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Practical Diabetes

Insulin Degludec, a Long-Acting Once-Daily Basal Analogue for Type 1 and Type 2 Diabetes Mellitus

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ABSTRACT

Here, we discuss certain practical issues related to use of insulin degludec, a new long-acting basal insulin analogue. Degludec provides uniform ("peakless") action that extends over more than 24 hours and is highly consistent from dose to dose. Like the 2 previously available basal analogues (detemir and glargine), degludec is expected to simplify dose adjustment and enable patients to reach their glycemic targets with reduced risk of hypoglycemia. Phase 3 clinical trials involving type 1 and type 2 diabetes have demonstrated that degludec was noninferior to glargine in allowing patients to reach a target glycated hemoglobin (A1C) of 7%, and nocturnal hypoglycemia occurred significantly less frequently with degludec. In addition, when dosing intervals vary substantially from day to day, degludec continues to be effective and to maintain a low rate of nocturnal hypoglycemia. Degludec thus has the potential to reduce risk of nocturnal hypoglycemia, to enhance the flexibility of the dosing schedule and to improve patient and caregiver confidence in the stability of glycemic control. A dedicated injector, the FlexTouch prefilled pen, containing degludec 200 units/mL, will be recommended for most patients with type 2 diabetes. Degludec will also be available as 100 units/mL cartridges, to be used in the NovoPen 4 by patients requiring smaller basal insulin doses, including most patients with type 1 diabetes.

Mots clés :
insuline basale
dégludec
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injecteur d'insuline
hypoglycémie nocturne
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diabète de type 2

RÉSUMÉ

Dans cet article, nous traitons de certains problèmes pratiques liés à l'utilisation de l'insuline dégludec, un nouvel analogue de l'insuline basale à action prolongée. La dégludec procure une action uniforme (« sans pic ») qui s'étend sur plus de 24 heures et qui est très constante d'une dose à l'autre. Comme les 2 analogues de l'insuline basale déjà disponibles (détémir et glargine), la dégludec devrait simplifier l'ajustement de la dose et permettre aux patients d'atteindre leurs objectifs glycémiques et de diminuer le risque d'hypoglycémie. Les essais cliniques de phase III sur le diabète de type 1 et de type 2 ont démontré que la dégludec n'était pas inférieure à la glargine en ce qui concerne l'atteinte par les patients d'une hémoglobine glyquée (A1c) cible de 7 % et qu'elle réduisait significativement la fréquence de l'hypoglycémie nocturne. De plus, lorsque les intervalles posologiques varient considérablement d'un jour à l'autre, la dégludec maintient son efficacité et son faible taux d'hypoglycémie nocturne. La dégludec a donc le potentiel de réduire le risque d'hypoglycémie nocturne, d'accroître la flexibilité du schéma posologique et de renforcer la confiance du patient et du soignant quant à la stabilité de la régulation de la glycémie. L'injecteur FlexTouch, un stylo prérempli contenant la dégludec à 200 U/ml, sera recommandé à la plupart des patients souffrant de diabète de type 2. La dégludec sera également disponible en cartouches de 100 U/ml afin d'être utilisée avec le NovoPen 4 par les patients dont de plus petites doses d'insuline basale sont nécessaires, dont la plupart des patients ayant le diabète de type 1.

Introduction

Basal glycemia control is essential for all patients with type 1 or type 2 diabetes mellitus. For type 2 diabetes patients, introduction of a basal insulin is a common first choice after failure of oral agents (1). Owing to its moderate cost, moderate coverage and familiar use, neutral protamine Hagedorn (NPH) insulin is frequently the first basal insulin prescribed (2). However, long-acting insulin analogues detemir and glargine have been engineered to provide extended coverage, with a flatter action profile and greater consistency of action from dose to dose than is possible with NPH insulin (3,4). As a result, these analogues are associated with reduced frequency of overall and nocturnal hypoglycemia, relative to NPH insulin (3,5,6).

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Degludec is a novel basal analogue providing more extended action than glargine, with a more predictable effect (7), and it is consistently associated with reduced nocturnal hypoglycemia rates (8–11). Here, we discuss some of degludec's distinguishing features, focusing on practical issues that diabetes educators may need to communicate to their patients as this new analogue becomes available in Canada. In particular, we consider the clinical record of degludec, including safety issues related to hypoglycemia and nocturnal hypoglycemia. We also discuss the possibility of flexibly timed daily dosing, as well as issues of dose titration and the selection of appropriate injection devices for patients receiving degludec.

Two cases

Case 1: Inadequate glycemia control in a 22-year-old man with type 1 diabetes

H.D., a 22-year-old man weighing 77 kg (body mass index [BMI] 24 kg/m^2), was first diagnosed with type 1 diabetes at 12 years of age. He is currently taking glargine 10 units twice daily, plus bolus mealtime insulin aspart. He has a history of poor glycemic control. On this visit, H.D.'s laboratory results reveal glycated hemoglobin (A1C) of 9.5% and fasting plasma glucose (FPG) of 9.7 mmol/L. He states that his FPG numbers range from 2 mmol/L to sometimes as high as 18 mmol/L. In an effort to prevent nocturnal hypoglycemic episodes, which he has experienced frequently in the past year, he skips his insulin dose when he is concerned that he has eaten less than usual. H.D. works at the student cafeteria 2 nights per week and frequently has evening classes. Although he carries an insulin pen in his backpack, he acknowledges that he sometimes delays taking his evening basal dose when he is busy or in class. He feels unsure about taking his injection at a later time, when it would be more convenient, so he occasionally omits this dose entirely.

Case 2: Initiation of basal insulin in a middle-aged man with type 2 diabetes

F.L. is a 55-year-old businessman who travels frequently from Canada to Southeast Asia. He weighs 95 kg (BMI 34 kg/m^2) and has a history of hypertension and elevated low-density lipoprotein cholesterol. He was diagnosed with type 2 diabetes mellitus at age 45 and currently is on a daily regimen of glyburide (10 mg twice daily), metformin (1000 mg twice daily) and sitagliptin (100 mg once daily). The dosages of his oral antidiabetic medications have increased steadily over the past 3 years to their current maximums. Despite these efforts, his most recent A1C level was 9.7%, and today's FPG was 9.2 mmol/L. F.L. is reluctant to initiate insulin, citing his fear of hypoglycemia and uncertainty about how to manage regular insulin injections while travelling frequently and crossing time zones.

Insulin Degludec

Degludec is a long-acting insulin analogue engineered to address the problem of variable insulin exposure, which patients experience with NPH insulin or basal analogues (6,12). Several novel features of this basal analogue were identified in the clinical research reported to date.

Pharmacology

After injection, degludec molecules cluster, forming large assemblies (multihexamers) inside the subcutaneous depot. Although the multihexamers are too large to be absorbed into the circulation, degludec monomers gradually dissociate from these multihexamers. The monomers cross into the capillary blood and from there to target tissues, such as the liver, fat and muscle. The result is a slow, even delivery of insulin, without peaks, with consistent day-to-day exposure (13).

The half-life of degludec is almost exactly twice that of glargine (25.4 hours vs. 12.5 hours), and it can be found in the bloodstream for a considerably longer time after a single injection (>120 hours vs. 36 to 48 hours) (14). Over 24 hours, the glucose-lowering action of degludec is almost completely flat, even at higher doses (Fig. 1) (13). Day-to-day fluctuation of this effect is 4 times smaller than with glargine in patients with type 1 diabetes (coefficient of variability, 20% vs. 82%; $p<0.0001$) (15). These features (peakless action and predictability between doses) simplify dose titration (12) and are associated with reduced risk of hypoglycemia (4).

Although degludec's glucose-lowering action persists for more than 24 hours, there is no "stacking" of sequential once-daily doses. That is, insulin exposure does not continue to increase over time, but rather comes to a stable, steady-state level relatively quickly, after 2 to 3 doses; if the daily dose does not change, degludec exposure remains relatively constant thereafter (16). Because of this feature, it is not recommended that the dose of degludec be adjusted every day, as is commonly done with other basal insulins (17).

The pharmacology of degludec suggests that this analogue may reduce the risk of nocturnal hypoglycemia, below that seen with other basal insulins. It also opens the door to the option of flexibly timed daily dosing. Both of these ideas have been studied, and outcomes have been reported for several phase 3 clinical trials.

Efficacy and hypoglycemia outcomes

Key outcomes from 2 head-to-head comparison studies of degludec and glargine (18,19), extending to 2 years of observation, are presented Figure 2. These 2 open-label studies are representative of the other degludec reports, including the pivotal 1-year studies evaluating the safety and efficacy of degludec versus glargine in patients with type 1 diabetes or type 2 diabetes (8,9).

In terms of glycemic control (A1C and fasting glucose), degludec was noninferior (i.e. equivalently effective) to glargine in both trials (18,19). Mean A1C declined by approximately 0.25 percentage points in type 1 diabetes patients and by more than 1 percentage point in type 2 diabetes patients over 2 years, regardless of which basal insulin was used (Figure 2, upper panels). Weight gain in previously insulin-naïve type 2 diabetes patients was also comparable (2.7 kg vs. 2.4 kg; $p=0.31$) (19).

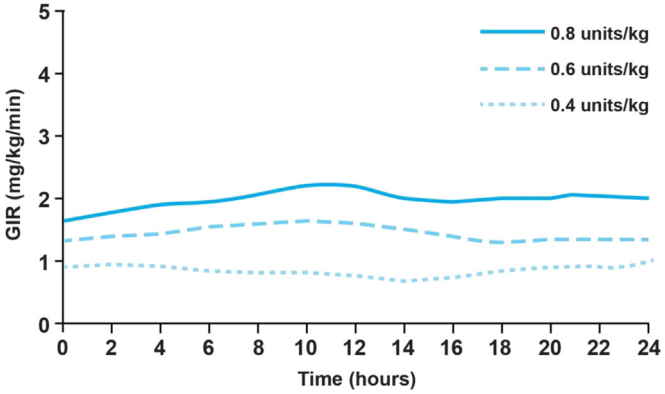

Figure 1. The glucose-lowering action of degludec lasts beyond 24 hours, with little variation over time, even at the highest dose tested. Solid blue line, 0.8 U/kg; dashed line, 0.6 U/kg; dotted line, 0.4 U/kg. GIR, glucose infusion rate. Reprinted with permission from Heise et al (13).

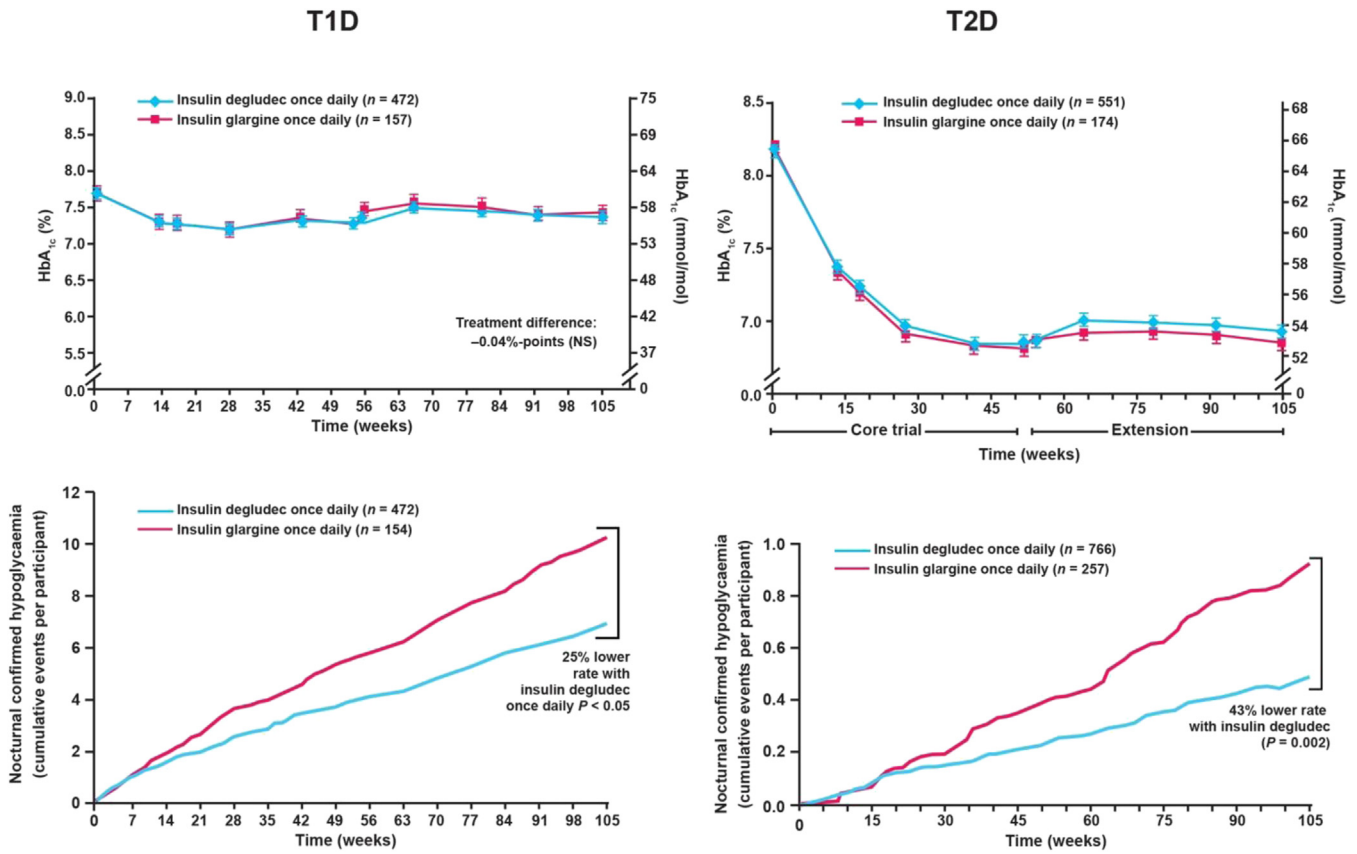

Figure 2. (Upper panels) Equivalent glycemic control with basal-bolus therapy using degludec or glargine in type 1 diabetes (T1D [left]) and type 2 diabetes (T2D [right]). (Lower panels) Rates of nocturnal hypoglycemia were significantly lower by 25% (p=0.02) in the degludec arm of the type 1 diabetes trial (left) and by 43% (p=0.002) in the type 2 diabetes trial (right). Blue lines, insulin degludec once daily; red lines, insulin glargine once daily. HbA, hemoglobin A1C; NS, nonsignificant. Reprinted with permission of the authors (18,19).

Overall, hypoglycemia rates did not differ significantly between the 2 treatments in either study. However, the nocturnal hypoglycemia rate (Figure 2, lower panels), which is more directly related to the basal component of the basal-bolus treatment, was approximately 25% lower with degludec than with glargine in the type 1 diabetes study, a statistically significant difference (3.9 vs. 5.3 episodes per patient-year; p=0.02) (18). In the type 2 study, nocturnal hypoglycemia was 43% less frequent with degludec (0.27 vs. 0.46 episodes per patient-year; p=0.002) (19). Similar findings have been observed consistently in other studies comparing degludec and glargine, as confirmed in a preplanned meta-analysis (11).

There was no significant difference in severe hypoglycemic events in the 2-year type 1 diabetes study (18). However, serious hypoglycemic events were statistically significantly less frequent with degludec in the type 2 diabetes study (0.006 vs. 0.021 episodes per patient-year; p=0.023) (19). Such events were rare in both studies.

Dosing flexibility

Additional research has explored the possibility of flexibly timed, once-daily degludec dosing. In studies of type 1 diabetes (20) or type 2 diabetes (21), patients were randomly allocated to use degludec either once daily at a consistent time or once daily with a changing dose interval. In the latter regimen, intervals between doses alternated between 8 and 40 hours; this schedule was designed to test the effects of administering degludec once daily, but not at regular 24-hour dosing intervals. In these studies, the changing daily dosing interval with degludec was associated with a similar decline in A1C and a similar or lower rate of nocturnal hypoglycemia, when compared with regular daily dosing with degludec (type 1 diabetes, 6.2 vs. 9.6 events per patient-year for irregular or regular daily dosing, respectively; type 2 diabetes, 0.6 vs. 0.6 events per patient-year) (20,21). These studies show that degludec can be administered, even at irregular intervals between 8 and 40 hours, with no significant change in glycemic control and no increase in nocturnal hypoglycemia risk (16).

Key practice point

While extreme variation in dosing intervals apparently causes no harm to patients on degludec, there is no reason to recommend it. Patients should be encouraged to establish a regular, easy-to-remember schedule for taking their daily degludec injection, but they should also be aware that if they forget or are unable to take their dose at the usual time, they can safely take it earlier or later in the day.

Practical Aspects of Degludec Treatment

Insulin dosing and dose titration are important considerations that affect patient acceptance and adherence (22,23) and, ultimately, the safety and effectiveness of the treatment (1,24). Below, we review what is known about the appropriate administration of degludec by patients with type 1 diabetes or type 2 diabetes.

Injection devices

Degludec will be available in a FlexTouch (Novo Nordisk, Bagsvaerd, Denmark) prefilled pen (25,26), which may be particularly suitable for the patient with type 2 diabetes. This pen features push-button dose delivery designed for comfort and ease of use, important considerations for patients with limited dexterity or hand strength (25). Dosing is accurate and highly consistent from injection to injection, regardless of dose size (27).

The prefilled FlexTouch pen contains 600 units of degludec in a total volume of 3 mL. With this 200 U/mL degludec formulation, the FlexTouch pen can administer a single dose of 2 to 160 units per injection, in 2-unit increments. With this concentration, there will be half the volume of fluid injected into the site, compared with standard 100 U/mL insulin formulations. This smaller volume may be of particular significance to type 2 diabetes patients who inject high doses of insulin. Comfort at the injection site and absorption issues are major considerations when choosing among the available insulins. Because degludec has a shelf life of 56 days at room temperature, the FlexTouch pen can be used without risk of insulin wastage as long as the patient requires an average daily dose ≥12 units.

For patients requiring basal insulin doses of <80 units daily, degludec cartridges are also available, to be used in a NovoPen 4 (Novo Nordisk). The cartridges contain degludec formulated at 100 U/mL, in a total volume of 3 mL. Doses range from 1 to 60 units per injection, in 1-unit increments. Regardless of the concentration of the insulin, the number dialled on the pens will reflect the actual units of insulin being given.

Starting dose, dose titration and dose adjustment with degludec

For patients with type 2 diabetes, basal insulin is now often initiated by starting with 10 units at bedtime and adjusting by 1 unit on subsequent nights until the glucose target is achieved—the "10+1" approach (17). However, 10+1 titration has not been tested in the case of degludec; daily dose adjustment (as in the 10+1 approach) is not expected to be feasible for this basal analogue, because the effect of an insulin dose change will only be fully evident when steady state is reached, which requires 2 to 3 days with degludec.

However, other titration schemes have been explored. In some trials, the starting doses of degludec or glargine were based on prior basal doses, although not always on a 1:1 unit basis. In pivotal studies, for patients already on once-daily insulin (basal or premix), the starting dose of degludec was chosen by replacing their prior basal insulin on a 1:1 unit basis (8,9). For patients previously on multiple daily doses of a basal insulin, the once-daily dose of glargine was reduced by 20% to 30%, whereas the once-daily dose of degludec had no such automatic reduction (8,9). In the 2-year type 2 diabetes study (19), starting dose for the insulin-naive patients was set at 10 units nightly.

In these trials, basal insulin doses were calibrated once weekly, for the mean of 3 sequential days of FPG levels, according to a predetermined algorithm that targeted fasting glucose of <5 mmol/L. However, this once-weekly dose adjustment scheme may not be suitable for use outside the clinical trial setting. A proposed titration schedule for degludec in type 2 diabetes is shown in Table 1. This approach is based on 2-unit dose adjustment increments, titrated twice per week and at least 3 days apart. This scheme targets fasting glucose to a range of 4.0 to 7.0 mmol/L, as recommended by current guidelines (28). Once the fasting glucose target has been reached, the dose of degludec is maintained. The dose can be increased or decreased by 2 units (1 click if using the prefilled FlexTouch pen) if glucose is above or below this range. The proposed approach is similar to a simple, once-weekly titration method that was recently described (29).

Table 1
Proposed scheme for twice-weekly dose adjustment with degludec for patients with type 2 diabetes

Fasting glucose on day of titration	Dose adjustment
<4.0 mmol/L	Decrease dose by 2 units.* Maintain reduced dose for next 3 to 4 days, until next scheduled titration day.
4.0 to 7.0 mmol/L	Maintain dose for next 3 to 4 days, until next scheduled titration day.
>7.0 mmol/L	Increase dose by 2 units.* Maintain increased dose for next 3 to 4 days, until next scheduled titration day.

* Two units of degludec corresponds to 1 click on the dose-adjustment dial of the FlexTouch pen, which may be used for patients requiring larger daily doses. Patients using a degludec cartridge in the NovoPen 4 will be able to adjust by increments of 1 unit. As suggested in the resolution to case 1, practitioners may choose in some cases to adjust the dose of degludec by 1-unit increments, again maintaining a twice-weekly schedule for dose adjustment (no more frequent than 1 adjustment per 3 days).

In some cases (e.g. in the lean elderly, in type 1 diabetes patients and in patients with severe renal impairment), the prescriber may prefer to titrate in 1-unit increments. This is not possible with the degludec FlexTouch pen (2-unit increments), but it is feasible if the patient is provided with a NovoPen 4 (1-unit increments), with degludec prescribed in cartridge form. Whatever the titration increments, degludec dose adjustment should be done twice weekly, rather than daily.

It is anticipated that the best way to implement this schedule will be to work with the patient to identify 2 consistent days per week to titrate (e.g. Mondays and Thursdays or Tuesdays and Fridays). Titration is based on the fasting glucose on the scheduled titration day. The daily dose is maintained between scheduled titration days and hence will be adjusted, at most, every 3 to 4 days. However, it is imperative for clinicians to individualize insulin dosing, considering the patient profile. For type 1 diabetes patients, we suggest that degludec be initiated as with any other basal insulin; titration can occur with 1-unit intervals, every 3 to 7 days, as determined by the physician. Dose adjustment for exercise with degludec is similar to that for other basal insulins. For patients using degludec in a basal-bolus regimen, food intake and mealtime insulin should be modulated to offset changes in exercise intensity.

Approaches to cases

Case 1: Inadequate glycemic control in a 22-year-old man with type 1 diabetes

H.D.'s difficulties with adherence are not unusual for a young, active person. Such a patient may find twice-daily insulin injection obtrusive and may be inconsistent in remembering to take even a single dose at the same time each day. Particularly in light of his recent experience with nocturnal hypoglycemia, degludec may be a reasonable option to increase the acceptability and potentially improve the safety of his basal insulin regimen. He is currently taking 20 units of glargine daily, in 2 equal doses in the morning and evening, with mealtime aspart. To transition to degludec, he should be prescribed a 100 U/mL degludec cartridge and a NovoPen 4, and he should begin with 20 units of degludec. For simplicity, his aspart regimen should remain unchanged, to be re-evaluated after he has established a new routine with once-daily degludec.

H.D. should be instructed to continue monitoring his blood glucose, but on a more frequent basis—at least 4 times a day while making the transition to the new basal regimen. He should then

adjust his dose twice a week, on Tuesdays and Fridays, as his weekday schedule is more regular and predictable than his weekend schedule. He has type 1 diabetes and has had significant difficulty with hypoglycemia. Because he may not need large doses of basal insulin, we are safer to provide him with the 100 U/mL cartridges, to make smaller changes. To reduce the risk of hypoglycemia, he will be instructed in a titration schedule of adding 1 unit for glucose levels >7 mmol/L and decreasing by 1 unit for glucose levels <4 mmol/L; he will call if he has any concerns. Alternatively, he could contact the clinic each week for several weeks, to ensure that he understands how to titrate his dose to the Canadian Diabetes Association target FPG of 4.0 to 7.0 mmol/L and to confirm that he is not experiencing any difficulties with his new regimen.

H.D. should choose a time for his regular daily injection of degludec, possibly a morning dose if this makes it easier for him to introduce the injection into his schedule. It is expected that he will continue to take his degludec injection on this schedule. However, he can be assured that if he forgets his dose or has any other reason to shift the timing of his degludec injection, he should take the missed dose at another time, ensuring that he continues to take his degludec injection on a daily basis and that all intervals between doses are at least 8 hours and no more than 40 hours long.

Case 2: Initiation of basal insulin in a middle-aged man with type 2 diabetes

F.L. is clearly a candidate for insulin treatment. However, he expresses some reluctance to make this transition because he is fearful about hypoglycemia and concerned about difficulties with dose timing during international travel. A basal-only treatment on a flexibly timed, once-daily schedule with degludec would be practical and address his concern regarding ease of use.

Owing to his weight and probable insulin resistance, F.L. may require a higher dose of insulin to achieve glycemic control. After instruction on the use of the pen, he should be instructed to take 10 units, at a consistent time each day if possible. Self-monitoring of blood glucose should be encouraged, with a minimum of once-daily FPG. He will increase his insulin twice a week, on Tuesdays and Fridays, as he usually has a large Sunday dinner, so Monday's FPG may be a higher-than-usual reading. He will use the titration schedule of adding 2 units for glucose levels >7 mmol/L and decreasing by 2 units for glucose levels <4 mmol/L (Table 2), based on the scheduled day for titration. He should not increase his insulin if he has more than 2 episodes of hypoglycemia in a week. If that should occur, he should call the clinic for instruction. Otherwise, he will call if he has any concerns and will return to the clinic in 6 weeks.

Table 2
Patient profiling for degludec therapy

Patient profile for degludec therapy includes any patient with type 1 diabetes or type 2 diabetes being considered for basal insulin analogues, particularly patients who:

- Have a history of, or an elevated risk for, nocturnal hypoglycemia
- Are unable, or find it burdensome, to administer basal insulin more than once daily
- Have irregular schedules, such as shift workers or students
- Travel frequently
- Benefit from use of the FlexTouch pen, including persons with dexterity issues and those who require large daily insulin doses (up to 160 units in a single injection)
- Rely on external resources to assist with insulin injection, such as home care patients and patients whose families assist insulin administration
- Are unable to achieve glycemic control on their current basal insulin therapy for risk of hypoglycemia or insulin variability

Conclusion

Insulin degludec, a long-acting basal analogue, was developed to address the need for more consistent, peakless insulin exposure over 24 hours (7). Degludec provides glycemic control similar to that of glargine but with a consistently, and statistically significant, lower risk of nocturnal hypoglycemia (18,19). This new analogue reaches steady-state levels after 2 to 3 daily injections. Degludec is used once daily, at any time that is convenient for the patient, and it is compatible with day-to-day variation in dosing intervals when needed (16). As is true for other patients on basal-bolus regimens who exercise, it is imperative to work with patients to adjust their mealtime analogue dose and food intake, to reduce risk of hypoglycemia.

Degludec appears to be a reasonable option for all patients who are being considered for treatment with basal insulin analogues. It may be especially advantageous for specific groups of patients, on the basis of their medical histories, personal habits and work or social schedules. Table 2 identifies patients who might particularly benefit from the combination of reduced nocturnal hypoglycemia risk and flexibly timed, once-daily injection with degludec.

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