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Ultra-long-acting insulins: A review of efficacy, safety, and implications for practice

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ABSTRACT

Background and purpose: In the past decade, there has been much advancement in oral antidiabetic agents, but few changes in insulin therapy. With the addition of the ultra-long-acting insulins, insulin glargine U300 (IGlar 300) and insulin degludec (IDeg 100 and IDeg 200), it is important to understand key aspects in the agents' clinical properties, efficacy, safety, dosing, packaging, and place in therapy.

Methods: A literature review was conducted using PubMed database and was limited to English, full-text articles published from January 2000 to January 2018. The following search terms were used: insulin glargine 300, insulin degludec, Toujeo, Tresiba, and ultra-long-acting insulin.

Conclusions: These agents are longer acting with sustained insulin coverage as compared with other basal insulins while having a low potential for hypoglycemia. Efficacy and safety profiles are quite good, and potential for weight gain was similar to IGlar 100.

Implications for practice: Depending on the patient's needs, these newer agents may offer some advantages. Insulin glargine U300 and IDeg 200 are concentrated, allowing for administration of large doses by less volume, thereby theoretically improving absorption. For patients needing flexible dosing, IDeg may be beneficial. The ultra-long-acting agents may also be useful if it is suspected that the basal insulin is not lasting the entire day.

Keywords: Basal insulin; diabetes mellitus; ultra-long-acting basal insulin.

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Introduction

The prevalence of diabetes is increasing globally. An estimated 422 million adults had diabetes in 2014, encompassing about 8.5% of the adult population worldwide (World Health Organization, 2016). Diabetes burdens 29.1 million people (9.3% of the population) in the United States. The total medical cost associated with diabetes is estimated to be $245 billion each year in the United States alone, which is about 2.3 times higher than for people not affected by the disease (Centers for Disease Control and Prevention, 2017). Not only is the prevalence increasing, but diabetes itself increases the risk of heart attack, stroke, kidney failure, leg amputation, vision loss, nerve damage, and complications related to pregnancy (World Health Organization, 2016). Glucose control is of utmost importance to decrease the risk of microvascular complications related to diabetes (Lachin et al., 2015).

In the past decade, there has been much advancement in oral antidiabetic agents, but few changes in insulin therapy. Despite this, insulin remains the mainstay of treatment for Type 1 diabetes and is often needed for Type 2 diabetes to adequately achieve glucose control (Cefalu, Rosenstock, LeRoith, & Riddle, 2015). In fact, the American Diabetes Association recommends initiating insulin for any patient with Type 2 diabetes who has not achieved their glycemic goals with other agents (American Diabetes Association, 2018).

Due to its convenience, basal insulin is generally recommended initially in combination with metformin or another noninsulin agent for uncontrolled Type 2 diabetes before progressing to basal–bolus insulin therapy.

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Until 2015, the only basal insulins available were U-100 neutral protamine Hagedorn (NPH), insulin glargine 100 units/ml (IGlar 100), insulin detemir, and human regular U-500, which has properties of both basal and bolus insulin. Insulin glargine U100 and detemir offer a clinical advantage over NPH secondary to a longer duration of action with less risk of hypoglycemia (Philis-Tsimikas et al., 2006; Yki-Jarvinen, Dressler, & Ziemen, 2000). Human regular U-500 provides a clinical advantage for patients with severe insulin resistance, requiring less volume per injection (Lane et al., 2009). Detemir, human regular U-500, and occasionally even IGlar 100, often require more than one dose each day for glucose control (Ashwell, Gebbie, & Home, 2006; Segal, Brunner, Burch, & Jackson, 2010; Swinnen et al., 2010).

The newer concentrated basal insulins are insulin glargine 300 units/ml (IGlar 300) and insulin degludec (IDeg). Insulin degludec is available in both 100 and 200 units/ml (IDeg 100 and IDeg 200, respectively). These higher concentrations allow for larger dosages of insulin to be administered with less volume per injection. They may also help to improve adherence for those injecting large doses of insulin (Davis, Lamos, & Younk, 2016). With the addition of these products, clinicians have many more options when selecting basal therapy, which can make it more difficult to determine the best agent for each patient. This article will review the new ultra-long-acting insulin products, IGlar 300, and IDeg 100 and IDeg 200, with a focus on pharmacokinetic and pharmacodynamic properties, efficacy, safety, dosing, packaging, and place in therapy.

Methods

Study authors conducted a comprehensive literature search using the PubMed database for clinical trials and review articles published from January 2000 to January 2018 using the following terms: insulin glargine 300, insulin degludec, Toujeo, Tresiba, and ultra-long-acting insulin. Eligibility criteria consisted of articles that were published in English and available in full text. Preference was given to randomized controlled trials, pharmacodynamics, and pharmacokinetics studies. Food and Drug Administration labeling, package inserts, treatment guidelines, medication prescribing guides (specifically for IGlar 300 and IDeg), and websites for drug pricing information were also reviewed and used sparingly to provide supporting information on dosing, packaging, and place in therapy.

Pharmacokinetics and pharmacodynamics

Compared with the original human insulin analogues, the ultra-long-acting basal insulins are designed for prolonged absorption into the systemic circulation, leading to a longer duration of action (Table 1). This protracted absorption of the ultra-long-acting basal insulins also results in a smoother, more consistent pharmacokinetic profile with blunted peak concentrations, thereby more closely mimicking the physiologic secretion of basal insulin from the pancreas in the fasting state. The blunted peak serum concentrations may also reduce the risk of hypoglycemia (Jonassen et al., 2012). This section will summarize the pharmacokinetic and pharmacodynamic properties of each of these agents.

Insulin glargine 300. Insulin glargine 300 is an analog of human insulin, differing by an exchange of the amino acid asparagine for glycine at position 21 of the insulin A chain, and the addition of two arginine residues at the C-terminus of the B chain (Becker et al., 2015; "Toujeo (insulin glargine injection) U-300 [package insert]," 2015). These structural alterations cause IGlar 300 to have a low pH of approximately 4, which is soluble in solution. After injection into the neutral pH of the subcutaneous tissue,

Table 1. Pharmacokinetics of select insulin products

Generic Name	Brand Name	Onset of Action (hr)	Time to Peak Effect (hr)	Duration of Action (hr)
Regular human insulin U-100	Humulin R, Novolin R	0.5–1	2–3	4–6
NPH insulin	Humulin N, Novolin N	2–4	4–10	8–16
Detemir	Levemir	~2	8	14–24
Glargine U-100	Lantus	2–4	8–12	20–24
Glargine U-300	Toujeo	6	[a]	30
Degludec U-100, U-200	Tresiba	~2	[a]	42
Regular human insulin U-500	Humulin R U-500	0.2–0.3	6	20

[a] *Minimal peak.*

Sources: Becker et al., 2015; de la Pena et al., 2011; Heise et al., 2016; 2012; "Humulin R U-500 [package insert].," 2016, "Toujeo (insulin glargine injection) U-300 [package insert]," 2015, "Tresiba (insulin deguldec injection) [package insert]," 2016; Korsatko et al., 2013; Powers & D'Alessio, 2011; Triplitt, Repas, & Alvarez, 2017.

the solution is neutralized, leading to the formation of microprecipitates that slowly dissolve and are released into circulation at a slow and continuous rate (de Galan, 2016). Insulin glargine U300 and IGlar 100 are structurally the same molecule, with the same amino acid sequence and the same active metabolites. Insulin glargine U300 is formulated at a concentration of 300 units/ml, which is three times the concentration of IGlar 100. This higher concentration allows for a smaller injection volume with a corresponding smaller surface area of the depot in the subcutaneous tissue. This smaller surface area results in a longer residence time and a slower redissolution rate compared with IGlar 100, leading to a more gradual and prolonged absorption into the systemic circulation (Wang, Zassman, & Goldberg, 2016).

The onset of action of IGlar 300 is approximately 6 hours, which is somewhat slower than that of IGlar 100 (3–4 hours). Insulin glargine U300 also has less of a peak effect than IGlar 100 (Becker et al., 2015; Steinstraesser, Schmidt, Bergmann, Dahmen, & Becker, 2014; "Toujeo (insulin glargine injection) U-300 [package insert]," 2015). Insulin glargine U300 reaches steady-state concentrations within 3–4 days and has an elimination half-life of approximately 19 hours (Becker et al., 2015). The median duration of action for IGlar 300 is 30 hours. This is approximately 5 hours longer, and more evenly distributed, than that of IGlar 100 (Becker et al., 2015; Bergenstal et al., 2017). Insulin glargine U300 demonstrates a more constant and sustained pharmacokinetic profile at steady state (Becker et al., 2015; Bergenstal et al., 2017; Steinstraesser et al., 2014).

Insulin degludec. Insulin degludec is similar to endogenous human insulin except for the removal of the C-terminus threonine at position 30 of the insulin B chain (ThrB30), which is replaced with a 16 carbon fatty acid and a glutamic acid spacer molecule. In solution, IDeg forms stable and soluble dihexamers that, upon injection, self-associate further into chains known as multihexamers, thereby creating a subcutaneous depot of insulin (Jonassen et al., 2012; "Tresiba (insulin deguldec injection) [package insert]," 2016). With the dissolution of zinc from the multihexamer structure, IDeg is slowly and continuously released from the subcutaneous tissue and into circulation, which contributes to its ultra-long duration of action (Jonassen et al., 2012).

Insulin degludec has an onset of action of approximately 2 hours and an elimination half-life of approximately 25 hours (Heise, Nosek, Bøttcher, Hastrup, & Haahr, 2012; Powers & D'Alessio, 2011). The slow and constant release from the depot is responsible for a duration of action of approximately 42 hours at steady state, which is achieved in 2–3 days with once-daily subcutaneous injections (Heise et al., 2016).

The glucose-lowering effect of IDeg has been shown to be flat, consistent, and evenly distributed throughout its 24-hour dosing interval. The glucose-lowering effect also increases linearly as the dosage is increased (Heise et al., 2012). Of note, the pharmacokinetic and pharmacodynamic profiles of IDeg observed in patients with diabetes are similar in patients with hepatic and renal dysfunction, as well as the older persons (Kiss et al., 2014; Korsatko et al., 2014; Kupčová et al., 2014). Despite there being two concentrations, IDeg 100 and IDeg 200, the pharmacokinetic and pharmacodynamic profiles of both concentrations are similar (Korsatko et al., 2013; Vora et al., 2015).

Efficacy

Insulin glargine 300. Clinical efficacy data for IGlar 300 compared with IGlar 100 comes from the EDITION trials (Bolli et al., 2015, 2017, Home et al., 2015, 2018, Riddle et al., 2014, 2015, Yki-Järvinen et al., 2014, 2015). The trials were designed as open-label, parallel group, and treat-to-target, which were based on a fasting plasma glucose (FPG) of 80–100 mg/dl. The EDITION 1, 2, and 3 trials focused on differing populations with Type 2 diabetes, whereas EDITION 4 trial focused on patients with Type 1 diabetes (Bolli et al., 2015, 2017, Home et al., 2015, 2018, Riddle et al., 2014, 2015, Yki-Järvinen et al., 2014, 2015). With a few exceptions, these trials consisted of mostly Caucasian, male patients who were approximately 60 years of age with a glycated hemoglobin (HbA1c) of around 8%. Patients in EDITION 3 were insulin naive and had a higher baseline HbA1c at 9.8% when compared with other IGlar 300 trials (Bolli et al., 2015, 2017; Home et al., 2015; Riddle et al., 2014, 2015, Yki-Järvinen et al., 2014, 2015). The EDITION 4 trial focused on patients with Type 1 diabetes with a similar trial design. These patients were younger than other IGlar 300 trials, with a mean age of 47 years, but they had a similar baseline HbA1c of around 8% (Home et al., 2015, 2018).

In all EDITION trials, IGlar 300 was determined to be noninferior to IGlar 100. This means that in clinical efficacy related to HbA1c, IGlar 300 and IGlar 100 are essentially equivalent. This is to be expected in a treat-to-target design (Bolli et al., 2015, 2017, Home et al., 2015, 2018, Riddle et al., 2014, 2015, Yki-Järvinen et al., 2014, 2015). In patients with Type 2 diabetes who were being treated with insulin, there was an approximate 0.5%–1.0% reduction in HbA1c and a 30 mg/dl reduction in fasting blood glucose. These results were maintained through the 12-month duration of the trials (Home et al., 2015, 2018, Riddle et al., 2015, 2014, Yki-Järvinen et al., 2014, 2015). In patients who were insulin naive, there was a more significant reduction in HbA1c at approximately −2.7%. This reduction was seen in both the IGlar 300 and the IGlar 100 groups and was sustained over 12 months (Bolli et al., 2015, 2017). The EDITION 4 trial compared patients who took IGlar 300 in the morning to those who took it in the evening. Largely, there were no differences in most efficacy endpoints, including fasting blood glucose. The key exception to this

was related to the HbA1c. At the end of 12 months, patients taking IGlar 300 in the morning had an HbA1c of 7.76% compared with 7.96% in those taking IGlar 300 in the evening. The authors stated that this could be related to higher insulin doses in those taking IGlar 300 in the morning. They also stated that this finding could be complicated by diurnal hormonal differences and patterns of physical activity (Home et al., 2015, 2018). At this point, it is recommended that IGlar 300 be administered at approximately the same time each day ("Toujeo (insulin glargine injection) U-300 [package insert]," 2015). Overall, reduction in HbA1c and FPG were similar between IGlar 300 and IGlar 100, but across all EDITION trials, patients on IGlar 300 required an approximately 10% higher basal insulin dose to achieve those results (Bolli et al., 2015, 2017, Home et al., 2015, 2018, Riddle et al., 2014, 2015, Yki-Järvinen et al., 2014, 2015).

Insulin degludec. The BEGIN trials are the major clinical trials related to IDeg. The majority of these trials were conducted using IDeg 100, but IDeg 200 is considered to be equivalent in glucose-lowering effects (Bode et al., 2014, 2013; Garber et al., 2012; Mathieu et al., 2013; Zinman et al., 2012). Additionally, the majority of these trials compared IDeg 100 with IGlar 100. To date, there are limited trials that directly compare IDeg 100 with IDeg 200. All the BEGIN trials had similar designs in that they were all open label, treat-to-target, noninferiority trials. Within the treat-to-target design, patients were initiated on their assigned insulin product and the dose was then titrated to achieve a fasting glucose less than 90 mg/dl (Bode et al., 2013; Garber et al., 2012; Zinman et al., 2012). The BEGIN trials focusing on patients with Type 2 diabetes enrolled patients who were approximately 58 years of age, primarily male, and Caucasian. The mean HbA1c was just above 8.0%, with a duration of diabetes for 8 years (Garber et al., 2012; Zinman et al., 2012). In the BEGIN trial that focused on patients with Type 1 diabetes, the mean age was younger at 43 years of age with slightly more male patients than female patients and a majority being Caucasian. These patients had Type 1 diabetes for approximately 19 years and had a mean HbA1c of 7.7% at baseline (Bode et al., 2013).

As one would expect in a treat-to-target design trial, there were few differences in efficacy in trials comparing IDeg 100 to IGlar 100, supporting their claim of noninferiority. In trials consisting of patients with Type 2 diabetes who had previously been treated with insulin, there was an approximate 1.0% reduction in HbA1c from baseline with consistent results over 24 months (Garber et al., 2012; Rodbard et al., 2013; Zinman et al., 2012). In insulin-naive patients with Type 2 diabetes, there was a similar 1.0% reduction in HbA1c, but there was a significantly greater reduction in FPG as compared with those on IGlar 100 (−69 vs. −60 mg/dl [p = .005], respectively) (Zinman et al., 2012). In the BEGIN trial focusing on patients with Type 1 diabetes, there was an overall smaller reduction in HbA1c at 0.40% over 12 months and a 0.27% reduction at the end of 24 months (Bode et al., 2013; Heller et al., 2012). The authors did not comment on this, but clinically, this difference is relatively insignificant. The lower effect seen in these patients is likely related to their lower initial HbA1c when compared with those studied with Type 2 diabetes.

As stated above, there are few trials with IDeg 200. BEGIN Low Volume was one of those trials, and it compared IDeg 200 to IGlar 100 in patients with Type 2 diabetes who were insulin naive over 26 weeks. Patients in both groups achieved a 1.3% reduction in HbA1c by the end of the trial period, but patients receiving IDeg 200 had an approximate 6 mg/dl greater reduction in FPG over those in the IGlar 100 group (Gough et al., 2013). These findings were similar to those found in the trial comparing IDeg 100 to IGlar 100. The only other trial including IDeg 200 was the BEGIN Compare trial, which compared IDeg 200 to IDeg 100 in a 22-week noninferiority trial. The key finding regarding HbA1c from this trial is that there was only a −0.11% (95% confidence interval [CI]: −0.28 to 0.05) estimated treatment difference between the groups (Bode et al., 2014). From this, it can be inferred that similar results can be seen if a patient is receiving either IDeg 200 or IDeg 100.

Safety and tolerability

Insulin glargine 300. ***Hypoglycemia.*** In EDITION 1, fewer participants reported ≥1 confirmed episodes of hypoglycemia (≤70 mg/dl) at any time of day (24 hours) with IGlar 300 (86%) compared with IGlar 100 (92%) over 12 months (relative risk 0.94 [95% CI: 0.89–0.99]) (Riddle et al., 2015). Overall, fewer participants reported episodes of hypoglycemia when comparing IGlar 300 to IGlar 100 in EDITION 2, 3, and 4, but this was not significantly different between the agents (Bolli et al., 2017; Home et al., 2018; Yki-Järvinen et al., 2015).

Nocturnal hypoglycemia. In EDITION 1, fewer participants reported ≥1 confirmed episode of nocturnal hypoglycemia (≤70 mg/dl) with IGlar 300 (54%) compared with IGlar 100 (65%) over 12 months (relative risk 0.84 [95% CI: 0.75–0.94]). Overall, fewer participants reported episodes of nocturnal hypoglycemia when comparing IGlar 300 to IGlar 100 in EDITION 2, 3, and 4, but this was not significantly different between the agents (Bolli et al., 2017; Home et al., 2018; Yki-Järvinen et al., 2015).

Severe hypoglycemia. Episodes of severe hypoglycemia occurred in only 1.4%–11% of participants in EDITION 1, 2, 3, and 4; however, there was no significant difference when comparing IGlar 300 with IGlar 100 (Bolli et al., 2017; Home et al., 2018; Riddle et al., 2015; Yki-Järvinen et al., 2015).

Weight gain. In EDITION 2, there was a significant between-group difference in mean change in body weight when comparing IGlar 300 (0.4 kg) with IGlar 100 (1.2 kg) at

month 12 (least square mean difference −0.7 [95% CI: −1.3 to −0.2], p = .009) (Yki-Järvinen et al., 2015). Although overall numerically less for IGlar 300, the increase in weight was small and similar for both IGlar 300 and IGlar 100 in EDITION 1, 3, and 4 (Bolli et al., 2017; Home et al., 2018; Riddle et al., 2015).

Insulin degludec. ***Hypoglycemia.*** In BEGIN Basal-Bolus Type 2, the overall rates of confirmed hypoglycemia were 11.1 episodes/patient-year exposure for IDeg 100 compared with 13.6 for IGlar 100, estimated rate ratio 0.82 (95% CI: 0.69–0.99), p = .0359 (Garber et al., 2012). In the other BEGIN trials, similar rates of hypoglycemia were reported for both IDeg 100 and IGlar 100 (Gough et al., 2013; Mathieu et al., 2013; Meneghini et al., 2013; Philis-Tsimikas, Brod, Niemeyer, Ocampo Francisco, & Rothman, 2013; Zinman et al., 2012).

Nocturnal hypoglycemia. In BEGIN Once Long, BEGIN Basal-Bolus Type 1, BEGIN Basal-Bolus Type 2, and BEGIN-Flex T1, there were few episodes of nocturnal hypoglycemia overall, but these occurred at a significantly lower rate with IDeg 100 versus IGlar 100 (Garber et al., 2012; Mathieu et al., 2013; Zinman et al., 2012). The other BEGIN trials demonstrated low but similar rates of hypoglycemia with IDeg 100 and IGlar 100.

Severe hypoglycemia. Overall, episodes of severe hypoglycemia occurred rarely in the BEGIN trials; however, only 0.3% of IDeg 100 participants in BEGIN Once Long reported 1 or more episodes of severe hypoglycemia compared with 1.9% in IGlar 100 participants, estimated rate ratio 0.14 (95% CI: 0.03–0.70), p = .017 (Garber et al., 2012; Gough et al., 2013; Mathieu et al., 2013; Meneghini et al., 2013; Philis-Tsimikas, Brod, Niemeyer, Francisco, & Rothman, 2013; Zinman et al., 2012).

Weight gain. Weight gain ranged from 1.1 to 3.6 kg for IDeg 100 and from 1.3 to 4.0 kg for IGlar 100 between 26 weeks and 2 years in the BEGIN trials; however, there were no significant differences found when comparing the two agents (Garber et al., 2012; Gough et al., 2013; Mathieu et al., 2013; Meneghini et al., 2013; Philis-Tsimikas et al., 2013; Zinman et al., 2012).

Implications for Practice

Dosing and administration. All three of these products are administered by subcutaneous injection and should not be used intramuscularly or intravenously nor should they be mixed with any other insulin product. Patients should be counseled to store unused pens in the refrigerator until the expiration date. Patients should also inspect the product before use to ensure there are no particles and that the solution is clear and colorless. According to the American Diabetes Association, 2018 Standards of Care, providers should initiate basal insulin at 10 units a day or 0.1–0.2 units/kg/d (American Diabetes Association, 2018). No dose conversions are necessary, as the pen devices allow the user to dial up the actual number of units to be delivered ("Toujeo (insulin glargine injection) U-300 [package insert]," 2015, "Tresiba (insulin deguldec injection) [package insert]," 2016).

Insulin glargine 300. Insulin glargine 300 is supplied as a 1.5-ml Solostar prefilled pen in a box of three pens, supplying the patient with 1,350 units per box. Insulin glargine 300 is provided in doses ranging from 1 to 80 units per injection. It is typically administered as a once-daily injection.

In insulin-naive patients with Type 1 diabetes, IGlar 300 should be dosed at one third to one half of the total daily dose of insulin, with the remainder used as short/rapid-acting insulin divided by each meal ("Toujeo (insulin glargine injection) U-300 [package insert]," 2015). In patients with Type 2 diabetes who are insulin naive, the recommended starting dose is 0.2 units/kg of body weight ("Toujeo (insulin glargine injection) U-300 [package insert]," 2015). Prescribers may need to consider adjusting doses of other concomitant medications to reduce the risk of hypoglycemia.

In patients with Type 1 and Type 2 diabetes already on once-daily long-acting or once-daily intermediate acting insulin, the same dose can be used of IGlar 300. If patients are taking twice-daily NPH insulin, the recommendation is to start IGlar 300 at 80% of the total daily NPH dose to reduce risk of hypoglycemia ("Toujeo (insulin glargine injection) U-300 [package insert]," 2015).

Prescribers should also note patients controlled on IGlar 100 may require a higher dose (10% higher dose seen in studies) of IGlar 300 to maintain glycemic control; however, it is not recommended to adjust the dose when initially changing from IGlar 100 to IGlar 300. It is also recommended to wait approximately 3–4 days to titrate the dose to reduce risk of hypoglycemia ("Toujeo (insulin glargine injection) U-300 [package insert]," 2015; Wang et al., 2016).

Insulin degludec. Insulin degludec 100 and IDeg 200 are supplied as a 3-ml FlexTouch prefilled pen in a box of five pens (for IDeg 100) and three pens (for IDeg 200), totaling 1,500 units and 1,800 units per box, respectively. Providers should make sure to specify which concentration they intend for their patient to receive. The maximum dose per injection with IDeg 100 is 80 units, which is comparable to the older basal insulin pen devices. The IDeg 200 pen device offers a distinct advantage for patients on insulin doses greater than 80 units per day, as the pen allows the patient to give up to 160 units in one injection, making this a great option for patients who are on large doses of basal insulin. It is important for providers to note that IDeg 100 dials in 1 unit increments, whereas IDeg 200 dials in 2 unit increments. If the patient is on IDeg 200, then their dose should always be an even number. The manufacturer recommends IDeg to be used as a once-daily injection at any time of the day, not increasing the dose more often than every 3–4 days. If a patient misses a dose, they should

administer the day missed, ensuring the spacing of the next dose by at least 8 hours ("Tresiba (insulin deguldec injection) [package insert]," 2016).

In insulin-naive patients with Type 1 diabetes, the starting dose should be one third to one half of the total daily dose of insulin. Patients with Type 2 diabetes who are insulin naive can initiate at 10 units of IDeg 200 once daily. In patients currently on insulin, the dose of IDeg 200 can be the same unit dose of the total daily long- or intermediate-acting insulin dose. Other antidiabetic medications may be altered if needed, to prevent hypoglycemia in insulin-naive patients ("Tresiba (insulin deguldec injection) [package insert]," 2016).

Place in therapy. ***Insulin glargine 300.*** Insulin glargine U300 offers a more constant and prolonged action profile when compared with its predecessor, IGlar 100, offering patients a basal option that lasts the entire day without fluctuations in levels (Riddle et al., 2016). Despite the insulin's duration of action being greater than 24 hours, IGlar 300 has low incidence of hypoglycemia and less reported nocturnal hypoglycemia compared with IGlar 100, which has a shorter duration of action (Freemantle et al., 2016). This can be especially helpful if a clinician suspects that a patient may be losing efficacy of their basal insulin toward the end of the day.

This is a highly concentrated insulin, which also makes it an attractive option for patients requiring large doses of insulin (where erratic absorption could be a concern). As mentioned previously, the pen device is limited to a maximum of 80 units per injection; therefore, a patient requiring greater than 80 units would need to administer two separate injections to receive their full dose (as this product is not available in a bulk vial formulation) ("Toujeo (insulin glargine injection) U-300 [package insert]," 2015). This may be a concern for patients desiring to minimize their number of injections.

Insulin degludec. The extended duration of action of IDeg can be a benefit for patients who may not be getting a full 24-hour coverage from their basal insulin. The unique formation of multihexamers, as described earlier, allows for a slow and continuous delivery of the molecule into circulation, resulting in prolonged and stable insulin absorption and low incidence of hypoglycemia (Heise et al., 2012; Kerlan, Thuillier, & Alavi, 2015).

One specific advantage of IDeg is the ability for flexible dosing. Efficacy and safety were considered noninferior when patients were allowed to vary dosing times each day versus administering at the same time every day (Kadowaki et al., 2016). This may be especially beneficial for shift workers or patients who often forget to take their insulin at the same time each day. The pen device also can be stored at room temperature for 56 days after being opened, which is the longest of all insulin products and may be helpful for patients who require lower doses ("Tresiba (insulin deguldec injection) [package insert]," 2016).

Conclusion

Although the increase in available insulin products can have a positive impact on diabetes management, more options can make it increasingly difficult when selecting an agent. Each of the agents highlighted in this review have distinct properties that may be beneficial for specific patients. Overall, they appear to be safe and efficacious when compared with other available basal insulin therapy (Bode et al., 2013; Garber et al., 2012; Gough et al., 2013; Mathieu et al., 2013; Meneghini et al., 2013; Philis-Tsimikas et al., 2013; Riddle et al., 2015; Steinstraesser et al., 2014; Zinman et al., 2012). The agents have an overall low risk of hypoglycemia and provide sustained insulin coverage throughout the entire day, making them all suitable options for basal coverage, especially for patients who may have issues with waning blood glucose control toward the end of the day (Freemantle et al., 2016; Kerlan et al., 2015).

Cost is typically a key factor in choosing a product. The average wholesale price of these insulin products are very similar to each other and to the pen devices for IGlar 100 and insulin detemir when compared unit for unit ("Lexi-Comp, Inc. (Lexi Drugs)," 2018). Actual out-of-pocket cost for each patient, however, varies depending on insurance coverage and the availability of manufacturer discount cards or other discount programs.

In summary, some key differences in clinical applicability of IGlar 300 and IDeg are that IGlar 300 and IDeg 100 have a maximum limit of 80 units per injection, whereas IDeg 200 has a limit of 160 units per injection, making it more convenient for patients requiring 81–160 units to administer a full dose in one daily injection. Furthermore, IDeg has been shown to maintain efficacy even when given at varying times during the day, which may be advantageous in certain patients such as shift workers or those who frequently vary their dosing schedule (Kadowaki et al., 2016; "Tresiba (insulin deguldec injection) [package insert]," 2016). The two concentrated basal insulins, IGlar 300 and IDeg 200, allow for greater doses to be administered with less volume, theoretically improving absorption in patients on large doses of insulin. In conclusion, these new ultra-long-acting insulins can certainly be a beneficial option for many patients, but as always, their utilization should be based on the characteristics of each product and the individual patient's needs.

Competing interests: *The authors report no conflicts of interest.*

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