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New Developments in Insulin Therapy for Type 2 Diabetes

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ABSTRACT

Insulin has classically been considered a treatment of last resort for individuals with type 2 diabetes, delayed until all other efforts by the patient and healthcare provider have failed. Recent treatment guidelines recommend the use of insulin, in particular basal insulin, as part of a treatment regimen earlier in the disease process. Many patients are reticent about initiating insulin, so therapies that allow insulin treatment to be more tailored to individual needs are likely to result in greater acceptance and patient adherence with therapy. To meet this need, a range of insulin products are in development that aim to increase absorption rate or prolong the duration of action, reduce peak variability and weight gain associated with insulin treatment, and offer alternative delivery methods. This review describes insulin products in clinical development, new combination therapies, and new devices for insulin delivery.

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KEYWORDS: Basal insulin; Insulin; Type 2 diabetes

Exogenous insulin is well established as the primary and lifesaving therapy for type 1 diabetes. Individuals with type 2 diabetes initially are treated with lifestyle changes including diet and exercise,[1-3] but treatment intensification because of declining beta-cell function usually is required and blood glucose may become inadequately controlled with oral glucose-lowering treatments or incretin-based therapies only. At this stage, supplementary insulin therapy typically is added, but insulin has classically been considered the final treatment option for individuals with type 2 diabetes.[1-3]

As treatment guidelines and insulin products are refined, however, it is increasingly being recognized that insulin may be used at an earlier stage in the management of type 2 diabetes. Recent treatment guidelines emphasize individualized therapy, acknowledging the difficulties associated with lifestyle therapy and the progressive nature of the disease. Some patients are recommended to include insulin, in particular basal insulin, as a component of treatment earlier in the disease process. In this way, the role of basal insulin changes from one of damage control in an inevitably progressive disease to one of preventative care, with the ability to modify the disease process in a positive way.[4]

Because many patients are reluctant to initiate multiple daily injections of insulin, insulin initiation often involves basal-only therapy in conjunction with existing oral glucose-lowering drugs. Used as supplementary therapy, insulin can rest beta-cells and facilitate recovery of the prandial response; however, early intensive therapy may offer advantages in beta-cell preservation in type 2 diabetes.[5] Patient-friendly, effective, and safe therapies that allow insulin treatment to be fully tailored to individual needs will significantly influence adherence to therapy. This review describes insulin products in clinical development, new combination therapies, and new devices for insulin delivery.

NEW BASAL INSULIN PRODUCTS

The currently available basal insulin analogs, insulin glargine (Lantus; Sanofi, Paris, France) and insulin detemir (Levemir; Novo Nordisk Inc, Plainsboro, NJ), offer an

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improvement over neutral protamine Hagedorn insulin in terms of duration of action and reduced peak effect.[6-8] However, they still demonstrate suboptimal/nonideal pharmacokinetic and pharmacodynamic properties.[9] A basal insulin ideally will provide a continuous and flat glucose-lowering effect over 24 hours in all patients, with low day-to-day variability (reducing the risk of hypoglycemia) and once-daily dosing for all. Both insulin glargine and insulin detemir need to be injected at the same time each day; this can make adherence difficult for patients who have varying daily schedules. As discussed by Tibaldi,[10] insulin degludec (Tresiba; Novo Nordisk Inc) is a novel basal insulin comprising recombinant DesB30 human insulin acylated at the LysB29 residue with a hexadecandioyl-γ-L-Glu side-chain that has a unique mode of protraction.[11,12] The pharmacokinetic/pharmacodynamic profile of insulin degludec confers reduced variability at similar efficacy to insulin glargine, with a lower risk of nocturnal hypoglycemia and the ability to dose more flexibly.[13-18] Insulin degludec is approved for use in several regions, including Europe, Japan, and Mexico, and regulatory filings in several other countries have been submitted. Approval in the United States is conditional on a satisfactory outcome in a dedicated cardiovascular safety trial.[19]

The molecular structure of insulin degludec permits the production of a co-formulation containing 70% insulin degludec and 30% insulin aspart (Ryzodeg; Novo Nordisk Inc), which has been approved in Europe, Japan, and Mexico, with product availability anticipated during 2014. In combining the long duration of action of insulin degludec with the rapid-acting insulin analog, insulin aspart (NovoRapid/NovoLog; Novo Nordisk Inc), this product aims to provide 24 hours of basal insulin coverage with additional post-prandial blood glucose control for 1 meal per day. Several new insulin products are in clinical development.

PEGYLATED INSULIN LISPRO (LY2605541)

Exogenously administered insulin is prone to glomerular filtration and therefore to significant renal clearance. PEGylated insulin lispro (PEG-lispro; Eli Lilly and Company, Indianapolis, Ind) is a novel basal insulin comprising lispro covalently bound to a 20 kDa polyethylene glycol chain (PEG) at lysine B28, resulting in a large hydrodynamic size. PEGylation appears to alter the tissue distribution of this insulin, delay absorption, and reduce renal clearance as incorporation of water molecules into hydrophilic structures increases the effective size of the molecule beyond the filtration potential of the kidney. These effects increase the duration of action to >36 hours.[20,21]

Endogenous insulin is secreted into the portal vein and travels directly to the liver, where approximately 80% is extracted.[22] Exogenous insulin is absorbed into the systemic circulation, leading to high concentrations in peripheral tissue, which may account for weight gain associated with insulin treatment.[23] It is proposed that the large size of PEG-lispro may reduce transport into peripheral tissue, such as adipose tissue.[24] Moore et al[25] have postulated that the fenestrated sinusoidal endothelium of the liver may allow preferential transport of PEG-lispro into the liver relative to peripheral tissues, and a clamp study in dogs suggested that PEG-lispro had a preferential hepatic versus peripheral effect on glucose metabolism.

Clamp studies have shown that PEG-lispro has a longer duration of action and less variability compared with insulin glargine.[21,26] In phase II trials, once-daily PEG-lispro (administered in the morning) provided similar blood glucose levels to insulin glargine, with less variability. In one study, the overall percentage of patients with type 2 diabetes reporting nocturnal hypoglycemia was similar with PEG-lispro and insulin glargine (25.6% vs 34.4%, $P = .127$); however, there was a rate reduction of 48% in favor of PEG-lispro when data were adjusted for baseline differences ($P = .021$).[24] Furthermore, patients receiving PEG-lispro lost weight (mean [standard deviation {SD}] weight loss, 0.6 [0.2] kg, $P = .007$), whereas patients receiving insulin glargine gained weight (mean [SD] weight gain, 0.3 [0.2] kg, $P = .662$; treatment difference: 0.8 kg, $P = .001$).

In a phase II study in patients with type 1 diabetes, the overall hypoglycemia rate was 12% higher with PEG-lispro than insulin glargine (mean [SD] events/patient/30-day period: 8.74 [7.70] vs 7.36 [6.80]; $P = .037$).[27] However, the nocturnal hypoglycemia rate was 25% lower with PEG-lispro in this study (0.88 [1.22] vs 1.13 [1.42] events/patient/30-day period; $P = .012$). Consistent with the study in patients with type 2 diabetes, PEG-lispro was associated with a mean weight loss of 1.20 kg ($P < .0001$), whereas insulin glargine was associated with a mean weight gain of 0.69 kg ($P = .0007$) (least-squares mean difference, −1.89 kg) ($P < .0001$).[27] In both studies, enzyme levels used for liver function tests (alanine aminotransferase and aspartate aminotransferase) were increased in the PEG-lispro versus the insulin glargine treatment groups.[24,27]

Larger phase III clinical trials with PEG-lispro are ongoing, including a randomized clinical trial of PEG-lispro used in basal−bolus therapy in type 2 diabetes (NCT 01468987[28]), which was completed in August 2013, and publication of data is awaited.

HIGH-DOSE FORMULATIONS

Many patients with type 2 diabetes are obese and may display insulin resistance, requiring high doses of insulin. Increasing the insulin concentration reduces the injection volume and potentially reduces the number of injections needed to deliver the required dose. However, changing the concentration may alter the pharmacodynamic profile because the surface area of the depot in contact with the interstitial fluid is reduced, which may slow absorption. A 500 U/mL formulation of human insulin was shown to have significantly delayed absorption in pigs when compared with a 100 U/mL formulation.[29]

Clinical studies of a 300 U/mL formulation of insulin glargine (U300) by Sanofi are under way, and phase I and II