baseline and after 24 weeks of therapy for safety and effectiveness. Adverse events (AE) noted during the course of therapy were recorded. Additionally Glycemic, non-glycemic parameters and quality of life indices were reported. Appropriate statistical analysis was carried out to assess the statistical significance.

Results: The Indian cohort of 2707 patients with T2DM treated with insulin detemir included 2336 (86.29%) insulin-naïve and 371 (13.71%) insulin-experienced patients. No adverse drug reaction (ADR) was noted over 24 weeks, one patient (out of 2707) reported serious adverse event. Major hypoglycemia was reported in 0.5% (0.08 events/patient year) patients and reduced to 0% (0 events/patient year) over 24 weeks. After 24 weeks' treatment with insulin detemir, an overall reduction in HbA_{1c} of 2.1% was noted ($p < 0.001$), with a 2.1% ($p < 0.001$) and 2% ($p < 0.001$) reduction in insulin-naïve and insulin-experienced groups, respectively. A significant reduction in fasting ([mean \pm SD] -3.8 ± 2.5 mmol/L) and postprandial (-5.2 ± 3.9 mmol/L) blood glucose (FPG and PPG) was also observed ($p < 0.001$ for both). At end of the study, 24.4% patients achieved the ADA target of $< 7.0\%$ and 14.3% patients achieved the AACE target of $< 6.5\%$ for HbA_{1c}. A significant improvement in quality of life indices like ED-5D (0.31 ± 0.29 ; $p < 0.001$) and EQ-VAS (21.7 ± 16.7 ; $p < 0.001$) was noticed.

Conclusion: In patients with T2DM not achieving their glycemic targets addition of basal insulin detemir was well tolerated and reported improvement in glycemic control.

Introduction

Type 2 diabetes mellitus (T2DM) is an important public health problem in India. A recently published ICMRINDIAB study reported a total of 62.4 million patients with T2DM in India.¹ Data from the 2011 IDF Diabetes Atlas observed this number will increase substantially so by 2030 it is expected that India may have 101.2 million patients with T2DM.²

The UKPDS highlighted the importance of glycemic control in preventing long-term complications associated with T2DM.³ This study reported that even a 1% reduction in HbA_{1c} would decrease significantly the risk of deaths associated with T2DM by 21%, myocardial infarction by 14%, and microvascular complications by 37%.³

Initially life style modification and oral antidiabetic drugs (OADs) are used as first line management in T2DM. As the disease progresses most of the patients will eventually require insulin for optimal glycemic control. However insulin therapy may cause adverse effects like weight gain and hypoglycemia.

Evidence suggests that insulin must be introduced when blood glucose fails to reach a target HbA_{1c} $< 7.5\%$ with lifestyle

modification and 2 – 3 OADs. However, in real-life situations, many patients with T2DM experience significant periods with HbA_{1c} $> 7\%$. This may be due to delayed introduction or titration of insulin therapy and underlying factors like fear about hypoglycemia and weight gain. Therefore modern insulin analogs were developed to address these drawbacks.⁴

The clinical safety and effectiveness of insulin analogues in a large and diverse population was assessed by the A₁chieve[®] study.⁴ We present data of a subgroup of the A₁chieve[®] observational study pertaining to India. These data are a post-hoc analysis of patients with T2DM who did not have adequate glycemic control and subsequently started or switched to basal insulin detemir in the A₁chieve[®] study.

Materials and Methods

Safety and effectiveness of premix (biphasic insulin aspart 30 [NovoMix 30]), basal (insulin detemir [Levemir]) and meal-time (insulin aspart [NovoRapid]) insulin analogs was assessed in people with T2DM in real-life practice. This was a prospective, multi-centre, open-label, non-interventional study of 24-weeks duration. The study was carried out in 28 countries across four continents. The design and methodology of the A₁chieve[®] study has been discussed previously in literature and in this issue in great detail^{4,5} and will not be described here.

We conducted a post-hoc, sub-group analysis of India-specific

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Table 1: Baseline Demographic Data

Sr. No	Parameter	All	Insulin naïve	Insulin experienced
1.	Number (N)	2707	2336	371
2.	Age, years (mean ± SD)	50.5 ± 10.1	49.9 ± 9.8	54.7 ± 11.0
3.	Male (%): Female (%)	62.4:37.6	61.0:39.0	71.4:28.6
4.	Duration of Diabetes, years (mean ± SD)	5.6 ± 4.1	5.1 ± 3.6	8.7 ± 5.6
5.	FPG, mmol/L (mean ± SD)	11.1 ± 2.9	11.2 ± 2.9	10.7 ± 2.8
6.	PPG, mmol/L (mean ± SD)	16.3 ± 3.5	16.3 ± 3.5	15.8 ± 3.6
7.	HbA _{1c} , % (mean ± SD)	9.4 ± 1.4	9.3 ± 1.4	9.5 ± 1.6
8.	Weight, kg (mean ± SD)	70.9 ± 11.0	70.9 ± 10.9	70.9 ± 11.3

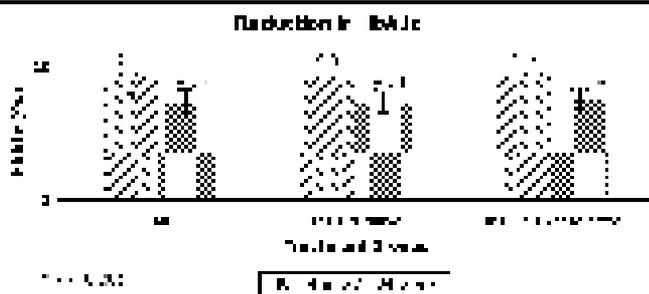


Fig. 1 : Reduction in HbA_{1c}

data from the A₁chieve[®] study in patients with T2DM who were started with or switched to insulin detemir in addition to OADs.

Patients were evaluated for adverse events. Similarly Glycemic parameters [HbA_{1c}, fasting plasma glucose (FPG), post-prandial plasma glucose (PPG)] were analyzed at baseline and after 24 weeks of treatment. Quality of life was analyzed by using the EQ-5D and EQ-VAS questionnaire at baseline and at the end of the study, description of these questionnaires have been described in detail in other article in this issue and will not be described here.

Statistical Methods

Results for continuous measurements are presented with mean ± SD and results for categorical measurements are presented by number (%). The paired t-test was applied to find the significance of change of continuous variables at baseline and after 24 weeks. The difference was considered as significant with a p value of < 0.05.

Results

We analyzed a sub-group of 2707 patients with T2DM treated with insulin detemir in addition to OADs, out of which 2336 (86.26%) patients were insulin naïve and 371 (13.71%) patients were insulin experienced (Table 1). The mean age was 50.5 years and mean duration of diabetes was 5.6years.

No adverse drug reaction was reported over 24 weeks. One serious adverse event (SAE) was noted with no withdrawal of drug. At baseline, 7.5% patients reported overall hypoglycemia with 1.29 events/patient year. The percentage of patients experiencing overall hypoglycemia was reduced to 0.9% (0.15 events/patient year) at 24 weeks. Similarly the percentage of patients experiencing nocturnal hypoglycemia and major hypoglycemia was reduced from 2.6% (0.37 event/patient

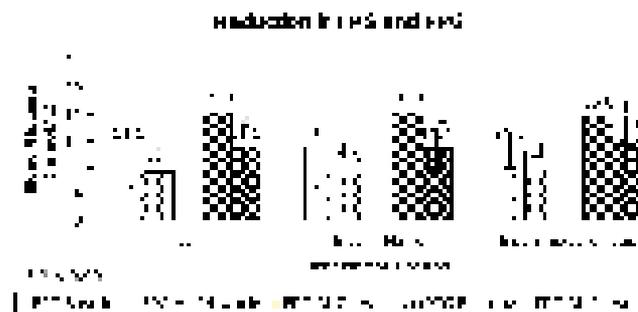


Fig. 2 : Reduction in FPG and PPG

Table 2 : Improvement in Lipid profile

	Number of patients	Baseline	Week 24	Change from baseline to week 24	p value
HDL-C, mmol/L (mean ± SD)	298	1.0 ± 0.3	1.1 ± 0.3	0.0 ± 0.3	0.88
LDL-C, mmol/L (mean ± SD)	292	3.1 ± 0.9	2.7 ± 0.8	-0.4 ± 0.6	< 0.001
TG, mmol/L (mean ± SD)	277	2.1 ± 0.9	1.8 ± 0.7	-0.3 ± 0.6	< 0.001
TC, mmol/L (mean ± SD)	151	5.1 ± 1.2	4.7 ± 0.9	-0.4 ± 0.7	< 0.001

HDL-C: High density lipoprotein, LDL-C: Low density lipoprotein, TG: Triglyceride; TC: Total Cholesterol. Table represents observations of all patients prescribed with insulin detemir which includes insulin naïve and insulin experienced patients.

year) and 0.5% (0.08 event/patient year) to 0% (0 event/patient) respectively after 24 weeks of insulin detemir therapy. Minor hypoglycemia was reduced from 7.4% (1.21 event/patient year) to 0.9% (0.15 event/patient) of patients. Thus insulin detemir was well tolerated.

After 24 weeks treatment with insulin detemir, overall reduction from baseline in HbA_{1c} of 2.1% was noticed (p<0.001). A mean reduction in HbA_{1c} of 2.1% (p<0.001) and 2.0% (p<0.001) was observed in insulin-naïve and insulin-experienced groups respectively (Figure 1).

Similarly significant reductions in FPG and PPG were noticed following 24 weeks treatment of insulin detemir. The mean reduction in FPG was 3.9 mmol/L (P <0.001) and 3.1 mmol/L (p <0.001) in the insulin-naïve and insulin-experienced groups, respectively. Similarly, a mean reduction in PPG of 5.4 mmol/L (P<0.001) and 3.5 mmol/L (P<0.001) was also seen in the insulin-naïve and insulin-experienced groups, respectively (Figure 2). At 24 weeks, 24.4% patients achieved the ADA target of HbA_{1c} <7% and 14.3% patients achieved AACE target of HbA_{1c} <6.5%.

Following 24 weeks of insulin detemir therapy a significant improvement in LDL, serum triglyceride and total cholesterol was noticed (Table 2). After 24 weeks of treatment mean 0.5 kg weight reduction was noted in this cohort (N=2707; p < 0.001).

A significant improvement in quality of life (EQ-5D, EQ-VAS) indices was noticed over 24 weeks of insulin detemir therapy

Table 3 : Improvement in quality of life indices

	Number of patients	Baseline	Week 24	Change from baseline to week 24	p value
ED-5D (mean ± SD)	2707	0.49 ± 0.28	0.80 ± 0.17	0.31 ± 0.29	<0.001
EQ-VAS	2100	55.2 ± 14.2	77.0 ± 9.4	21.7 ± 16.7	<0.001

Table represents observations of all patients prescribed with insulin detemir which includes insulin naive and insulin experienced patients.

(Table 3).

Pre-study 371 patients were receiving insulin out of which 50.7% patients were receiving twice daily and 39.4% patients were receiving once a daily while remaining were receiving thrice or more than thrice a day. At baseline, the majority of patients (81.5%) received insulin detemir once daily and few patients (18%) received it twice daily; very few patients received it thrice daily. The mean dose of insulin prior to study was 0.32 U/kg, at baseline mean insulin detemir dose was 0.26 U/kg and mean dose at week 12 and 24 was 0.27U/kg and 0.28/kg respectively.

Discussion

In this post-hoc analysis we evaluated safety and efficacy of insulin detemir in patients receiving OADs or other insulin and not achieving glycemic target.

This sub-group analysis reported following interpretations: In Indian patients with T2DM insulin detemir in addition to OADs was well tolerated. In subjects with high baseline glycemic parameters had clinically significant reductions in all glycemic parameters, together with improvements in the lipid profile and no significant weight gain and overall weight reduction of 0.5 kg. A robust reduction in HbA_{1c} of 2% with low incidence of hypoglycemia was noticed following 24 weeks of treatment. These interpretations may be of clinical significance.

Due to the progressive nature of the disease, many patients with T2DM ultimately require insulin to achieve glycemic control in addition to their existing anti-diabetic therapy. Basal insulin therapy provides constant low levels of insulin and thus maintains normal blood glucose level with minimal fluctuations. Usually, long acting basal insulin is administered either at bedtime or in the morning. Unfortunately in the majority of Indian patients insulin is started late during the course of disease with little residual beta cell function due to various factors viz:

clinical inertia, fear for hypoglycemia, accessibility to medical care etc.

Insulin detemir is a neutral, non-crystalline, clear, soluble insulin preparation with proven benefits in its efficacy and safety. Various clinical studies have demonstrated improvements in glycemic control, with lower risk of weight gain and hypoglycemia compared with NPH insulin and glargine.⁶

This study involved a large sample size, and a heterogeneous population across multiple centres and provides real-life experience with clinical management of diabetes in India; however, the observational nature of the study must be kept in mind while interpreting the results.

Conclusion

Starting or switching to insulin detemir was safe and associated with improved glycemic control in patients with T2DM not achieving their glycemic targets. Following the addition of insulin detemir, a clinically significant proportion of patients achieved ADA goals with favorable tolerability and improvement in quality of life. This post-hoc analysis in a real-life situation supports the use of basal insulin in patients taking antidiabetic drugs not achieving glycemic targets.

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