

Pediatric diabetes: Potential for insulin degludec

Sanjay Kalra, Ambika Gopalakrishnan Unnikrishnan¹, Rakesh Sahay²

Department of Endocrinology, Bharti Hospital and B.R.I.D.E., Karnal, Haryana, ¹Chellaram Diabetes Institute, Pune, Maharashtra, ²Department of Endocrinology, Osmania medical College, Hyderabad, Telangana, India

Comprehensive guidelines, published recently by the International Society for Pediatric and Adolescent Diabetes (ISPAD) describe the use of insulin in children and adolescents in great detail.^[1] These guidelines provide a bird's eye view of the subject, and also clarify micro management issues, which challenge the pediatric diabetes care provider from time to time. The guidelines detail not only the currently used insulin preparations (both human and analogue), but also identify newer molecules in varying stages of development. These include insulin degludec (I Deg), an ultra-long action basal insulin, which is available as monoformulation, and also as co-formulation with insulin aspart (I Asp).^[2]

In spite of development in insulin pharmacotherapeutics, important shortcomings still hamper optimal management of pediatric diabetes.^[3,4] Rigid schedules for timing of administration of insulin, high variability in action profiles of available insulins, the risk of hypoglycemia, and the absence of a truly once daily basal insulin are some challenges faced by children with diabetes. The ISPAD guidelines mention that insulin glargine (I Glar) may have to be injected once or twice a day while insulin detemir (I Det) is often administered twice daily.^[1] Given the unpredictable timings of exercise and variable timings as well as quantities of food taken by children and adolescents, they are probably more prone to hypoglycemia. As hypoglycemia may lead to cognitive dysfunction, and is most undesirable in growing children, its prevention is of prime importance in them. I Deg has the potential to address these important issues.

ADVANTAGES OF INSULIN DEGLUDEC

Insulin degludec is approved for use in many countries around the world, including India, in both type 1 and type 2 diabetes, in persons aged >18 years. Its pharmacokinetic properties of a long half-life (25 h), long duration of action (42 h), and lower variability (25% that of I Glar) differentiate it from other basal analogues. Its unique profile allows it to be used once daily while being injected without regard to meal timing or to the time of administration on the previous day.^[2] I Deg with its long-acting profile offers adequate basal coverage with just one injection/day, with the added advantage of flexibility in timing of administration. The long half-life also helps in counteracting the Dawn phenomenon, a common clinical challenge in type 1 diabetes, and reduces the risk of hyperglycemia or ketosis if a dose is inadvertently missed.

INSULIN DEGLUDEC IN TYPE 1 DIABETES

The pharmacokinetic properties of I Deg are retained in children and adolescents with diabetes. In a single center, randomized, single dose, double blind, two period crossover trial conducted in children aged six and above, I Deg was compared with I Glar. The total exposure to I Deg was numerically greater in children (estimated ratio children: Adults 1.48 [0.98–2024] and statistically greater in adolescents (estimated adolescents: Adults ratio 1.33 [1.08–1.64]) than in adults. The maximum concentration of I Deg was similar in all age groups. A flat, stable I Deg exposure was suggested across a 24 h dosing period, with the drug being detected in serum up to 72 h after administration.^[5]

Recently, Thalange *et al.* reported long term efficacy and safety of I Deg, in combination with I Asp, in children and adolescents aged 1–17 years. The I Deg + I Asp based regime improved glycemic control, in spite of using lower basal insulin doses (0.38U/kg of I Deg vs. 0.55 u/kg of

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Corresponding Author: Dr. Sanjay Kalra, Department of Endocrinology, Bharti Hospital and B.R.I.D.E., Karnal, Haryana, India.
E-mail: brideknl@gmail.com

I Det). The I Deg group experience similar rates of overall and nocturnal hypoglycemia; lower rates of hyperglycemia with ketosis; and higher chances of severe hypoglycemia, than the comparator group, which used I Det once or twice daily, with I Asp.^[6] This data are in addition to the efficacy, safety and tolerability of I Deg that has been reported in adults with type 1 diabetes.^[7]

In our center (SK), over the past year we have used I Deg in 12 children aged 5–17 years, who were unable to achieve stable glycemic control on a five dose regime (three doses of regular or rapid-acting insulin + two doses of long-acting insulin basal analog), or were unwilling to continue a five dose regime. In all these children, save one, we have been able to achieve satisfactory glycemic levels with four doses, (i.e. three doses of regular insulin and one of I Deg). There has been a marked reduction in basal insulin requirement, from 0.40 U/kg/day to 0.30 U/kg/day, with no episodes of severe hypoglycemia. While unpublished data is generally not presented in such articles, we believe this initial, single center experience with degludec is worth sharing with our peers.

Thus, I Deg, with its long-acting profile offers adequate basal coverage with just one injection/day, with the added advantage of child-friendly (and parent-friendly!) flexibility in timing of administration. Currently, I Deg is not approved for use in children aged <18 years. However, publication of favorable pharmacokinetic and clinical data should prompt approval for its use in pediatric patients as well. A Cochrane review is underway to assess the efficacy and safety of ultra-long acting insulin analogues relative to basal insulins.^[8]

ADVANTAGES OF INSULIN DEGLUDEC ASPART CO-FORMULATION

Children with type 1 diabetes also complain of having to inject insulin multiple times. The ISPAD guidelines clearly discourage the use of premixed insulin.^[1]

Insulin degludec Asp is a co-formulation (as opposed to a premixed combination) of I Deg and I Asp, in which both components maintain their distinct character.^[9] Using I Deg Asp, instead of two separate doses of I Deg and I Asp, helps reduce the number of injections in a basal-bolus regime by 25%.

INSULIN DEGLUDEC ASPART IN TYPE 1 DIABETES

Insulin degludec I Asp has been studied in adult type 1 diabetes subjects as part of a three-dose regime. In this

study, subjects were given one injection of I Deg Asp, with a major meal, and two injections of I Asp, with other meals. The timing of administration could be changed at will. This regime (I Deg Asp) was compared with a traditional basal-bolus regime of three I Asp and one or two I Deg doses (total four or five doses/day). The I Deg Asp based regime was non-inferior to the standard basal-bolus regimen in terms of hemoglobin A1c (HbA1c) reduction, with a 13% lower dose requirement (69 U and 0.86 U/kg vs. I Det 79 U and 1.00 U/kg; $P < 0.0001$), and 37% less nocturnal confirmed hypoglycemia (I Deg Asp 3.71 vs. standard basal-bolus regime 5.72 events/year, [$P < 0.05$]).^[10]

No published data is available on the use of I Deg Asp in pediatric diabetes so far is a multinational phase III study (NCT01835431), to investigate the efficacy and safety of I Deg Asp once daily + I Asp for the remaining meals versus I Det once or twice daily + meal time I Asp in 346 children and adolescents with type 1 diabetes mellitus is nearing completion.^[11] The primary outcome is a change from baseline in HbA1c at week 16.

Results from this study, if favorable, will help children with type 1 diabetes achieve optimal glycemic control with a lesser number of injections than before. Though not studied yet, I Deg Asp creates the hope for use of a convenient regimen, using two doses of I Deg Asp,^[9] along with a modified meal pattern (2 major meals = 3–4 snacks) in children who are unwilling to inject more frequently.

Currently, I Deg Asp is not approved for use in children below the age of 18. However, its unique pharmacokinetic and dynamic profile, with coverage of both basal and prandial glycemia, may see its use in pediatric diabetes in the near future.

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