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Effect of Insulin Detemir (Levemir®) on Risk of Hypoglycaemia and Glycaemic Parameters: Experience from Real Life Practice in Indonesian Patients with Diabetes Mellitus

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Abstract

Objective. To evaluate the safety and efficacy of insulin detemir in patients with diabetes mellitus in Indonesia.

Methods. This was a multi-centre, prospective, 12-week observational study in patients with diabetes mellitus conducted in Indonesia.

Results. A non-randomized sample of 1290 patients with diabetes mellitus in which most of them were type 2 diabetes (1285 patients, 57.4% males, mean age 54.1 ± 9.0 years, mean BMI 23.5 ± 4.1 kg/m^2, mean duration of diabetes 6.5 ± 4.9 years) were recruited from 121 sites. No serious adverse drug reactions (SADRs) including major hypoglycaemic episodes were reported at 12 weeks. The rate of total and major hypoglycaemic episodes decreased from 0.0248 to 0.0031 episodes/patient years and from 0.0022 to 0 episodes/patient years from baseline to 12 weeks, respectively. Treatment with insulin detemir was associated with a reduction in HbA_{1c} of -2.0%-point (95% CI, -2.13 to -1.93) from baseline to 12 weeks. Insulin detemir also improved FPG. A slight increase of 0.12 kg (95% CI, -0.05 to 0.29) in body weight was observed from baseline to 12 weeks.

Conclusions. 12-week treatment with insulin detemir was safe and well-tolerated in Indonesian patients with type 2 diabetes. It improved glycaemic control, decreased the risk of hypoglycaemia and was relatively weight neutral.

Key Words: Insulin detemir; Indonesia; Safety, Efficacy

Introduction

Diabetes mellitus is a chronic and progressive disease, and is associated with a series of macro- and micro-vascular complications. The Diabetes Control and Complications Trial (DCCT) demonstrated that good metabolic control, resulting from intensive insulin therapy, reduced the risk of development and/or progression of retinopathy, nephropathy and neuropathy in type 1 diabetes[1]. The United Kingdom Prospective Diabetes Study (UKPDS) and other studies showed that intensive glycaemic control in type 2 diabetes could significantly reduce the risk of development and/or deterioration of micro-vascular complications[2,3] and may improve cardiovascular outcomes[3]. An important new insight is the existence of so-called 'glycaemic metabolic memory.' Both DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) and UKPDS follow-up studies[4,5] demonstrated that the level of glucose control in the early years of disease would impact dramatically on the development of later complications. In both studies, in comparison with patients who were not optimally controlled, patients with tighter glycaemic control during the study would develop less micro- and macrovascular complications more than 10 years after discontinuation of the study. These observations emphasize the need to control glycaemia as tight and as early in the disease process as possible.

Insulin treatment is the cornerstone of diabetes management. It is the only means of achieving glycaemic control in insulin deficient patients with type 1 diabetes. It is also the only effective treatment for many patients with type 2 diabetes when deterioration of beta cells has progressed to the point that diet and oral agents have become inadequate to control hyperglycaemia. However, the main limitations to human insulin treatment include weight gain and an increased risk of hypoglycaemia. Furthermore, the desired relatively constant basal insulin level is difficult to obtain with the currently available intermediate-acting insulin preparations.

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Insulin detemir is a long-acting insulin analogue with improved pharmacological properties providing 24 hour basal insulin coverage. It has been demonstrated that insulin detemir treatment can result in more predictability (lower within-patient variability) of fasting blood glucose values[6,7], reduction of hypoglycaemic episodes[8,9], neutral or less weight gain both in type 1 diabetes and type 2 diabetes[6-9].

Asia is the major site of a rapidly emerging diabetes epidemic[10]. India and China will remain the two countries with the highest numbers of people with diabetes (79.4 million and 42.3 million, respectively) by 2030[10]. In a national study from June 2007 through May 2008 which was designed to estimate the prevalence of diabetes among Chinese adults, 92.4 million adults had diabetes[11]. Additionally, among top ten countries with bigger number of patients with diabetes, four of them are located in Asia: Indonesia, Pakistan, Bangladesh, and the Philippines. The prevalence of diabetes in urban Indonesia was 5.7%, consisting of diagnosed diabetes mellitus 1.5%, estimated undiagnosed diabetes mellitus 4.2% and IGT 10.2%.[12] Due to the high prevalence in Indonesia, diabetes will be a heavy social burden for the country. Until now no clinical data on use of insulin detemir in Indonesian patients was available. Therefore, the study was undertaken to evaluate the safety and effectiveness of treatment of insulin detemir in Indonesian patients with type 1 or type 2 diabetes in clinical setting.

Methods and Materials

Study design

This was a multi-centre, prospective 12-week observational study in patients with type 1 or type 2 diabetes mellitus conducted in Indonesia. Data was collected from the patients' records or self-monitored blood glucose diary or patients' own recollection at baseline and at approximately 12 weeks after starting insulin detemir. Patients were encouraged to comply with the protocol and come for the follow-up visits as per the schedule. All patients were to be prescribed insulin detemir at the discretion of the physician. There was no comparator group and patients served as their own controls (from baseline). Written informed consent was obtained for all patients before any study-related activity. The study was performed in accordance with the Declaration of Helsinki[13] and International Conference on Harmonisation Good Clinical Practice[14].

Patients

Patients with type 1 or type 2 diabetes mellitus including newly diagnosed patients, were included in this study. Patients who were unlikely to comply with protocol, e.g. uncooperative attitude, inability to return for the final visit, patients who had hypersensitivity to insulin detemir or any of the excipients were excluded from the study. Patients were to be withdrawn from the study if they became pregnant or at the discretion of the investigator. At all visits, the number of hypoglycaemic episodes experienced during the past 4 weeks, including the timing (daytime vs. nocturnal) and the number of major episodes, and the 6 most recent fasting plasma glucose values (from patient's self-monitored blood glucose diary) were recorded. Any adjustments to the timing and dose of insulin detemir therapy, including any change to concomitant insulin or oral hypoglycaemic agents were recorded.

Endpoints

The primary endpoint was the incidence of serious adverse drug reactions (SADRs), including major hypoglycaemic episodes, during 12 weeks of insulin detemir therapy. The secondary endpoints included the number and incidence of hypoglycaemic episodes in the 4 weeks preceding the final visit (12 weeks); incidence of adverse drug reactions (ADRs) and number of serious adverse event (SAE), change in body weight, HbA_{1c}, fasting plasma glucose (FPG) and the variability in FPG.

Major hypoglycaemic episode was defined as an episode with blood glucose <50 mg/dl (2.8 mmol/l), and with severe central nervous system symptoms consistent with hypoglycaemia in which the patient was unable to treat himself/herself, or reversal of symptoms after either food intake or glucagon or intravenous glucose administration.

Statistical analyses

Statistical analyses were performed for all patients, previous treatment with oral anti-diabetic drugs (OAD) and previous treatment with OAD+insulin. The summary of the baseline characteristics and safety data and the analysis of the efficacy outcome variables were based on Full Analysis Set (FAS), which consisted of all patients with a baseline visit, had been treated with insulin detemir at least once and did not use insulin detemir before the start of the study.

All results were interpreted in a descriptive manner. Hypoglycaemic events were expressed as absolute number and the number of episodes/ patient years. All testing used two-sided tests with significance level α= 0.05 and were performed using SAS, Version 9.1 (SAS Institute, Cary, NC).

Results

Baseline demographics and diabetes therapy

Patient demography is summarised in Table 1. Total 1290 patients were recruited in this study – 5 with type 1 diabetes and 1285 with type 2 diabetes. As most of the patient population had type 2 diabetes, this article presents data of type 2 diabetes patients only. In these 1285 patients, 52 patients were on no prior therapy, 832 patients (65.2%) were on only OAD and 232 patients (18.1%) were on OAD+Insulin. However, there were 582 patients (out of 832) who had OAD only at recruitment, shifted to OAD + basal insulin at baseline and continued

Table 1. Baseline Characteristics – type 2 diabetes

	Patients previously on 'OAD + insulin' therapy	Patients previously on 'OAD therapy only'	Total
N	182	582	1285
Age (Mean ±SD), years	56.0 (7.6)	55.4 (8.0)	54.1 (9.0)
Gender, M/F (%)	57.7/42.3	56.2/43.8	57.4/42.6
Weight (Mean ±SD), kg	58.1 (11.1)	63.2 (10.9)	61.9 (11.4)
BMI (Mean ±SD), kg/m^2	22.6 (4.9)	23.9 (3.8)	23.5 (4.1)
HbA_{1c} (Mean ±SD), %	9.2 (1.5)	9.5 (1.7)	9.4 (1.8)
Diabetes duration (Mean ±SD), years	7.3 (5.4)	6.2 (4.7)	6.5 (4.9)
Reason(s) for starting a new therapy, n (%)			
i) Improve glycaemic control	117 (64.3)	551 (94.7)	1078 (83.9)
ii) Try new insulin	144 (79.1)	324 (55.7)	762 (59.3)
iii) Improve weight control	41 (22.5)	259 (44.5)	488 (38.0)
iv) Patient dissatisfaction with current therapy	31 (17.0)	190 (32.6)	373 (29.0)
v) Reduce plasma glucose variability	26 (14.3)	212 (36.4)	348 (27.1)
vi) Unstable diabetes	25 (13.7)	176 (30.2)	306 (23.8)
vii) Reduce risk of hypoglycaemia	62 (34.1)	118 (20.3)	289 (22.5)
viii) Side effects from current therapy	9 (4.9)	56 (9.6)	138 (10.7)
ix) Change due to insulin pen	12 (6.6)	52 (8.9)	130 (10.1)

SD: Standard deviation; Percentages are based on the number of subjects with non-missing values; A subject may have findings in more than one category in 'Reason(s) for starting a new therapy'; BMI: Body Mass Index

on OAD + Basal insulin upto theend of study. Similarly, there were 182 patients (out of 232) on OAD + Basal at recruitment, till the end of study therapy. Only these patients have been included here.

The mean daily dose of insulin detemir at baseline was 13.2U and increased to 14.7U after 12 weeks of treatment. 98.6% patients received insulin detemir once daily at baseline and 97.1% patients were administered insulin detemir once daily after 12 weeks of treatment.

Safety

Adverse events

No SADRs were reported during the study. Two ADRs were reported in this study and both were hypoglycemia. One death was reported. The patient died due to chronic renal failure. The event was assessed as unlikely related to study product.

Body weight

The estimated mean change in body weight from baseline to end of treatment was 0.12 kg (95% CI,-0.05 to 0.29) in all patients. In patients previously treated with OAD only, after transferring to insulin detemir (OAD group), the estimated mean change in body weight from baseline to end of treatment was 0.24 kg (95% CI, 0.01 to 0.46). In patients previously treated with OAD+insulin, after switching to insulin detemir (OAD+insulin group), the estimated mean change in body weight from baseline to end of treatment was -0.91 kg (95% CI, -1.44 to -0.37).

Hypoglycaemic events

The number of hypoglycaemic episodes after 12 weeks of treatment was reduced for overall and major hypoglycaemic episodes by categories of total and time of occurrence (daytime or nocturnal) for all patients, OAD group and OAD+insulin group. (Table 2)

Efficacy

HbA_{1c}

In all patients, the estimated mean change in HbA_{1c} from baseline to end of treatment was -2.0% (95% CI, -2.13 to -1.93). In OAD group, the estimated mean change in HbA_{1c} from baseline to end of treatment was -2.1% (95% CI, -2.23 to -1.97), while in OAD+insulin group, it was -1.6% (95% CI, -2.10 to -1.36). (Table 3)

FPG

In all patients, the estimated mean change in FPG from baseline to end of treatment was -72.9 mg/dL (95% CI, -103 to -60.1) (Table 3). The mean FPG variability was after 12 weeks of treatment reduced by 5.6 mg/dL from baseline. In OAD group, the mean FPG variability was reduced by 4.6 mg/dL from baseline after 12 weeks of treatment. In OAD+insulin group, the mean FPG variability was reduced by 7.6 mg/dL from baseline after 12 weeks of treatment.

Discussion

The results of this cohort of patients from Indonesia with type 2 diabetes suggest that 12-week treatment with insulin detemir improves glycaemic control without increasing the risk of hypoglycaemia and is relatively weight neutral. There were no SADRs, including major hypoglycaemic episodes reported during the study. The rate of SADRs in the Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVE) European study cohort was 1%[15]. The lower rate of hypoglycaemic events in the Indonesian patients could be due to the lower dose of insulin detemir administered in this study and the fact the dose remained almost constant during 12-weeks. In general, the safety profile observed in this study was however consistent with the safety profile in PREDICTIVE Europe as well as in clinical trials where, insulin detemir has been shown to have a low risk of

Table 2. Hypoglycaemia Reported during Treatment

	Total hypoglycaemia		Daytime hypoglycaemia		Nocturnal hypoglycaemia	
	All events	Major events	All events	Major events	All events	Major events
Previously on OAD + insulin						
Baseline, N=182						
N (%)	10 (5.5%)	1 (0.5%)	10 (5.5%)	1 (0.5%)	8 (4.4%)	0 (0.0%)
Episodes/patient years	0.0247	0.0014	0.0137	0.0014	0.0110	0.0000
Week 12, N=182						
N (%)	2 (1.1%)	0 (0.0%)	2 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Episodes/patient years	0.0055	0.0000	0.0055	0.0000	0.0000	0.0000
Previously on OAD						
Baseline, N=582						
N (%)	23 (4.0%)	2 (0.3%)	21 (3.6%)	2 (0.3%)	19 (3.3%)	0 (0.0%)
Episodes/patient years	0.0202	0.0009	0.0112	0.0009	0.0090	0.0000
Week 12, N=582						
N (%)	5 (0.9%)	0 (0.0%)	5 (0.9%)	0 (0.0%)	2 (0.3%)	0 (0.0%)
Episodes/patient years	0.0047	0.0000	0.0039	0.0000	0.0009	0.0000
All patients						
Baseline, N=1285						
N (%)	60 (4.7%)	8 (0.6%)	56 (4.4%)	7 (0.5%)	47 (3.7%)	3 (0.2%)
Episodes/patient years	0.0248	0.0022	0.0153	0.0016	0.0096	0.0006
Week 12, N=1278						
N (%)	8 (0.6%)	0 (0.0%)	8 (0.6%)	0 (0.0%)	2 (0.2%)	0 (0.0%)
Episodes/patient years	0.0031	0.0000	0.0027	0.0000	0.0004	0.0000

Table 3. HbA_{1C} and FPG Change during Treatment

Variable (SD)	N	Baseline	Final visit	Absolute change
Previously on OAD + insulin				
HbA_{1c}, %	9	9.0 (1.6)	7.4 (0.8)	-1.6 (0.8)
FPG, mg/dL	59	206.3 (94.8)	140.7 (29.9)	-65.6 (84.9)
Previously on OAD				
HbA_{1c}, %	147	9.5 (1.7)	7.4 (1.0)	-2.1 (1.4)
FPG, mg/dL	342	207.6 (62.6)	134.9 (34.2)	-72.7 (57.1)
All patients				
HbA_{1c}, %	306	9.4 (1.7)	7.4 (0.9)	-2.0 (1.7)
FPG, mg/dL	615	209.3 (64.8)	136.4 (33.0)	-72.9 (61.1)

Data presented as Mean (SD)

hypoglycaemia, in particular, low risk of nocturnal hypoglycaemic episodes.

Furthermore, insulin detemir was weight neutral in the Indonesian study. A small increase in body weight of +0.12 kg was observed after 12 weeks of treatment with insulin detemir in all type 2 diabetes patients treated with insulin detemir. Also this finding is in general, consistent with the finding in the PREDICTIVE European cohort (type 2: -0.4kg)[15-18]. As the Indonesian patient cohort was not as overweight (mean BMI was 23.5 kg/m^2) at baseline compared with the European patients at baseline (mean BMI was 29.5 kg/m^2 for type 2). Furthermore, patients previously treated with OAD showed an increase of 0.24 kg and patients previously treated with OAD+insulin showed a reduction of -0.91 kg in body weight, respectively. These results show the difference between adding insulin detemir to OAD and switching from another insulin to insulin detemir in combination with OAD and suggested that treatment with insulin detemir was weight neutral. Insulin therapy is often associated with weight gain[19]. While the mechanism underlying insulin-associated weight gain is not fully understood, it may result from higher peripheral versus hepatic insulin levels in patients receiving exogenous insulin, more efficient insulin-stimulated lipogenesis, and decreased glycosuria. Body weight is also modulated by the action of insulin at receptors in the brain that, when activated, decrease appetite and food consumption. It may be that the lower weight gains observed in patients treated with insulin detemir versus NPH insulin are related to its avid binding to albumin. Albumin passes freely into the liver via hepatic sinusoids and this may result in increased hepatic and decreased peripheral action for insulin detemir, leading to less weight gain. Binding of insulin detemir to albumin may also enhance its penetration through the blood-brain barrier and action at insulin receptors in the brain[19,20].

The number of total, daytime and nocturnal hypoglycaemic episodes decreased in overall patients after 12 weeks of treatment. This finding is consistent with the observation in other PREDICTIVE cohort studies[16-18] where the frequency of hypoglycaemic episodes decreased after 14 weeks of treatment. Owing to the unique physicochemical structure, insulin detemir shows a relatively flat pharmacokinetic/pharmacodynamic profile and low within-patient variability which may result in reduction in hypoglycaemic events, particularly nocturnal hypoglycaemic events as compared to older basal insulin preparations[21].

Treatment with insulin detemir enabled Indonesian patients with type 2 diabetes to reduce mean HbA_{1c} from 9.4% at baseline to 7.5% after 12 weeks of treatment with a mean reduction of 2.0%-point. In the subgroup analysis, a larger reduction of the mean HbA_{1c} was observed in the subgroup with OAD only as pre-treatment (2.1%)

compared to that in the subgroup with OAD+insulin as pre-treatment (1.6%). However, at the end of treatment HbA_{1c} was comparable in two subgroups (mean HbA1c: 7.4%). The improved glycaemic control observed in the present observational study is strongly supportive of the original physicians' decision to initiate treatment with insulin detemir, which is to improve glycaemic control. Heterogeneity of real-life populations and the absence of a control group in observational studies may limit the conclusions we can draw from them. Furthermore, response rate in terms of HbA_{1c} and FPG measurement (28.6% and 53.1%, respectively) was also low in this study, hence, we should interpret these results carefully. Nevertheless, beneficial information on safety, efficacy and pattern of use of a drug in an extensive patient population can be gained from observational studies.

Conclusion

In conclusion, 12-week treatment with insulin detemir was safe and well-tolerated in Indonesian patients with type 2 diabetes. It improved glycaemic control without increasing the risk of hypoglycaemia and was relatively weight neutral.

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Appendix

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