

Artificial Pancreas May Help in Meeting Targets

BY BRUCE JANCIN

EXPERT OPINION FROM A
CONFERENCE ON MANAGEMENT
OF DIABETES IN YOUTH

KEYSTONE, COLO. – Why are the Juvenile Diabetes Research Foundation and many of the nation's foremost diabetes researchers pressing full speed ahead to develop an artificial pancreas?

Quite simply, because multiple real-

world studies show that current usual therapy of type 1 diabetes fails to achieve target hemoglobin A_{1c} levels in more than half of patients.

And while more intensified management using insulin pumps and frequent daily or continuous glucose monitoring (CGM) effectively lowers HbA_{1c} values for some patients outside the artificial world of clinical trials, it does not work for everybody – especially teenagers,

many of whom do not want to have to deal with diabetes continuously, Dr. Georgeanna J. Klingensmith said at the conference, sponsored by the Children's Diabetes Foundation at Denver.

"An artificial pancreas may remove enough of the human error and hassle factor to allow more patients to achieve success, we hope. A cure for adolescence would also help," quipped Dr. Klingensmith, chief of the pediatric clinic at the

Barbara Davis Center for Childhood Diabetes and professor of pediatrics at the University of Colorado, Denver.

A JDRF-sponsored study of CGM as it is used in routine clinical care underscores the adolescent adherence problem. Patients were instructed in the use of the device and were in frequent contact with their health care provider for the first month, then told to call as needed. By 6 months, 64% of the patients who were aged 25 years or older were using their CGM sensor at least 6 days a week, as instructed. So were 25% of 8- to 14-year-olds, but only 19% of 15- to 24-year-olds. Moreover, 21% of all 15- to 24-year-olds were not wearing the device at all in month 6 (*Diabetes Care* 2010;33:17-22).

Predictors of successful use of CGM at month 6 included age 25 years or greater, more frequent self-testing of blood glucose prior to going on CGM, wearing the device 6 days or more a week during the first month, and success in keeping blood glucose readings in the 70- to 180-mg/dL range during month 1.

Dr. Klingensmith cited among several examples of the state of real-world diabetes care the Hvidøre Study Group. In this 21-center study of roughly 2,000 pediatric type 1 diabetes patients, mostly in Europe, only a single center met the 2009 International Society for Pediatric and Adolescent Diabetes (ISPAD) consensus guideline that all children should have an HbA_{1c} below 7.5%. The mean HbA_{1c} was 8.2% (*Diabetes Care* 2007;30:2245-50).

Similarly, in 2,999 type 1 diabetes patients at six U.S. centers participating in the SEARCH for Diabetes in Youth Study, in which Dr. Klingensmith was a co-investigator, mean HbA_{1c} was 8.3%, with only 44% of type 1 patients meeting American Diabetes Association HbA_{1c} age-based targets (*J. Pediatr.* 2009;155:668-72).

Most of the factors associated with HbA_{1c} in a multivariate analysis of SEARCH were nonmodifiable: age, diabetes duration, race, parental education, insurance status, household income. The only two independent modifiable factors were insulin regimen – patients on pump therapy had a mean HbA_{1c} of 8.0%, significantly lower than any other regimen – and frequency of blood glucose testing.

In 2009, at the Barbara Davis Center for Childhood Diabetes in Denver, of 2,437 patients diagnosed with type 1 diabetes more than 3 months earlier, the median HbA_{1c} was 8.2% in children younger than 6 years old, 8.2% in 6- to 12-year-olds, and 8.7% in those aged 13-18 years. Plus, teens accounted for 75% of all patients with a median HbA_{1c} greater than 10%, Dr. Klingensmith continued.

An artificial pancreas, or "closed loop" system, would entail reliable automated guidance of insulin pump dosing based on input from CGM coupled with predictive algorithms for avoidance of severe hypoglycemia, she said. ■

Disclosures: Dr. Klingensmith said her work is supported by research grants from the National Institutes of Health and Centers for Disease Control and Prevention.

Postmarketing Experience—The following adverse reactions have been identified during postapproval use of FORTEO. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- **Osteosarcoma:** Cases of bone tumor and osteosarcoma have been reported rarely in the postmarketing period. The causality to FORTEO use is unclear. Long term osteosarcoma surveillance studies are ongoing.
- **Hypercalcemia:** Hypercalcemia greater than 13.0 mg/dL has been reported with FORTEO use.

Adverse events reported since market introduction that were temporally (but not necessarily causally) related to FORTEO therapy include the following:

- **Allergic Reactions:** Anaphylactic reactions, drug hypersensitivity, angioedema, urticaria;
- **Investigations:** Hyperuricemia;
- **Respiratory System:** Acute dyspnea, chest pain;
- **Musculoskeletal:** Muscle spasms of the leg or back;
- **Other:** Injection site reactions including injection site pain, swelling and bruising; oro-facial edema.

USE IN SPECIFIC POPULATIONS: Pregnancy Category C—There are no adequate and well-controlled studies of FORTEO in pregnant women. In animal studies, teriparatide increased skeletal deviations and variations in mouse offspring at doses more than 60 times the equivalent human dose and produced mild growth retardation and reduced motor activity in rat offspring at doses more than 120 times the equivalent human dose. FORTEO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In animal studies, pregnant mice received teriparatide during organogenesis at subcutaneous doses 8 to 267 times the human dose. At doses \geq 60 times the human dose, the fetuses showed an increased incidence of skeletal deviations or variations (interrupted rib, extra vertebra or rib). When pregnant rats received subcutaneous teriparatide during organogenesis at doses 16 to 540 times the human dose, the fetuses showed no abnormal findings.

In a perinatal/postnatal study, pregnant rats received subcutaneous teriparatide from organogenesis through lactation. Mild growth retardation in female offspring at doses \geq 120 times the human dose (based on surface area, mcg/m²). Mild growth retardation in male offspring and reduced motor activity in both male and female offspring occurred at maternal doses 540 times the human dose. There were no developmental or reproductive effects in mice or rats at doses 8 or 16 times the human dose, respectively.

Exposure multiples were normalized based on body surface area (mcg/m²). Actual animal doses: mice (30 to 1000 mcg/kg/day); rats (30 to 1000 mcg/kg/day).

Nursing Mothers—It is not known whether teriparatide is excreted in human milk. Because of the potential for tumorigenicity shown for teriparatide in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use—The safety and efficacy of FORTEO have not been established in any pediatric population. FORTEO should not be prescribed in patients at an increased baseline risk of osteosarcoma which include pediatric and young adult patients with open epiphyses. Therefore, FORTEO is not indicated for use in pediatric or young adult patients with open epiphyses.

Geriatric Use—Of the patients receiving FORTEO in the osteoporosis trial of 1637 postmenopausal women, 75% were 65 years of age and over and 23% were 75 years of age and over. Of the patients receiving FORTEO in the osteoporosis trial of 437 men, 39% were 65 years of age and over and 13% were 75 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment—No studies have been performed in patients with hepatic impairment.

Renal Impairment—In 5 patients with severe renal impairment (CrCl \leq 30 mL/min), the AUC and T_{1/2} of teriparatide were increased by 73% and 77%, respectively. Maximum serum concentration of teriparatide was not increased.

OVERDOSAGE: Incidents of overdose in humans have not been reported in clinical trials. Teriparatide has been administered in single doses of up to 100 mcg and in repeated doses of up to 60 mcg/day for 6 weeks. The effects of overdose that might be expected include a delayed hypercalcemic effect and risk of orthostatic hypotension. Nausea, vomiting, dizziness, and headache might also occur.

FORTEO® (teriparatide [rDNA origin] injection)

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In postmarketing spontaneous reports, there have been cases of medication errors in which the entire contents (up to 800 mcg) of the FORTEO delivery device (pen) have been administered as a single dose. Transient events reported have included nausea, weakness/lethargy and hypotension. In some cases, no adverse events occurred as a result of the overdose. No fatalities associated with overdose have been reported.

Overdose Management—There is no specific antidote for teriparatide. Treatment of suspected overdose should include discontinuation of FORTEO, monitoring of serum calcium and phosphorus, and implementation of appropriate supportive measures, such as hydration.

DOSAGE FORMS AND STRENGTHS: Multi-dose prefilled delivery device (pen) for subcutaneous injection containing 28 daily doses of 20 mcg.

PATIENT COUNSELING INFORMATION: Patients should read the FDA-approved *Medication Guide* and delivery device (pen) *User Manual* before starting therapy with FORTEO and re-read them each time the prescription is renewed. Patients need to understand and follow the instructions in the FORTEO delivery device *User Manual*. Failure to do so may result in inaccurate dosing.

**PLEASE SEE FULL PRESCRIBING INFORMATION
FOR ADDITIONAL INFORMATION.**

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