Vaccine for Type 1 Diabetes Shows Promise

Swedish biotech company signs development and marketing deal with Johnson & Johnson.

BY BRUCE JANCIN

FROM A CONFERENCE ON MANAGEMENT OF DIABETES IN YOUTH

KEYSTONE, COLO. – Right now, Diamyd Medical's GAD vaccine is in the sweet spot in the developmental pipeline – an interim period of enormous optimism that this novel autoantigen-based immunotherapy will safely prevent many cases of type 1 diabetes.

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The results of three phase II studies look quite promising. Two large phase III clinical trials are well underway in Europe and the United States. The safety experience with the 65-kD isoform of GAD (glutamic acid decarboxylase-65) vaccine has been outstanding. The subcutaneous two-injection series is easy to administer. Acceptance of the vaccine by patients and their families is high.

The vaccine targets a serious disease whose incidence is steadily climbing by 3%-5% per year in developed countries. And most patients with recently diagnosed type 1 diabetes possess GAD autoantibodies, so the Diamyd vaccine would be widely applicable.

All of that was good enough for Johnson & Johnson, which in June inked a huge development and marketing deal for the GAD vaccine with small Swedish biotech company Diamyd Medical. Under the deal, Diamyd receives $45 million upfront, milestone payments of up to $580 million, and tiered royalties after that. The Federal Trade Commission's antitrust division has approved the deal.

But during this blissful interlude, one key question remains: Is the Diamyd vaccine effective?

"It's too early to say if this works. Absolutely too early. We have a phase III trial in Europe with results due next spring. And the TrialNet study [is] going on here in the U.S. So we will know in a year or 2," Dr. Johnny L. Ludvigsson said at the conference, which was sponsored by the Children's Diabetes Foundation at Denver.

Dr. Ludvigsson, professor of pediatrics at the University of Linkoping (Sweden), led the phase III European trial evaluating whether the GAD vaccine preserves beta-cell function and residual insulin secretion in patients with type 1 diabetes diagnosed within 3 months of starting treatment. He also headed a phase II study that caused a favorable buzz within the diabetes research community (N. Engl. J. Med. 2008;359:1909-20) and for which he is now analyzing 5-year follow-up data.

And while the forthcoming phase III trial results will tell the tale as to clinical efficacy, at this time some useful interim observations can be made about the GAD vaccine, according to Dr. Ludvigsson:

▶ **The vaccine has demonstrated excellent safety.** Experience with the vaccine to date totals 850 patient-years in adults and 350 patient-years in children, with no adverse events reported. This is enormously reassuring because GAD transforms glutamate into GABA, an important neurotransmitter. Lack of GAD in the CNS leads to muscle rigidity and convulsions, while stimulation of CNS GAD results in inhibition of neurotransmission. The absence of any such adverse events indicates the vaccine is working, as designed, to affect only the activated T cells that have targeted pancreatic beta cells for destruction, Dr. Ludvigsson said.

▶ **The vaccine has demonstrated prolonged immunologic effects.** The immunologic response to the Diamyd vaccine lasts surprisingly long – approaching 5 years and still counting. It's a GAD-specific, cell-mediated, and humoral immune response characterized by increased GAD autoantibodies, a Th2 shift marked by reduction in activated T cells and an increase in regulatory T cells, a sharp and sustained rise in levels of interleukins-2, -5, -10, -13, and -17, and GAD tolerance.

Eventually, fasting C-peptide levels start to fall off in parallel to the placebo group.

DR. SKYLER

▶ **"The earlier we treat, the better the outcome."** That's why the phase III European trial is restricted to patients diagnosed with type 1 diabetes within the past 3 months. It's also the impetus for ongoing prevention trials in individuals at very high genetic risk for type 1 diabetes who have GAD autoantibodies but have not developed overt disease.

For the future, the GAD vaccine alone probably is not the solution to type 1 diabetes, Dr. Ludvigsson said candidly.

"I believe this opens the door to using different antigens, like in allergy. Allergists don't use just cat antigen in patients who have cat, dog, and house dust mite allergies. I suppose we may also learn to combine autoantigens, together with possible stimulation of beta cells in combination with drugs that promote beta-cell regeneration," he continued.

The likely necessity for a combined approach addressing multiple pathways was underscored in a separate presentation by Dr. Jay S. Skyler, chairman of the type 1 Diabetes TrialNet, a National Institutes of Health-funded international network of centers conducting clinical trials of diabetes therapies.

The GAD vaccine appears to have the same limitation as the other immunomodulatory therapies evaluated to date in clinical trials, including the B cell–depleting anti-CD20 agent rituximab, and the anti-CD3 biologics teplizumab and otelixizumab: Namely, they preserve beta-cell function for a while, but the effect is transient. Eventually, fasting C-peptide levels start to fall off in parallel to the placebo group. That's why combination therapy will probably be required in order to cure or prevent type 1 diabetes, according to Dr. Skyler, professor of medicine, pediatrics and psychology at the University of Miami.

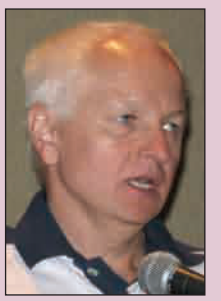
Ideally, a combination therapy should be multipronged, with three goals: Stop immune destruction, preserve beta-cell mass, and replace or regenerate beta cells. Such a regimen might start off with a potent anti-inflammatory therapy – perhaps an anti-interleukin-1beta agent or tumor necrosis factor inhibitor – to quell the metabolic stress surrounding the pancreatic islets. This might well need to be given on a continuing basis.

Dr. Ludvigsson reported receiving research grant support from Diamyd. Dr. Skyler has served as a consultant to and/or received research grants from numerous pharmaceutical companies. ■

VIEW ON THE NEWS

More Than One Type of Prevention

Elimination of the environmental agent(s) responsible for type 1 diabetes (T1D) would be the most efficient approach to *primary prevention*; however, more work is needed to identify the environmental agents and to develop effective interventions.



Blocking progression from islet autoimmunity to clinical diabetes or *secondary prevention* has been attempted, so far to no avail, by a number of groups, including large randomized trials.

Trials in patients with newly diagnosed T1D aim at *tertiary prevention*, such as preservation of remaining islet beta cells to induce and prolong partial remission. Unfortunately, most islets have already been destroyed by the time diabetes is diagnosed and complete reversal of diabetes is highly unlikely. Benefits may include a simpler insulin regimen, lower hemoglobin A_{1c}, and reduced risk of hypoglycemia and microvascular complications. The gain may be even greater if the intervention is applied as soon as the patient shows asymptomatic "dysglycemia."

While new interventions are often tested first in patients with established diabetes, and, when proven safe, applied to patients with pre-T1D, efficacy after diagnosis of diabetes is not to be a precondition to application in pre-T1D, as there may be a "point of no return" in the destruction of the islets, rendering some interventions effective only at the earlier stages of the process.

Among several approaches to prevention of T1D, "vaccination" using islet autoantigens (intact or altered peptides derived from insulin, GAD_{65} or other proteins) stands out as potentially inducing long-term tolerance by induction of regulatory T cells that down-regulate immunity to autoantigens. Until recently, trials of insulin administered parenterally, orally, or intranasally have been unsuccessful. Therefore, the initial results from trials of the Diamyd vaccine, as reviewed here, were greeted with huge interest and excitement. The vaccine includes the whole recombinant human GAD_{65} ($rhGAD_{65}$) molecule suspended in alum. The protective effect was most pronounced in patients treated within 3 months of diagnosis, and no serious side effects were observed.

Insulin-related molecules continue to attract great interest in vaccine development. Phase I studies have been completed or are nearing completion for a proinsulin peptide C19-A3, an insulin peptide with incomplete Freund adjuvant, and a plasmid encoding proinsulin.

Combination therapies may enhance efficacy while lowering risk of adverse events if utilizing therapies from different treatment pathways. While more targeted therapies are being employed, immunomodulatory agents are still relatively nonspecific and potentially toxic to some of the trial participants.

In the long run, primary prevention will likely be the optimal approach to the prevention of T1D. Once more than one islet autoantibody is present, most individuals progress to diabetes in 5-10 years. The TrialNet consortium (www.diabetestrialnet.org) systematically evaluates therapies in new-onset patients as well as in prediabetic subjects, and invites proposals from the research community at large.

MARIAN REWERS, M.D., PH.D., *is professor of pediatrics and preventive medicine at the Barbara Davis Center for Childhood Diabetes, University of Colorado, Denver. He is on an advisory board for GlaxoSmithKline and provided medical-legal consultation for AstraZeneca.*