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REVIEW ARTICLE

Safety, efficacy, and early clinical experience of insulin degludec in Japanese people with diabetes mellitus: A first-year report from Japan

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ABSTRACT

In Japan, insulin therapy is recommended for the treatment of type 2 diabetes mellitus either directly after diet, exercise and lifestyle improvements, or if the target for glycemic control is not achieved with other hypoglycemic agents. Insulin degludec is an ultra-long-acting insulin that was launched in Japan in 2013, having shown good efficacy and safety in its clinical development program. It has now been used in clinical practice for more than 1 year. During this time, clinicians and researchers have identified possible factors that could influence the decision as to which patients might be appropriate for insulin degludec treatment. In the present review, we describe how to initiate and manage insulin degludec therapy in routine clinical practice. We also discuss several important topics related to the use of insulin degludec, including patient selection, dosing, handling of bolus insulin, hypoglycemia and other potential safety considerations.

INTRODUCTION

Type 2 diabetes mellitus is a progressive disease characterized by the gradual decline of β-cell function and the increasing need to intensify therapy over time with the aim of better glycemic control. Studies indicate that approximately 50% of patients with type 2 diabetes mellitus may require insulin therapy in addition to oral anti-diabetic drugs (OADs) at some point after their diagnosis[1–3]. By contrast, patients with established type 1 diabetes mellitus depend on exogenous insulin for their survival and to maintain their essential metabolic and biologic functions.

The current clinical practice guidelines of the Japan Diabetes Society recommend a glycated hemoglobin (HbA1c) target of <7% while minimizing undesired effects, such as hypoglycemia, in order to minimize the risk of diabetes-related complications. The Japan Diabetes Society recommends initiating insulin therapy in patients with type 2 diabetes mellitus either directly after diet, exercise and lifestyle improvements, or if the glycemic control target is not achieved despite using OADs[4]. However, these guidelines do not recommend a time after which insulin should be administered. Therefore, insulin might be initiated simultaneously with OADs and titrated at any time during the management of patients with type 2 diabetes mellitus.

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Despite the availability of a wide variety of insulin preparations for use in Japan, the existing preparations do not adequately fulfil a number of unmet needs[5–7]. In particular, there is a need for newer basal insulins, which could further reduce the risk of hypoglycemia, elicit less variable and more consistent glycemic responses, and allow convenient once-daily administration in patients with diabetes.

Insulin degludec is a novel basal insulin that has been available in Japan since March 2013. The extensive phase 3a global clinical development program of insulin degludec confirmed its safe and effective use in patients with type 1 diabetes mellitus and type 2 diabetes mellitus[8–18]. Insulin degludec shows unique pharmacological properties, including a flat, stable profile and a very long duration of action compared with other insulins[19]. When injected subcutaneously, insulin degludec forms a depot of soluble multihexamers, which dissociate from the depot slowly, producing less variability and more consistent glycemic effects. The molecular design and mechanism of protracting the pharmacodynamics of insulin degludec differ from the existing basal insulin analogs. Therefore, it is critically important to understand how the properties of insulin degludec might influence its clinical use.

Now that insulin degludec has been available for more than 1 year in Japan, it is important that we critically assess whether the results of controlled clinical trials are also observed in real-life clinical practice[20–23]. It is also important that we address

possible challenges raised by clinicians and patients in relation to the initiation of insulin degludec, and account for factors that should be considered during its use. Therefore, the aim of the present review was to provide a timely update on the appropriate and safe use of insulin degludec in Japanese patients. This report provides a summary of the observed properties of this insulin in routine clinical practice relative to the available data from phase 3 controlled clinical trials, as well as the results from real-life, independent, routine clinical experiences of both type 1 diabetes mellitus and type 2 diabetes mellitus using insulin degludec published by diabetes care centers in Japan[20–23].

EFFICACY AND SAFETY OF INSULIN DEGLUDEC IN JAPANESE PATIENTS AND INTERNATIONAL PHASE 3 TRIALS

An extensive phase 3 clinical development program of insulin degludec has been completed, with numerous studies carried out in many countries, including Japan, of patients with type 1 diabetes mellitus or type 2 diabetes mellitus.

In a 6-week randomized controlled trial of Japanese patients with type 1 diabetes mellitus previously treated with mealtime insulin aspart together with a basal insulin[24], insulin degludec reduced the mean fasting plasma glucose (FPG) from 181.8 to 146.7 mg/dL. Hypoglycemia occurred in 30/33 patients (90.9%; 315 episodes), including nocturnal hypoglycemia in 12 patients (36.4%; 25 episodes). However, no severe hypoglycemia occurred. In a 26-week international study, in which type 1 diabetes mellitus patients received insulin degludec in combination with insulin aspart[10], HbA1c decreased by 0.40%. The overall rates of confirmed hypoglycemia and nocturnal hypoglycemia were 42.54 and 4.41 episodes/patient year, respectively. Additionally, the rate of confirmed nocturnal hypoglycemia was lower in patients treated with degludec than in those treated with the comparator basal insulin.

One 26-week international, open-label, randomized study[25] enrolled Japanese patients among patients of other nationalities. In that study, the efficacy and safety of insulin degludec as basal treatment were compared with those of insulin detemir in participants with type 1 diabetes mellitus. Overall improvements were observed in HbA1c (0.73% [degludec] *vs* 0.65% [detemir]) and mean FPG in both groups, but the improvements were greater in the group treated with insulin degludec. Hypoglycemia rates and adverse event profiles were similar in both groups, but the incidence of confirmed nocturnal hypoglycemia was significantly lower in the insulin degludec group than in the insulin detemir group (4.14 and 5.93 episodes/patient year, respectively; $P = 0.0049$). Generally, the results in Japanese patients were consistent with those for Caucasian patients.

In a 26-week, Pan-Asian study of patients with type 2 diabetes mellitus inadequately controlled by OAD[14], insulin degludec reduced HbA1c by 1.24% from a baseline of 8.4% (Figure 1). The overall rates of confirmed hypoglycemia and nocturnal hypoglycemia were 3.0 and 0.8 episodes/patient year, respectively (Figure 2). In a global study of insulin-naïve patients[17], insulin degludec reduced HbA1c by 1.06% from a baseline of 8.2% (Figure 3). The rates of confirmed hypoglycemia and nocturnal hypoglycemia were 1.52 and 0.25 episodes/patient year, respectively (Figure 4). In that study, the rate of confirmed nocturnal hypoglycemia was lower in patients treated with degludec than in those treated with the comparator basal insulin.

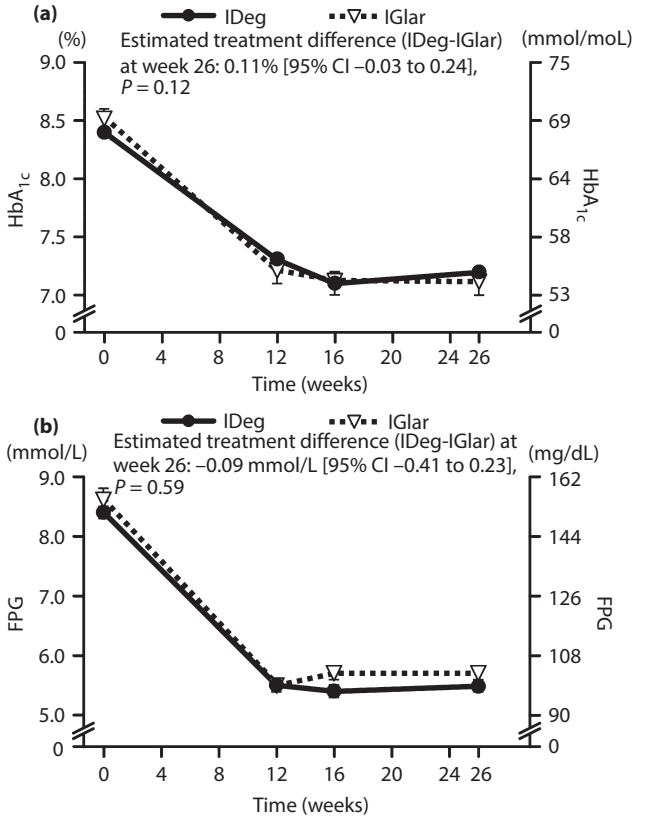

Figure 1 | Mean (a) glycated hemoglobin (HbA1c) and (b) fasting plasma glucose (FPG) over time. Data are observed mean values for all randomized participants (last observation carried forward is used for each post-baseline time-point). Error bars show standard errors of the mean. CI, confidence interval; FPG, fasting plasma glucose; IDeg, insulin degludec; IGlar insulin glargine. Reprinted from Onishi *et al.*[14] with permission.

These results suggest that insulin degludec has similar efficacy in terms of the HbA1c reduction and hypoglycemia profiles between Japanese/Asian patients and non-Asian patients.

SELECTING APPROPRIATE PATIENTS

Insulin degludec was used as the basal insulin in a basal–bolus regimen in most clinical settings in Japan to treat patients with type 1 diabetes mellitus or in combination with OADs in patients with type 2 diabetes mellitus[14–17,25]. Patients already using a basal insulin or premix insulin might benefit from switching to insulin degludec if they are unable to achieve the

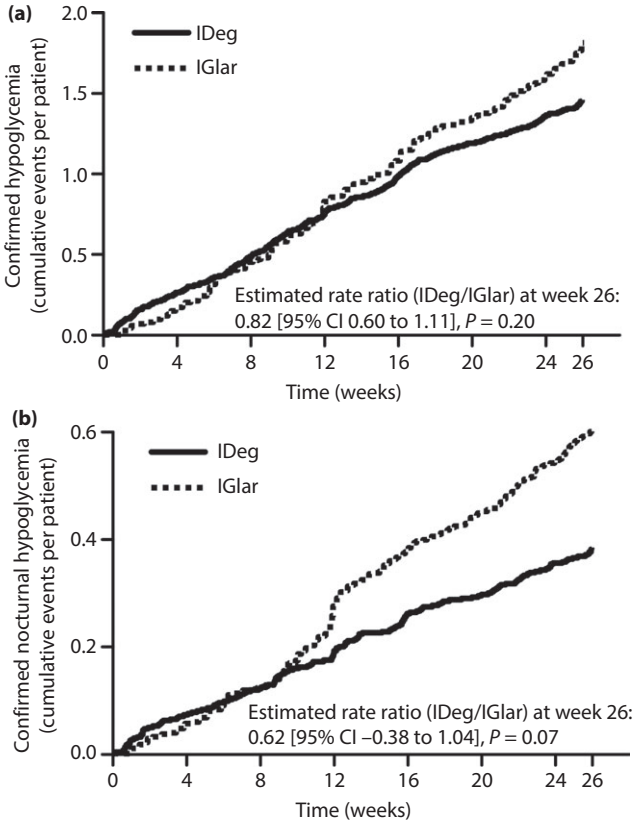

Figure 2 | Cumulative number of (a) confirmed hypoglycemic episodes and (b) confirmed nocturnal hypoglycemic episodes. CI, confidence interval; IDeg, insulin degludec; IGlar insulin glargine. Reprinted from Onishi *et al.*[14] with permission.

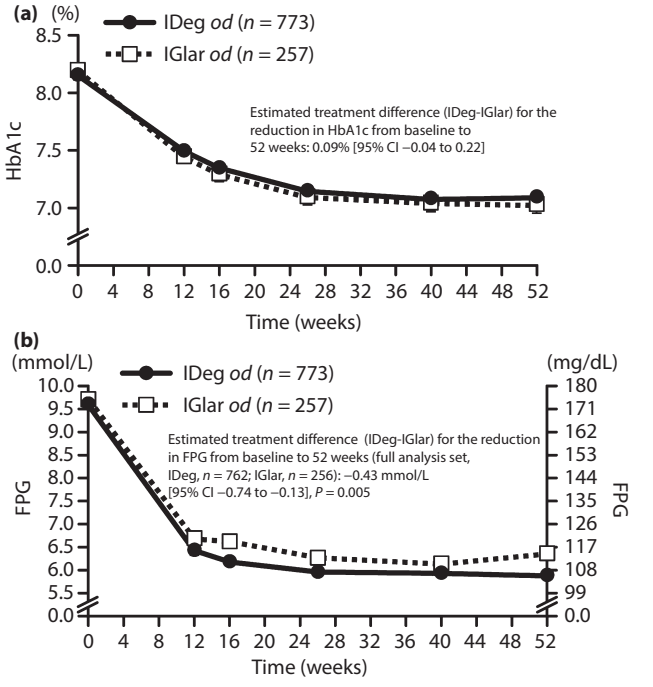

Figure 3 | (a) Mean glycated hemoglobin (HbA1c) with time. (b) Mean fasting plasma glucose (FPG) with time. Data are reported as the means ± standard error of the mean. Missing data after baseline were imputed with the last observation carried forward approach. Ideg, insulin degludec; IGlar, insulin glargine; od, once daily. Modified from Zinman *et al.*[17] with permission.

HbA1c target despite titrating the prior basal or premix insulin dose; patients with consistently high FPG or fasting blood glucose (FBG) concentrations; patients with significant glycemic variability while using another basal or premix insulin; patients with a high risk of hypoglycemia; and patients who are expected to benefit from switching from twice-daily injections of their prior insulin to once-daily injection of insulin degludec[26].

INITIATION AND DOSING OF INSULIN DEGLUDEC

Insulin Degludec as Initial Insulin Therapy

For adults initiating treatment with insulin degludec, it should generally be started at a dose of 4–20 units once-daily by a subcutaneous injection[26]. The dose should be selected and adjusted depending on the patient's glycemic control status, symptoms, and glucose test results. The dose of insulin degludec is usually adjusted to achieve FBG levels of 80–110 mg/dL. In Japanese clinical practice, the dose of insulin degludec was increased by 1–2 units if the FBG concentration was >110 mg/dL, and was decreased by 1–2 units if the FBG concentration was <80 mg/dL. Insulin degludec is normally administered once-daily at any time of the day, provided the timing of administration is maintained at regular intervals.

Based on the Japanese clinical experience of insulin degludec, it can be safely initiated for the following groups of patients, at the physician's discretion: (i) patients with type 1 diabetes mellitus who might be treated with multiple daily insulin injections, including mealtime (bolus) insulin doses; (ii) type 2 diabetes mellitus patients who do not achieve glycemic control targets despite receiving education on diet, exercise and lifestyle improvements; and (iii) type 2 diabetes mellitus patients who do not achieve glycemic control targets despite using other OADs or insulin.

In Japan, insulin degludec is approved for use alone or in combination with OADs or with mealtime insulin in patients with type 2 diabetes mellitus. Nevertheless, the treatment policy should be customized to the individual patient's needs, and should take into consideration the treatment targets recommended by the Japan Diabetes Society.

Switching to Insulin Degludec From Another Insulin

In patients who switched from another once-daily basal insulin to once-daily insulin degludec, we observed that the insulin doses were generally switched on a unit-to-unit basis. This is consistent with independent routine clinical practice in Japan[21,23] and the currently approved Japanese label[26]. However, the physician should carefully assess whether this

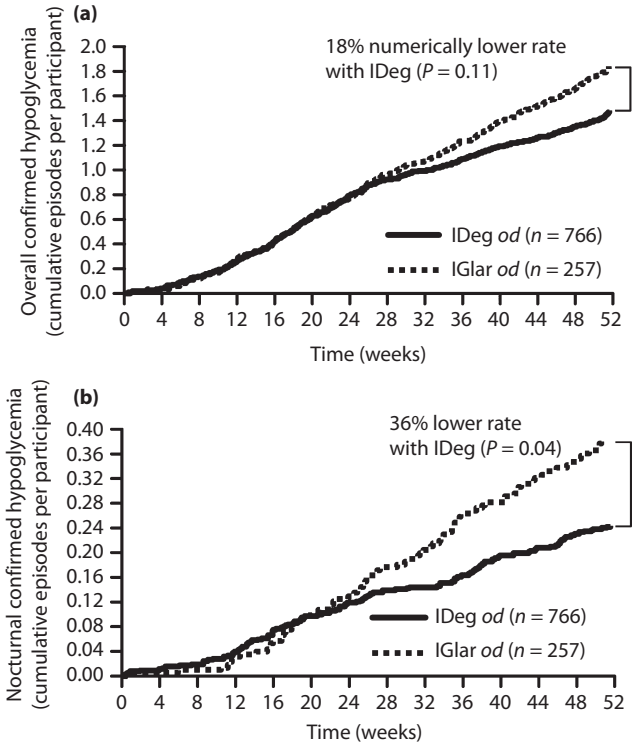

Figure 4 | Confirmed hypoglycemic episodes. (a) Overall confirmed hypoglycemic episodes. (b) Nocturnal confirmed hypoglycemic episodes. IDeg, insulin degludec; IGlar, insulin glargine; od, once daily. Reprinted from Zinman *et al.*[17] with permission.

approach is suitable for individual patients taking into consideration the patient's condition, and possible differences in the effect and duration of action of insulin degludec compared with the prior basal insulin. Based on their clinical experience, some Japanese physicians tend to lower the dose by 5–10%, even in patients switching from once-daily basal insulin to once-daily insulin degludec. Although this approach is not consistent with the Japanese label, which recommends unit-to-unit switching in patients using once-daily insulin, a lower starting dose might be necessary in some patients, especially those at high risk of hypoglycemia. The physician must subsequently ensure that the insulin degludec dose is titrated according to the patient's glycemic response.

Some basal insulins might need to be injected twice-daily to achieve glycemic control targets and/or because of frequent hypoglycemic episodes if administered once daily. As with other basal insulins[27] and the clinical observations in real-life clinical practice, when switching from a twice-daily basal insulin to once-daily insulin degludec, the starting insulin degludec dose should be approximately 20–30% lower than the total daily basal dose of the prior insulin regimen. A dose decrease of 30% is generally more common for patients with lower HbA1c (e.g., <8%) at the time of switching to insulin degludec. Based on data from Japanese patients with type 1 diabetes mellitus[20], it seems that switching to insulin degludec avoids the need for twice-daily injections of the basal insulin, and reduces the risk of hypoglycemia compared with other basal insulins. Additionally, patients who switched from twice-daily injections of a basal insulin to any once-daily basal injection frequently expressed increased satisfaction, because the number of daily injections was reduced[28].

Based on real-life clinical experience to date, it is important to manage patients' expectations. When switching from another basal insulin to insulin degludec, the FBG might not decrease to the desired level within the first 24 h. However, these short-term changes are to be expected when starting a new basal insulin owing to the time generally required for long-acting insulins to reach therapeutic plasma concentrations. Indeed, insulin degludec reaches steady-state concentrations within 2–3 days of once-daily administration[19,26]. Therefore, it is important that clinicians inform their patients of these expected changes and reassure them that their glycemic control will improve quickly, and that dose adjustment might be necessary thereafter. The time required for insulin degludec to reach steady-state concentrations is similar to that for other basal insulin analogs. Therefore, a cautious approach is generally advisable when switching from any basal insulin to another. Accordingly, for successful initiation of insulin degludec or any other long-acting insulin in the outpatient setting, it is essential that the clinician and patient wait for several days to see the full effect before drawing any conclusion about treatment effectiveness.

The early clinical experience of insulin degludec in Japan shows that most patients can be switched to insulin degludec with no major safety concerns. Furthermore, several Japanese studies have shown that many patients are able to achieve better glycemic control with or without a reduction in the daily basal dose or the total daily dose of insulin within a few months of switching to insulin degludec[21,23,29]. However, some patients might not achieve improvements in glycemic control after switching from another insulin to the same or a lower dose of insulin degludec. In these patients, it is necessary to slowly titrate the dose of insulin degludec. In routine clinical practice, the doses of insulin degludec are generally titrated weekly. The ability to titrate the insulin degludec dose is based on its low risk of hypoglycemia (especially nocturnal hypoglycemia), as shown in controlled clinical trials[14,16,17], allowing safe and effective titration if deemed appropriate or necessary by the physician.

Patients Who Might Benefit From Switching From Another Long-Acting Basal Insulin to Insulin Degludec

In general, Japanese clinicians who decided to switch their patients to insulin degludec did so because their patients were either dissatisfied with their previous basal insulin and/or did not achieve the glycemic targets. Based on our experience, it seems that switching from another basal insulin to insulin degludec might be warranted for the following types of patients:

(i) patients who do not achieve glycemic targets (FBG or HbA1c) despite titrating their prior basal insulin; (ii) patients who achieve the HbA1c target, but frequently experience hypoglycemia, especially nocturnal hypoglycemia; (iii) patients with significant day-to-day variations in their FBG, which limits the ability to safely titrate their basal insulin; (iv) patients who inject their basal insulin twice-daily, but wish to switch to a once-daily regimen; and (v) patients who sometimes miss or delay their basal insulin injection because of unavoidable circumstances[30,31].

Timing of the Insulin Degludec Dose

Insulin degludec should be administered once-daily, at any time of the day, providing it is injected at the same time each day[19,26]. If the patient missed a dose, flexible timing of injection is possible because of the very long duration of action of insulin degludec combined with its flat, peakless profile[19,30,31]. Many Japanese physicians recommend injecting insulin degludec in the morning, although it can be administered in the evening, bedtime or at any other time, taking into consideration the patient's lifestyle, size and content of meals, degree of glycemic control, whether the dawn phenomenon was observed with the patient's prior basal insulin, and other factors. Nevertheless, adjusting the timing of injection might be beneficial for some patients to provide further improvements in control and/or avoid hypoglycemia. For example, some patients could have higher daytime insulin requirements, especially patients who regularly consume large meals. These patients might benefit from morning dosing, especially if their glucose level tends to drop during the night. Meanwhile, patients who frequently experience the dawn phenomenon with elevated glucose concentrations overnight could benefit from injecting insulin degludec in the evening, as described below.

Effects of the Dawn and Dusk Phenomena on Insulin Degludec Dosing

The early continuous glucose monitoring (CGM) data in Japanese patients showed a difference in the effect of insulin degludec compared with other basal insulins in terms of the rises in blood glucose levels at dawn and at dusk[21]. In some patients treated with other basal insulins, if the insulin was injected at bedtime, the CGM data showed that the early morning rise in blood glucose was suppressed, but the early evening rise in blood glucose at the end of the dosing interval was not (i.e., at the end of the 24-h period between two injections), which is known as the dusk phenomenon. Conversely, basal insulins injected in the morning were sometimes unable to suppress the early morning rise in blood glucose, which is known as the dawn phenomenon. These two observations could be explained by a slightly shorter than expected duration of action (i.e., not lasting for the full 24 h) of some once-daily basal insulins[5,32,33]. The previously observed rises in blood glucose concentrations at dawn and dusk disappeared within a few days after switching to insulin degludec, and the blood glucose profiles stabilized with less pronounced peaks across the 24-h dosing period. This effect could be related to the longer duration of action of insulin degludec, which lasts for >24 h and allows for more consistent glycemic profiles over the 24-h dosing period.

Initiation of Insulin Degludec in the Hospital Setting

In Japan, patients can electively be admitted to the hospital for the purpose of initiating insulin. For these patients, insulin degludec has been used safely and effectively as a basal insulin option. In general, insulin degludec reaches a steady state within a similar period of time compared with other basal insulin analogs. During the first 24 h after the first injection, the time to reach maximum plasma concentration with basal insulin analogs might vary owing to the differences in their molecular design and mechanism of action. However, clamp studies and observations from clinical practice showed that insulin degludec quickly reaches the desired therapeutic effect (steady state) within a similar period compared with other basal insulin analogues[19,34,35,36]. It is our understanding that insulin degludec is an appropriate tool for achieving glycemic control in the hospital setting, and it has been used for this purpose in many centers in Japan. Based on its steady-state condition, clinical pharmacology studies show that insulin degludec has a flatter, less variable and more consistent glycemic effect. The lower variability of insulin degludec in steady state allows safer and more effective titration both within the hospital setting as well as in the outpatient setting.

MANAGING THE BOLUS INSULIN

Most patients with type 1 diabetes mellitus and some patients with type 2 diabetes mellitus might be treated with a basal–bolus insulin regimen. If the physician decides to switch the basal component to insulin degludec, the physician must first select the starting dose of insulin degludec, and then consider changes to the bolus insulin dose depending on the patient's glycemic control and potential risk of hypoglycemia.

There are several factors that need to be considered when adjusting the doses of the basal and bolus insulins in these patients. First, the duration of action of insulin degludec might be longer than the patient's previous basal insulin. Therefore, some patients who switch to a morning dose of insulin degludec might require a lower bolus insulin dose in the morning than that necessary with the previous basal insulin. This is because the morning bolus dose may have been increased to compensate for a shorter-acting prior basal insulin, and switching to insulin degludec, with a longer duration of action than the prior insulin, could eliminate the need for the higher bolus dose. This concept might apply to the other bolus doses depending on the timing of administration.

Second, the peakless profile of insulin degludec might actually require a slight increase in some bolus doses. In some patients administering their basal insulin dose in the morning, a slight peak in the prior basal insulin concentration before

lunch or dinner could necessitate reductions in the bolus insulin doses at lunch and/or dinner with the prior basal insulin. Accordingly, after switching to insulin degludec in the morning, although the morning bolus might need to be lowered, the lunch and/or dinner bolus doses may need to be increased compared with the doses used with the prior basal insulin. The opposite might be true with evening basal injection. These factors should be carefully considered by the physician, and changes in the basal and bolus insulin doses should be made with continued observation of the patient's glycemic responses.

USE IN SPECIAL POPULATIONS

A preplanned meta-analysis was carried out in elderly patients aged ≥65 years[37]. In that analysis, insulin degludec showed similar glycemic effects to another basal insulin, but the rates of overall confirmed hypoglycemia and nocturnal hypoglycemia were lower with insulin degludec.

Insulin degludec was also studied in patients with different degrees of renal impairment[38]. The pharmacokinetic properties of insulin degludec were similar between patients with renal impairment and patients with normal renal function[38]. Furthermore, hemodialysis did not affect the clearance of insulin degludec[38].

Insulin degludec has been used clinically in patients who undergo endoscopic or surgical procedures in routine practice. Most of these experiences have not yet been fully documented in the published literature. One small Japanese study reported the use of insulin degludec in patients who underwent a total colonoscopy (TCS) associated with screening for colon cancer[39]. A total of 12 patients with type 2 diabetes mellitus treated with insulin degludec and scheduled for TCS were enrolled. The patients fasted for 24 h after having supper (at 18.00 hours) on the day before TCS until supper (at 18.00 hours) on the day of TCS. The last dose of insulin degludec was given at 08.00 hours on the day before TCS. All other antidiabetic medications were discontinued on the day of TCS. Insulin degludec dosing was resumed at 08.00 hours on the day after TCS. Continuous glucose monitoring was carried out starting on the day before the procedure until after insulin degludec dosing was resumed. Despite the 24-h fasting period, patients taking insulin degludec who underwent TCS did not experience any episodes of hypoglycemia on the day before, of, or after the procedure. Although the means and standard deviations of glucose levels were significantly lower during the fasting period than during the non-fasting period ($P < 0.006$, $P < 0.003$, respectively), the glucose variability (mean changes in glucose levels) during both periods was significantly correlated ($r = -0.8$, $P = 0.008$). These clinical findings are consistent with the long and stable profile of insulin degludec, and seem to be reassuring for its use in relation to hospital procedures.

Although the safety and efficacy of insulin degludec have not been assessed in pediatric patients, a clinical pharmacology study has shown that the pharmacodynamic profiles of insulin degludec in children and adolescents are consistent with those in adults[40].

Finally, insulin is required in pregnant women with type 1 diabetes mellitus or with gestational diabetes. Studies evaluating treatment with insulin degludec in pregnant women have not yet been carried out. As with other insulins, pregnant women should consult their physician, because the body's insulin requirements can change substantially during pregnancy, and in the perinatal and lactation periods.

PRECAUTIONS AND SAFETY CONSIDERATIONS

Hypoglycemia

As with other insulins, it is important to aim for a balance between achieving the best possible glycemic control and minimizing the risk of hypoglycemia. The phase 3a clinical development program showed non-inferiority of insulin degludec to other basal insulins in terms of the reduction in HbA1c[9,10,14,17]. Additionally, the rate of nocturnal hypoglycemia was consistently lower with insulin degludec, whereas the overall hypoglycemia rate did not seem to differ[9,10,14,17,41]. The early clinical experience with insulin degludec in Japanese patients seems to be consistent with these observations[42]. However, it is important that patients and clinicians are aware that the half-life and the duration of action of insulin degludec might differ from those of other basal insulins, and they should take into consideration these differences between other insulins and insulin degludec to minimize the risk of hypoglycemia. It is recommended to start at a conservative dose and adjust the dose according to the patient's level of glycemic control to avoid hypoglycemia.

Insulin degludec has a distinct molecular design and mode of protraction. The long duration of action could lead to a perception of the accumulation or stacking of each dose. However, this has not been observed in our clinical experience or in the controlled phase 3 clinical studies. In addition, the counter-regulatory responses with insulin degludec were examined in a stepwise hypoglycemic clamp study[43]. The results of that study showed that insulin degludec preserved the endogenous counter-regulatory responses with significantly less glucose infusion required to maintain plasma glucose at target. In real-life settings, this should reduce the risk of severe hypoglycemia, because the body retains the ability to respond to low glucose levels by increasing glucose availability.

Exercise-related hypoglycemia was investigated in seven randomized treat-to-target trials involving insulin degludec[44]. The proportions of patients who experienced exercise-related confirmed or nocturnal hypoglycemia were similar between insulin degludec and another basal insulin. In a separate meta-analysis of three randomized treat-to-target trials[45], there was no statistically significant difference between insulin degludec and another basal insulin in terms of the duration, impact or recovery time of hypoglycemic episodes.

Other Possible Safety Considerations

The phase 3a clinical development program of insulin degludec involved more than 10,000 patients in 40 countries[8–17]. Several important safety parameters were studied, including immunogenicity, antibody formation, affinity for insulin-like growth factor-1 receptors, mitogenicity, cardiovascular events and injection-site reactions. The results obtained in this program show that insulin degludec exhibits an acceptable safety profile similar to that of other basal insulins, with no statistical or clinical differences in any of these parameters[8–17].

In the study by Onishi *et al.*[14] comparing insulin degludec and insulin glargine in an Asian population, 59% and 65% of patients in the insulin degludec and insulin glargine groups, respectively, reported at least one adverse event, of which ~99% were mild or moderate. Rates of serious adverse events were similar between groups (both: 0.1 events/patient-year of exposure [PYE]). Few patients reported injection-site reactions with insulin degludec (1.8% of patients) or insulin glargine (2.1% of patients); all reactions were mild in severity.

In a recent study by Hollander *et al.*[46], similar proportions of patients reported adverse events in the insulin degludec (84%) and insulin glargine (83%) groups. The rates of major adverse cardiovascular events for insulin degludec and insulin glargine were low (0.03 and 0.02 events/PYE, respectively). The rates of injection-site reactions for insulin degludec and insulin glargine were also low (0.05 and 0.02 events/PYE, respectively). Most of the adverse events in each group were mild, and the most frequently reported serious adverse events in both groups were hypoglycemia (0.01 event/PYE) and coronary artery disease (0.01 event/PYE).

Considering the unique properties of each insulin, and because patients might respond differently to different insulin preparations, physicians should carefully monitor their patients when starting new medications or changing therapies to detect possible safety issues. A number of post-marketing surveillance studies of insulin degludec are currently underway in Japan and other countries. Furthermore, insulin degludec is under review by the Food and Drug Administration (FDA) in the USA. After their initial review, the FDA requested additional cardiovascular data from a dedicated cardiovascular trial. The cardiovascular safety of insulin degludec was evaluated in the phase 3a development program. There were no significant differences in the prespecified primary analysis of major adverse cardiovascular events in patients treated with insulin degludec or insulin degludec/aspart compared with those treated with the active control[47]. The FDA requested a number of additional and post-hoc analyses, some of which showed varied risk levels and wide confidence intervals above the upper limit of the FDA criteria. Although insulin degludec has already been approved in Europe, Japan and a number of other countries, the FDA decided to review the data from the cardiovascular trial before making their final decision. This cardiovascular outcomes study is currently ongoing globally under the name DEVOTE. DEVOTE is a randomized, double-blind, controlled clinical trial comparing the cardiovascular safety of insulin degludec with that of insulin glargine in 7,500 subjects with type 2 diabetes at high risk of cardiovascular events. The trial was initiated in October 2013. It is event-driven, and has an anticipated duration of up to 5 years. DEVOTE will include subjects from Japan and more than 20 other countries[48]. These additional studies and routine post-marketing surveillances are expected to provide further data on the safety, efficacy and utility of this new basal insulin.

CONCLUSIONS

Insulin degludec is a novel basal insulin analog product that has been available in Japan since March 2013. It has been reported to be safely and effectively used in patients with type 1 diabetes mellitus and type 2 diabetes mellitus both in the in-hospital as well as the outpatient setting in Japan based on real-life clinical experience and published clinical trial data reports from several Japanese institutions[14,20–24]. Insulin degludec shows a distinct mechanism of action resulting in a flat, stable profile and a very long duration of action. It is important to understand the implications and relevance of the findings from the controlled clinical trial programs in the real-life clinical settings. This is of particular clinical value for Japanese patients who might have different levels of sensitivity and responsiveness to insulin compared with Caucasians[49]. Overall, the early real-life clinical experience with insulin degludec in Japanese patients[20–23] confirms the findings from the clinical pharmacology and the large phase 3 clinical trials with this agent. Insulin degludec showed a longer duration of action with more consistent glycemic effects in Japanese patients compared with other currently available basal insulins. These features allow insulin degludec to have a more favorable effect in minimizing hyperglycemic spikes during dawn, dusk and throughout the day as evidenced by CGM measurements in Japanese patients[20,21]. The same features could also explain the observed lower risk of hypoglycemia, particularly in terms of fewer nocturnal episodes. Additional larger studies would be useful to compare the effect of insulin degludec in different titration algorithms in Japanese patients. Although such studies are ongoing as part of the phase 3b development program of insulin degludec, it is important to increase the real-life clinical experience with insulin degludec in Japanese patients to gain further understanding of the utility of this new agent and the appropriate patients who might benefit the most from its administration.

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DISCLOSURE

KK has served on speaker bureaus for Takeda, Kowa, Novo Nordisk, Novartis, MSD and Dainippon Sumitomo; has consulted for Novo Nordisk, Takeda, Sanwa Kagaku Kenkyusho,

Chugai, AstraZeneca and Taisho; and has received research support from Takeda, Novo Nordisk, Daiichi-Sankyo, Sanofi, MSD, Novartis, AstraZeneca, Chugai and Boehringer Ingelheim. MAE is a medical doctor and an employee of Novo Nordisk Japan, serving as Chief Medical Officer and Head of Medical & Scientific Affairs.

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