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Original Article

Insulin detemir improves glycemic control and reduces hypoglycemia in children with type 1 diabetes: findings from the Turkish cohort of the PREDICTIVE™ observational study

Kurtoglu S, Atabek ME, Dizdarer C, Pirgon O, Isguven P, Emek S. Insulin detemir improves glycemic control and reduces hypoglycemia in children with type 1 diabetes: findings from the Turkish cohort of the PREDICTIVE™ observational study.
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Background: Insulin detemir is a basal insulin analog designed to produce a superior pharmacokinetic profile to basal formulations of human insulin. It has shown consistently improved tolerability in comparison to neutral protamine Hagedorn (NPH) insulin in adult cohorts, but there are relatively few publications involving pediatric cohorts.
Methods: The efficacy and safety of insulin detemir in children with type 1 diabetes was assessed using data from the Turkish cohort of PREDICTIVE™ (a large, multinational, observational) study. The children investigated were using basal–bolus therapy involving NPH insulin or insulin glargine at baseline but were switched to insulin detemir as part of routine clinical care by their physicians.
Results: Twelve weeks of treatment with insulin detemir significantly reduced mean hemoglobin A1c (9.7–8.9%, $p < 0.001$) and mean fasting glucose [185–162 mg/dL (10.3–9 mmol/L), $p < 0.01$]. Fasting glucose variability was also lower after treatment with insulin detemir than previously (on either NPH or glargine, $p < 0.05$). The frequencies of total, major and nocturnal hypoglycemic events were significantly reduced with insulin detemir relative to baseline, with an estimated mean of 6.89 fewer events/patient/yr overall ($p < 0.001$) and 2.6 fewer nocturnal events/patient/yr ($p < 0.01$). Weight and insulin dose remained relatively unchanged.
Conclusions: Twelve weeks of treatment with insulin detemir improved glycemic control and reduced hypoglycemia in children with type 1 diabetes. This improved tolerability might allow further dose titration and therefore additional improvements in glucose control.

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*See Appendix.

The importance of glycemic control in the management of type 1 diabetes is well established (1), although attaining and maintaining good glucose control is not always straightforward. Achieving glycemic targets in children with type 1 diabetes can be particularly challenging for several reasons. First, major hypoglycemia appears to be more common in children than in adults (2–4) and is a source of great concern for their parents and carers as well as for the children themselves (3, 4). Nocturnal hypoglycemia may be especially feared and act as a barrier to insulin titration. In addition to the short-term consequences of hypoglycemia, there are

concerns that hypoglycemia in children may adversely affect neural development (3, 4).

Second, children usually have more varied lifestyles and less regimented eating patterns than adults, and teenagers with diabetes may particularly struggle with fitting insulin injections into their lifestyle as they come to terms with adulthood and take responsibility for self-management. Third, younger children (i.e., those aged less than 10–11 yr) usually need support from carers to administer injections and so may only be able to take insulin twice daily.

Insulin detemir is a basal insulin analog launched in Turkey in 2005 and indicated for use in children with diabetes aged 6–18 yr. Data from a randomized controlled clinical trial suggest that insulin detemir may be able to help children overcome some of the barriers to glycemic control that they face (5). In this 26-wk study, children aged 6–17 yr with type 1 diabetes were randomized to insulin detemir or neutral protamine Hagedorn (NPH) insulin as the basal component of a basal–bolus regimen. Insulin detemir was associated with a 26% lower risk of nocturnal hypoglycemia and resulted in more normal body mass index (BMI) measurements than NPH insulin (indicative of less unwanted weight gain). Mean fasting plasma glucose (FPG) and mean within-subject variation in FPG were also significantly lower in insulin detemir-treated patients than in NPH-insulin-treated patients, although there was no difference in hemoglobin A1c (HbA1c). These findings in children are supported by studies of adults with type 1 diabetes showing reduced risk of nocturnal hypoglycemia at equivalent or improved levels of glycemic control (6–10) and less weight gain (6, 7, 9, 10) with insulin detemir than with NPH insulin. Such reductions in hypoglycemia, more predictable glucose control and less weight gain may allow more of the estimated 4300 children with type 1 diabetes in Turkey (aged <14 yr) (11) to attain desired glucose control.

Observational studies are an important means of validating the clinical results of randomized controlled trials in large, heterogeneous real-life samples. The PREDICTIVE™ (Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation) study is a large, international, observational study to assess the safety and efficacy of insulin detemir in patients with type 1 or type 2 diabetes. In this study, we report data from children with type 1 diabetes enrolled as part of the Turkish cohort, with the intention of providing further insights into the efficacy and safety of insulin detemir in this particular patient group.

Materials and methods

The PREDICTIVE study is a large-scale, prospective multinational observational study that has recruited more than 35 000 patients with type 1 or type 2 diabetes from more than 25 countries. Eleven European countries are involved providing data from more than 20 000 patients (12). In this study, we present data from pediatric patients with type 1 diabetes in the Turkish cohort after 12 wk of treatment with insulin detemir.

Participants

This analysis of data from the PREDICTIVE study includes children and young people with type 1 diabetes (aged 6–18 yr), who were using basal–bolus regimens not involving insulin detemir at baseline. As the aim of the study was to investigate insulin detemir in the real-life setting, exclusion criteria were limited to the contraindications of the product labeling.

Study design

Participants were prescribed insulin detemir as part of their normal clinical evaluation, and participating physicians determined the starting dose, injection frequency and any subsequent regimen changes. Patients were not provided with any additional educational support or interventions other than those deemed necessary by their physician as a part of usual clinical practice. Informed consent was obtained for participants, and ethical approval was obtained in accordance with local practice.

The primary end-point was the number of serious adverse drug reactions, including major hypoglycemic episodes [defined as episodes involving symptoms that could not be self-treated and that included blood glucose <50 mg/dL (2.8 mmol/L) or symptom reversal after food intake, glucagon or intravenous glucose]. Secondary end-points included mean weight change (evaluated using SD scores) and the frequency of total and nocturnal (between bedtime and normal waking time) hypoglycemic events. For this purpose, events were recorded in the 4 wk preceding baseline and the 12-wk follow-up visit, with data converted into the more meaningful unit of events/patient/yr (calculated by multiplying by 13). Nocturnal hypoglycemia was defined as a hypoglycemic event (based on patient reporting) occurring between bedtime after the evening injection and before rising. Patients were asked to measure blood glucose levels if they experienced symptoms of hypoglycemia. Efficacy end-points included HbA1c, fasting glucose and variability in fasting glucose (calculated for each participant as the SD of the last 2–6 self-measured fasting glucose values taken at baseline and before end-point). These measurements were taken in accordance with standard clinical practice. A detailed methodology for the PREDICTIVE study has been published (13).

Physicians were also asked to provide their reason(s) for switching their patients to insulin detemir.

Statistical analysis

Descriptive statistics were used to describe demographic parameters, HbA1c, mean fasting glucose and hypoglycemic episodes. Changes from baseline were analyzed using paired *t*-tests for HbA1c and mean fasting glucose. Hypoglycemia was analyzed using the Wilcoxon paired sign-rank sum test. Weights are presented as SD scores using weight distribution data from a referenced comparator group as a control (14). A p value of <0.05 was considered statistically significant.

Results

This analysis includes data from 106 children and young people with type 1 diabetes from 29 centers in Turkey; 48% of participants were female. Mean age (±SD) was 12.6 yr (3.2) with 39 children aged 6–11 yr and the remaining 67 aged 12–18 yr. Mean BMI was 19.9 kg/m^2 (±3.4), and mean diabetes duration was 3.9 yr (±3.3). At study start, 80 (76%) participants were using NPH insulin as their basal insulin and 26 (24%) were using insulin glargine. The most frequently cited reason for switching a patient to insulin detemir was to improve glycemic control (91% of responders). Other commonly cited reasons included 'reducing the risk of hypoglycemia' (53%), 'improving weight control' (24%) and 'reducing blood glucose variability' (57%) (Table 1).

Twelve weeks of insulin detemir treatment significantly improved glycemic control: HbA1c decreased from 9.7% at baseline to 8.9% ($p < 0.001$) and fasting glucose decreased from 185 to 162 mg/dL (10.3–9 mmol/L) ($p < 0.01$) (Fig. 1). Variability in fasting glucose was also significantly lower with insulin detemir treatment [mean of variability of fasting glucose decreased from 59 to 43 mg/dL (3.3–2.4 mmol/L), $p < 0.05$; Fig. 1]. Table 2 reports data for the overall group subdivided by age; younger children (aged 6–11 yr inclusive) and older (aged 12–18 yr inclusive). A modest increase in mean weight change, also shown in Table 2, was standardized for SD scores, and no significant differences were observed.

Table 1. Reasons for switching to insulin detemir*

Reason cited	Proportion of physicians citing reason, n (%)
Improve patients glycemic control	108 (90.8)
Reduce risk of hypoglycemia	63 (52.9)
Reduce blood glucose variability	68 (57.1)
Try new insulin	50 (42.0)
Improve weight control	29 (24.4)

*Physicians were asked to cite their reasons for transferring their patients to insulin detemir from their existing basal insulin (neutral protamine Hagedorn insulin or insulin glargine). Physicians could give more than one reason for switching treatment.

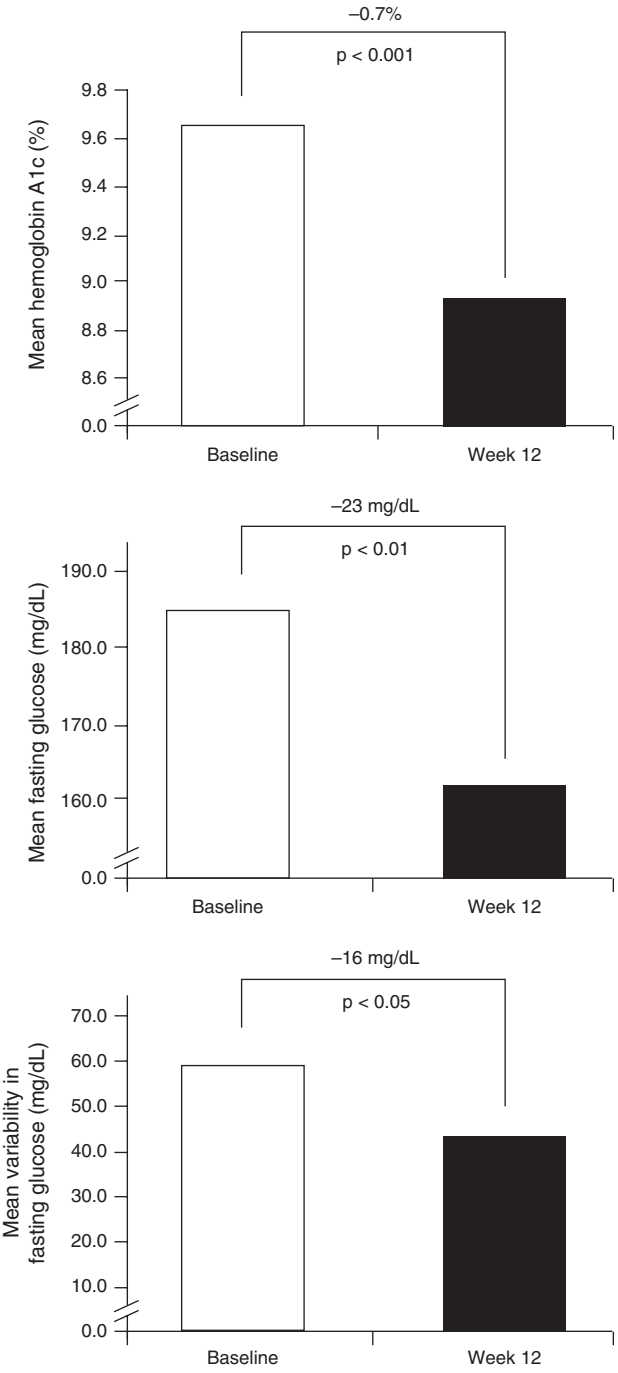

Fig. 1. Measures of glucose control before and after 12 wk of treatment with insulin detemir.

Hypoglycemia (total, nocturnal and major) occurred significantly less often in the 4 wk preceding wk 12 of insulin detemir treatment than in the 4 wk preceding baseline (Fig. 2). Five (5%) patients experienced one or more major hypoglycemic events. There were no other serious adverse drug reactions. Table 3 shows these data subdivided between different age groups.

Mean weight-adjusted total insulin dose, basal insulin dose and bolus insulin dose were relatively unchanged from baseline to study end (Table 4). Most

Table 2. Efficacy and weight end-points subdivided by age group

End-point	6–11 yr inclusive			12–18 yr inclusive		
	Baseline	Week 12	Change	Baseline	Week 12	Change
HbA1c (%)	10.17 ± 2.44	9.29 ± 1.57	−0.88 ± 1.84*	9.29 ± 2.09	8.65 ± 1.71	−0.64 ± 1.34*
Fasting blood glucose, mg/dL (mmol/L)	181 ± 56 (10.08 ± 3.33)	169 ± 61 (9.39 ± 3.38)	−12 ± 16.5 (−0.69 ± 4.25)	188 ± 62 (10.44 ± 3.44)	153 ± 51 (8.51 ± 2.81)	−35 ± 58 (−1.93 ± 3.21*)
Fasting blood glucose variability, mg/dL (SD mmol/L)	76 ± 43 (4.24 ± 2.37)	55 ± 36 (3.04 ± 1.99)	−22 ± 58 (−1.20 ± 3.22*)	48 ± 32 (2.67 ± 1.77)	30 ± 23 (1.66 ± 1.25)	−18 ± 28 (−1.01 ± 1.53*)
Weight (kg)	47.5 ± 15.6	48.7 ± 15.6	+1.2	56.6 ± 11.7	57.3 ± 11.8	+ 0.7
Weight SDS	−0.02 ± 1.23	−0.02 ± 1.36	0.0	0.07 ± 1.18	−0.01 ± 1.26	−0.08 ± 0.65

*$p \leq 0.01$.
SDS, standard deviation score

Fig. 2. Mean number of hypoglycemic events/patient/yr at baseline and after 12 wk of treatment with insulin detemir (hypoglycemic events/patient/yr were calculated from data collected in the 4 wk preceding baseline and week 12).

patients used one daily basal insulin injection before and 12 wk after switching to insulin detemir (92 and 93%, respectively).

Discussion

This analysis of the Turkish PREDICTIVE study data included children and young people with type 1 diabetes treated at baseline with a basal–bolus insulin regimen involving NPH insulin or insulin glargine as the basal component. Switching to a basal–bolus regimen including insulin detemir resulted in significant improvements in glycemic control after 12 wk: HbA1c

Table 3. Hypoglycemia subdivided by age group

Hypoglycemia: events per 4-wk period	6–11 yr inclusive			12–18 yr inclusive		
	Baseline	Week 12	Change	Baseline	Week 12	Change
Total	0.82	0.41	−0.41*	1.16	0.65	−0.51**
Major	0.33	0.02	−0.31**	0.31	0.07	−0.24*
Nocturnal	0.20	0.02	−0.18	0.31	0.10	−0.21

*$p < 0.05$.
**$p \leq 0.01$.

Table 4. Insulin dose at baseline (before starting insulin detemir) and after 12 wk of follow-up

	Baseline	Week 12	Change
Total insulin daily dose (U/kg, mean ± SD, n = 89)	0.97 ± 0.34	1.01 ± 0.53	0.04 ± 0.54
Basal insulin daily dose (U/kg, mean ± SD, n = 89)	0.35 ± 0.22	0.34 ± 0.17	−0.01 ± 0.23
Bolus insulin daily dose (U/kg, mean ± SD, n = 89)	0.62 ± 0.22	0.67 ± 0.39	0.05 ± 0.39

and fasting glucose were reduced and fasting glucose was less variable. Total, major and nocturnal hypoglycemic events occurred significantly less frequently at this time than at baseline. This improvement in glycemic control occurred without marked increases in insulin dose or indications of undesirable weight increase.

Our findings are broadly consistent with those of controlled trials involving insulin detemir in children and adolescents. For example, Danne et al. (15) reported that the pharmacokinetic profile of insulin detemir in children with type 1 diabetes (aged 6–12 and 13–17 yr) was less variable than that of NPH insulin. Furthermore, Robertson et al. (5) reported that after 26 wk of treatment with insulin detemir as part of a basal–bolus regimen, children (aged 6–17 yr) with type 1 diabetes had significantly lower and less variable fasting glucose and a reduced risk of nocturnal hypoglycemia compared with those using NPH insulin as part of a basal–bolus regimen. Clinical studies in adults with type 1 diabetes also suggest that insulin detemir can reduce the risk of hypoglycemia while maintaining or improving other measures of glycemic control (6–10). That this present study found significant improvements in all measures of glycemic control is consistent with the other results reported from the PREDICTIVE study (12, 16).

The HbA1c reduction of 0.7% (representing a 7.3% reduction in magnitude from baseline) shown in this study is likely to be clinically important as the Diabetes Control and Complications Trial showed that a 10% reduction in HbA1c equated to a 40–50% lower risk of retinopathy or its progression (17). Nevertheless, the final mean HbA1c of 8.9% remains somewhat higher than desired treatment targets. However, it should be noted that this study was of fairly short duration (12 wk), hence continued treatment may result in further improvements in glucose control. Within this context, of particular note is the observation that the mean insulin dose remained relatively unchanged during the study. There is, therefore, scope to titrate the insulin dose more aggressively with the aim of achieving further improvements in control, and the reduction in hypoglycemia implies this could be possible.

Attaining good glucose control in children may be more difficult than in adults (18). However, several features of insulin detemir suggest that it may be particularly suitable for helping them in overcoming barriers to glycemic control. For example, the less variable glucose and reduced risk of hypoglycemia shown in this study [and in the randomized controlled trial (5)] is particularly relevant given that hypoglycemia appears to be more common in children than in adults and is feared by both patients and parents (2–4). When the data are subdivided by age group, both subgroups experienced significant benefits in HbA1c and fasting glucose variability; however, younger children (aged 6–12 yr) did not share the same significant benefits in fasting glucose reduction as did adolescents (aged 12–18 yr). This finding may, in part, be explained by different timings of injections and blood glucose readings: younger children may have had different bedtimes to older children. Alternatively, this finding may be statistically anomalous given the comparatively lower numbers included in the subgroups compared with the data set as a whole. Our findings broadly support the work of Robertson et al. (5) who showed that insulin detemir is less likely to cause unwanted weight gain in children.

Observational studies such as PREDICTIVE provide a valuable insight into the efficacy and safety of treatments in routine clinical practice and are an important and necessary complement to the information provided in randomized clinical trials. However, it should be noted that at least some of the improvements

reported in this study may be because of a study effect or selection bias rather than insulin detemir *per se*. In particular, patients included in this analysis were in poor control at baseline and may therefore have been particularly susceptible to study effects [especially given the observation that the main reason for inclusion into PREDICTIVE was to improve glycemic control (12)].

Despite this reservation, these data provide an insight into the efficacy and safety of insulin detemir in children when used in standard clinical practice at physician-determined doses. This analysis suggests that, for young patients with poorly controlled blood glucose levels on a basal–bolus regimen with NPH insulin or insulin glargine, switching to insulin detemir may bring about clinically significant improvements in glycemic control and hypoglycemia without major dose adjustment.

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