IS DEGLUDEC THE INSULIN OF TOMORROW?

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ABSTRACT
In an effort to develop better basal insulin with a profile that may cause less hypoglycaemia, Degludec an analogue with a decanoic acid side chain involved. Like Detemir and Liraglutide it binds to albumin in the subcutaneous tissue and blood. It forms multimers which break down slowly, thereby leading to a gradual release. Degludec is more long acting than the current long acting insulins that are present in the market and therefore from phase 2 and phase 3 trials appear to have a better 24 hour profile with a hypoglycemic profile which is comparable. In combination with short acting insulin, Degludec plus (IDegAsp) can be used on a once daily basis at night to control sugars reasonably well with better control of postprandial sugars when compared to Glargine arm in phase 2 studies.

INTRODUCTION
The advent of Insulin was a landmark in the treatment of Diabetes Mellitus. The change in therapeutic policy from Porcine and Bovine insulin to Human Insulin, through the process of genetic engineering, was able to tackle many adverse effects of animal related insulin which included including hypersensitivity and lipoatrophy. Research advances in this field had seen the entry of intermediate and long acting insulins into the market.

The human body secretes basal insulin and bouts of bolus insulin after each meal. The intermediate and long acting insulins were used as an attempt to mimic this physiologic basal-bolus regimen. However they have not been able to achieve this effect with a similar impact in a number of patients. The reason for this is that most of the longer acting exogenous insulins have a “peak” effect in contrast to the “peak-less” action of endogenous basal insulin. In addition, many of them precipitated hypoglycemia due to their delayed “peak” effect. Drugs initially used in an attempt to maximize the basal impact including Ultralente were also unable to withstand the test of time and have been withdrawn from the market, since hypoglycaemia was a major problem. Glargine was initially thought to be a peak less insulin; however some recent studies seem to suggest that this is not entirely the case. With this backdrop we like to discuss the possibility of Insulin Degludec as a long acting insulin analogue.

FACTORS THAT WARRANT BETTER LONG ACTING INSULIN
The benefits for the patient on ideal long acting insulin include the ability to achieve a more physiological control of blood glucose and thereby achieve fewer side effects which include hypoglycemia. Many patients and physicians are often reluctant to start or intensify insulin therapy because of a perceived fear of painful injections, hypoglycemia, weight gain, impairment of quality of life, complexity of insulin regimens, and drug costs. Studies have also suggested that hypoglycemia is more common with insulin when compared to sulphonylureas especially in those subjects with a prolonged duration of diabetes (Figure 1). Therefore, a thrice weekly regimen is more likely to improve the compliance and improve the control with better HbA1c levels, subsequently preventing micro vascular complications on the long run. Studies have shown that satisfaction with the appropriate treatment modality would improve the quality of life amongst diabetes patients.

Hypoglycemia and fear of hypoglycemia are considered to be the major barriers to achieving good
Is Degludec the Insulin of Tomorrow?

Fig. 1: Hypoglycaemia risk increases with the duration of Diabetes

glycaemic control by patients and clinicians. Amongst the insulins in the market, Glargine is the one with the smallest peak, but is still not peakless. Given the benefit Glargine has in reducing hypoglycaemia’s, the flat time action profile action of long acting insulins like Degludec may reduce the incidence of hypoglycaemia’s even further.

Lesser inter-subject variability of insulin is helpful in titrating the insulin dosage correctly. It is well known that Glargine has a better profile than NPH insulin in this regard. However the potential still exists for longer acting insulins with an even lower inter-subject variability.

By and large neither Glargine nor Detemir have been successfully used on a once daily basis and are able to reliably provide a 24 hour basal insulin replacement in Type 1 Diabetes. Studies have shown that a twice daily regimen of Glargine is required in some patients to reduce the number of hypoglycemic attacks as compared to once daily usage. There is thus a need for a truly reliable 24 hour acting insulin warranting only once daily usage.

Most insulins cause weight gain. However Detemir has been found to have a statistically significant weight loss of 1 kg as compared to NPH and Glargine. Given that most treatment intensive regimens cause weight gain attempts are required to develop insulin that does not cause weight gain.

Observational studies had suggested that Glargine may have a dose related increase in cancer compared to Human Insulin; however by and large this is probably not a significant problem on careful assessment of the data. However, it would be preferable that any newer insulin should have a low affinity for the IGF-1 receptor to avoid concerns in connection with potential carcinogenicity.

Degludec

- Insulin backbone
- Side chain: fatty acid + linker
  - Allows formation of multi-hexamers
  - Confers albumin binding

DEGLUDEC INSULIN

Studies have shown Degludec to be equally effective when compared to glargine, in reducing the HBA1c Levels in both Type 1 and Type 2 patients, but with a thrice weekly regimen as compared to the daily administration of Glargine when used in treating Type 1 diabetes.

The molecular structure of Degludec retains the human insulin amino acid sequence, but for the deletion of Threonine in the B30 position of the chain, and the addition of a 16-carbon fatty diacid attached to Lysine in the B29 position via a glutamic acid spacer. (Figure 2)

Insulin Degludec forms a soluble multihexamer at the injection site and is slowly released as insulin monomers, thus prolonging the duration of action. It also binds to albumin thereby causing a slow and stable release of monomers. (Figure 3)

STUDIES ON INSULIN DEGLUDEC

Clinical pharmacology

The clinical pharmacology, in particular the pharmacokinetics are usually studied using a hyperinsulinemic euglycemic pancreatic clamp. The principle of the clamp is to clamp the endogenous production of hormones from the pancreas and supplement hormones from outside so as to ascertain the level of glucose needed to achieve euglycemic state during steady state. The glucose infusion thus needed for maintaining euglycemia, after administering fixed levels of the extrinsic insulin, would be then used to ascertain the levels of the extrinsic insulin during various time periods of the study (Figure 4).

Degludec, On account of a smooth and stable pharmacokinetic profile at a steady state, causes less within-subject variability. As discussed earlier a drug that shows a longer duration of action and lower inter-subject variation is the need of the
Fig. 3: Hexamer formation in Degludec due to linker

Degludec ligand carboxy group binds to Zn in hexamer

The side chain (linker) forms an accurate fit between Degludec hexamers to form multi-hexamers

Fig. 4: Principle of Clamp study

Insulin injection

Blood glucose

Blood glucose

IV glucose infusion rate

Time (min)

Fig. 5: Graph showing 24 hour action of Degludec

Source: NN1250-1876, PK/PD MD study in T1D

There was a difference in rate of Hypoglycemia (RR=0.72), in particular with regards to confirmed nocturnal hypoglycemic attacks (RR=0.42) in the two groups in favor of Degludec. However there was no difference in HbA1c, FPG or mean daily dose of insulin seen in the two groups, implying that Degludec was as efficacious as Glargine with regard to these parameters. The body weight was also maintained over the 16 week period.

**TYPE 2 DIABETES**

A multicentric trial among Type 2 Diabetes Mellitus patients was done to compare once daily Glargine with once daily or thrice weekly Degludec.

236 subjects in between 18 and 75 years of age, having at least 3 months duration of Type 2 Diabetes Mellitus were included in the study. Only those who were on up to two oral antidiabetic drugs for at least 2 months were included in the study. Those who were on thiazolidines or insulins were excluded from the study. Only those with BMI between 23 and 42 and HbA1c between 7% and 11% were included in the study.

The subjects were divided into 3 groups with 2 groups on once daily 10 U Degludec, one group on thrice weekly 20 U Degludec insulin (1U =9 nmol), and the third group on once daily 10 U Glargine concentrations (1U =6 nmol)

They were then followed up for a period of 6 weeks and HbA1c, hypoglycemic attacks, body weight and BMI over this period and the data was compared amongst the groups (Figure 7).

The study found no significant differences in the rate of confirmed hypoglycemic events, amongst once daily or thrice weekly Degludec as compared to glargine. The efficacy outcome measures, including mean weekly insulin dose was similar across all the groups. Thus it is thought that with half the injections weekly, similar glucose control and lesser hypoglycemia could be obtained with Degludec as compared to Glargine.

**DEGLUDEC PLUS**

Degludec plus (IDegAsp) is a combination of Degludec and
Aspart in a 70:30 formulation. Studies have been done to compare Degludec plus and other alternative formulations (AF) of Degludec Aspart (55:45) with Glargine (IGlar) in Type 2 Diabetes Mellitus, all in combination with Metformin. Insulin was administered before the evening meal and dose-titrated to a fasting plasma glucose (FPG) target of 4.0–6.0 mmol/L.

After 16 weeks, mean A1C decreased in all groups to comparable levels. Mean 2-h post dinner plasma glucose increase was lower for IDegAsp and AF than IGlar, whereas mean Fasting Plasma Glucose was similar. Hypoglycemia rates were lower for IDegAsp and IGlar than AF. Nocturnal hypoglycemic events occurred rarely for IDegAsp and IGlar compared with AF.

Thus no significant difference in HbA1c and fasting blood glucose seen between the three groups. However those on IDegAsp had a mean decrease in post prandial sugar of 27 mg/dl as compared to those on Glargine. The daily mean insulin dose was also lesser by 7 u/kg in the former as compared to the latter.

**CONCLUSION**

Degludec gives a comparable glycemic control with Glargine
at a similar molar and unit dose in both Type 1 and Type 2 Diabetes. There was lower rate of hypoglycemic events in those patients on once daily Degludec compared to those on once daily glargine in type 2 Diabetes. In type 1 Diabetes, the rate of hypoglycemia was significantly lower in those on Degludec once daily when compared to Glargine once daily.

The longer 24 hour action of Degludec may also pave the way for a flexible once daily dosing of insulin at any time of the day. Phase 3 trials are in progress and preliminary reports show that a thrice weekly administration of Degludec appeared promising. Once daily dosage of Degludec resulted in significantly lower plasma glucose, and a reduction in hypoglycemic episodes, in 52 week trials in type 2 diabetes when Degludec was compared with once daily glargine. Amongst type 1 diabetes a lower risk of nocturnal Hypoglycemia was seen with once daily Degludec as against Glargine on a daily basis.

REFERENCES


