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REVIEW

Clinical Use of Degludec in Children and Adolescents with T1D: A Narrative Review with Fictionalized Case Reports

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ABSTRACT

The use of insulin in children and adolescents with type 1 diabetes (T1D) is a challenge because of the heterogeneity of these patients and their lifestyles, with consequent unpredictability in blood glucose levels. A new ultra-long-acting basal insulin, insulin degludec (degludec), has the potential to mitigate some of these challenges, notably variability in the glucose-lowering action of the basal insulin component of an insulin regimen, and consequent risks of hypo- and hyperglycemia. However, the protracted half-life and steady state pharmacokinetics of degludec potentially bring some new challenges. In particular, the adjustment of therapy in response to commonly encountered clinical situations might require a different approach when degludec is used in place of other currently used basal insulins in this challenging patient population. The purpose of this article is to guide clinicians through a series of case histories in the use of this insulin. These include, but are not limited to, how to initiate, titrate, switch from other basal insulin or pump therapy; how to alleviate difficulties arising as a result of unpredictable lifestyle/habits; and how to maintain treatment following diabetic ketoacidosis. The guidance presented in this review illustrates that degludec is a good option for a diverse range of children and adolescents with T1D, providing much needed flexibility in the treatment of this challenging patient population.
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Keywords: Blood glucose; Diabetic ketoacidosis; Insulin analogue; Long-acting insulin; Self-monitoring; Type 1 diabetes

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INTRODUCTION

Challenges of the Pediatric Population with T1D

Type 1 diabetes (T1D) is primarily diagnosed in children and adolescents (i.e., patients aged less than 20 years) [1]. The incidence of T1D is rising and this is most notable in prepubertal children, where the rise is greatest [1]. Projections incorporating this rising incidence estimate a tripling of new cases of T1D in this group from 2010 to 2050 [2].

Children and adolescents with T1D present a challenge to clinicians because of their developmental immaturity (physiological and psychological), their heterogeneous and often unpredictable lifestyles (diet, exercise, support in management of diabetes, and sleeping patterns), and long periods without their usual parent/guardian carer [3, 4]. While guidelines such as those from the International Society for Pediatric and Adolescent Diabetes (ISPAD) are developed to support clinicians requiring guidance for many of the common challenges in this population of patients, it is not within the scope of the guidelines to provide tailored recommendations for the numerous prandial and basal insulins on the market [5]. Therefore, clinicians seeking advice beyond the information in the product label may turn to clinical trial data to learn more about the practicalities of using a basal insulin. However, there are few clinical trials investigating the use of basal insulin in children and adolescents with T1D in daily life, and because data from clinical trials in adults with T1D are not applicable to the pediatric population such as differences in insulin exposure [4], different basal/bolus ratio, and insulin resistance and there is an unmet need regarding guidance on how to use basal insulins safely and effectively in different clinical scenarios. Despite being essential for these patients (i.e., without administration of exogenous insulin, T1D is a fatal condition), the limited evidence base for safe use means that many modern basal insulins analogs are not (or were only recently) approved for use in the full age spectrum for the pediatric population with T1D (birth to less than 18 years old).

Insulin degludec (degludec) is one exception to these generalizations, representing the only ultra-long-acting insulin analog indicated for T1D and type 2 diabetes (T2D) in children as young as 1 year of age [6, 7], with clinical studies demonstrating its equivalent pharmacokinetics (PK) to adults [4] and comparative effectiveness compared with other basal insulins [8]. Degludec is available in both 100 units/mL or 200 units/mL FlexTouch® pens, depending on country.

The purpose of this article is to inform clinicians about the unique characteristics of degludec and how to adapt/employ these in the treatment of children and adolescents with T1D. To this end, we provide detailed guidance based on a range of fictionalized case histories drawn from real life. These examples illustrate how best to use degludec when initiating or switching basal insulin, how to titrate dose in the event of poor control, hypoglycemia, or following an episode of diabetic ketoacidosis (DKA), and how to adapt degludec administration when there is inconsistency in care or lifestyle. However, it should be noted that it is important to check the Summary of Product Characteristics for individual countries to confirm conditions of use and also any relevant local or national regulations concerning reimbursement in children and adolescents. This paper does not contain any experimental studies using human participants or animals performed by any of the authors. Rather, it utilizes the authors' practical experience of clinical use of degludec in children and adolescents.

PK Profile of Degludec

To fully understand the clinical profile of degludec, and the reasons why it differs from other basal insulins, requires an understanding of its unique pharmacological properties. Although the relatively very long half-life of degludec (Table 1) may appear intimidating, this actually affords patients and prescribers a greater degree of flexibility [9, 10] when confronting issues common to the pediatric population, such as delayed or missed doses and administration of smaller dose increments during titration [11].

The long half-life and hence long duration of action of degludec is achieved through a unique mechanism of protraction [12]. Degludec is present as a solute in a formulation in which the individual insulin molecules are self-associated into stable dihexamers. After injection, the diffusion of phenol causes these structures to polymerize into multihexamer chains, forming a subcutaneous (SC) depot. As zinc slowly dissociates, these structures then slowly and predictably release bioactive insulin monomers (at a slow and steady rate), which are readily

Table 1 Pharmacokinetic properties of available basal insulins

	Degludec [13, 14] (0.4–0.8 U/kg)	**IDet [70, 71] (0.4–0.8 U/kg)**	**Glargine U100 [13, 72–75] (0.3–0.8 U/kg)**	**Glargine U300 [72, 76] (0.4 U/kg)**	**NPH insulin [75, 77] (0.3–0.4 U/kg)**
Peak action, h	Minimal peak	2–3[a]	8–12[b]	Minimal peak	5
Mean half-life, h	24–27	5.0–7[c]	12–14	19	4.0
Duration of action, h	> 42	20–23[a]	20–26[d]	30–36	13[a]
Recommended dosing interval	Once per day	Once or twice per day	Once per day	Once per day	Once or twice per day

Degludec insulin degludec, *IDet* insulin detemir, *glargine U100* insulin glargine 100 units/mL, *glargine U300* insulin glargine 300 units/mL, *NPH* neutral protamine Hagedorn

[a] Duration may be shorter

[b] Peaks were compared across several studies from 0.3 to 0.8 U/kg

[c] Depending on dose

[d] Reported range at 0.3 U/kg

absorbed from the depot into the circulation. As a result, degludec exhibits slow and consistent absorption kinetics, resulting in a protracted duration of action, with half-life exceeding 24 h, and a total duration of action exceeding 42 h [13, 14]. The total duration of action of an insulin depends on dose and the individual patient's insulin sensitivity, but in clamp studies of adult patients with T1D, a total duration of action exceeding 42 h was reported for all patients at doses of 0.6 and 0.8 U/kg, and a duration of at least 33 h (but often exceeding 42 h) was reported at a dose of 0.4 U/kg [15].

Other basal insulins, when administered once daily, do not achieve consistent and stable glucose lowering or fail to cover the full 24 h (Table 1), having a variable peak and a waning glucose-lowering effect prior to the next injection. Consequently, these insulins need to be dosed consistently at 24-h intervals, with little variability in injection timing, and adjustments are required in bolus insulin to compensate for this. In addition, some basal insulins are only available for treatment of adults [16]. In contrast, degludec, with its half-life greater than 24 h, reaches near steady-state levels (greater than 90%) [13] within 72 h of initiation [17]. The consistent glucose-lowering effect of degludec over 24 h typically results in a reduced basal and bolus insulin requirement when patients are switched from their previous basal insulin [18]. However, dose adjustments with degludec take 48–72 h to have clinical effect. The half-life of degludec is also longer relative to its dosing interval compared with other basal insulins (Table 1), and subsequently clinicians may be concerned about accumulation or "stacking" of degludec. However, the accumulation of insulin degludec with successive doses is precisely matched by its clearance with the attainment of "steady state". The clearance rate of insulin is directly proportional to the circulating concentration, thus stacking does not occur with degludec and steady state plasma concentrations are quickly attained (Fig. 1) [19]. Consequently, the long half-life of degludec means that once steady state is reached, there will be much reduced peak–trough fluctuations, translating into a more consistent glucose-lowering action (flatter time–action profile) over a 24-h period [19, 20].

Not only does the protraction mechanism (and dosing interval) of degludec minimize PK/pharmacodynamic (PD) fluctuations over the day but it also results in a consistent PK/PD profile from injection-to-injection and hence a

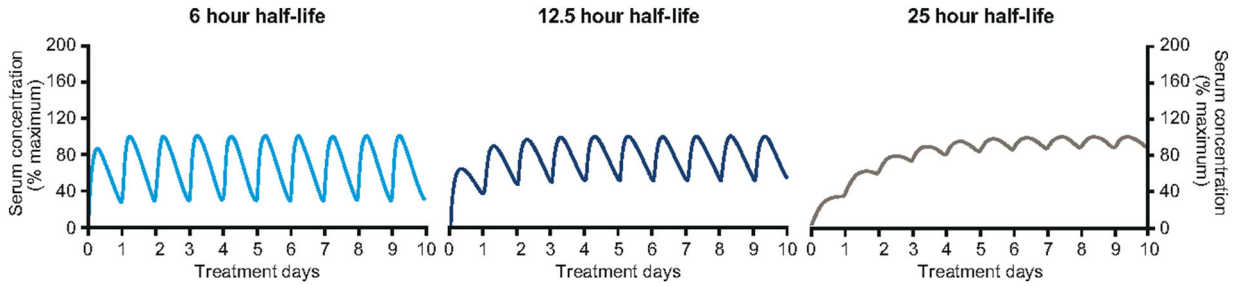

Fig. 1 Hypothetical accumulation of insulin from first dose to steady state for insulins with various half-lives with once-daily dosing. Reproduced from *Endocrine Practice*, 201, Heise T and Meneghini L, Insulin stacking versus therapeutic accumulation: understanding the differences, 75–83, Copyright 2014, with permission from the American Association of Clinical Endocrinologists [19]

predicable glucose-lowering response [15]. As the PK of degludec is equivalent in adults and children [4], it is worth noting, despite the physiological differences between these age groups, the results of the Flex T1 study in adults with T1D. The Flex T1 study demonstrated that once steady state is achieved, there is considerable latitude to vary the dosing interval at the patient's convenience (± 16 h giving a range of 8–40 h between injections), provided that the patient continues to receive, on average, one injection every 24 h [10]. These properties give degludec a flexibility in dose timing that is not available with other basal insulins that have a shorter half-life. Hence, inconsistences in the dosing of degludec (e.g., missed doses, mistimed doses, and excess doses) will have a greatly attenuated impact on the circulating basal insulin concentration. Once initiated, in addition to the lower rates of hypoglycemia demonstrated in treat-to-target clinical trials [21], in real-world clinical practice, in adults, degludec is capable of achieving better glycemic control at a lower insulin dose and with lower rates of hypoglycemia compared with other basal insulins [22, 23].

GUIDANCE AND CLINICAL CASES

Broad Guidance for Clinicians

The first week on any insulin regimen is an important time as this period is used to establish the baseline doses that will be used during ongoing treatment. It is often a period of learning for the child or caregiver. Following diagnosis of T1D, the immediate goals of treatment are patient education in self-management, eliminating ketosis, and titrating insulin doses to restore blood glucose to within the target range without hypoglycemia or excessive hyperglycemia. Long term, this will prevent the harmful impacts of hyperglycemia and ketosis from causing long-lasting complications [5]. It is very difficult to formally evaluate such patients in clinical trials, which typically exclude patients less than 3–12 months from diagnosis. As a result, there is a lack of clinical evidence regarding the use of degludec in children at diagnosis (as is the case with other basal insulins) [18]. Additionally, no randomized clinical trials have formally evaluated basal insulin in infancy.

Case 1: How to Initiate a Patient on Degludec/Starting Dose

Patient case 1 Initiating with degludec following diagnosis

Name: Olivia A1C: 13.0% (118.9 mmol/mol)

Age: 13.3 years

Body weight: 48.6 kg

Previous dose: None

Case history

Olivia has a new diagnosis of diabetes. She has hyperglycemia (18.1 mmol/L [326 mg/dL]), and ketosis, but is not acidotic. She does lots of sport. Olivia is in puberty, and had menarche 2 months ago

Patient case 1 continued

Guidance

Olivia was initiated on degludec 14 units (0.29 units/kg) daily with insulin aspart as bolus insulin, with an ICR of 1 unit to 15 g carbohydrate, with a correction factor of 1 unit to 3 mmol/L (55 mg/dL), aiming for fasting plasma glucose of 5.0–7.4 mmol/L (90–130 mg/dL)

ICR insulin to carbohydrate ratio

Broad Guidance for Clinicians

In children and adolescents, degludec is initiated as a basal insulin component from diagnosis to help restore glycemic control (see patient case 1 for guidance). To ensure that the dose of degludec can be safely titrated toward the maintenance dose, it is important to start at a fraction of the predicted total daily dose (basal + bolus) and dose degludec according to the child's body weight. In practice, degludec should be initiated at 30–50% of the predicted total daily dose (basal + bolus). The total daily dose (units/kg/day) will be selected (or estimated after intravenous (IV) insulin treatment) on the basis of a patient's fasting blood glucose (BG) targets but also depends on the stage of T1D; with high doses (greater than 0.7 units/kg/day) sometimes required following diagnosis, and lower doses (total daily dose less than 0.5 units/kg/day) in patients in remission [24]. Nevertheless, the insulin requirement following diagnosis is highly variable depending on the age of child, BMI, puberty status, mode of presentation (e.g., DKA versus no DKA), etc. For example, a thin, young child without DKA and A1C of 7% may need a total daily insulin dose of at most 0.25 units/kg per day, whereas an overweight adolescent who presents with DKA may need at least 1 unit/kg per day. Depending on target A1C (usually less than 7.0% [53 mmol/mol]), these targets typically reside within the range of 4.0–7.0 mmol/L (72–126 mg/dL) for fasting plasma glucose and 5.0–9.0 mmol/L (90–162 mg/dL) for postprandial glucose [25].

Once a dose is selected, it is important to dose degludec every 24 h for the first 2–3 days, without unduly varying the timing until steady state is achieved [17]. Hyperglycemia is straightforwardly overcome with bolus corrections and this is the case whichever basal insulin is used.

Case 2: How to Switch a Patient to Degludec from Other Basal Insulins

Patient case 2 Switching from glargine U100 as a result of issues with painful injections and poor adherence

Name: Alice A1C: 8.0% (63.9 mmol/mol)

Age: 7 years ICR: 1 unit per 15 g at breakfast; 1 unit per 20 g at other meals

Body weight: 22.8 kg

Previous dose: Glargine U100 8 units/day (0.35 units/kg); insulin aspart 12 units across 3 meals

Case history

Alice was diagnosed 6 months ago and started on a basal–bolus injection regimen with glargine U100. Alice is very distressed by her current insulin injections, with complaints about painful injections. Her basal injections are at bedtime, and this is leading to huge anxiety and proving very disruptive to family life and the daily routine. In particular, there is a high burden on Alice's mother, as she is the only person Alice will allow to give the injection. Alice is apprehensive, but okay with her bolus injections

Patient case 2 continued

Guidance

The more neutral pH of degludec (degludec; pH 7.6) compared with that of glargine U100 (pH 4.0) [6, 26] may help alleviate the negative association with daily basal insulin injections

On the basis of her case notes and the lower dose requirement with degludec, a dose reduction of 1 unit was made making Alice's first dose with degludec 7 units/day

In addition, Alice's previous bolus insulin dose was also reduced

Following the switch, Alice's fasting BG testing was used to inform further adjustments in degludec dose. As this information may often be lacking in older children/troubled adolescents, use of CGM or flash glucose monitoring is invaluable

As degludec reaches steady state over a 2- to 3-day period, care was taken to emphasize that doses need to be taken at the same time each day during this period. If this is not possible, the variability in glucose exposure may be corrected for by giving a slightly higher dose of degludec on the first day of switch, or simply correcting with additional bolus insulin over this period

The ICR for Alice's evening meal was reduced from 1 unit per 20 g to 1 unit per 25 g, as degludec has been shown to result in lower postprandial glucose measurements compared with detemir in children with T1D (especially after breakfast and dinner) [8] as well as in adults [27]

Broad Guidance for Clinicians

Patients may be switched to degludec from another basal insulin for a variety of reasons (Table 2), and initially a dose reduction of up to 20% of their daily basal insulin dose is advised [18]. This recommendation is supported by studies of children and adults with T1D comparing degludec with insulin glargine 100 units/mL (glargine U100) [22, 23, 28], and insulin detemir (IDet) [8, 22, 23] that consistently show approximately 10–20% lower basal insulin requirement with degludec. This has also proven to be the case when comparing degludec with insulin glargine 300 units/mL (glargine U300) in patients with T2D [29].

The lower insulin requirement with degludec is partly due to the ability of degludec to be dosed once daily, when the previous basal insulin might have been dosed twice daily, but also due to degludec's greater potency when compared with insulins such as glargine U300 [30]. In practice, dose reductions are also required when switching from glargine U300 or IDet for the bolus dose (see patient case 2 for guidance) as well as the basal dose. Typically, this is a 10–30% reduction as evidenced by studies in adults [22, 23, 28, 29] and children [8].

Table 2 Potential reasons for switching from another basal insulin to degludec

Common reasons for switching to degludec
To reduce the risk of hypoglycemia
To permit setting of lower glycemic targets considering the risk of hypoglycemia
To provide more stable overnight glucose control because of variable and unpredictable fasting plasma glucose levels, or other indications of glucose variability with a previous basal insulin
To address issues with adherence because of the inflexibility of a previous regimen or the injection process/device
To reduce number of basal injections to simplify the lives of children and caregivers
Allergic reactions to other basal analogs

Case 3: How to Switch a Patient to Degludec Previously Using Pump Therapy

Patient case 3a Switching to degludec as a result of poor adherence to pump therapy

Name: Miguel A1C: 9.8% (83.6 mmol/mol)

Age: 15 years ICR: 1 unit per 10 g

Body weight: 65 kg

Previous basal dose: 28 units/day (0.43 units/kg)

Total daily dose: 44 units/day

Case history

Miguel recently had a hospital admission with DKA. His adherence to bolus insulin dosing is not optimal (1–2 boluses per day) and his glucose testing is inadequate (0–2 tests daily), hence he did not recognize his pump had failed as a result of cannula occlusion. Miguel agreed that a pump was not the best option for him at present

Guidance

As Miguel has had issues with adherence, particularly with self-measuring of BG, his basal insulin requirement was recalculated and he received appropriate psychological support and education to help him meet his glycemic targets. As there is often limited information available from non-adherent patients, the added complexity often makes it advisable to start afresh with weight-based insulin dosing (e.g., 40% of body weight for the basal insulin dose). Miguel has a high proportion of his total daily dose determined by his basal insulin (> 60% when it should optimally be 40–50% of total); likely increased to make up for skipped bolus injections

As Miguel was on too much basal insulin, he was started on 25 units/day (0.38 units/kg) of insulin degludec 100 units/mL and 1 unit insulin aspart per 10 g carbohydrate. Flash glucose monitoring was used to facilitate titration of his insulin doses

Patient case 3b Switching to degludec from pump therapy due to a desire for a more discreet treatment

Name: Anna A1C: 8.0% (63.9 mmol/mol)

Age: 17 years ICR: 1 unit per 8 g with breakfast, 1 unit per 10 g with other meals; 1 unit per 12 g before or after exercise

Body weight: 57 kg

Previous basal dose: 24 units/day

Case history

Anna is an active teenager and has been living with diabetes for 8 years. She has been on a pump most of that time, but is keen to have a less "visible" therapy. In general, she is moderately adherent to her diabetes care, performing 3–4 SMBG measurements daily. She remembers insulin boluses, unless she is on a night out with friends, when she will tend to skip boluses, because of anxiety about possible hypoglycemia. Although Anna has suboptimal glycemic control, she changes pump catheter regularly and does not interrupt basal rate. Therefore, the switch to degludec can be based on her previous daily basal dose

Guidance

Although pump therapy has been reported to improve glycemic control and reduce the risk of hypoglycemia and hospitalization for DKA [31, 32], Anna is not in good control as a result of skipped boluses. Instead of using frequent prandial and correction bolus doses, which is associated with better HbA1c, she applies infrequent large corrections. Consequently, Anna still has marked hypo- and hyperglycemia, and potentially DKA. Her fasting glucose was usually satisfactory. Switching to degludec was advised

Anna was commenced on degludec 24 units once daily (0.42 units/kg) (no dose reduction because of still pubertal high insulin need) with the same ICR

She was strongly encouraged not to skip bolus doses

She was educated about alcohol and diabetes, and also counseled regarding pregnancy and diabetes

Clinical Perspective and Rationale for Switching

Utilization of continuous glucose monitoring (CGM) with devices capable of continuous SC insulin infusion (CSII) (pump therapy) currently represents the optimal form of diabetes management [33]. Studies comparing outcomes in patients using pump therapy with multiple daily injections (MDIs) have shown either similar glycemic control and rates of hypoglycemia, or an improvement in glycemic control and risk of hypoglycemia when comparing pump therapy with MDIs [31, 34], whereas one trial (not involving degludec) indicated that in newly diagnosed patients, MDI was superior to CSII [35]. However, pump therapy is not without issues and despite its wide adoption it may not be the best option for all patients, and presently there are no data comparing outcomes in patients treated with pump therapy or with MDI with degludec. Disadvantages of insulin pumps and potential reasons patients or caregivers may wish to switch to insulin injections include issues with pump failure, expense of pump therapy, skin sensitivity/infections, psychological factors (stress from complexity of pump usage and maintenance), weight gain, ketonuria or DKA and poor adherence (forgetting bolus doses or BG testing) [33], or just personal choice. In addition, as children move to adolescence, a shift in responsibility occurs with pump therapy that if not handled correctly can result in declining adherence [36, 37] and the poor glycemic control that is associated with this population [38]. Given that older children and adolescents struggle to remain adherent to self-measuring of blood glucose (SMBG), they may forget to add bolus doses around mealtimes or snacks [39, 40] or just do not want the pump device the whole day on the body (especially the case for adolescent girls) [41]. Therefore, it may be necessary to discontinue pump therapy on safety grounds (see patient cases 3a and 3b for guidance).

Broad Guidance for Clinicians

Pump users require a lower total daily insulin dose than patients administering MDI [39]. When switching from a pump to conventional MDI therapy, a 20% increase in total daily dose will typically be required (usually achieved through rapid titration). The basis for calculating the insulin requirement during initiation of degludec treatment depends on the pre-existing insulin requirement observed with CSII and the level of glycemic control. In children with good glycemic control and low frequency of hypoglycemia, the total dose of degludec may remain unchanged as the reduced proportion of basal insulin in CSII is offsetting any need to reduce the dose of degludec as is customary when switching to degludec from basal insulins. When initiating degludec from another injectable basal insulin, a reduction in the degludec dose is usually required.

Case 4: How to Titrate Degludec in Patients Initiated or Switched from Another Insulin

Patient case 4 Titration of degludec after switching due to prior hypoglycemia

Name: Michael	A1C: 8.5% (69.4 mmol/mol)
Age: 4 years	
Body weight: 14 kg	
Previous MDIs: Biphasic lispro and neutral protamine Hagedorn (NPH) insulin (25:75) given as 7 U (am) and 4 U (pm)	

Patient case 4 continued

Case history

Michael was diagnosed with T1D when he was 3 years old and has been treated with biphasic lispro (25:75 for insulin lispro/insulin lispro protamine) twice daily. Initially, he was very well controlled with a low insulin requirement, but over the last year his control has deteriorated, partly because his parents were unwilling to consider a more intensive insulin regimen. However, he recently experienced an episode of severe nocturnal hypoglycemia and professional CGM documented previously unsuspected nocturnal hypoglycemia, persuading his parents that for their son's safety, a change was required. Additionally, he consistently had elevated fasting glucose potentially due to previously unrecognized nocturnal hypoglycemia and rebound morning hyperglycemia (Somogyi phenomenon) or the "dawn phenomenon" [42]. CGM confirmed that he was experiencing reactive hyperglycemia secondary to unsuspected hypoglycemia, demonstrating that the basal insulin component within his fixed biphasic insulin mixture was too high

Guidance

Michael's parents were advised to increase the frequency of BG monitoring, especially at bedtime and overnight (3–4 h after bedtime) to minimize risk of nocturnal hypoglycemia and a switch to degludec was proposed

The initial dose of degludec (based on his total daily requirement) was reduced from the level used with NPH insulin and set to 30% of his daily dose (0.3 U/kg)

Beginning on 4 U/day (0.29 units/kg) of degludec, the titration algorithm of the BEGIN: Young 1 was applied [8] and on the basis of his lowest pre-breakfast fasting plasma glucose of 10.9 mmol/L (196 mg/dL), his first dose adjustment was an increase of 1 U to 5 U/day

Over the course of 2 weeks, Michael reached his new target of 4–8 mmol/L (70–145 mg/dL), achieved with 4.5 U (0.32 units/day) of degludec and he experienced no recurrence of nocturnal severe hypoglycemia

Glycemic Targets

Current ISPAD guidelines (2018) recommended an A1C target of less than 7.0% (53 mmol/mol) for children with T1D using analog insulins, advanced insulin delivery technology, and who are able to check BG regularly (i.e., use of CGM) [25]. A higher A1C target of 7.5% (58 mmol/mol) is advised in children who are unaware, or unable to articulate hypoglycemia, those at risk of severe hypoglycemia, and in areas where access to modern analogs and technology is more limited [25]. In particular, children younger than 6 years of age should receive special consideration when setting glycemic targets as they are more susceptible to the adverse effects of hypoglycemia on brain development because they may be unable to recognize, articulate, and/or manage episodes of hypoglycemia [43].

With greater emphasis on individualizing glucose targets, current ISPAD guidelines no longer specify fixed glucose targets throughout the day [25] as provided in previous guidelines (Table 3). For CGM users, time in range is considered a more optimal measure of glycemic control [44].

In patients using CGM, additional targets include the proportion of time that BG remains within target range (3.9–10.0 mmol/L [70–180 mg/dL]) in relation to the amount of time BG reflects a state of hypoglycemia (less than 3.9 mmol/L [less than 70 mg/dL]) [25]. Time in range greater than 70% is considered optimal, but while it is acknowledged that these new glucose target metrics may be used for goal setting in the future, currently there are few data available in children and it therefore remains unknown how time in range targets will benefit long-term outcomes [25].

Treat-to-Target Titration of Degludec

As with other basal insulins, the degludec dose should be individualized according to the patient's metabolic needs, BG monitoring results, and glycemic targets [6, 18]. In the pediatric trial of degludec (BEGIN: Young 1 trial) the pre-meal BG target was 5.0–8.0 mmol/L

Table 3 Insulin titration algorithms from BEGIN: Young 1 [8]. Reproduced with permission from Thalange et al. [8]. Published by John Wiley & Sons, Inc

Insulin dose	Basal dose			Bolus dose	
	< 5 U	5–15 U	> 15 U	≤ 5 U	> 5 U
Pre-breakfast or pre-dinner BG, mmol/L (mg/dL)	Dose adjustment			Dose adjustment	
< 5.0 (< 90)	− 0.5	− 1	− 2	− 1	− 2
5.0–8.0 (90–145)	0	0	0	0	0
8.1–10.0 (146–180)	+ 0.5	+ 1	+ 2	+ 0.5	+ 1
10.1–15.0 (181–270)	+ 1	+ 2	+ 4	+ 1	+ 2
15.0 (> 270)	+ 1.5	+ 3	+ 6	+ 1.5	+ 3

BG blood glucose

(90–145 mg/dL) [8]; however, the current ISPAD guidelines recommend that the glucose target should be individualized according to the patient's needs [25]. As a rule of thumb, titration of degludec weekly is practical and effective. Titration of degludec must be made no more frequently than every 3–4 days to ensure steady state is reached before calculating any changes in dose [6] unless there is an episode of fasting hypoglycemia during this time when a dose reduction should be applied.

Although the long half-life of degludec makes it more flexible concerning the injection time than other insulins (by permitting varied once-daily injection time) [4, 9, 10, 13], dosing is generally recommended to be at the same time each day to because a regular routine may help prevent missed doses by obtaining a daily routine. Other basal insulins have a higher peak to trough ratio (Table 1; Fig. 1) and insulin exposure is highly susceptible to mistimed doses [19], requiring that these insulins are dosed at the same time of day. In addition, owing to the low day-to-day variability in glucose-lowering effect of degludec and the lower risk of hypoglycemia, it should be possible to titrate to lower SMBG targets while achieving a comparable risk of hypoglycemia to other basal insulins (or to similar targets with lower risk of hypoglycemia; see patient case 4 for guidance) [20]. This may be beneficial to children, not just because of the lower risk of hypoglycemia but also as a result of the potential to minimize exposure to hyperglycemia associated with microvascular complications shown to affect the brain, kidney, and heart in preclinical studies [45–47].

One challenge with applying the algorithm from the BEGIN: Young 1 trial (Table 3) is that as with Michael (case 4) some children may require titration in 0.5-U increments and this is only possible with NovoPen Echo® and its 3-mL Penfill® cartridges. This was possible with Michael as he resided in the EU, where Penfill® was available; however, outside of Europe, equivalent dosing may be achieved through use of alternate-day dosing with the FlexTouch® U100 to achieve intermediate doses—in Michael's case, alternating doses from 4 to 5 units could have been employed. The long duration of action/half-life of degludec means it is possible to use this approach. Novel modelling analyses supports this approach (Fig. 2; T. Heise, unpublished data), demonstrating that while the peak-to-trough insulin exposure will naturally increase when alternating doses from 1 to 2 U/day, on average the exposure will be equivalent to using a dose of 1.5 U/day. By this variation of ± 1 U from day to day, the model shows that half-unit steps are available by this "trick". In addition, the circulating basal insulin level is still far more stable when alternating the degludec dose compared with the variability in insulin levels achieved with shorter half-life insulins (Fig. 1) that would be incapable of achieving stability with alternating doses.

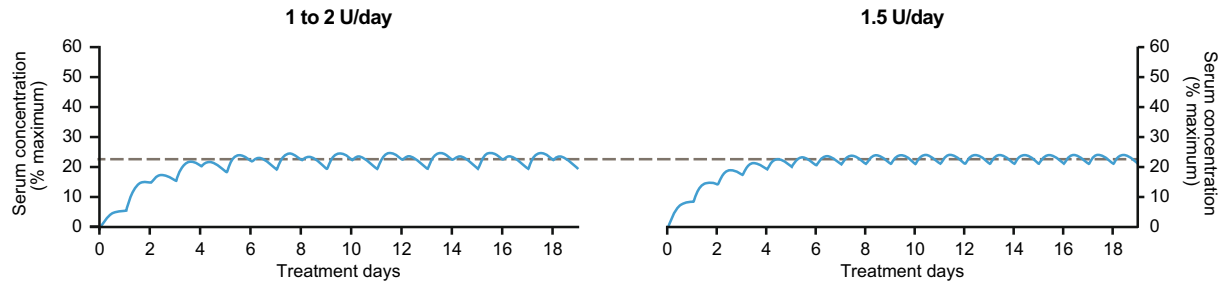

Fig. 2 Hypothetical accumulation of ultra-long-acting insulin from first dose to steady state for different dosing regimens. The different settings (alternate dosing) were visualized in a single-compartment model, and the figures were provided as a courtesy by Tim Heise, unpublished data © 2018. Similar model data has been published previously [78]

Case 5: How to Use Degludec in Patients Who Have Unpredictable Levels of Physical Activity That May Impact Glycemic Control

Patient case 5 Adolescent patient playing in a football tournament for a week, with sustained levels of physical activity each day (e.g., 6 h)

Name: Thomas A1C: 7.1% (54.1 mmol/mol)

Age: 14 years ICR: 1 unit per 10 g and 1 unit per 15 g (pre- and post-exercise)

Body weight: 53 kg

Current MDIs: Degludec with insulin aspart (18 U and 26 U)

Case history

Thomas is an avid footballer, and in addition to physical education classes, he has football practice once a week (ca. 90 min) and on most weeks, a 60-min match. Recently his team was invited to participate in an overseas football tournament. He would be away from home for 4 days. During this time he will play approximately 5–7 h of football a day. While his parents are keen that Thomas participates in the tournament, they are concerned he may neglect his diabetes care and are particularly concerned regarding possible hypoglycemia. Should hypoglycemia happen while he is away, his parents are concerned that this may lead to a reluctance to participate in future tournaments or sport in general. This would likely impact his physical and mental well-being

Patient case 5 continued

Guidance

While Thomas is experienced with taking responsibility for his BG levels and the adults responsible for his care on the trip are familiar with his condition, given the combination of travel, higher levels of exercise, and potentially unregulated diet necessitate consideration and careful planning

Adequate provision of BG test strips, high glycemic index snacks, and hypoglycemia remedies (e.g., glucose tablets) is essential [48]

As the week includes some periods of moderate- to high-intensity exercise, it is recommended that 3 days before the tournament his degludec dose is reduced by 30%, with any hyperglycemia managed by bolus corrections

Flash glucose monitoring was recommended to facilitate timely glucose checks

Current recommendations advocate children and adolescents with T1D to participate in 60 min of at least moderate-intensity exercise, daily [49]. Although patients with T1D are encouraged to exercise because of the potential improvements in health and disease status, because the glycemic response to exercise varies with each individual, care needs to be taken to minimize increased risk of hypoglycemia that occurs with exercise that is over 30 min [48] or when exercise is more intense than usual [49, 50].

Patients should understand that during or after intense exercise, there is a risk of hypoglycemia and it is important to perform SMBG prior to exercise; use SMBG data to adjust food intake or exercise levels; and use oral glucose before mild hypoglycemic episodes become more severe [18, 49]. During exercise and if available, use of CGM in combination with carbohydrate intake algorithms help to maintain euglycemia [51]. However, all patients with diabetes remain susceptible to hypo- or hyperglycemia with exercise, and an individualized approach is needed to minimize risk—particularly in high-performance athletes.

To limit the risk of post-exercise hypoglycemia it may be desirable to consider the duration and intensity of exercise [52] and make suitable adjustments to the carbohydrate intake, e.g., 0.2–1.5 g/kg/h prior to and during the exercise [48]. For short duration (less than 30 min) exercise or when pre-exercise insulin doses are decreased, carbohydrate might not be required. However, when exercise is longer and particularly when insulin has not been reduced beforehand, 0.2–0.5 g/kg/h may be required for low- to moderate-intensity exercise with higher levels of carbohydrate (1–1.5 g/kg/h) required for longer or more strenuous exercise (e.g., football, jogging, cycling, and swimming) [48]. In general, unless hyperglycemic, exercise should be always be followed (within 1–2 h) by an appropriate meal to replenish glycogen stores and reduce post-exercise hypoglycemia [48].

Guidance with Insulin Prior to and During Exercise

Broad advice from ISPAD is that the insulin regimen should be tailored to the type of exercise undertaken and that individual injections should be given at a muscular site that is not heavily involved in the activity [48]. Whilst this is true of glargine and NPH insulin, detemir and degludec are not affected in this way owing to their differing modes of protraction. The PK of the basal or bolus insulin should always be considered when timing doses prior to exercise to ensure that the peak exposure does not coincide with the period of exercise; if this is the case, a marked dose reduction is recommended [48].

Bolus Dose

The type and duration of exercise undertaken (aerobic/mixed intensity aerobic and anaerobic exercise) are key in determining the appropriate pre-exercise bolus dose. For example, a 25% reduction in the bolus dose is recommended for mixed aerobic activity lasting between 30 and 45 min, increasing to approximately 50% if activity is of a longer duration. For continuous aerobic activities lasting between 30 and 45 min a reduction of 25–50% is recommended and this increases to 50–75% when exceeding 45 min. For post-exercise bolus doses, the type and duration of the activity are less important and the guidelines recommended reductions of up to 50% [48]. In addition to the increased risk of hypoglycemia, following a period of short intense anaerobic exercise, the increased sympathetic nervous system response that occurs with intense anaerobic exercise resulting in increased epinephrine levels may lead to hyperglycemia that may require adjustment of the bolus insulin dose. According to ISPAD recommendations this would be a 50% correction bolus for BG levels above 14 mmol/L (252 mg/dL) [48]. To further mitigate the increased risk of nocturnal hypoglycemia, a low glycemic index (GI) snack can be consumed prior to bedtime (0.4 g carbohydrates/kg) [48].

Basal Dose

Exercise increases the risk of nocturnal and next-day hypoglycemia [53], and it is common practice to advise reducing basal insulin doses by 20% on the day of exercise; however, this strategy is not effective in patients on insulin degludec as adjustments would need to be made 3 days prior to any planned major change in activity level [13, 17]. Accordingly, it is necessary to manage risk of hypoglycemia through a combination of carbohydrate intake and bolus insulin adjustment [48].

Exercise and Degludec

As described above, typically patients can accommodate periods of physical activity by managing carbohydrate intake and adjusting bolus insulin. However, the dose of degludec should be reconsidered if there is a change in the level of exercise, stress, diet, body weight, or with illness [18]. This is particularly the case leading up to planned endurance exercise, such as adventure holidays, football camps, marathons, or other endurance exercise. Broad advice in this setting is a reduction of 20–30% in the total daily insulin dose (see patient case 5 for guidance) [54]. Arguably the possibility of using a temporary basal rate with CSII gives the most physiological way to adapt insulin substitution which is offset by discomfort of wearing a device during physical exercise. In comparison with glargine U100, IDet, or NPH insulin, degludec will require dose reductions 3 days before planned activity. While degludec requires additional time/planning before periods of longer duration or higher intensity exercise, if titrated appropriately to the level of exercise and carbohydrate intake, the risk of hypoglycemia is similar to that of other long-acting basal insulins [55].

Case 6: How to Maintain Treatment with Degludec in Patients Following an Episode of DKA

Patient case 6 Poor adherence to treatment and SMBG resulting in DKA

Name: Matthew A1C: 11.3% (100 mmol/mol)

Age: 10 years

Body weight: 28 kg

Current MDIs: NPH insulin with insulin aspart

Patient case 6 continued

Case history

Matthew was been raised under difficult social circumstances and had a troubled relationship with his family. He lived with his mother, step-father, and five half-siblings; despite his young age, he was entrusted with management of his diabetes, with no adult supervision. He experienced an episode of very severe DKA (pH 6.88). Management included standard therapy with IV fluids and insulin and in addition degludec was commenced within 6 h of admission

His DKA episode resulted in him being placed in foster care. It was clear that he was severely neglected, being grossly underweight. His parents had not collected diabetes supplies, including insulin, for several months

Guidance

The PK properties of degludec, described previously, mean that the circulating concentration will not drop quickly and will not drop to zero even if a dose is missed. In fact, a patient would likely have to miss two to three daily doses of degludec to be at any risk of DKA. In addition, in a trial of children with T1D treated with IDet or degludec, degludec resulted in significantly lower rates of hyperglycemia with ketosis [8]

Since degludec is more forgiving regarding missed injections and carries a lower risk of hypoglycemia with ketosis when compared with insulins such as IDet [8], Matthew was switched from NPH insulin to degludec

It was emphasized that his diabetes care be appropriately supervised by a responsible adult

DKA is a life-threatening condition that results from severe insulin deficiency. Around a third of children and adolescents with T1D will be diagnosed with this life-threatening condition [56], which is the leading cause of diabetes-related death in childhood [57]. DKA always arises from insufficient insulin, hence lack of adherence to insulin treatment or delayed diagnosis represent common risk factors for children and adolescents with T1D [57–59].

When DKA has resolved, the switch from insulin infusion to (or back to) SC insulin therapy needs to be carefully considered. Frequent BG monitoring is recommended to prevent the risk of hypoglycemia and also the risk of rebound hyperglycemia [59], which may prolong recovery from DKA and as a result increased length of stay and risk of mortality [60]. To minimize the risk of rebound hyperglycemia, the timing of switch needs to be considered on the basis of the half-life of the SC basal insulin [59]. For example, with longer-acting insulins starting earlier (e.g., evening before/ca. 12 h accompanied by lowering of IV insulin) than shorter/rapid-acting insulins, which should be delayed until nearer to the point of switch (15 min to 2 h) so that there is adequate insulin coverage [59].

Alternatively, as with Matthew, SC basal insulin therapy may be continued during IV insulin therapy with the insulin and/or glucose content of IV fluids being titrated according to the patient's BG. Research has shown that this practice is safe and beneficial [60, 61]. Early introduction of a basal insulin with a long half-life may help prevent the deleterious impact of technical errors during the transition from short-acting IV insulin to the post-IV SC basal insulin [61]. As long-acting insulins have proven to result in lower rates of hypoglycemia compared with short-acting insulins [62–64], it is unsurprising that addition of a long-acting SC basal insulin to IV insulin infusion causes no increased risk of hypoglycemia [61]. Furthermore, when given earlier, e.g., within 6 h of admission, dual IV and SC insulin therapy has the potential to reduce duration with DKA, insulin infusion time, hospital stay, and associated costs [65]. However, despite no increased risk of cerebral edema with dual IV and SC insulin therapy, there is an increased risk of hypokalemia that requires appropriate potassium replacement during IV fluid administration [66]. For degludec, which takes 2–3 days to reach steady state [17], commencement could begin early on, e.g., the first evening of the DKA episode (see patient case 6 for guidance).

Case 7: How to Use Degludec When There May Be Multiple Demands on a Patient's Care Resulting in Unpredictable Variations in BG

Patient case 7 First holiday/trip away from parents

Name: Angela	A1C: 7.8% (61.7 mmol/mol)
Age: 17 years	ICR: 1 unit per 8 g
Body weight: 65 kg	

Current MDIs: Degludec with insulin aspart

Case history

Angela has been using degludec and managing her diabetes for a few years and has grown quite independent and confident in managing her diabetes. Recently she has attended some pop concerts and would like to go away for a 3-day music festival. Her parents are concerned and have sought advice because it will be her first time away and they are concerned that she may experience episodes of hypoglycemia due to alcohol consumption, increased physical activity, and more unpredictable eating

Guidance

She was advised that during the festival, to limit consumption of alcohol, increased physical activity and erratic timing of meals could be handled by ensuring that her BG is monitored regularly; that alcohol is only consumed with carbohydrates and bolus insulin is adjusted to smooth hyper- and hypoglycemic fluctuations in BG (particularly pre-breakfast). Angela was advised not to compromise her good glucose control by lowering her dose of degludec. She was further counseled regarding contraception/safe sex and effects of illicit drugs on glycemia

Although school term time provides some structure and routine for the day-to-day lives of children and adolescents, summer holidays remove this routine and can impact adherence and glycemic control [67]. The flexibility of degludec, stemming from its long half-life and establishment of stable basal insulin levels [9, 10, 13], helps maintain adequate insulin coverage/glycemic control when doses cannot be taken at the same time each day (see patient case 7 for guidance). Accidental missed doses

can be remedied by administering the missed dose within 40 h of the previous injection. The next injection needs to be at least 8 h after this (two injections within 48 h) [18]. Compared with other basal insulins, degludec has greater flexibility in this regard. Children forgetting a nighttime degludec dose will have negligible likelihood of hyperglycemia or ketosis (due to use of degludec) [8] and can take their missed dose in the morning.

Alcohol consumption in adolescents with T1D may also create a challenge, with alcohol breakdown hindering gluconeogenesis and increasing the risk of hypoglycemia [68]. In the absence of evidence-based recommendations, guidance for patients with T1D wishing to consume alcohol is sparse and limited to alignment with broader advice to limit alcohol consumption and to ensure that alcohol is consumed with food [68]. However, patients should be informed not just of the risks during alcohol consumption but also of the prolonged risk extending into the following morning [69].

SUMMARY

The currently available basal insulin analogs in children and adolescents under 18 years old are glargine, detemir, and degludec, which have different modes of action. Basal analogs are more expensive than NPH but show a more predictable insulin effect with less day-to-day variation, compared to NPH insulin [5]. In this narrative review of degludec use in children and adolescents with T1D we have illustrated how the unique PK profile of degludec offers solutions to a wide spectrum of issues faced by this challenging patient population. The stability and flexibility of degludec can help patients and caregivers address issues most commonly associated with this population, i.e., unpredictable lifestyle, poor treatment adherence, and higher risk of hypoglycemia.

RESOURCES

For clinicians seeking additional resources for patients and caregivers, a wealth of resources are available at the Pediatric Resource Center for Tresiba®.

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Data Availability. Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Further information regarding the figure provided by Tim Heise can be requested from the corresponding author of the present review.

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