Basal Insulin Analogues –
A Review of Recent Data on Efficacy and Safety
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Abstract
Conventional basal insulin preparations have to be resuspended prior to injection and have low therapeutic efficacy and drawbacks like nocturnal hypoglycaemia. There is evidence supporting improved pharmacokinetic and pharmacodynamic profiles of basal insulin analogues, glargine and detemir as compared with NPH. Initiation and titration of basal insulin analogues helps patients to improve compliance due to low injection frequency compared to the conventional basal insulin. The unique protraction mechanism adds advantage to insulin detemir in terms of high predictability. Also these analogues have better patient adherence, improved quality of life and higher treatment satisfaction. So basal insulin analogues particularly are better treatment options for treatment of Diabetes.

Introduction
The progressive nature of type 2 diabetes and continuous declining of beta cell function necessitates different types of treatment at different stages of the disease. Most clinician prefer a stepwise therapy of diet, exercise, oral antidiabetic drugs (OADs) and Insulins. In situations, where patients can no longer be managed by diet and exercise, there are recommendations for the use of OAD and newer therapies. OADs, despite maximal doses, offers control of HbA1c for a limited time, and still remains the key challenge in clinical practice. OAD failure is a well recognised phenomenon in clinical practice and studies have shown that this often results in a delay in insulin initiation. This is one of the predominant causes for a majority of patients with a longer duration of diabetes to remaining sub-optimally controlled.

Insulin is frequently reserved for a later stage of the disease and often prescribed for multiple OAD failure cases. Although insulin is the most effective treatment for insulin deficient type 2 diabetes, with proven efficacy in lowering HbA1c, there is strong resistance to introduce Insulin at an earlier stage of the disease. The barriers contributing to patient reluctance to start insulin therapy are fear of hypoglycaemia, weight gain worry, ‘needle anxiety’ and feelings of guilt and failure.

The clinical inertia, which is also due to the physician’s perceived complexity of therapy adds to the existing resistance. The extra time needed to educate the patients to safely implement insulin into the diabetic drug treatment often impedes the enthusiasm for insulin therapy.

Peakless Insulin Concept
Physiological insulin secretion has two phases, viz meal related and basal. The basal component is the trough concentration of insulin secreted between meals and overnight fasting period. Basal insulin formulations attempt to recreate the normal physiology, which is often impaired in diabetes. The challenge here is to provide insulin which requires low injection frequency, preferably once a day with a desired flat and reproducible pharmacodynamic (PD) profile of normal basal insulin secretion. It is well known that the conventional basal insulin preparations [Ultralente and neutral protamine Hagedorn (NPH) insulin] fall short of these desired properties. These are available as suspensions and have to be thoroughly resuspended prior to injection, which is often ignored in the self injection treatment plan. The pronounced peak effect predisposes to nocturnal hypoglycaemia, is yet another issue, which makes these preparations undesirable in routine clinical practice. The high variability in PD profile along with the suboptimal duration of action leads to low therapeutic efficacy. Studies have shown that NPH has shorter duration of action and the end of action occurs at 12-14 hrs. Therefore, NPH insulin will not be able to substitute basal insulin, unless given at least twice daily. In view of these shortfalls, attempt has been made to produce long acting insulins. In the recent years, technology has improved and with the advent of analogue insulins, more potent and longer acting basal insulins are introduced.

Basal Insulin Analogues
It is desired to have insulin that mimics physiological profile and has 24 h action. Insulin detemir and insulin glargine are the two basal analogues available currently for therapeutic use in patients with diabetes. Basal insulin analogues have PD profile that matches endogenous basal insulin secretion by controlling blood glucose levels at night-time and between meals. Therefore, basal insulin analogues control blood glucose more effectively and reduce the risk of hypoglycaemia by providing a steady release of insulin in patients with diabetes. These PD profiles of basal insulin analogues are destined to overcome the limitations of the traditional basal insulin NPH, viz., pronounced peak effect, increased risk of hypoglycaemic events, substantial within-patient variability, shorter duration of action and the potential need for multiple daily dosing.

Mechanism of Protraction
Insulin glargine has a single amino acid substitution at the terminal residue (A21) of the A chain, with two arginine residues added to the B chain terminus (B31,32). Although these modifications make the molecule soluble in acidic environments, it forms precipitates in the neutral subcutaneous depot. The precipitation might lead to undesirable within-subject variability.

Insulin detemir has a deletion of the terminal B chain amino acid (B30), and a fatty acid side chain (myristic acid) is attached at B29. This region of the molecule is involved in self-association, but not in insulin receptor interaction. In addition, these changes facilitates the dihexameric complexes to form in the injection depot, while it also enables reversible albumin binding. Hence, insulin detemir can be retained in the injection depot for a longer duration and further albumin binding serves to retard it in the circulation and buffers the effect of any sudden change in the absorption rate.
Efficacy

PD profiles are similar in these two basal insulin analogues, which is evident by the euglycemic clamp studies in type 2 diabetes. The PD data show no significant differences in dose response, control of blood glucose, glucose infusion rate or duration of action for both analogues (around 24 hours), validating that insulins detemir and glargine meet the need of an ideal basal insulin analogue with the pharmacokinetic potential of up 24-hour efficacy. In a 52 week treat to target trial, both insulins detemir and glargine were found to have same therapeutic efficacy. Similar proportion of patients with type 2 diabetes reached an HbA1C target of ≤7.0% for insulins detemir (33%) and glargine (35%).

These finding are further confirmed by clinical studies that have demonstrated improvements in glycemic control with the different basal insulin analogues. Studies of varying duration of 20- to 52-weeks have shown comparable glycemic control (HbA1C reductions of 1.5-1.9%) for insulins NPH, glargine and detemir. The use of insulin detemir or insulin glargine as add-on to oral glucose-lowering therapy also resulted in comparable HbA1C reduction with a very low risk for hypoglycaemia. It is interesting to note that morning administration of insulin detemir produced similar overall glycemic control at a slightly higher dose, with a low incidence of nocturnal hypoglycaemia.

Therefore, the timing of administration of insulin detemir can be tailored to individual patients' needs and insulin detemir can be offered either in the morning or at bed time. Though initial studies were conducted with twice daily detemir, recent evidence from glucose clamp studies, continuous glucose monitoring (CGM), randomized clinical trials and routine clinical practice studies have shown that detemir is once daily. Latest AACE / ACE consensus statement 2009 also considers detemir as once daily basal insulin with addition benefits of better predictability and less weight gain than other insulins. European medicines agency (EMEA) recommends once daily detemir for the treatment of type 2 diabetes.

Safety

The safety profile, in terms of reduced hypoglycaemic events of both insulin detemir and insulin glargine has been impressive. Both the analogues are associated with a reduced risk of hypoglycaemic episodes, including nocturnal hypoglycaemia, to half the level seen with insulin NPH. The unique protraction property, supports the observation that insulin detemir is characterized by significantly lower within-subject variability in blood glucose-lowering action from injection to injection compared with NPH insulin and insulin glargine. Hypoglycaemic episodes, has the potential to modify dietary pattern of the patients. Often it leads to defensive eating behaviour, which further increases insulin requirement. Hence, the potential advantage of insulin detemir in clinical practice is the low risk of hypoglycaemia (<0.0001) when compared with insulin NPH and insulin glargine. One of the common undesired outcomes of conventional insulin therapy is weight gain. Studies have shown that insulin detemir has weight-sparing effect compared with insulin NPH and its counterpart, insulin glargine.

In a randomized control trial, it was shown that weight gain with insulin detemir was less than half of that for NPH insulin. Another interesting observation is the more pronounced weight neutrality in obese patients. Weight neutrality is likely to be welcomed by obese patients requiring insulin therapy, who wish to limit weight increases. In an observational study, it was shown that patients with a BMI < 25 kg/m2 gained a small amount of weight (0.55 kg), while patients with a BMI ≥ 25 kg/m2 experienced weight reduction that was proportional to baseline BMI. However, the patients with baseline BMI ≥ 31 kg/m2 category had the greatest reduction in weight (1.5 kg). The lack of weight gain with insulin detemir usage can be due to the combined effects such as, less hypoglycaemic episodes with less defensive eating, hepatoselective action causing less adipogenesis and direct central action which reduces appetite.

Dose Titration - Glargine and Detemir

Injection fear is a cause of concern in insulin therapy. Compliance and patient acceptance is better with less frequent dosing regimens. This warrants a simplistic insulin regimen, preferably once-daily insulin dosing. The efficacy and safety of insulin therapy for type 2 diabetes are studied using the Treat-to-Target (TTT) concept, whereby patients aim to achieve a set fasting plasma glucose (FPG) target continuously, using regular dose adjustments. TTT method although improves glycemic control shows a similar HbA1C improvements for the comparators since the same titration targets are applied. If any differences are observed, they are generally with regard to hypoglycaemia or weight. These adjustments can be performed either by the physician or by the patients themselves. Simple titration schedules have been utilized to increase patient self-management of their diabetes, enabling them to effectively adjust the insulin dose themselves.

Studies performed using insulin glargine suggest that the escalation of dose can be done with less incidence of adverse effects when compared with conventional basal insulin regimens. M.C. Riddle et al (2003) demonstrated the effectiveness of once daily regimen of insulin glargine in a TTT study. They also found a reduced risk of hypoglycaemia using once daily, evening basal dose of insulin glargine. In the same study, insulins glargine and NPH were initiated, while continuing the previous OAD regimen to reach the HbA1C target below 7%. Forced titration of fasting plasma glucose (FPG) below 5.5 mmol/L was done using one of the insulin. In this TTT study, approximately 60% of individuals reached the target HbA1C levels and a high adherence was found in the glargine group. In yet another TTT study with insulin detemir and NPH over 24 weeks, insulin doses were titrated toward an FPG target of below 6.0 mmol/L (108 mg/dL) prebreakfast and predinner.

In both treatment groups, 70% of patients achieved the target HbA1C levels. In comparison to evening NPH, 24-hour and nocturnal hypoglycaemia were reduced by 53% (P = 0.019) and 65% (P = 0.031), respectively, with evening detemir. Weight gain with evening detemir was 0.7 kg in comparison to 1.6 kg with NPH (P = 0.005 for evening detemir vs NPH). The TTT method therefore, is a simple and practical regimen for the initiation and optimisation of basal insulin therapy in patients with T2DM in daily clinical practice.

The LANMET study and the LAPTOP study compared the efficacy of insulin glargine with NPH and premixed insulins respectively. Although both glargine and NPH regimens were equally effective, the glargine group achieved the reduction in HbA1C with significantly less hypoglycaemia during the first 12 weeks. However, there was no difference in the frequency of hypoglycaemia episodes the two treatment groups afterwards. In both studies, concomitant OAD (Metformin and glibenpiride) were used along with insulin glargine, but OAD was not used in the comparator group of the LAPTOP study. Therefore, this
were more effective in getting to the target HbA1c endpoint. However, patients in the 3.9–5.0 mmol/L target arm (-1.1%; FBG: -3.4 vs. -3.2 mmol/L).

Studies have also looked at the titration strategies. In the ATLANTUS study, the TTT algorithm of insulin glargine managed by physician (adjusted weekly) was compared with that of the patient (adjusted every 3 days) managed algorithm. In this study, a greater reduction in HbA1C with the patient-led algorithm versus the physician- led algorithm (HbA1C: -1.2 vs. -1.1%; FBG: -3.4 vs. -3.2 mmol/L). In the PREDICTIVE 303 study, self-titration of insulin detemir (303 algorithm; dose titration every 3 days; increase insulin dose by 3 units if the mean FPG was >6.1 mmol/L, no change with FPG 4.4–6.1, decrease by 3 units with FPG<4.4 mmol/L) achieved better glycemic control than patients whose doses were titrated by physicians (standard of care). It is interesting to note that the hypoglycaemic events were significantly reduced (P = 0.0039) in the self-titration of insulin detemir in comparison to the standard of care.

Following the effective use of the simple 303 patient self-titration algorithm in the PREDICTIVE 303 study, the TITRATE study assessed two different FPG targets for patient-directed titration of insulin detemir over 20 weeks while continuing prior OAD therapy. In the TITRATE study, the patients were randomized to the target 3.9–5.0 mmol/L (70–90 mg/dL) or 4.4–6.1 mmol/L (80–110 mg/dL) and the simple 303 titration algorithm (Fig. 1) was used by patients to adjust their once-daily dose of insulin detemir. Patients self-adjusted their dose every 3 days based on the average of three self-measured FPG values. Overall, > 50% patients achieved the target HbA1C of <7.0% by study endpoint. However, patients in the 3.9–5.0 mmol/L target arm were more effective in getting to the target HbA1C than those in the higher target arm (p = 0.04) and an overall mean reduction in HbA1c was 1.2% at endpoint. These findings suggest that the lower FPG targets in self-titration strategy, encourage patient to titrate the dose of insulin detemir more aggressively to achieve the HbA1C goals, without significantly increasing the risk of hypoglycaemia or weight gain.

Both the PREDICTIVE 303 and TITRATE studies showed very low incidence of hypoglycaemic events including nocturnal hypoglycaemia. Mean changes in body weight from baseline were small and not statistically significant between the study groups. These observations highlights that the easy titration method used in insulin detemir self-titration strategy achieves clinically important improvements in glycemic control along with very low incidence of hypoglycaemia and less weight gain.

Cancer Risk

Cancer and diabetes shares the potential risk factors for their development, viz., age, sex, obesity, physical activity, diet, alcohol, and smoking. Even though diabetic individuals are more prone for various types of cancer, the potential biologic links between the two diseases are incompletely understood. The insulin receptor, in addition to its metabolic functions, is also capable of stimulating cancer cell proliferation and metastasis. Majority of cancer cells express insulin and IGF-I receptors. Although stimulation of IGF-I receptors are necessary for mitogenesis, studies have shown that the activation of the A receptor isoform of insulin receptor in IGF-I receptor deficient cells is adequate to promote insulin-mediated mitogenesis. Hence there is a theoretical cancer risk in insulin treated patients.

Research in the past, looked at the differences between human insulin and analogue insulin with respect to binding affinity to the IGF-I receptor. Recent evidence suggests that insulin glargine has much higher affinity, and higher mitogenic potency, than human insulin or other analogues in both in vitro or in vivo studies. Though registry based studies showed a possible association of glargine use with increased incidence of malignancies, particularly with breast cancer, these studies had several limitations like retrospective analysis, short duration etc. The cancer incidence was also under debate due some methodological limitation and in their statistical management. Moreover the diversity in clinical characteristics of patients potentially account for confounding factors in cancer incidence. Furthermore, the diversities in the treatment regimen including basal-bolus regimen does not reflect the cancer incidence exclusive to insulin glargine.

A recent meta-analysis concluded that insulin detemir does not increase the incidence of cancer when compared with treatment with either NPH insulin or insulin glargine. The researchers found significantly lower odds for having a cancer diagnosis in the detemir group compared with the NPH insulin group. Although the meta-analysis is based on a limited data set, the intrinsic validity is high, as it is derived from randomised, controlled insulin detemir trials. Hence, it can be concluded that there is no evidence of a signal of any increased cancer risk in patients treated with insulin detemir compared with either NPH insulin or insulin glargine.

Quality of Life: Basal Analogues

Basal analogues have clearly demonstrated a satisfactory glycaemic control with low rates of overall and nocturnal hypoglycaemia, but their effects on long term effects on mortality and morbidity is yet to be ascertained. In addition to this glargine or detemir have shown better patient adherence, improved quality of life and higher treatment satisfaction.

Conclusions

Evidence supports that the basal insulin analogues, glargine and detemir, offer improved pharmacokinetic and pharmacodynamic profiles compared with NPH. Initiation and titration of basal insulin analogues may help patients to improve compliance due to low injection frequency compared to the conventional basal insulin. The unique protraction mechanism adds advantage to insulin detemir in terms of high predictability.

References
