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REVIEW

Recent Advances in Insulin Therapy

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Abstract

Insulin therapy has advanced remarkably over the past few decades. Ultra-rapid-acting and ultra-long-acting insulin analogs are now commercially available. Many additional insulin formulations are in development. This review outlines recent advances in insulin therapy and novel therapies in development.

Keywords: Insulin analog, Basal insulin, Inhaled insulin, Ultra-fast acting insulin analogs, Oral insulin.

Introduction

More than 30 million people in the United States are living with diabetes.[1] Over 15% of people living with diabetes use insulin therapy.[2] For those living with type 1 diabetes (T1D), insulin is the mainstay of therapy. Since the discovery of insulin in 1921, numerous insulin analogs and novel formulations have been developed. Recent advances in insulin therapy include ultra-rapid-acting insulin and ultra-long-acting basal insulin therapies. The focus of basal insulin development is toward longer and flatter profiles of action to reduce hypoglycemia and provide more flexibility with timing of dosing. The focus of rapid-acting insulin (RAI) development is toward faster onset and offset of glucose-lowering action. Despite these advances, there still remain issues with available insulin therapy. These include the challenge of postprandial hyperglycemia due to the delayed onset of subcutaneous insulin,[3] the significant risks of hypoglycemia[4] and weight gain,[5] the burden of injection therapy,[6] and cost.[7] In this review, we focus on insulin therapies that have been commercialized in the past 5 years and insulin therapies that are in development.

Basal Insulin Therapy

Insulin glargine U-300

Insulin glargine U-300 (Sanofi) gained Food and Drug Administration (FDA)-approval on February 25, 2015, making it the first approved ultra-long-acting basal insulin. The advantage of this concentrated form of insulin glargine over insulin glargine U-100 is a more constant and evenly distributed glucose-lowering effect as well as longer duration of action. Insulin glargine U-300 maintained glucose control (≤105 mg/dL) for ~5 h longer than insulin glargine U-100 with a median time of 30 h.[8] In a 6-month parallel-group study of 807 adults with type 2 diabetes (T2D) on multiple daily insulin injections (EDITION 1), use of insulin glargine U-300 resulted in similar HbA1c levels compared with insulin glargine U-100, but with significantly less nocturnal hypoglycemia.[9] Thirty-six percent of participants had one or more confirmed hypoglycemic event (≤3.9 mmol/L) or severe nocturnal hypoglycemic events between weeks 9 and month 6 with insulin glargine U-300 compared with 46% with the use of insulin glargine U-100 (relative risk 0.79 [95% confidence interval (CI) 0.67–0.93]; $P < 0.005$). A reduction in nocturnal hypoglycemia with insulin glargine U-300 compared with U-100 was shown again in EDITION 2 in adults with T2D.[10] The efficacy and safety of insulin glargine U-300 were not compromised when insulin was injected up to 3 h before or after the usual time of administration.[11] It should be noted that on average, insulin requirements are higher with insulin glargine U-300 compared with insulin glargine U-100. In EDITION 1, the insulin doses were 9% higher with insulin glargine U-300 compared with insulin glargine U-100.

Insulin degludec

Insulin degludec (Novo Nordisk) is an ultra-long-acting insulin analogue with a glutamic acid and fatty acid side chain. Insulin degludec gained FDA approval on September 25, 2015, becoming the second ultra-long-acting basal insulin approved in the United States. After 8 days of once-daily insulin degludec injections, the glucose-lowering effect of the final injection lasted at least 42 h.[12] Compared with glargine U-100, insulin degludec was shown to have four times lower day-to-day variability in glucose-lowering effect (coefficient variation of 20% vs. 82%).[13] The extended duration of insulin degludec allows it to be administered at

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varying times in the day. Administering insulin degludec at extreme dosing intervals of 8–40 h between doses did not raise glycosylated hemoglobin levels or hypoglycemia rates compared with once-daily insulin glargine U-100 in adults with T2D[14] or T1D.[15]

In a randomized crossover trial of 501 adults with T1D (SWITCH 1), insulin degludec resulted in fewer symptomatic hypoglycemic episodes (<56 mg/dL) compared with insulin glargine and fewer nocturnal symptomatic hypoglycemic episodes (277.1 vs. 426.8 episodes per 100 person-years exposure).[16] A randomized crossover trial of 721 adults with T2D (SWITCH 2) similarly showed a reduction in symptomatic hypoglycemic episodes and nocturnal symptomatic hypoglycemic episodes with insulin degludec compared with insulin glargine U-100.[17] In a study of 7637 adults with T2D at high risk of cardiovascular events (DEVOTE), insulin degludec was shown to be noninferior to insulin glargine U-100 in terms of incidence of major cardiovascular events (hazard ratio 0.91 for first occurrence of a major cardiovascular event with insulin degludec [95% CI 0.78–1.06]).[18]

Insulin glargine U-300 and insulin degludec have been compared in multiple clinical trials. In a crossover study of 57 adults with T1D, insulin degludec was shown to have lower between-day and within-day variability in glucose-lowering effect compared with insulin glargine U-300.[19] In a randomized 24-week noninferiority study of 929 adults with uncontrolled T2D (BRIGHT), insulin glargine U-300 was noninferior to insulin degludec U-100 in lowering glycosylated hemoglobin levels, with lower rates of hypoglycemia during the titration period (0–12 weeks), but comparable rates of hypoglycemia over the full study periods.[20] In a randomized study of 1609 adults with T2D (CONCLUDE), the rates of nocturnal symptomatic and severe hypoglycemia were modestly lower with degludec U-200 compared with glargine U-300, with no significant difference in the rate of overall symptomatic hypoglycemia.[21]

One possible advantage of ultra-long-acting basal insulin is reducing the risk of diabetic ketoacidosis in people with T1D. In one observational study, insulin omission was one of the main contributors to the development of diabetic ketoacidosis.[22] In theory, ultra-long-acting basal insulin therapies could reduce the risk of diabetic ketoacidosis in people with T1D who intermittently omit insulin doses. Future clinical trials are required to determine if this is the case.

Insulin 287

A once-weekly insulin would significantly reduce the burden of injectable basal insulin and is being developed by Novo Nordisk in the form of insulin 287. A study assessing the pharmacokinetics and pharmacodynamics of insulin 287, a once-weekly basal insulin, was completed in adults with T2D in June of 2015 (NCT0214886) and in adults with T1D in December of 2019 (NCT03766854). Insulin 287 was also studied in combination with semaglutide (NCT03789578).

Oral insulin

Administering insulin orally would remove the burden of injections. In a phase 2 trial, an oral basal insulin, insulin 338 (Novo Nordisk), resulted in similar glucose control as injected insulin glargine in adults with T2D.[23] Novo Nordisk ceased development of insulin 338 because the doses required to achieve glucose control were high, making it not commercially viable. ORMD-0801 (Oramed Ltd.) is another oral insulin,[24] which is currently in phase 2 trials for adults with T1D and T2D.

Basal insulin peglispro

In normal physiology, endogenous insulin is secreted by pancreatic beta-cells into the portal circulation. In contrast, conventional subcutaneous insulin results in peripheral hyperinsulinemia.

Basal insulin peglispro (Lilly) is a PEGylated molecule that was designed with targeted hepatic activity, but was found to increase triglyceride and transaminase levels.[25] In 2015, Lilly ceased development of insulin peglispro due to the potential adverse effects.

Ultra-RAI Therapy

Fiasp

Fiasp (Novo Nordisk) was approved by the FDA in 2017.[26] It is formulated with two excipients: vitamin B3 (niacinamide) to increase speed of absorption and L-arginine for stability.[27] These excipients are included in the FDA database of allowed inactive ingredients at higher concentrations than present in Fiasp.[28] Aspart insulin contains a single amino acid substitution from regular human insulin to allow for more rapid dissociation of insulin hexamers into dimers and monomers to increase speed of absorption of a subcutaneous depot.[29] Niacinamide acts as a hydrotrope to further shift the balance from hexamers toward monomers that are more readily available for absorption. Niacinamide also serves as a vasodilator to increase blood flow to the injection site.

This earlier absorption of Fiasp compared with aspart results in an incremental increase in early insulin action. A meta-analysis of pharmacokinetic/pharmacodynamic studies in adults with T1D demonstrated faster appearance in venous blood (4 vs. 9 min), with greater concentration, and greater insulin action in the first 30 min compared with insulin aspart.[29] A 26-week phase 3 study in people with T1D was randomized to premeal Fiasp, postmeal Fiasp (20 min postmeal), or premeal standard aspart. This study demonstrated noninferiority of Fiasp for both mealtime and postmeal dosing with slightly more frequent early postprandial hypoglycemia than the comparison group, whereas postprandial hypoglycemia rates (2–4 h after meals) were lower, leading to similar overall rates of hypoglycemia. This study also demonstrated superiority for 1 and 2 h postprandial glucose control on a meal test compared with aspart (estimated treatment difference of −21.21 mg/dL at 1 h [95% CI −29.65 to −12.77]; $P < 0.0001$).[30] In a phase 3 study of people with T2D only on basal insulin at baseline, the addition of Fiasp was noninferior with regard to change A1c compared with aspart.[31] In addition, this study showed improved 1 h postprandial glucose control with similar hypoglycemia rates.

A randomized blinded crossover study using Fiasp in the Medtronic 670G system, a hybrid closed-loop system, showed noninferiority of the Fiasp insulin.[32] A similar study with the iLet automated insulin delivery system also showed

noninferiority of glucose control with Fiasp.[33] One reason why no difference was found may have been that these studies did not adjust the insulin delivery algorithm to account for the faster insulin profile of Fiasp. A study was recently completed using Fiasp in the iLet system with two different insulin delivery settings (NCT03816761). The results are yet to be published.

In these clinical trials, adverse events with Fiasp are similar to other RAIs. There may be slightly more mild injection-site reactions and slightly more frequent postprandial hypoglycemia than the comparison group, although the overall rates of hypoglycemia are similar.

Inhaled insulin

Technosphere® insulin (Afrezza; MannKind Corporation) is a drug/device product approved by the FDA in 2014.[34–37] Afrezza insulin is a dry powder formulation of human insulin adsorbed onto Technosphere (fumaryl diketopiperazine) microparticles. These microparticles reach the deep lung on inhalation where they are rapidly dissolved into the bloodstream. Following inhalation by adults with T2D, serum insulin levels increased rapidly within 5 min and peaked at 15 min.[38] A meta-analysis of 12 trials concluded that the glycemic efficacy of Technosphere-inhaled insulin is lower than that of subcutaneous insulin, but inhaled insulin carries a lower risk of severe hypoglycemia and weight gain.[39] The authors recommended reserving the use of Technosphere insulin for adults with diabetes without pulmonary disease who require insulin therapy but are unable or unwilling to use subcutaneous insulin therapy. In addition, select patients prefer to use Technosphere when they desire rapid correction from hyperglycemia, given its rapid onset of action. This type of insulin should not be used in those with lung disease or those who smoke. Pulmonary function tests should be performed before initiation, 6 months after initiation, and then yearly.

Dance 501 inhaled insulin (Aerami Therapeutics) is a novel liquid human insulin formulation with a small handheld aerosol device for inhalation. The company's website indicates this insulin is ready to enter phase 3 trials.[40] The relative biopotency compared with subcutaneous RAI is 13%. Data presented at the 2019 Diabetes Technology Meeting in people with T2D showed a linear dose relationship and a more rapid onset of action (6.5 vs. 20 min, $P < 0.02$) compared with lispro insulin,[41] with similar results in adults with T1D[42] presented at the 2019 American Diabetes Association Scientific Sessions.

LY900014 lispro

LY900014 (URLi) is novel ultrarapid insulin (Eli Lilly) that recently completed phase 3 trials in T1D and T2D, with results presented at the 2019 American Diabetes Association Scientific Sessions.[43–48] A double-blind, treat-to-target 26-week trial in 1222 adults with T2D evaluated the efficacy and safety of ultrarapid lispro compared with lispro. This demonstrated noninferiority for change in A1c and no significant differences in rates of serious hypoglycemia. URLi demonstrated lower hypoglycemia rates in the period >4 h after a meal and superior 1 and 2 h postprandial glucose excursions on a meal test. These improvements in the postprandial periods were also seen on ambulatory glucose profiles from blinded Dexcom G4 CGM. URLi showed noninferiority for change in A1c in the companion study in 673 participants with T2D and also superior 1 and 2 h postprandial glucose excursions on a meal test. No differences in local tolerability have been reported with this insulin.

BioChaperone Lispro insulin

BioChaperone Lispro insulin (BCLIS; Adocia) is ready to enter phase 3 trials.[49] This insulin contains a novel excipient with a modified oligosaccharide molecule, BioChaperone BC222, for faster absorption as well as citrate to speed absorption.[50] There are U100 and U200 formulations. Studies with BCLIS delivered through an insulin pump showed faster onset of absorption and action compared with standard aspart, on par with Fiasp.[51] Another study in adults with T1D with BCLIS self-administered at the start of a mixed meal test demonstrated lower 1 and 2 h postprandial glucose excursions compared with lispro; the area under the curve for this time frame was 31% lower with BCLIS than lispro.[50] Adocia is also developing a long-acting/short-acting combined formulation using BioChaperone 147, a polyanionic amphiphilic polymer, with insulin glargine that allows glargine to be mixed with BCLIS. This combination product showed moderate improvements in postprandial parameters compared with NPH/lispro mixed insulin and separate injections of glargine and lispro in people with T2D who consumed a solid mixed meal.[52] No differences in local tolerability have been reported with this insulin.

"Superfast" insulin aspart

AT247 (Arecor Limited) is a formulation of aspart using excipients with metal ion binding capacity. Data presented in abstract form for swine studies showed modestly faster glucose lowering than RAI.[53] As of December 2019, they announced completion of a phase 1 clinical study comparing AT247 with aspart and Fiasp, with plans to present these data in 2020.[54]

Pramlintide with insulin

Amylin is cosecreted from beta-cells with insulin, achieving 20–40-fold lower plasma level after a mixed meal than insulin.[55] The secretion of amylin is also lost in T1D.[56] Pramlintide, a synthetic analogue of human amylin, can reduce postprandial glucose spikes presumably by slowing gastric emptying.[57] A 52-week double-blind study with 480 participants with premeal administration of pramlintide and insulin reduced A1c 0.67% from baseline compared with 0.16% in the placebo group ($P < 0.0001$).[58] Fixed premeal doses of 30 mcg SQ pramlintide used in conjunction with an insulin-only closed-loop system requiring meal announcement resulted in improved postprandial glucose levels and reduced area under the curve for the glucose excursions.[59] Most recently, a dual-hormone system delivering a fixed ratio of pramlintide to insulin (6 mcg/unit) significantly improved time-in-target range (70–180 mg/dL) and glucose variability compared with a single-hormone closed-loop system.[60]

Prior studies with pramlintide required a second subcutaneous injection to administer this medication along with insulin before each meal, as mixing pramlintide with insulin can cause precipitation. In order for this approach to be

clinically feasible, several pharmaceutical companies are working on formulations of a combined pramlintide-insulin product. Adocia is developing BioChaperone Pramlintide Insulin.[61] Xeris is also developing a stable coformulation.[62] Postprandial hypoglycemia can occur when initiating pramlintide, a dose reduction of the mealtime insulin is recommended. Nausea is a common side effect as pramlintide is known to delay gastric emptying.

Cone snail insulin

A new paradigm for faster acting insulin analogs might come from the animal kingdom.[63] In 2015, it was found that a fish-hunting cone snail (*Conus geographus*) uses a venomized form of insulin to target its prey. This snail releases a monomeric form of insulin into the water to cause a hypoglycemic reaction in its prey. Subsequently, seven other unique insulin sequences were discovered in related snails. Despite structural differences in the insulin molecule, these forms of insulin can bind to the human insulin receptor, although with lower affinity than human insulin, and lower blood glucose in mouse and fish models of diabetes. These monomeric insulins may be able to overcome delays in absorption that arise from the hexamer to monomer breakdown that must occur with current subcutaneous insulins.

Other approaches

Oral insulin. Oral insulin will need to overcome very low absorption across the intestinal epithelium as well as degradation by proteolytic enzymes. Various methods have been developed, including permeation enhancers,[64] nanoparticle encapsulation,[65] and mucosa adhering patches.[66] One new approach is with a luminal unfolding microneedle injector (LUMI) device.[67] This orally delivered device bypasses the mucosal barrier by physically inserting insulin-loaded microneedles into the small intestine. The LUMI device is a 9×30 mm coated capsule that dissolves in the gut and deploys the microneedle device. Future work will be needed to assess bowel perforation and obstruction risk. Despite many years of research into orally delivered insulin, these formulations remain in early studies.[68]

Hepatic-directed insulin lispro. Hepatic-directed insulin lispro (Diasome Pharmaceuticals, Inc.) is a subcutaneously delivered formulation that uses a hepatocyte targeting moiety, biotin-phosphatidylethanolamine in a phospholipid matrix, which passively binds $\sim$100 insulin molecules.[69] A recently completed 26-week, multicenter randomized, double-blinded treat-to-target trial compared hepatic-directed insulin lispro to standard insulin lispro in participants with T1D.[70] This study showed noninferiority for A1c lowering, no hepatic safety concerns, and no difference in overall hypoglycemia rates.

Glucose responsive insulins. This concept refers to the controlled release of insulin triggered by glucose conditions. One approach uses encapsulation of insulin with controlled delivery from biomimetic systems. The matrices carrying the insulin range from hydrogels to vesicles to micro- or nanoparticles that encapsulate and then release insulin by a variety of methods, including swelling, shrinking, or changes in porosity.

These systems typically use one of three biomimetic mechanisms for glucose responsivity: (1) glucose oxidase, (2) glucose binding proteins (i.e., lectins, concanavalin A [Con A]), or (3) phenylboronic acids (PBA) and their derivatives.[71,72] Glucose oxidase catalyzes a reaction of glucose with oxygen and water to generate gluconic acid and hydrogen peroxide, thus creating a locally acidic environment.[71] This is the same reaction used by continuous glucose monitors for proportional amperometric signals to detect glucose levels. The glucose oxidase approach has disadvantages of potential immune reaction to a xenogenic enzyme, local toxicity from the hydrogen peroxide by-

Table 1. External Methods for Insulin Release

Mechanism	*Description*
Ultrasound	• Low-frequency ultrasound promotes uptake of insulin by inducing air pockets in the keratinocytes of the stratum corneum and disruption of lipid layers without effecting barrier properties of the skin.[76] • Ultrasound-responsive shells[77] and injectable nanonetworks[78] for regulated release of encapsulated insulin.
NIR light	• Various approaches with photoactivated depot of insulin for light regulated release.[79] • Gold nanorod complexes with a surfactant are being used to store insulin. Gold nanorods absorb NIR, which causes the light energy to be converted to heat to break the stratum corneum.[80] • Gold nanoparticles containing an insulin reservoir, NIR leads to collapse of the nanoparticle network and insulin release.[81]
Temperature	• Thermal-responsive polymers,[82,83] beads,[84] and microneedle[85] patches for temperature-dependent insulin release.
Site warming devices	• Warming the site of insulin injection improves local blood flow, increases insulin absorption. • Infusion site warming devices have been shown to reduce time-to-peak insulin action in human studies.[86]
Mirconeedle devices	• Microneedle patches (solid, hollow, or drug loaded) could allow glucose responsive insulin delivery in combination with biomimetic systems or external trigger systems.[87] • Consist of micron-sized needles attached to a transdermal patch that allow for painless subcutaneous delivery of drug delivery.[88]

NIR, near-infrared.

product, and inherent degradation of the enzyme over time.[71] Glucose binding proteins such as Con A bind saccharides with high affinity and specificity. Con A forms aggregates that can be used as a glucose responsive cross-linking molecule. Subsequent studies have suggested that immunogenicity and mitogenicity concerns with ConA have diminished enthusiasm for its clinical utility.[73] PBA are nonbiologic small molecules that can reversibly bind glucose to form glucose responsive hydrogels. The pKa of PBA (8–9) is much higher than physiologic pH requiring addition of moieties to PBA to shift toward more physiologic pHs. In general, glucose responsive insulin approaches will need to overcome several issues before clinical translation, including insufficient insulin release profiles, delayed responsivity, insulin leakage, biocompatibility, and accumulation of carrier materials.[71]

Another approach to glucose responsivity is through modification of the insulin molecule itself. MK-2640 is an insulin molecule that is glycosylated to allow for binding and clearance by the mannose receptor C type 1 (MRC1) while maintaining insulin receptor action.[74] In theory, glucose has competitive binding for MRC1 such that at high glucose concentrations, less of the insulin analogue is cleared via MRC1 (thus more is available for insulin receptor signaling), whereas at low glucose concentrations, a larger portion of the insulin analogue is cleared resulting in lower insulin receptor binding and signaling.[75] MK-2640 was recently evaluated in human studies.[74] Interestingly, they were unable to demonstrate a glucose-dependent change in MK-2640 clearance, but they did see a glucose-dependent increase in glucose disposal, suggestive of an increased pharmacodynamic effect at higher glucose concentrations.

External methods for insulin release

An alternative tactic for glucose responsive insulin delivery is through external remote triggers for insulin release that could be used along with continuous glucose monitors to allow for an alternative to infusion pumps in a closed-loop system (Table 1).

Conclusions

Recent advances in bolus and basal insulin therapy provide some incremental and some more substantial improvements over prior insulin formulations. In clinical studies, ultra-long-acting basal insulin therapies have demonstrated significantly less nocturnal hypoglycemia and allow for flexibility in timing of dosing. New bolus insulin therapies on the market and in development focus on faster absorption for better early insulin action mainly through additives to improve postprandial hyperglycemia due to the delayed onset of subcutaneous insulin. Although the newer products (Fiasp, Technosphere insulin) have yet to demonstrate superior long-term outcomes such as significant A1c lowering or diabetes complication rates. Future approaches, including pramlintide-insulin combination products and cone snail insulin, offer promise for more physiologic postprandial glucose control. Oral, hepatically directed, and glucose-responsive insulins remain important avenues of research but could face some challenges and are unlikely to be ready for use in patients in the foreseeable future.

Author Disclosure Statement

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