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Clinical experience with insulin detemir: Results from the Indonesian cohort of the international A_1chieve study

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ABSTRACT

Aim: To determine the safety and efficacy of insulin detemir in Indonesian patients with type 2 diabetes (T2D) as a sub-analysis of the 24-week, prospective, multinational, non-interventional A_1chieve study.

Methods: This study included 477 Indonesian T2D patients starting insulin detemir at the discretion of their physicians. Safety and efficacy was measured in routine clinical practice at baseline, interim (around 12 weeks from baseline) and final (around 24 weeks from baseline) visit.

Results: At baseline the mean age, duration of diabetes and mean BMI were 55.3±8.5 years, 5.9±4.0 years and 24±3.6 kg/m^2, respectively. Of these patients, 78% were insulin-naive and 22% were prior insulin users. Glycaemic control was poor at baseline. After 24 weeks, significant reductions were observed in mean HbA_{1c} (2.2%, $p < 0.001$), fasting plasma glucose (90.0 mg/dL, $p < 0.001$) and postprandial plasma glucose (115.4 mg/dL, $p < 0.001$) levels, in the entire cohort. Similar significant reductions were also seen in insulin-naive patients and prior insulin users. In the entire cohort, 32.5% patients achieved HbA_{1c} levels <7.0% while 32.0% insulin-naive patients and 33.9% prior insulin users achieved this target after 24 weeks. No hypoglycaemic events were reported in the entire cohort. Modest increase in body weight was noted in the insulin-naive group, while mean body weight decreased in prior insulin users after 24 weeks of insulin detemir therapy.

Conclusion: This sub-analysis suggests that insulin detemir can be a safe and effective option for initiating insulin therapy in people with T2D in Indonesia.

1. Introduction

The prevalence of type 2 diabetes (T2D) is increasing worldwide, but the increase is particularly rapid in Asian countries. This current trend also proposes that 60% of the world's diabetic population will be in Asia. The epidemic increase in T2D is primarily attributed to lifestyle changes as a result of rapid socioeconomic growth especially in countries including Indonesia that report a high rate of urbanization [1]. The International Diabetes Federation places Indonesia among the top 10 countries worldwide with a diabetes prevalence of 7.6 million in 2012 [2].

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The stepwise approach in the management of T2D includes lifestyle modifications, use of oral glucose lowering drugs (OGLDs) and insulin. Due to the progressive nature of the disease, the majority T2D patients are unable to maintain HbA_{1c} targets on a regimen of lifestyle changes and OGLDs, alone [3]. Results from an epidemiological study demonstrated that HbA_{1c} values were as high as 9.0% (75 mmol/mol) and 10.0% (86 mmol/mol) before treatment intensification to combination OGLDs or the initiation of insulin, respectively [4]. In patients with severe β-cell dysfunction, exogenous insulin treatment is essential for controlling glycaemia and reducing risks of diabetes-related complications and mortality [5]. The American Diabetes Association 2012 guidelines recommend insulin therapy, with or without additional agents, in newly diagnosed patients having markedly symptomatic and/or elevated blood glucose levels or HbA_{1c}, from the outset [6].

Insulin replacement therapies are limited in their capacity to match physiologic conditions due to the complexity of normal insulin secretion patterns and various pharmacokinetic factors. For example, intermediate-acting preparations, or neutral protamine Hagedorn (NPH) insulin, are associated with unpredictable peaks. Furthermore, patients and healthcare providers are often reluctant to initiate insulin due to concerns over injections, fear of hypoglycaemia and additional weight gain, and also because insulin treatment is perceived as complex [7]. The reluctance of physicians and patients to initiate insulin therapy can contribute to periods of poor glycaemic control in individuals with T2D, ultimately increasing the risk of micro- and macrovascular complications.

The newly introduced insulin analogues help patients and physicians overcome these barriers [5]. It has been shown that a very simple approach of adding a basal insulin analogue to a current OGLD regimen can improve glycaemic control with a reduced frequency of hypoglycaemia in insulin-naive T2D patients [8].

Insulin detemir, a biosynthetic long-acting insulin analogue, has been developed to provide a predictable, protracted and flat pharmacodynamic profile, limiting the risk of hypoglycaemia. It is structurally modified to self-associate and bind reversibly to albumin and is soluble at a neutral pH. These characteristics mediate insulin detemir's slow absorption from the subcutaneous administration site and result in a protracted duration of action compared with conventional human insulin formulations. Also, insulin detemir has duration of action of up to 24 hours [9]. Data from randomized controlled trials (RCTs) and observational studies have shown that use of insulin detemir significantly reduces HbA_{1c} and blood glucose levels, is associated with a very low risk of hypoglycaemia and have a weight neutral effect [3,8,10–12].

The beneficial effects reported in RCTs require validation during routine clinical practice in large patient populations, with varying stages of the disease, having other co-morbidities and on multiple medications [13]. To evaluate the clinical safety of various insulin analogues in people with T2D in routine clinical practice, the multinational A_1chieve trial was conducted [3]. Complete study results are now available online under www.A1chieve.com. The study was carried out in 28 countries across four continents. Here we present a subgroup analysis of the A_1chieve study which examined the safety and efficacy of insulin detemir in the Indonesian T2D population. It also evaluated the effect of insulin detemir on quality of life in individuals with T2D.

2. Methods

2.1. Study design

A_1chieve [3] was a 24-week, international, prospective, non-interventional study of Indonesian T2D patients who had begun using biphasic insulin aspart 30 (premix), insulin aspart, or insulin detemir with or without OGLDs. This sub-analysis was conducted to determine the safety and efficacy of insulin detemir in T2D patients recruited between October 2009 and August 2010 at 65 centers in Indonesia. The local ethics committee approval was obtained and all patients signed informed consent. The prescription for insulin detemir and use of concurrent OGLDs as well as all subsequent treatment decisions was at the discretion of the physician in accordance with local practice. Patients were free to withdraw from the study at any time. There were no defined study-related procedures. Safety and effectiveness of therapy were determined from measurements made at usual clinic visits. Data points were captured at baseline, interim (around 12 weeks from baseline) and final (around 24 weeks from baseline) visit. The time period of 4 weeks prior to the baseline visit, was defined as a pre-study period. Information was gathered from the physician's usual clinical notes, the participants' recall and self-monitoring glucose diary at each visit and transferred to a standard case report form (CRF).

2.2. Inclusion and exclusion criteria

All patients with T2D, who had not used any of the study insulins previously or who had been started on any of the insulins in the 4 weeks prior to the study, were included in the study. Patients who had once participated in the study were not enrolled again during the study period. Also patients with hypersensitivity to the study insulins or excipients were excluded, as were the women who were pregnant, breast-feeding, or who intended to become pregnant within 6 months of the study.

2.3. Primary and secondary endpoints

The primary endpoint was the number of serious adverse drug reactions (SADRs) including major hypoglycaemic events recorded from baseline to final visit. Secondary safety endpoints included the change in the number of minor, major, and nocturnal hypoglycaemic events between baseline and the final visit. If the study insulin was started 4 weeks before the baseline visit date, the number of hypoglycaemic events in the last 4 weeks before the final visit was compared to the number of events in the

Table 1 – Demography of the Indonesian cohort

Parameter	Entire cohort (n = 477)	Insulin-naive (n = 372)	Prior insulin users (n = 105)
Gender (male/female), %	49.3/50.7	48.7/51.3	51.4/48.6
Age, years	55.3 (8.5)	55.1 (8.8)	55.8 (7.6)
Duration of diabetes, years	5.9 (4.0)	5.9 (4.4)	5.7 (2.7)
Body weight, kg	62.8 (10.6)	61.6 (11.0)	65.8 (8.2)
BMI, kg/m^2	24.0 (3.6)	23.5 (3.7)	25.5 (2.9)
HbA_{1c}, %	9.5 (1.7)	9.5 (1.7)	9.3 (1.4)
HbA_{1c}, mmol/mol	80 (19)	80 (19)	78 (15)

BMI, Body Mass Index.
Data are presented as mean (SD) unless specified otherwise.

last 4 weeks before the baseline visit. Secondary efficacy endpoints included change in: (1) HbA_{1c}, fasting plasma glucose (FPG), and postprandial plasma glucose (PPPG) at interim visit and final visit compared with baseline; (2) Body weight, blood pressure, and serum lipids at final visit compared with baseline; (3) Health-related quality of life (QoL).

Major hypoglycaemia was defined as an event with severe central nervous system symptoms consistent with hypoglycaemia in which the affected individual was unable to treat himself/herself and had one of the following characteristics: (1) plasma glucose < 3.1 mmol/L or 56 mg/dL or (2) reversal of symptoms after either food intake or glucagon or intravenous glucose administration. All other hypoglycaemic events were classified as minor. Hypoglycaemic events occurring between bedtime and before getting up in the morning were classified as nocturnal.

QoL was measured using the EQ-5D questionnaire and EQ visual analogue scale (EQ VAS) at baseline and after 24 weeks of therapy with insulin analogues. EQ-5D consisted of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) having three severity levels each. EQ VAS is a standard vertical 20 cm scale on which the best health state is marked as 100 and the worst state as 0.

2.4. Statistical methods

The sample size calculation for the entire A_1chieve cohort was based on the number of patients (60,000) exposed for 6 months required to confirm a frequency of $\geqslant$15 events/100,000 patient-years of any one SADR, including major hypoglycaemic events, at the 95% confidence level. Statistical analyses were performed for the entire cohort and for the entire cohort classified as insulin-naive or prior insulin users. Descriptive statistics were used to summarize continuous variables and frequency tables (number and percentage) were used for discrete variables. All statistical analyses were two-sided, with 5% significance level, unless otherwise stated. For the change in hypoglycaemia from baseline, the percentage of patients reporting at least one event was analyzed using McNemar's test. The change from baseline in HbA_{1c}, FPG, PPPG, SBP, body weight, blood lipids and QoL was analyzed using a paired t-test using baseline and end-of-study values. Data analyses were performed by Novo Nordisk using SAS (Version 9.1.3).

3. Results

3.1. Demography of the Indonesian cohort

A total of 477 patients were recruited and analyzed in the insulin detemir subgroup of the Indonesian cohort, out of which 372 were insulin-naive (including 22 treatment-naive) and 105 patients were prior insulin users. The treatment-naive group included those patients who had not received any anti-diabetic therapy (insulin or OGLD) prior to enrolment. The male/female ratio was equal in all groups. The average duration of diabetes was 5.9 years for entire cohort. The mean body weight was 62.8 kg. Detailed demographic characteristics are reported in Table 1.

Metformin was the most commonly prescribed OGLD pre-study (74.9%), at baseline (72.6%) and at the end of study (85.8%). Sulfonylureas were the second most commonly prescribed OGLDs (69.4%, 38.6% and 40.9% pre-study, at baseline and at Week 24, respectively). Thiazolidinediones were prescribed in 11.4% of patients pre-study, 3.2% at baseline and 0.5% at Week 24. Combinations of $\geqslant$2 OGLDs were prescribed in 39.6% patients at baseline and 26% patients at the end of study.

3.2. SADRs and hypoglycaemia

No SADRs were reported during the study. At baseline, overall hypoglycaemic episodes were experienced by 5.9%, patients in the entire cohort, 5.1% insulin-naive patients and 8.6% prior insulin users. In the entire cohort, 0.2% and 5.7% patients reported major and nocturnal hypoglycaemic episodes respectively at baseline. After 24 weeks of insulin detemir therapy no hypoglycaemic events were reported in this cohort (Table 2).

3.3. Glycaemic control and insulin detemir dosage

The entire cohort had poor glycaemic control at baseline with a mean±SD HbA_{1c} 9.5±1.7% (80±11 mmol/mol). Insulin-naive patients had mean HbA_{1c} levels of 9.5±1.7% (80±11 mmol/mol) while the prior insulin users had HbA_{1c} levels of 9.3±1.4% (78±15 mmol/mol). Baseline FPG for the

Table 2 – Proportion of patients experiencing hypoglycaemia

Hypoglycaemia	Percent with at least one event			
		Entire cohort (n = 477)	Insulin naive (n = 372)	Prior insulin users (n = 105)
Overall	Baseline	5.9	5.1	8.6
	24 weeks	0	0	0
	p	<0.0001	<0.0001	0.0027
Minor	Baseline	5.9	5.1	8.6
	Week 24	0	0	0
	p	<0.0001	<0.0001	0.0027
Major	Baseline	0.2	0.3	0
	Week 24	0	0	0
	p	0.3173	0.3173	–[a]
Nocturnal	Baseline	5.7	4.8	8.6
	Week 24	0	0	0
	p	<0.0001	<0.0001	0.0027

p-values are from McNemar's test on paired proportions of patients experiencing hypoglycaemia.
[a] No value available.

Table 3 – Glucose control, insulin dose and body weight

Parameter		Entire cohort (n = 477)	Insulin naive (n = 372)	Prior insulin users (n = 105)
HbA_{1c}, %	n	175	147	28
	Baseline	9.5 (1.7)	9.5 (1.7)	9.3 (1.4)
	Week 24	7.3 (1.0)	7.3 (1.0)	7.1 (0.7)
	p	<0.001	<0.001	–[a]
HbA_{1c}, mmol/mol	n	175	147	28
	Baseline	80 (19)	80 (19)	78 (15)
	Week 24	57 (11)	57 (11)	54 (8)
	p	<0.001	<0.001	–[a]
Proportion with HbA_{1c} <7%, %	Baseline	2.7	2.6	3.2
	Week 24	32.5	32	33.9
Fasting plasma glucose, mg/dL	n	383	317	66
	Baseline	209.0 (66.0)	219.1 (63.3)	160.5 (56.7)
	Week 24	119.0 (20.6)	118.5 (20.9)	121.2 (18.9)
	p	<0.001	<0.001	–[a]
Post-prandial plasma glucose, mg/dL	n	377	295	82
	Baseline	263.7 (81.6)	263.0 (78.1)	266.0 (93.5)
	Week 24	148.3 (39.6)	147.8 (41.0)	149.8 (34.3)
	p	<0.001	<0.001	–[a]
Insulin dose, U/kg	Pre-study	0.37 (0.20)	–	0.37 (0.20)
	Baseline	0.22 (0.16)	0.21 (0.08)	0.26 (0.30)
	Week 24	0.34 (0.17)	0.34 (0.17)	0.36 (0.18)
Body weight, kg	n	431	337	94
	Baseline	62.5 (10.6)	61.6 (11.0)	65.8 (8.2)
	Week 24	63.2 (9.3)	62.6 (9.5)	65.4 (7.9)
	p	0.003	<0.001	0.351

Data are presented as mean (SD).
[a] p-value not reported since n < 100.

entire cohort was 209.0±66.0 mg/dL. Insulin-naive patients and prior insulin users had mean FPG levels of 219.1±63.3 and 160.5±56.7 mg/dL, respectively. PPPG levels were also high at baseline, 263.7±81.6 mg/dL for the entire cohort and 263.0±78.1 and 266.0±93.5 mg/dL for insulin-naive and prior insulin users groups, respectively (Table 3).

After 24 weeks of treatment with insulin detemir, there was significant improvement in all parameters of glycaemic control. Mean HbA_{1c} level for the entire cohort was reduced to 7.3±1.0% (57±11 mmol/mol) with a change of 2.2% (24 mmol/mol) from baseline ($p < 0.001$). Insulin-naive patients showed a significant improvement of 2.2% (24 mmol/mol) from baseline ($p < 0.001$). Prior insulin users also showed a similar HbA_{1c} improvement of 2.2% (24 mmol/mol) from baseline to Week 24. On further analysis into insulin-naive group, a reduction of

1.7±2.0%, 19±22 mmol/mol (from 8.2±1.8 [66±20 mmol/mol] to 6.6±1.2% [49±13 mmol/mol]) was seen in treatment naive patients. Mean FPG and PPPG levels decreased significantly in the entire cohort and in the insulin-naive group ($p < 0.001$). Prior insulin users also experienced a reduction of 39.3±51.6 mg/dL in FPG and 116.2±84.9 mg/dL in PPPG after 24 weeks of therapy. More than 32% patients were able to achieve target HbA_{1c} of <7.0% (53 mmol/mol) at the end of study (Table 3).

Among insulin-naive patients, the mean starting dose of insulin detemir at baseline was 0.21±0.08 U/kg which was titrated to 0.34±0.17 U/kg during the course of 24 weeks. The baseline insulin detemir dose in prior insulin users was titrated to 0.36±0.18 U/day at Week 24 from a baseline dose of 0.26±0.30 U/kg (Table 3).

3.4. Body weight, blood lipids and blood pressure measurements

Prior insulin users had a mean weight loss of 0.4 kg after 24 weeks while the entire cohort and the insulin-naive group showed a mean weight gain of 0.7 kg and 0.9 kg, respectively (Table 3). These small changes in weight were clinically insignificant. Total cholesterol levels decreased from 5.4 to 4.7 mmol/L after 24 weeks (–0.7 mmol/L) and LDL cholesterol levels decreased from 3.3±1.1 to 2.8±0.7 mmol/L (–0.5 mmol/L) in the entire cohort. Reduction in systolic blood pressure, from 129.2±15.9 to 123.5±13.9 mmHg, was significant for the entire cohort (–5.7 mmHg, $p < 0.001$).

3.5. QoL

EQ VAS scores increased significantly by 11.6 points ($p < 0.001$) i.e. from 70.3 points at baseline to 81.9 points after 24 weeks. The highest improvement (12.4 points, $p < 0.001$) was seen in insulin-naive group. A significantly greater proportion of subjects reported that they were not as anxious or depressed at 24 weeks as compared to baseline (86.3% vs 74.6%, $p < 0.0001$). The majority of patients (96.4%) stated that they have no problems with self-care after 24 weeks, as compared to 87.7% at the baseline ($p < 0.0001$). A total of 74.6% patients reported no problems with performing their usual activities at the baseline, while the number rose to 90.8% at the end of study ($p < 0.0001$). No pain or discomfort was reported in 86.1% patients at Week 24 as compared to 69.1% patients at baseline ($p < 0.0001$).

4. Discussion

Basal insulin with or without OGLDs is an effective option for insulin initiation. Long-acting insulins, such as insulin detemir, could be regarded as one of the foundation insulins for building glycaemic control, especially as a once-daily regimen. However, data on the safety and effectiveness of insulin detemir was not available in the Indonesian population. This is the first study to evaluate safety and efficacy of insulin detemir and its effect on quality of life in Indonesian T2D patients.

Overall, this Indonesian T2D cohort demonstrated poor glycaemic control with HbA_{1c} in the range of 9.5% (80 mmol/mol) at baseline. This observation was also made in the DiabCare study suggesting an immediate need to intensify pharmacotherapy while adopting multi-disciplinary T2D management approaches in Indonesia [14]. In order to effectively reduce the micro/macrovascular complications of diabetes, the American Diabetes Association suggests a target HbA_{1c} <7.0% (53 mmol/mol) [6]. At baseline, only 2.7% patients had HbA_{1c} levels <7.0% (53 mmol/mol) while after 24 weeks of insulin detemir therapy 32.5% patients achieved the target.

Insulin detemir has been shown to reduce HbA_{1c} levels effectively. The 26-week, randomized, controlled PREDICTIVE study reported a decrease in mean HbA_{1c} value from 8.9% (74 mmol/mol) to 7.8% (62 mmol/mol) with once-daily insulin detemir [15]. In another randomized, open-label, multi-center trial of patients with poorly controlled T2D, morning (pre breakfast) and evening insulin detemir doses were associated with 1.58% (17 mmol/mol) and 1.48% (16 mmol/mol), reductions in HbA_{1c} respectively [16]. TITRATE, a 20-week, randomized, controlled, open-label, multi-center, treat-to-target study of insulin-naive T2D patients, showed a 1.2% (13 mmol/mol) reduction in HbA_{1c} levels [17]. The current sub-group analysis from the A_1chieve study shows a 2.2% (24 mmol/mol) decrease in HbA_{1c} levels in Indonesian patients. This decrease will have multifold effects on risk reduction for diabetic complications as each 1% reduction in mean HbA_{1c} has been shown to reduce the risk of deaths by 21%, the risk of myocardial infarction by 14% and reduce microvascular complications by 37% [18]. Additionally, this Indonesian cohort of the A_1chieve study showed a clinically significant decrease of 90.0 mg/dL (5.0 mmol/L) in FPG levels with a numerically higher decrease of 100.6 mg/dL (5.6 mmol/L) in the insulin-naive group. A subgroup analysis of the PREDICTIVE study had shown a reduction of 3.7 mmol/L in FPG after 14 weeks of insulin detemir treatment [19]. Similarly, FPG improved from 10.8 to 7.1 mmol/L in a 52 weeks multinational, randomized, open-labeled treat-to-target trial comparing insulin detemir with insulin glargine when administered as add-on to OGLDs in insulin-naive patients [20].

Hypoglycaemia remains a major side effect of attempts to improve glycaemic control in diabetes. The deleterious effects of hypoglycaemia in diabetes include vasoconstriction, tachycardia, and platelet aggregation due to the sympatho-adrenal epinephrine response. All of these effects are thought to increase risk for acute coronary events and sudden cardiac death in high-risk cardiovascular patients with diabetes suffering frequent or severe hypoglycaemia [21–23]. Minimizing hypoglycaemia, is thus of utmost importance when treating diabetes and considering appropriate glycaemic goals patients. Across the trials that reported incidences of hypoglycaemic event in patients with type 1 diabetes or T2D, episodes of major hypoglycaemia were documented in fewer than 10% of patients receiving insulin detemir [24]. In the A_1chieve study, 5.9% of the 66,726 patients enrolled experienced at least

one episode of hypoglycaemia during the study [3]. In this Indonesian cohort none of the patients experienced hypoglycaemia. However, due to the observational study design, recall bias may have led to an under-reporting of hypoglycaemic events.

Weight gain is also an important concern as a potential side effect of treatment for patients with T2D receiving certain oral therapies or insulin. The increase in body weight associated with anti-diabetic therapy may blunt the clinical benefit of improved glycaemic control associated with such therapy. A report of data pooled from two randomized, parallel group trials of 22 and 24 weeks' duration reported that patients treated with insulin detemir had minimal weight gain (mean <1 kg) regardless of their BMI at entry; whereas, in patients treated with NPH insulin, weight gain increased with BMI after treatment (mean weight gain approx. 2.4 kg) [25]. In this Indonesian cohort receiving insulin detemir, the mean weight gain was 0.7 kg. Interestingly, prior insulin users actually lost 0.4 kg of weight. The decreased risk of hypoglycaemia with insulin detemir and a more consistent and reliable delivery of the desired dose, can be a possible mechanism that contributes to decreased defensive snacking and in turn helps to limit weight gain. Improved lipid profile and blood pressure control at the end of the study further reduce cardiovascular risk in T2D patients.

Duration and type of diabetes are not consistently associated with quality of life. It is difficult to ascertain which part of disease or management affects the quality of life. However, having better glycaemic control is associated with better quality of life [26]. Statistically significant improvement was observed in most measures of quality of life with insulin detemir in the Indonesian cohort. Better glycaemic control with decreased episodes of hypoglycaemia may be the contributors in improved quality of life.

Although this subgroup analysis has provided novel insight about T2D population status, safety and efficacy of insulin detemir in Indonesia, being an observational study, there are some inherent limitations. Concomitant medications were not controlled. The study was non-randomized and no standardized treatment protocol was enforced. The study lacked a control arm and most safety parameters were based on participant recall or diaries.

In conclusion, this study has shown that insulin detemir was effective in poorly controlled T2D patients from Indonesia. The safety and efficacy of insulin detemir has been established in both insulin-naive patients as well as prior insulin users. Furthermore, it may also help in improving other metabolic parameters and improve patients' QoL. The observations of this study may help overcome the fear of hypoglycaemia and clinical inertia in early initiation of insulin in T2D patients.

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Conflict of interest statement

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