

ABSTRACT

Achieving good glycaemic control while avoiding hypoglycaemia, in order to delay or prevent the long term complications in patients with type 1 or 2 diabetes mellitus is important. Although, insulin plays a vital role in the management of diabetes, conventional human basal insulins like NPH have certain limitations, which have led to the development of more stable and peak less analogues. Although the first generation basal insulin analogues, insulin glargine and insulin detemir are an improvement over NPH, they still exhibit subtle peak effect and some patients may need twice daily administration. Insulin degludec (Tresiba®) is an ultra-long acting basal insulin analogue with flat, stable glucose lowering profile with half-life of >25 hours and duration of action of > 42 hours and less within patient day-to-day variability compared to long acting insulin analogue insulin glargine. A co-formulation of insulin degludec with rapid acting insulin aspart (Insulin degludec/Insulin Aspart) [Ryzodeg®] is also available, comprising 70% insulin degludec and 30% insulin aspart. This article reviews the clinical impact of these newer insulins in the management of Type 2 diabetes.

INTRODUCTION

Diabetes is a global epidemic with estimated 415 million individuals currently living with diabetes. By 2040, this number is projected to reach 642 million¹. Good glycaemic control significantly and importantly reduces the risk of long-term complications of both type 1 and type 2 diabetes. The benefits of tight glycaemic control have been confirmed by the DCCT (Diabetes Control and Complications Trial)/EDIC (Epidemiology of Diabetes Interventions and Complications) in type 1 diabetes and UKPDS (United Kingdom Prospective Diabetes Study) trials in type 2 diabetes, respectively²⁻⁴. Intensive glucose lowering therapy was associated with significantly reduced risks of myocardial infarction, stroke and heart failure in an epidemiological analysis of the follow-up to the UKPDS study³. Although, benefits of good glycaemic control have been emphasized, action is needed to increase the proportion of individuals achieving recommended glycaemic goals.

Insulin therapy continues to play a vital role in the treatment of patients with diabetes mellitus. Basal insulin has been an important treatment option for patients with diabetes mellitus (DM) and, has undergone major improvements in terms of purity and similarity to the action of physiologic human insulin. Lente and Ultralente

formulations were used for decades but are no longer available. The use of neutral protamine Hagedorn (NPH) insulin is also being replaced with the basal insulin analogs detemir and glargine⁵. Basal insulin analogs generally cause less severe and nocturnal hypoglycemia compared with NPH insulin owing to their improved pharmacologic profiles⁶⁻⁸. In comparison to NPH insulin, insulin glargine causes similar weight gain, whereas insulin detemir causes less weight gain. In addition, insulin detemir has been associated with a glucose-lowering effect that is more predictable than that of NPH insulin. Despite the improvements observed with basal insulin analogs, their time-action profiles are not completely flat and are shorter than 24 hours in many patients^{9,10}. Ideal basal insulin is the one which delivers a steady, stable, peakless, continuous insulin concentration for at least 24 hours, in a predictable manner, with low intraindividual and interindividual variability and minimal hypoglycaemia¹¹.

Type 2 DM is a progressive disease and meal time glucose control impairment is an early feature of disease progression in Type 2 DM and control of post prandial glycaemia needs to be addressed. But some reluctance to initiate or intensify insulin therapy has been noted among primary care physicians because of fear of hypoglycemia and weight gain, and perceived problems of dependency on the medication and complexity of multiple injections and titration of regimens¹²⁻¹⁴. Combination therapies in the form of basal insulin plus bolus insulin at the major meal, basal-bolus (Basal insulin and bolus insulin at all meals) or premix strategies were traditionally considered following successful titration with basal insulin only. Although regimens based on injections of premixed biphasic insulin can provide prandial coverage for several meals, they may also be associated with an increased rate of nocturnal hypoglycemia¹⁵ as the interaction between the soluble and protaminated insulin components (shoulder effect) produces a prolonged and uneven peak glucose-lowering effect compared with rapid-acting insulins. Therefore, insulin combinations comprising a long-acting basal and a distinct rapid-acting prandial insulin in a single pen, suitable for once-daily (OD) or twice-daily (BID) administration, may be suitable insulin initiation and intensification approach.

This article reviews the pharmacological properties, efficacy and tolerability of insulin degludec and insulin degludec/insulin aspart in type 2 DM patients.

Table 1: Pharmacological properties of Insulin Degludec

Pharmacological Property	Insulin Degludec
Terminal Half-life	25.4 Hrs
Duration of action	>42 Hours
Glycaemic variability	75% lower than insulin glargine
Glucose lowering effect over 24 Hours	Consistent and evenly distributed
Pharmacokinetics in renal failure and hepatic failure patients	Ultra-long pharmacokinetics are preserved in renal failure and hepatic failure patients
Miscibility with bolus insulin and GLP-1 analogues	Yes

INSULIN DEGLUDEC IN TYPE 2 DM PATIENTS

Pharmacological properties

Insulin degludec is a soluble ultra-long acting basal insulin analogue that has same amino acid sequence as human insulin, apart from deletion of Threonine amino acid residue at B30 and addition of 16 carbon fatty acid (Hexadecanedioic acid) to Lysine at B29 through a glutamic acid spacer. Due to its structure and formulation, insulin degludec forms stable and soluble multihexamers upon injection. Insulin monomers then slowly and gradually dissociate from the multihexamers and are subsequently absorbed into the bloodstream to provide an ultra-long duration of action¹⁶. The terminal half-life of IDeg was approximately 25 hr at steady state and the duration of action was found to be >42 Hours^{17,18}. A double-blind, two-period, incomplete block cross-over trial which investigated the pharmacodynamic and pharmacokinetic properties of IDeg at steady state (SS) in people with type 2 diabetes, concluded that the mean glucose infusion rate (GIR) profiles were flat and stable for all dose levels. The glucose-lowering effect of IDeg was evenly distributed over the dosing interval τ , with area under the curve (AUC) for each of the four 6-h intervals being approximately 25% of the total AUC (AUCGIR, τ ,SS)¹⁹. The glycaemic variability of insulin degludec is found to be four times lesser than that of insulin glargine²⁰. The pharmacokinetic and pharmacodynamic properties of insulin degludec are enumerated in Table 1.

Efficacy and safety

The efficacy of insulin degludec in Type 2 DM patients was compared with insulin glargine in four randomized, open label, multi-centre phase 3 trials including insulin naïve patients and insulin experienced patients²¹⁻²⁴. Another randomised, open-label, multi-centre, 26 Weeks, Phase 3 trial examined the efficacy of a flexible insulin degludec dosing regimen²⁵. The results of the trials have been enumerated in Table 2. In terms of HbA1C reduction, insulin degludec was non-inferior to insulin glargine in insulin naïve and insulin experienced patients.

A patient level meta-analysis was done to obtain a comprehensive overview of differences between the two preparations (insulin degludec and insulin glargine). End points analysed were glycosylated hemoglobin (HbA_{1c}), fasting plasma glucose (FPG), insulin dose and hypoglycemic rates analysed in mutually exclusive groups: non-severe nocturnal, nonsevere daytime, and severe²⁶. The results from the meta-analysis for Type 2 DM patients are enumerated in Table 3.

The injection timing of insulin degludec can be varied without compromising glycaemic control in Type 2 DM patients according to the results from BEGIN Flex study. In this study there was no significant difference between patients receiving insulin degludec according to flexible dose regimen and those receiving insulin degludec with their evening meal in mean reduction in HbA_{1c}, proportion of patients achieving HbA_{1c} of < 7% or mean FPG²⁵.

Subcutaneous insulin degludec was generally well tolerated in patients with Type 2 DM. The majority of adverse events among insulin degludec recipients were of mild to moderate severity and were not considered to be related to treatment. The most commonly reported treatment emergent adverse events included nasopharyngitis, upper respiratory tract infection, head ache and diarrhoea²¹⁻²⁴.

Although there was initial concerns on the cardiovascular safety of insulin degludec, FDA has concluded that currently available data is suggest that the risk associated with insulin degludec is similar to that of other long-acting insulin analog products and has given approval for insulin degludec and insulin degludec/insulin aspart on 25th September 2015²⁷.

The potential limitations of insulin degludec clinical development program was, the lack of blinding, inclusion of non-symptomatic hypoglycemia in the hypoglycemia endpoints, exclusion of patients with one or more hypoglycemia risk factors, and no recording of the timing of IGLar administration. So, a randomized, double-blind, crossover, multicenter, treat-to target phase 3b clinical trial conducted in patients with T2D (Switch 2 Study). Patients previously treated with basal insulin with or without oral antidiabetic drugs were randomised 1:1 to 100 U/mL (U100) of IDeg or IGLar once daily and 1:1 to administer basal insulin in the morning or evening throughout the trial. The primary objective was to confirm superiority of IDeg compared with IGLar in the rates of severe or blood glucose (BG)-confirmed symptomatic hypoglycemia during the maintenance period (after 16 weeks of treatment)²⁸. The results of the study are enumerated in Table 4.

Early evidence from the real world has also been encouraging²⁹⁻³². The results from the real world studies have been enumerated in Table 5.

Table 2: Summary of Phase 3a clinical trials of insulin degludec versus insulin glargine in Type 2 DM patients

Trial	Population/comparator	Duration (wks)	Efficacy		Hypoglycaemia	
			Non-inf. HbA _{1c}	FPG mmol/L [mg/dL]	Total	Nocturnal
ONCE LONG (core and extn)	Insulin naïve, T2D	104	Yes	-0.38 [-6.84]*	↓ 16%	↓ 43%*
BB	Previously treated with insulin, T2D	52	Yes	-0.29 [-5.22]	↓ 18%*	↓ 25%*
FLEX*	Insulin naïve and insulin treated, T2D	26	Yes	-0.42 [-7.56]*	↑ 3%	↓ 23%
Low Volume	Insulin naïve, T2D	26	Yes	-0.42 [-7.56]*	↓ 14%	↓ 36%
Once Asia	Insulin naïve, T2D	26		-0.09 [-1.62]	↓ 18%	↓ 38%

*Statistically significant

Table 3: Summary of results (Meta-Analysis of Endpoints in Phase 3a Trials for insulin degludec versus insulin glargine in Type 2 DM patients)

Category	Change in HbA _{1c} ; Ideg-Iglar Estimate(95% CI)	Change in FPG; IDeg-IGlar Estimate(95% CI)	Daily insulin dose Estimated treatment ratio (95% CI)	Nocturnal hypoglycaemia	
				Full trial period Estimated rate ratio IDeg/IGlar (95% CI)	Maintenance period Estimated rate ratio IDeg/IGlar (95% CI)
T2DM insulin-naïve	0.08(-0.01; 0.16)	-0.34(-0.54;0.15)	0.90 (0.85; 0.96)	0.64 (0.47; 0.86)	0.51 (0.36; 0.72)
T2DM B/B	0.08 (0.05; 0.21)	-0.29(-0.65; 0.06)	1.03 (0.97; 1.10)	0.75 (0.57; 0.98)	0.71 (0.51; 0.99)

Table 4: Summary of results of Switch 2 Study

Parameter	Result
Non-inferiority in HbA _{1c} reduction	Yes
Severe or BG confirmed symptomatic hypoglycaemia – maintenance phase (rates)	30% Lesser
Severe or BG confirmed symptomatic nocturnal hypoglycaemia – maintenance phase (rates)	42% lesser
Severe Hypoglycaemia maintenance phase rates	46% Lesser

Table 5: Post approval studies of insulin degludec

Properties	Sweden	UK	India
Reduction in HbA _{1c} (%)	0.30	0.70	0.36
Reduction in insulin dosage (%)	14	-	27
Reduction in overall hypoglycaemia (%)	22	90	70

INSULIN DEGLUDEC/INSULIN ASPART (IDEGASP) IN TYPE 2 DM

Pharmacological properties

The co-formulation of IDeg and IAsp in IDegAsp is a clear, colourless, neutral pH solution. The molecular structure of two components of IDegAsp (insulin degludec and insulin aspart) allows them to co-exist without affecting their individual PK/PD profile. The basal component, IDeg, exists in the form of stable di-hexamers in the pharmaceutical preparation, forming long multi-hexamer chains after subcutaneous administration. Subsequently, continual release of IDeg monomers from the ends of the chains ensures a flat PK/PD profile, lasting long enough to meet basal insulin requirements over 24 h once at steady state. In contrast, IAsp in IDegAsp exists

as hexamers in the vial, which rapidly dissociate into monomers after subcutaneous administration, providing a near-physiological meal-time concentration profile. This has been confirmed by size-exclusion chromatography, in conditions simulating pharmaceutical preparations as well as after subcutaneous administration, clearly showing the existence of two separate components that do not affect each other's PK/PD profile, either in solution or once injected³³. Furthermore, a clamp study carried out in people with type 1 diabetes mellitus (T₁DM) at steady state demonstrated the basal and meal-time effects of the two components in a dose-dependent manner³⁴. Also, no clinically relevant differences in the pharmacokinetics of IDegAsp in older people (≥65 years) were found compared to young adults (18-35 years)³⁵. In addition, no clinically relevant differences have been observed in the PK or PD of IDeg or IAsp in patients with renal or hepatic failure^{36,37,38}.

Table 6: Summary of pharmacological properties of IDegAsp

Pharmacological Property	IDegAsp
Components	Insulin Degludec and Insulin Aspart in a ratio of 70:30
Glucose lowering effect	Pharmacokinetics of insulin degludec and insulin aspart distinct in the co-formulation
Glycaemic variability	75% lower than insulin glargine
Dose proportionality	Total exposure proportionally increases with dose

Efficacy and safety

The efficacy of IDegAsp in Type 2 DM patients was compared with insulin glargine/Biphasic insulin Aspart/Basal-bolus therapy in four randomized, open label, multi-centre phase 3 trials including insulin naïve patients and insulin experienced patients. The results of the trials have been enumerated in Table 6.

IDegAsp in insulin naïve patients

In comparison to insulin glargine, when IDegAsp was administered once daily in insulin naïve patients with Type 2 DM patients, there was superiority in lowering HbA_{1c} with numerically lower nocturnal hypoglycaemic episodes although the difference was not statistically significant³⁹. In a global study in insulin-naïve people comparing twice-daily IDegAsp with twice-daily BAsp 30, there was no difference in HbA_{1c}, despite FPG being 1.0 mmol/l lower ($p < 0.001$). However, in this study there was a 75% reduction in nocturnal con-confirmed hypoglycaemia in favour of IDegAsp, together with a 54% reduction in any-time hypoglycaemia⁴⁰.

IDegAsp in prior insulin users (Table 7)

In studies comparing twice-daily administration of IDegAsp with BAsp 30, one in a global population and one in an Asian population, IDegAsp was non-inferior to BAsp 30 for change in HbA_{1c}, but superior in lowering FPG and at a lower daily insulin dose. IDegAsp demonstrated a 32% reduction in confirmed hypoglycaemia rate ($p = 0.005$) and a 73% reduction in the rate of nocturnal confirmed hypoglycaemia ($p < 0.001$)⁴¹. In the Asian population, there was no effect on any time (confirmed) hypoglycaemia and the rate ratio or nocturnal confirmed hypoglycaemia (reduction of 33%) did not meet statistical significance⁴².

A study comparing twice daily administration of IDegAsp versus basal plus meal time insulin therapy in prior insulin users, the final HbA_{1c} was comparable although non-inferiority was not achieved. But, the insulin dose was 12% lower using combination insulin and confirmed and nocturnal hypoglycaemia were 19% and 20% lower respectively⁴³.

Subcutaneous insulin degludec/insulin aspart was

generally well tolerated in Type 2 DM patients. The majority of adverse events were mild to moderate in severity.

Dosing and titration of IDeg and IDegAsp

Insulin degludec is indicated for treatment of diabetes in adults. On occasions when administration at the same time every day is not possible, insulin degludec allows for flexibility in the timing of insulin administration; it should be ensured that there is a minimum of 8h gap between 2 injections. For insulin-naïve T₂DM patients the recommended daily starting dose is 10 U followed by individual dosage adjustments. In insulin experienced patients, Unit-to-unit switch from any basal insulin OD or BID or basal component of prior basal-bolus or premix insulin can be considered. A 20% dose reduction may be considered when switching from BID insulin. During the transition period, patients may observe higher blood glucose values for 3–5 days following the switch to IDeg. Once-weekly titration based on the average of two preceding FPG measurements is recommended⁴⁴.

Insulin Degludec/Insulin aspart is indicated for once or twice daily subcutaneous administration with the main meals. If needed the timing of administration can be changed as long as IDegAsp is administered with the largest meal when taken once daily. In insulin naïve Type 2 DM patients total daily starting dose for IDegAsp is 10 units with main meal(s) followed by individual dosage adjustments. In insulin experienced Type 2 DM patients, patients receiving OD/BD basal or premix insulins can be converted to IDegAsp at the same total insulin dose as the patients previous total daily dose. Patients with T₂DM switching from basal and bolus insulin therapy to IDegAsp will need to convert their dose based on individual needs. In general, patients are initiated on the same number of basal units. Adjust breakfast or lunch dose based on the average of 3 preceding pre-main evening meal SMBG values and main evening meal dose based on the average of 3 preceding pre-breakfast SMBG values⁴⁵.

CONCLUSION

Insulin degludec is a novel basal insulin analogue with a unique mode of protraction which ensures a flat and stable glucose-lowering effect with half-life of more than 25 hours and duration of action beyond 42 hours. The glucose lowering effect of insulin degludec is consistent over a period of 24 hours compared to insulin glargine and its day-to-day variability is four times lower than that of insulin glargine. The ultra-long pharmacokinetic properties of insulin degludec are preserved in subjects with renal impairment and hepatic impairment. Insulin degludec can be administered at any time of the day, but at the same time every day.

IDegAsp is a novel co-formulation that may offer in patients with progressive T₂DM a simpler, injectable insulin regimen with fewer injections as compared to basal bolus/basal plus therapy. As compared to premix insulin therapy, IDegAsp shows better reductions in fasting plasma glucose and significant reductions in confirmed

Table 7: Summary of Phase 3 clinical trials of IDegAsp

Study	Dosing	Comparator	HbA1C difference	Hypoglycaemia difference
Onishi et al. 26 week open label, treat to target study in T2DM insulin naïve Japanese patients	Once daily	Insulin Glargine	-0.28 (-0.46 to -0.10), p < 0.01 Superior	Overall Hypoglycaemia - 27% Reduction Nocturnal hypoglycaemia - 25% Reduction
Franek et al 26 week, open label, treat to target study in T2DM insulin naïve patients	Twice daily	Biphasic insulin Aspart	0.02 (✓ 0.12 to 0.17), non-inferior	Overall Hypoglycaemia - 54% reduction Nocturnal hypoglycaemia - 75% Reduction
Fulcher et al 26 week, open label, treat to target study in T2DM insulin experienced patients	Twice daily	Biphasic insulin Aspart	-0.03% (-0.18 to 0.13), non-inferior	Overall Hypoglycaemia - 32% reduction Nocturnal Hypoglycaemia - 73% reduction
Kaneko et al. 26 week, open label, treat to target study T2DM insulin experienced Asian patients	Twice daily	Biphasic insulin Aspart	0.05 (-0.10 to 0.20), non-inferior	Nocturnal Hypoglycaemia - 33% Lesser
Rodbard et al 26 week, open label, treat to target study T2DM insulin experienced patients	Twice daily	Insulin Degludec + insulin aspart (2-5 times daily)	0.18 (✓ 0.04 to 0.41), p = NS Non-inferiority not confirmed	Overall Hypoglycaemia - 19% reduction Nocturnal Hypoglycaemia - 20% reduction

and nocturnal confirmed hypoglycaemic episodes as compared to biphasic insulin aspart. Both IDeg and IDegAsp have been useful addition in the therapeutic armamentarium for the management of Type 2 diabetes.

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