Since its first clinical use in 1920s, insulin remains the cornerstone in the management of both type 1 and type 2 diabetes mellitus. Further, in late 1970s, insulin therapy was complimented by the availability of recombinant human insulin,[1] which was a more acceptable form of insulin as it had fewer side effects. Subsequently, recombinant technology led to development of insulin analogs, in which structural modifications were introduced in the amino acid sequences to human insulin so as to get the desired pharmacokinetic and pharmacodynamic profile.

The strategy behind insulin therapy is to simulate the body’s physiological insulin secretion. In this, there is a basal insulin secretion that constitutes approximately 40% of the total insulin secretion over 24-h period along with short bursts of insulin secretion that occurs with meals.[2] The main function of the basal insulin secretion is to inhibit hepatic glycogenolysis, ketogenesis, and gluconeogenesis and that of prandial insulin secretion is to combat the meal-related surge in glucose levels.[2] Our aim is to approximate this physiological insulin profile by providing a long-acting insulin that mimics the basal insulin secretion and to provide short-acting insulin with meals that approximates the insulin bursts occurring with meals [Figure 1].

**Evolution of Basal Insulins**

An ideal, basal insulin should have a peak-less pharmacodynamic profile, at least 24 h of duration of action, very low risk of hypoglycemia, should be tolerated well in both type 1 and type 2 diabetes mellitus, and should have predictable action without any intra and inter individual variability.[3] The quest for the search of such an ideal basal insulin continues.

Intermediate acting insulin neutral protamine hagedorn (NPH) and lente insulin has been used as basal insulin by giving two doses so as to give the basal insulin...
coverage for a period of 24 h. They have a gradual onset of action of 1-3 h with a peak of 4-8 h and a duration of action of 13-20 h.[4] NPH consists of protamine that ensures slow release of insulin and zinc, which allows protamine to form crystals with insulin. These insulin have a peak action that may overlap with the peaks of short-acting analogs and may result in frequent hypoglycemic episodes, especially at night.[3] They also have huge intra patient and inter patient variability in their pharmacokinetic and pharmacodynamic profile.[5] Ultralente insulin has longer duration of action than lente insulin and NPH, but it is associated with larger day to day variability, erratic peaks, and frequent hypoglycemic episodes.[14] Among all those mentioned above, only NPH is being used in clinical practice presently. These drawbacks necessitated more research that led to the discovery of long-acting analogs, namely glargine and detemir [Figure 2].

**GLARGINE**

The structure of glargine differs from that of human insulin such that, in A21 of A chain, there is substitution of aspargine with glycine, and, in position B30 of B chain, there is addition of two arginine residues.[6] It is stable in acidic solution, and, once it is injected into skin at neutral pH, it precipitates causing delays in its absorption and taking longer duration for action.[7] Its onset of action is 1-3 h up to 24 h, it has a peak-less profile, less variability in pharmacological profile,[8] and less hypoglycemia when compared with NPH.[9] The reduction of HbA1C is almost comparable with that of NPH.[10] The major drawback of glargine is the weight gain that occurs after prolonged use.[11] Also, there is a concern about cancer risk with this agent.

**DETEMIR**

The structure of detemir differs from that of human insulin in two perspectives: Deletion of amino acid threonine at position 30 of beta chain and addition of 14 carbon aliphatic fatty acid to epsilon amino group of lysine in position B29.[12] These changes enable detemir to bind with albumin reversibly and to form multimeric complexes within subcutaneous tissue, which prolongs its duration of action.[13] Its pharmacological profile is very similar to that of glargine, except that it may require 2 doses in some patients to provide optimal basal coverage, which occurs rarely with glargine.[14] Furthermore, it is weight neutral, which makes it more preferable in obese population.[15] It seems to have lesser cancer risks, and has less inter individual variability when compared with glargine.[16]

**DEGLUDEC—IDEAL BASAL INSULIN?**

In recent times, degludec has attracted the attention of many people with its extended duration of action and thrice weekly injection to give full coverage of basal insulin. The structure of degludec differs from that of human insulin with the deletion of threonine of B30 and addition of 16 chain carbon fatty di-acid to lysine of B29 with a glutamic acid as a spacer. This formulation allows degludec to form multiple hexamers, which makes them dissociate slowly after subcutaneous injection and thus take longer duration for action. In addition, binding to albumin also compliments its longevity.[15] It results in long, flat, extended insulin profile, released smoothly without any peaks and has no inter subject variability. Its levels are detectable even after 96 h of injection.[18] The advantage over glargine and detemir is that it has ultra-long acting profile that reduces the number of doses for basal coverage. They showed that degludec provided comparable results between once daily and thrice weekly doses without any significant difference in adverse effects or glycemic control.[19] Also, it has less occurrence of hypoglycemia in type 1 diabetes[20] and better control of postprandial blood sugars in type 2 diabetes when compared to glargine.[10] The drug has completed phase III trial and is awaiting FDA approval.

Degludec can be formulated with aspart, a short-acting insulin. Two formulations are available: 70-30% and 55-45%.[21] It can be used in the treatment of both type 1 and type 2 diabetes as basal bolus regimen with aspart, and, in type 2, it can be used alone with other oral hypoglycemic agents.[22] The common adverse drug reactions are nausea, vomiting, rash, headache, hypoglycemia, weight gain, and upper respiratory tract infections.[22]

With the amount of evidence that is evolving, it is very likely that glucedec may replace the existing long-acting analogs in the near future [Figures 3 and 4].
POTENTIAL CARCINOGENIC RISK

The mystery regarding the role of long-acting insulin analogs in carcinogenesis remains to be unraveled. Insulin analogs having modifications in beta chain of insulin of B26 to B30 have increased affinity of binding towards IGF-1 receptor, which may play a role in mitogenic potential.[23] These insulin also show prolonged occupancy time of binding to insulin receptor, which may lead to abnormal activation of downstream pathways, that may lead to cell proliferation.[24,25] Although many evidences support the mitogenic potential of the insulin analogs, it may be amplified by the fact that diabetes, obesity, and insulin resistance itself can act as risk factor of many cancers, which may confound the results.[26]

Of all the analogs, glargine has the highest affinity toward IGF-1 receptor[27] and has greater concern. Several studies have identified the association of glargine with breast cancer risks.[28,29] Furthermore, a recent study demonstrated that the risk of cancer with glargine does not occur with its short-term use, rather it is associated with prolonged use of >5 years, in the context of using other forms of insulin therapy before starting glargine.[29] UKPDS and DIAGAMI-2 trial describes only increased mortality of cancer patients who are on insulin therapy and does not comment upon the incidence of cancer.[29,30] ORIGIN trial reassures the use of glargine and that it does not increase the overall cancer risks significantly.[31] We need more evidences to know the exact relation between the insulin analogs and cancer potential.

ROLE OF BASAL INSULIN IN SPECIAL SITUATIONS

Children

Glargine is the most frequent basal insulin used in children, but its safety is not yet established. Compared with glargine, detemir has shown more consistent pharmacokinetic profile in children,[2,14,32]

Pregnancy

Due to potential risks of embryo toxicity, teratogenicity, mitogenicity, and lack of adequate data, these long-acting agents are not approved for treatment in pregnancy.[2,33-35] Its role is yet to be clearly defined in pregnancy, although FDA now mentions this as a Class C indication in this situation.

EVOLVING BASAL ANALOGS

New formulations of glargine that are under development are LY2963016, which has completed phase III, and BIOD adjustable basal, which is in phase I. The advantage of the latter is that it can be mixed with other insulin preparations unlike conventional glargine preparations.[36,37] A protaminated form of insulin lispro is also under pipeline, which can be used as basal insulin.[38]

An unique ultra-long acting insulin FT-105 being developed, in which insulin is attached to polyglutamate peptide which in turn is attached to vitamin E, is under phase 1 clinical trials.[39] An unique ultra-long acting insulin FT-105 being developed, in which insulin is attached to polyglutamate peptide which in turn is attached to vitamin E, is under phase 1 clinical trials.[39] This formulation will cause aggregation of insulin particles that retards absorption.

Another novel basal analogue LY2605541 is presently undergoing phase 2 clinical trials.[3]

The formulation of combining basal insulin molecules with non-insulin such as GLP is also being investigated.[22] “Smart” insulin are specialized insulin preparations that release insulin according to concentration of glucose in tissue levels, thereby alleviating the risk of hypoglycemia.[36]
In summary, it would appear that glargine and detemir, which had largely replaced NPH insulin as basal insulin of choice today, will continue to be used as effective basal insulin in the near future. Their potential for increased cancer risk is yet to be established. Unless studies supporting clear links are reported, they will be continued to be used as basal insulin. However, both glargine and detemir may not provide full coverage of basal insulin for 24 h with single doses in some patients and may require a 2nd dose. Degludec appears to be more promising agent that can be used in thrice weekly doses besides providing full and more effective basal coverage for 24 h when given as once a day injection. If the consistency of the thrice weekly dose of degludec is proven by further studies, degludec will certainly replace the existing agents as an ideal basal insulin in the future. With lot of newer basal insulin in the pipeline, especially smart insulin, which are very promising, degludec should expect tougher competition from future insulin also.

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