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MONOGRAPH

rhGAD65

Diabetes Vaccine

Diamyd®

Recombinant human glutamic acid decarboxylase (GAD) 65 kD isoform

EN: 285080

SUMMARY

Therapeutic vaccines have emerged as a promising alternative in the prevention and treatment of autoimmune diabetes, a progressive autoimmune destruction of insulin-producing β-cells in the pancreas. Thus, using autoantigens that drive the immune-mediated pathology, diabetes vaccination attempts to induce immune tolerance, thereby delaying or arresting disease progression. The 65-kD isoform of glutamic acid decarboxylase (GAD65) is a major autoantigen in the two autoimmune forms of diabetes: type 1 diabetes and latent adult-onset autoimmune diabetes (LADA). Diamyd® is a vaccine candidate containing recombinant human GAD65 (rhGAD65) that has proven to slow down the destruction of insulin-producing β-cells in preclinical and clinical studies. Phase II clinical studies in children with recent-onset type 1 diabetes and children and adults with LADA have demonstrated the safety of Diamyd® and long-term protection of β-cell function. Currently ongoing phase III trials will determine whether Diamyd® can preserve residual β-cell function in young patients with recent-onset type 1 diabetes.

BACKGROUND

Type 1 diabetes is a chronic disease characterized by progressive T-cell-mediated autoimmune destruction of insulin-secreting β-cells found in the islets of Langerhans in the pancreas. It accounts for 5-10% of all reported cases of diabetes. One or more biomarkers of β-cell immune destruction, which include autoantibodies to islet cells, insulin, tyrosine phosphatases IA-2 and IA-2β and the 65-kD isoform of glutamic acid decarboxylase (GAD65), may be found in 85-90% of newly diagnosed cases (1). GAD65 autoantigen appears to be essential in mediating islet inflammation (insulitis) in humans and nonobese diabetic (NOD) mice, a spontaneous murine type 1 diabetes model (2). In addition, it has been suggested that β-cell destruction is preferentially caused by the T helper 1 (Th1) phenotype of $CD4^+$ T cells via the secretion of interferon gamma (IFN-γ) and interleukin-2 (IL-2), while Th2 cells would exhibit a protective or regulatory function by secreting IL-4, IL-5 and IL-10, which are antagonistic to Th1 cytokines (3).

Latent adult-onset autoimmune diabetes (LADA) is an autoimmune form of diabetes that initiates in adulthood, has a slow rate of progression to insulin dependence, and shows genetic susceptibility and type 1 diabetes autoantibodies, typically islet cell and GAD65 autoantibodies. Although often regarded as a transitional state between type 1 and type 2 diabetes, LADA presents unique clinical features and therefore may be considered a separate clinical entity. Thus, unlike subjects with type 1 diabetes, LADA patients exhibit greater body mass index, elevated triglycerides and HDL cholesterol, greater insulin resistance and greater plasma C-peptide concentrations, indicating higher insulin production. In fact, one of the diagnostic criteria in LADA is that insulin therapy is not required for at least 6 months after diagnosis, although insulin requirements increase as long as autoimmune β-cell destruction progresses (4).

Immunomodulatory approaches leading to a Th1 to Th2 shift have been suggested to protect against autoimmune diabetic disease. Studies in NOD mice have demonstrated that immunotherapy with GAD65 peptides can prevent the development of diabetes by shifting the Th1/Th2 balance towards a Th2 response (decreased IFN-γ and increased IL-5 secretion) (5). Further investigations have shown that immunization of NOD mice with GAD65-specific peptides was able to stop the onset of insulitis and posterior development of overt disease in young 4-week-old animals not showing signs of the disease. Moreover, administration of a specific combination of GAD65-specific peptides to 12-week-old NOD mice already exhibiting significant β-cell autoimmunity suppressed the progression to overt disease through the induction of regulatory Th2 cells, as shown by decreased IFN-γ and increased IL-4 and IL-5 levels. Interestingly, protection against the development of diabetes was proven to be dependent on the production of IL-4 by Th2 cells, as shown by experiments in IL-4-defective young and old NOD mice, which despite immunization developed overt disease (6).

Recombinant human GAD65 (rhGAD65, Diamyd®) is a human DNA vaccine that was originally developed at the University of California, Los Angeles, and subsequently licensed to Diamyd Medical. It has recently been granted orphan drug designation by the FDA for the treatment of type 1 diabetes with residual β-cell function.

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PRECLINICAL PHARMACOLOGY

The effects and mechanism of action of rhGAD65 in preventing diabetes in NOD mice were investigated in a study in which 4-week-old female NOD mice were assigned to i.m. injections of rhGAD65 (50 μg), pcDNA (50 μg) or PBS, and cumulative diabetes incidence was measured up to 30 weeks of age. At this time point, rhGAD65-treated mice showed a significantly lower diabetes incidence than the PBS group (61.9% vs. 95.2%; *P* = 0.008), as well as a significant decrease in insulitis scores and apoptotic β-cell rates. Upregulation of IL-4 levels and the cytosolic component of the nuclear factor of activated T-cells (NF-ATc), accompanied by downregulation of the pre-existing component of NF-AT (NF-ATp), thus favoring the formation of Th2 cells, was also observed (7).

CLINICAL STUDIES

The safety of alum-formulated rhGAD65 was evaluated in a dose-escalating phase II clinical study that recruited 47 LADA patients randomly assigned to alum alone as placebo or to s.c. injection of rhGAD65 (4, 20, 100 or 500 μg) 4 weeks apart (8, 9). Vaccination with rhGAD65 was well tolerated, most adverse events being mild and no significant drug-related adverse events being reported. Moreover, the 20-μg dose was associated with significant increases from baseline in fasting and mixed-meal tolerance test (MMTT)-stimulated C-peptide levels at 6 months (median percent change of 36% and 19%, respectively). The change in these two parameters was positively correlated with an increased fraction of regulatory T cells ($CD4^+CD25^+$; Treg) over 6 months.

Long-term safety and effects on β-cell function were also assessed in a study that prospectively followed for 5 years a total of 40 of the 47 LADA patients included in the dose-escalating phase II study (10). None of the serious adverse events reported (eight in the rhGAD65 group) were considered to be treatment-related and no neurological abnormalities were detected during the 5-year follow-up. Fasting C-peptide levels in the 20-μg dose group, which significantly increased within the first year compared with baseline, remained elevated at 5 years, although this difference was not statistically significant. However, the 5-year change in fasting C-peptide levels suffered a significant decline in the placebo and the 500-μg dose group, but not in the 4-, 20- and 100-μg dose groups. In fact, patients receiving 20 μg increased their fasting C-peptide levels over 5 years compared with placebo (0.04 vs. 0.28, respectively; 95% confidence interval [CI]: −0.12 to 0.19 log nmol/L and 0.04-0.51 log nmol/L, respectively), supporting investigation of this dose in further trials. After 5 years following the initial injection, patients receiving the 20- or 100-μg dose showed a significantly lower risk of starting insulin treatment (hazard ratio [HR]: 0.29; 95% CI: 0.10-0.90).

Alum-formulated rhGAD65 was found to delay the loss of residual β-cell function without modifying insulin requirements in pediatric patients with recent-onset type 1 diabetes. Participants in this phase II trial were 10-18 years of age (N = 70), had residual fasting C-peptide levels of 0.1 nmol/L or more and were positive for GAD autoantibodies (> 23 WHO U/mL). They were randomized to receive an s.c. injection of 20 μg of rhGAD65 (n = 35) or alum alone as placebo (n = 35) on days 1 and 30. Baseline clinical characteristics and distribution of HLA genotypes (low-, moderate- or high-risk) were comparable between both groups. Efficacy results showed no significant treatment effect on the primary efficacy endpoint, i.e., change between baseline and month 15 in the fasting C-peptide level, but rhGAD65 vaccination led to a significantly lower decline in fasting C-peptide levels at month 30 (secondary efficacy endpoint) compared to the placebo group (−0.21 nmol/L vs. −0.27 nmol/L; *P* = 0.045). MMTT-stimulated C-peptide secretion, measured as the area under the curve (AUC), was also markedly reduced in patients treated with study drug by month 15 (−0.38 nmol/L vs. −0.75 nmol/L per 2 h; *P* = 0.01) and by month 30 (−0.72 nmol/L vs. −1.02 nmol/L per 2 h; *P* = 0.04), compared with those receiving placebo. No differences in insulin requirements, which increased throughout the study, and in glycated hemoglobin values were found between the groups. However, the protective effect of rhGAD65 treatment did not hold in patients treated 6 months or more after diagnosis. Immunization with rhGAD65 led to increased GAD autoantibody levels, which reached peak values at 3 months, decreasing thereafter but still remaining significantly higher after 30 months than with placebo. After in vitro stimulation with GAD65, specific immune responses 15 months after rhGAD65 vaccination were observed in cells from treated children, including enhanced secretion of IL-5, IL-10, IL-13 and IL-17, IFN-γ and TNF-α, but not of IL-6 and IL-12. Cell expression of FOXP3 mRNA and TGF-β was also higher in the rhGAD65 group compared with placebo. An analysis performed 3 months after the first injection showed that samples from GAD-vaccinated children exhibited similar percentages of T cells expressing regulatory T-cell (Treg) markers ($CD4^+CD25^+$ high cells expressing neuropilin/CTLA-4) to those of a healthy age- and gender-matched reference group, while the percentage of Treg cells increased in the placebo group (11). Following in vitro GAD65 stimulation, a reduction in the number of $CD14^+$ monocytes, as well as an increase in costimulatory molecules (CD80/CD58) in $CD14^+$ monocytic cells, were seen in samples from rhGAD65-treated children. These changes were also accompanied by increased chemokine levels (MCP-1, MIP-1α and MIP-1β) in the supernatants of treated cells (12).

Subsequently, a double-blind, randomized, placebo-controlled confirmatory phase IIb study was designed to screen type 2 diabetes for GAD65 autoantibodies (GADA) and then administer 20 μg rhGAD65 s.c. or placebo as a prime and a boost 4 weeks apart in order to assess safety, metabolic control and β-cell function. A total of 2,096 type 2 diabetes patients were diagnosed within 5 years, 226 of whom were GADA-positive. Administration of 20 μg rhGAD65 or placebo to 160 eligible patients resulted in no serious treatment-related adverse events reported over 1 year after treatment, in agreement with previous safety results (13). With regard to safety, seven and five serious adverse events occurred in the rhGAD65 and placebo group, respectively, but none was related to study treatment. The frequency and nature of adverse events were similar in both groups, with upper respiratory tract infection, nasopharyngitis, gastroenteritis and headache being the most frequently reported adverse events. Neurological assessment revealed no differences in neurological function between both groups (14).

Given the positive results obtained in phase II trials, Diamyd Medical is currently conducting an international phase III clinical program in the European Union (15) and in the U.S. (16), which is expected to recruit a total of 640 patients, to investigate whether rhGAD65 can halt or slow the autoimmune destruction of β-cells in patients with newly diagnosed type 1 diabetes.

SOURCE

Diamyd Medical AB (SE).

DISCLOSURES

The author is a freelance medical writer who renders writing services to Thomson Reuters and is not associated in any way with the manufacturer.

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