What's New in Insulins and Delivery Systems

Intranasal, buccal, oral, peritoneal, and even rectal insulins are in various stages of development.

BY BRUCE JANCIN

FROM A CONFERENCE ON THE MANAGEMENT OF DIABETES IN YOUTH

KEYSTONE, COLO. – Pfizer Inc.'s Exubera earned marketing approval to enormous fanfare in 2006 as the first inhaled insulin. Expectations were high for what was expected to be a blockbuster product. Yet Exubera was pulled from the market the next year, brought down not by safety issues, but because it was a spectacular commercial failure.

The Exubera flameout has not dissuaded other pharmaceutical companies from pursuing development of intranasal, buccal, oral, peritoneal, and even rectal insulins, according to Dr. Jay S. Skyler. He presented an update on many of these novel insulins and new delivery systems at the conference, which was sponsored by the University of Colorado, Denver, and the Children's Diabetes Foundation at Denver:

▶ **Inhaled insulin.** Afrezza, MannKind Corp.'s investigational inhaled insulin with fumaryl diketopiperazine, reaches peak plasma insulin concentrations in just 10 minutes, far faster than currently available rapid-acting insulins. And the Afrezza inhaler is no bigger than a thumb, in contrast to the bulky and awkward Exubera inhaler.

"Everybody criticizes Afrezza. They say, 'Exubera failed.' Well, it probably failed in the marketplace because of its delivery system and lack of pharmacokinetic advantages compared to existing insulins, whereas with Afrezza you get both the pharmacokinetic advantage and convenience of delivery," said Dr. Skyler, professor of medicine, pediatrics, and psychology and former director of the division of endocrinology, diabetes, and metabolism at the University of Miami.

Afrezza is now under review by the Food and Drug Administration for possible marketing approval.

▶ **Intraperitoneal insulin delivery.** In the mid-1990s, Dr. Skyler and coworkers demonstrated that when insulin was delivered intraperitoneally, 51% of it was rapidly absorbed into the portal circulation and went straight to the liver.

The redesigned DiaPort percutaneously implanted peritoneal port system, under development by Roche, can be connected to an external insulin pump, according to two unpublished studies: In a recent 6-month study, patients who were randomized to standard insulin pump therapy with continuous subcutaneous insulin infusion gained an average of 1.5 kg, whereas those assigned to the DiaPort system experienced no change in body weight. And in another trial, episodes of recurrent severe hypoglycemia in patients using the DiaPort system were reduced sevenfold, compared with baseline, even though their hemoglobin A_{1c} fell by nearly 2%.

"I think the peritoneal approach is one we need to seriously think about as we move into automated systems," the endocrinologist said.

▶ **Oral insulins.** These agents' Achilles heel has been poor bioavailability, typically less than 1%. Proposed solutions include using liposomal coatings, absorption promoters, or protease inhibitors, and packaging the oral insulin in hydrogels or microspheres to stabilize it against degradation.

Oral insulins in the developmental pipeline that appear to achieve rapid peak plasma insulin concentrations include Emisphere Technologies' oral insulin (Diabetes Care 2010;33:1288-90) and Biocon's IN-105 oral insulin polymer (J. Diabetes Sci. Technol. 2009;3:568-84).

In contrast, Capsulin, under development by Diabetology Ltd., a U.K. company, has a far less impressive early plasma effect (Diabetes Obes. Metab. 2010;12:82-7).

"This one doesn't look like it's going anywhere as a rapid-acting insulin, but it might actually work as a basal insulin, given orally," Dr. Skyler said.

Another product with a delayed effect is the oral insulin capsule being developed by Oramed Pharmaceuticals, an Israeli company. This product, known as ORMD 0801, is designed for intestinal absorption. Phase II studies have been completed in patients with type 2 diabetes.

▶ **Novel basal insulins.** Novo Nordisk A/S's ultralong-acting insulin degludec has a half-life in excess of 24 hours and can be detected in the circulation at least 96 hours post injection. It can be given once daily or three times per week, although Dr. Skyler suspects that many patients would have difficulty sticking to the latter schedule.

The Exubera flameout has not dissuaded other pharmaceutical companies from pursuing the development of other novel insulins and new delivery systems.

Insulin degludec achieves protracted absorption in subcutaneous tissue by utilizing a soluble multihexamer formation rather than the standard single hexamer formation. Insulin degludec will be studied in the pivotal phase III BEGIN and BOOST trials, which together will involve more than 10,000 patients and will be the largest-ever clinical trial program for insulin therapy in diabetes.

Eli Lilly & Co.'s insulin lispro protamine suspension has been studied with favorable results as part of a basal-bolus approach in patients with type 1 diabetes (Diabet. Med. 2010;27:563-9), as well as in insulin-naive patients with type 2 diabetes that is poorly controlled with oral agents (Diabet. Med. 2010;27:181-8). This insulin is already marketed in some parts of the world.

A French company, Flamel Technologies Inc., is developing FT-105, a basal insulin consisting of a vitamin E and glutamic acid polyaminoacid polymer linked to the insulin protein. When administered by subcutaneous injection, FT-105 aggregates into dense microparticles that take a long time to dissolve.

Altea Therapeutics Corp.'s PassPort is a transdermal insulin delivery system. The patient applies a proprietary patch on the skin, presses an attached button to create micropores, then slaps an insulin-containing patch over the site. Studies indicate that the system provides protracted availability of basal insulin with resultant plasma insulin levels that are proportionate to the various insulin concentrations available in the patch reservoir.

Valeritas Inc.'s insulin device V-Go consists of a small, patchlike insulin pump that contains no electronic components. The disposable skin patch lasts 24 hours, during which it provides basal insulin at a steady rate. The patient can push a small button to release a few extra units of insulin at a time, as a premeal bolus. In addition, Sanofi-Aventis has a very long-acting insulin analogue in phase I studies, and Eli Lilly has a new basal insulin in phase I as well.

▶ **New rapid-acting prandial insulins.** Development of such products would help to control the daunting problem of postprandial hyperglycemia. One possible solution is Becton, Dickinson & Co.'s device for intradermal injection of insulin lispro, which capitalizes on the fact that insulin is consistently absorbed more rapidly intradermally than subcutaneously. The Becton, Dickinson device consists of a skin patch containing an array of tiny intradermal needles, each of which is no longer than the E in the "E Pluribus Unum" on the back of a penny.

Yet another intradermal insulin product in development is Debiotech SA's Jewel micropump, which is mounted to a disposable skin patch. The system, which is considerably smaller than a fingertip, is now under FDA review.

▶ **Ultrarapid-acting insulins.** Afrezza is one. The DiaPort system for intraperitoneal delivery is another ultrarapid-acting solution.Yet another is Biodel Inc.'s VIAject, which comprises insulin with ethylenediaminetetraacetic acid and citric acid that forms rapidly absorbed monomers upon subcutaneous injection. In a 16-patient crossover study, peak insulin concentrations were achieved in 34 minutes with VIAject, compared with 63 minutes for insulin lispro and 139 minutes for regular human insulin.

Whether that's quick enough to make for a commercial success remains to be seen, Dr. Skyler said. VIAject is now in phase III testing.

Halozyme Therapeutics' insulin-PH20 technology combines currently available mealtime insulins with recombinant human PH20 hyaluronidase, which results in greatly accelerated insulin action.

▶ **Buccal insulin.** "The buccal route has been argued about for many, many years," Dr. Skyler observed. One device for buccal administration that has drawn research and commercial attention recently (Diabetes Obes. Metab. 2010;12:91-6) is Generex Biotechnology Corp.'s Oral-lyn insulin spray, an aerosolized aqueous solution of regular human insulin. The device delivers 10 units per puff to the oral cavity at a velocity of 100 mph. Oral-lyn is marketed only in Ecuador, which Dr. Skyler considers a less-than-ringing endorsement.

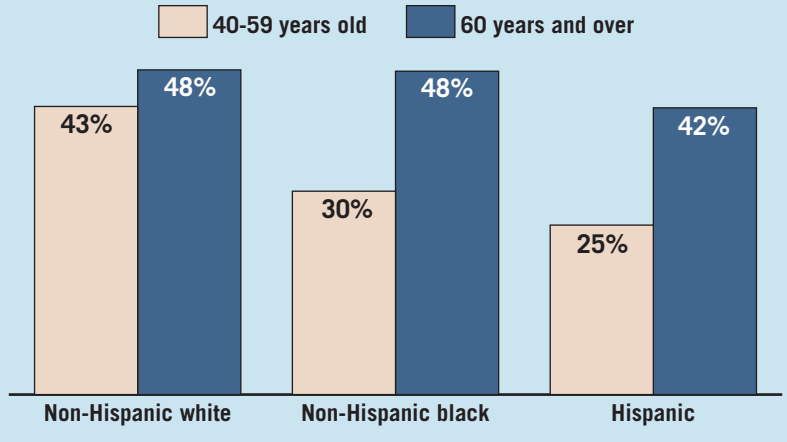
▶ **"Smart" insulins.** Insulin with a built-in glucose sensor was first proposed in the 1970s. The concept is to harness an insulin polymer conjugate to a multivalent glucose-binding molecule. Upon contact with blood glucose, the glucose displaces the insulin in the polymer, freeing the insulin to go into the circulation.

"I'd be quite thrilled to see this kind of insulin come to the market, but I'm a bit skeptical," Dr. Skyler said.

Dr. Skyler disclosed that he has served as a consultant to and/or received research grants from numerous pharmaceutical companies. ■

DATA WATCH

Diabetes Patients Aged 40 and Over Who Received All Three Recommended Services* for Diabetes in 2006



*Hemoglobin A_{1c} measurement, dilated eye examination, foot examination
Source: Agency for Healthcare Research and Quality Medical Expenditure Panel Survey