Review of Clinical Profile of IDegAsp

AG Unnikrishnan¹, Awadhesh Kumar Singh², KD Modi³, Banshi Saboo⁴, Shilpa Chugh Garcha⁵, Paturi Vishnupriya Rao⁶

Abstract
In patients with diabetes, treatment intensification requires basal and bolus insulin injections to control the fasting and prandial insulin needs. To overcome the burden of multiple daily injections, co-formulating basal and bolus insulins in single injection could allow a simple regimen with fewer injections. Current premixed insulin analogues are limited by the protaminated insulin component, which cannot provide effective basal coverage. While, long-acting insulin analogues like insulin glargine and insulin detemir cannot be combined with rapid-acting insulin analogues due to physiochemical incompatibility. Insulin degludec/insulin aspart (IDegAsp) is a soluble co-formulation of two distinct insulin analogues in the ratio of 70% ultra-long-acting insulin degludec (IDeg) and 30% rapid-acting insulin aspart (IAsp). The distinct PK/PD properties of IDeg and IAsp components are preserved in the co-formulation, with the rapid absorption characteristics of IAsp and flat and stable profile of IDeg maintained separately. Size exclusion chromatography studies of IDegAsp indicate that IDeg and IAsp exist as stable di-hexamers and hexamers, respectively in the formulation. Moreover, at steady state, the prandial and basal glucose lowering effects of IDeg and IAsp were distinct and clearly separated. A clear dose-response relationship was observed in patients with type 1 and type 2 diabetes treated with IDegAsp. The glucose lowering effects of basal and prandial components of IDegAsp are maintained in elderly (≥ 65 years of age) patients with type 1 diabetes. In addition, the PK and clearance of IDeg and IAsp are not affected by mild, moderate or severe renal or hepatic impairment. Presence of two distinct insulin analogues, as a soluble co-formulation with basal component with an ultra-long duration of action makes IDegAsp an advance to premix insulins.

Introduction
Despite therapeutic advances in the diabetes management, insulin therapy remains the mainstay of treatment in patients with type 1 and type 2 diabetes mellitus. The goal of exogenous insulin therapy is to mimic the physiologic insulin secretion to control both fasting and post-prandial glucose levels while achieving desired glycated haemoglobin (HbA1c) levels.¹ ² Conventional insulin formulations are unable to resemble the physiological insulin secretion patterns partly due to their pharmacokinetic disadvantages.

Therefore, to optimize these insulins for therapeutic benefits, newer insulin analogues which mimic the profile of endogenous insulin more closely than conventional insulin preparations may be considered a step closer to the concept of ideal insulin regimen.³ Rapid-acting insulin analogues (insulin aspart, glulisine, lispro) with faster absorption profile and shorter duration of action (Table 1) show better post-prandial glycaemic control than regular human insulin. Long-acting insulin analogues (insulin glargine, detemir) with prolonged duration of action and less within-subject variability⁴ ⁵ show superior basal glycaemic control and better fasting plasma glucose (FPG) control (thereby reduces the risk of hypoglycaemia) than NPH insulin. Novel long-acting insulin degludec (IDeg) has a longer half-life and four times lower pharmacodynamic variability than glargine.⁶ However, use of these insulin analogues separately as part of basal-bolus therapy requires multiple daily injections (MDIs)⁷ ⁸ which together with fear of hypoglycaemia⁹ ¹⁰ adds on to perceived treatment burden limiting treatment adherence of patients.¹⁰

A combination of basal and bolus insulins with a complementary pharmacokinetic/pharmacodynamic (PK/PD) profile could allow for a simple and safe regimen providing both basal and mealtime insulin coverage with fewer injections.¹¹ As the current premix insulin analogues are fixed mixtures of rapid acting insulin and protaminated rapid acting insulin analogues,² they may not provide stable glucose lowering effect due to protaminated nature of basal component, which is not

¹Chief Endocrinologist and CEO, Chellaram Diabetes Institute, Pune, Maharashtra; ²Consultant Endocrinologist, GD Hospital and Diabetes Institute, Kolkata, West Bengal; Sun Valley Diabetes Research Center, Guwahati; ³Endocrinologist, Dr. Modis Clinic, CARE Hospital, Hyderabad; ⁴Diabetologist-Endocrine and Metabolic Physician, Diabetes care and Hormone Clinic, Ahmedabad, Gujarat; ⁵Medical Advisor, Novo Nordisk India Pvt. Ltd. Bangalore, Karnataka; ⁶Dept. of Endocrinology, Nizam’s Institute of Medical Sciences, Hyderabad.
<table>
<thead>
<tr>
<th>Table 1: Pharmacokinetics of conventional and analogue insulins</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulin</strong></td>
</tr>
<tr>
<td>Conventional insulin therapies</td>
</tr>
<tr>
<td>Regular human insulin</td>
</tr>
<tr>
<td>NPH</td>
</tr>
<tr>
<td>Premixed NPH/regular human insulin (70% NPH/30% regular human insulin)</td>
</tr>
<tr>
<td>Rapid-acting insulin analogues</td>
</tr>
<tr>
<td>Insulin lispro</td>
</tr>
<tr>
<td>Insulin aspart</td>
</tr>
<tr>
<td>Insulin glulisine</td>
</tr>
<tr>
<td>Long-acting insulin analogues</td>
</tr>
<tr>
<td>Insulin glargine</td>
</tr>
<tr>
<td>Insulin detemir</td>
</tr>
<tr>
<td>Insulin degludec</td>
</tr>
<tr>
<td>Premixed insulin analogues</td>
</tr>
<tr>
<td>75% NPL/25% lispro</td>
</tr>
<tr>
<td>50% NPL/50% lispro</td>
</tr>
<tr>
<td>70% insulin aspart protamine/30% aspart</td>
</tr>
<tr>
<td>Insulin degludec/Insulin aspart</td>
</tr>
</tbody>
</table>

*Median values NPH = Neutral Protamine Hagedorn; NPL = Neutral Protamine Lispro*

a true long-acting insulin, but an intermediate insulin (Table 1).

### Co-formulation of Long-Acting Insulin with Rapid-Acting Insulin

Co-formulation of long-acting insulin analogues with rapid-acting insulin analogues was not possible in the past due to the physicochemical incompatibilities. The long acting insulin analogue, insulin glargine (IGlar) is soluble at an acidic pH of 4.0 whereas commercially available rapid acting insulin analogues are soluble at pH 7.4. Therefore, if IGlar is co-formulated with a rapid-acting insulin analogue, it will precipitate, and thus is incompatible to combine them in one formulation.

On the other hand, long acting insulin analogue, insulin detemir (IDet) is soluble at neutral pH. Upon subcutaneous injection, it forms a soluble depot of hexamers and di-hexamers, which are less stable than the di-hexamers of insulin degludec. Therefore, when co-formulated with a rapid-acting insulin analogue, IDet can form mixed hexamers of the two insulins with inappropriate and/or unpredictable PK/PD profiles. Thus a co-formulation of IDet and a rapid-acting insulin analogue is not possible.

IDeg is a basal insulin analogue with an ultra-long duration of action that exists as clear solution at pH 7.4. It retains the amino acid sequence of human insulin, except for the deletion of ThrB30 and addition of a 16-carbon fatty diacid sidechain to LysB29 via a glutamic acid spacer. IAsp, a rapid-acting insulin analogue, differs from human insulin by the replacement of ProB28 with aspartic acid. Insulin degludec/insulin aspart (IDegAsp) is the first soluble co-formulation of two different insulin analogues (70% IDeg, as basal insulin and 30% IAsp, as prandial insulin). In the formulation, IDeg exists as stable di-hexamers, and IAsp remains as distinct hexamers. Whereas under conditions that mimic subcutaneous environment (with phenol and zinc present), IDeg and IAsp exist as separate molecular entities. The IDeg component forms stable di-hexamers in the presence of phenol at both ends, and IAsp remains as distinct hexamers. Whereas under conditions that mimic subcutaneous environment (with phenol excluded), as examined by SEC, the two components of IDegAsp elute separately; an initial peak representing the large multi-hexamers of IDeg followed by a peak representing the monomers of IAsp only (Figure 1). Consequently, the IDeg component forms a depot of soluble and stable multi-hexamers at the site of injection (due to the binding of fatty diacid sidechain of one IDeg di-hexamer to the zinc ion situated on another di-hexamer), from where IDeg monomers gradually separate and are slowly and continuously absorbed into the circulation. At the same time, IAsp hexamers dissociate into monomers which are rapidly absorbed and reach the target organs, where it activates the insulin receptors (IRs). This represents the primary mechanism for the dual duration action of IDegAsp.

IDegAsp is commercially available as Ryzodeg®. It is approved as FlexTouch®, and as PenFill® in some countries.

### Clinical Profile of IDegAsp

The PK and PD profile of IDegAsp has been investigated in phase 1 trials in patients with type 1 diabetes mellitus (T1DM), both as single dose and at steady state. Patients with T1DM were the most appropriate for clamp studies as these subjects were relatively homogeneous, and study data was not confounded by endogenous insulin production or acquired insulin resistance.

Using size exclusion chromatography (SEC), it is observed that under conditions that mimic the pharmaceutical formulation (with phenol and zinc present), IDeg and IAsp exist as separate molecular entities. The IDeg component forms stable di-hexamers in the presence of phenol at both ends, and IAsp remains as distinct hexamers. Whereas under conditions that mimic subcutaneous environment (with phenol excluded), as examined by SEC, the two components of IDegAsp elute separately; an initial peak representing the large multi-hexamers of IDeg followed by a peak representing the monomers of IAsp only (Figure 1). Consequently, the IDeg component forms a depot of soluble and stable multi-hexamers at the site of injection (due to the binding of fatty diacid sidechain of one IDeg di-hexamer to the zinc ion situated on another di-hexamer), from where IDeg monomers gradually separate and are slowly and continuously absorbed into the circulation. At the same time, IAsp hexamers dissociate into monomers which are rapidly absorbed and reach the target organs, where it activates the insulin receptors (IRs). This represents the primary mechanism for the dual duration action of IDegAsp.
of protraction of IDegAsp which provides distinct and separate glucose lowering effects of IAsp and IDEg components (Figure 2). Further, IDEg monomers are bound strongly but reversibly to serum albumin in the bloodstream. This represents the secondary protraction mechanism of IDEg component. IDEg monomers readily activate IRs on target cells, owing to their higher affinity to IRs as compared to albumin.

Heise et al evaluated the PD and PK effects of IDEgAsp (0.6 U/kg) at steady state in patients (n=22) with T1DM. The mean total serum exposure (AUCIAsp,0–12h) of IAsp was 1,087 pmol h/L and the time to reach maximum concentration (tmax,IAsp) was 80 min (median). The PK properties of prandial component in IDEgAsp were found to be similar to that of individual insulin aspart. IDEg, the basal insulin component of IDEgAsp showed a flat and evenly distributed exposure over one dosing interval with an AUCIDEg,SS of 72,084 pmol h/L at steady state. Exposure to IDEg component of IDEgAsp was found to be similar in the first and second 12 h periods of administration. IDEg reaches a steady state after 2-3 days of once-daily (OD) dosing and the mean ratio of AUCIDEg,0–12h,SS/AUCIDEg,SS was 0.51, indicating an evenly distributed PK profile over 24 h. The PK properties of basal

Fig. 1: Size-exclusion chromatography of insulin degludec/insulin aspart in conditions simulating the sub-cutaneous environment. IAsp: Insulin aspart IDEg: Insulin degludec. Source: Adapted from Havelund et al. 2013

Fig. 2: Mechanism of protraction of insulin degludec/insulin aspart. Source: Adapted from Heise et al. 2014

Fig. 3: Pharmacodynamic profile of insulin degludec/insulin aspart. Mean glucose infusion rate profile of (a) once-daily and (b) simulated twice daily at steady state of insulin degludec/insulin aspart administered in subjects with type 1 diabetes mellitus. IDEgAsp, Insulin degludec/insulin aspart; BID, twice daily. Source: Adapted from Ma et al. 2012, Heise et al. 2014
component in IDegAsp were found to be similar to that of individual IDeg.16,26

IDegAsp can be administered OD or twice daily (BID) with main meals depending upon the patient’s glycaemic control. Due to the ultra-long duration of action of IDeg component, the PD of IDegAsp has been investigated after achieving steady state. At steady state concentrations, in patients with T1DM, when a single dose (0.6 U/kg) of IDegAsp was administered, area under glucose infusion rate (GIR) curve (AUC GIR,0-24h,SS) (geometric mean, coefficient of variation [CV]) of 3859 mg/kg (33%) and time for reaching maximum GIR (t GIRmax,SS ) (median [CV]) of 2.5 h (29.9) were observed. 20 The GIR profile demonstrated a rapid onset of action through a distinct peak of IAsp followed by a flat basal action of IDeg, sustaining beyond 24 hours. Individual effects of rapid-acting and long-acting components were clear and distinct maintaining both prandial and basal glycaemic coverage (Figure 3).3,20

IDegAsp in Special Population

Since the PK profiles of IDeg and IAsp components of IDegAsp were found to be distinct, their PK profiles were investigated separately with single dose in subjects with normal and varying degrees of renal/hepatic impairment.27-29 No significant interactions between any PK parameter and creatinine clearance were observed with single dose (0.08 U/kg body weight) of IAsp in patients with renal impairment. Similarly, no significant changes in PK parameters with respect to Child-Pugh Score were observed with single dose (0.06 U/kg body weight) of IAsp in patients with hepatic impairment.27 Single dose (0.4 U/kg body weight) of IDeg showed no significant difference in total exposure (AUC0-120h,SD), maximum concentration (Cmax,SD) or apparent clearance (CL/F,SD ) in subjects with normal and impaired renal function. The PK profiles of IDeg were similar, without any safety issues for subjects with end-stage renal disease (ESRD), irrespective of their haemodialysis acceptance.28 Likewise, IDeg was well-tolerated in subjects with normal or impaired hepatic function and the ultra-long PK properties were preserved, with no significant differences in absorption or clearance (Figure 4).29

To determine if variations in dosing recommendations are required in patients of different age groups, the PD profile of IDegAsp were investigated in elderly and young adults with T1DM. In a study, fifteen elderly subjects, aged more than 65 years, and thirteen young adults, aged between 18 to 35 years were administered with a single dose (0.5 U/kg) of IDegAsp. The mean AUCGIR,0-24h,SD for 24-hours was similar for elderly (geometric mean [CV]: 1794 mg/kg [62%]) and young adults (1786 mg/kg [28%]). The mean AUCGIR,0-24h,SD ratio for elderly/young adults was 1.01 (95% confidence interval: 0.69; 1.47) and prandial coverage (AUCGIR,0-6h,SD ) was comparable between the elderly (geometric mean 909 mg/kg [45%]) and young adults (1001 mg/kg [25%]).30

Further, IDegAsp displays a proportional dose–response relationship in glucose lowering effect across three clinically relevant dose levels (0.4, 0.6, 0.8 U/kg). In patients with T1DM, the AUCGIR,0-24h,5D and GIRmax,5D increased significantly and proportionally with increase in the dose of IDegAsp.31 Similar linear relation was also observed in patients with type 2 diabetes with increase in the dose of IDegAsp.31
Differences between IDegAsp and Premixed Insulin

IDegAsp markedly differs with premixed insulin (biphasic insulin aspart 30/70 [BIAsp 30]) in the PK and PD properties. A comparison of the GIR profile of IDegAsp single dose (0.6 U/kg) and BIAsp 30 single dose (0.6 U/kg) in patients with T1DM found that IDegAsp displayed a GIR profile with initial peak action of IAsp followed by a separate, stable and sustained GIR, reflecting the IDeg component.19 Whereas with BIAsp 30, a dual-release formulation with 30% soluble and 70% protaminated IAsp, the GIR returns to baseline values 18–22 h after injection. Further, due to the overlapping effects of the two forms of IAsp, a ‘shoulder’ effect was observed with BIAsp 30 between approx. 6 and 12 h.19 The distinct GIR profile of IDegAsp is due to the ultra-long duration of action of IDeg, the basal component of IDegAsp, extending beyond 24 hours at steady state.20 The preserved PD properties of IDegAsp showed potential improvements in FPG and reductions in hypoglycaemia compared to premixed insulins. IDegAsp showed superior reductions in FPG, comparable HbA1c and reduced daily insulin dose at end of trial compared with BIAsp 30. Moreover, the rates of overall confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were both significantly lower with IDegAsp.20,32 Therefore, IDegAsp at steady state could provide better basal and prandial insulin coverage than BIAsp 30 owing to distinct PK profiles of two separate (basal and bolus) insulin analogues (Figure 5).19

Summary

IDegAsp is a soluble co-formulation, in which the rapid-acting properties of IAsp and ultra-long acting properties of IDeg are preserved separately. This is due to the stable di-hexamers of IDeg, which do not interact with hexamers of IAsp within the formulation. The presence of distinct individual components is confirmed in size exclusion chromatography experiments both in the conditions mimicking formulation (as described above) and also in the model of the subcutaneous environment. Also the pharmacokinetic profiles of two components are preserved in renal and hepatic impaired patients and can be used safely in these patients. A clear dose–response relationship in PK and PD (proportional in T1DM and linear in T2DM) profiles of once daily IDegAsp has been established in patients with type 1 and type 2 diabetes. The glucose lowering effects are also preserved in elderly and young patients with diabetes. Although the PD profile of once daily and simulated model of twice daily IDegAsp are similar, twice daily dosing is beneficial in patients requiring adequate glycaemic control covering two main meals of the day.

The advantage of distinct basal and prandial PD profile of IDegAsp could translate into potential reductions in hypoglycaemia and improved fasting plasma glucose levels in patients with diabetes.3 IDegAsp may help patients and health care professionals to overcome the barriers of intensifying insulin therapy, potentially enabling more patients to achieve glycaemic target with lower risk of hypoglycaemia. The flexibility of dose time coupled with clinical profile could make IDegAsp be an important treatment option for future diabetes therapy in patients requiring insulin intensification.

References


