Beta cell function and metabolic control during two years of follow-up after GAD65 dose-escalation immunomodulation in adult-onset autoimmune diabetes

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Conclusion

Our two-year follow-up of the 47 LADA patients who were given Diamyd™ at escalating dosages demonstrates that the increase fasting and stimulated c-peptide and decrease in HbA1c previously reported for six months remained during the two year follow-up. As there were no treatment-related SAE we suggest that further exploration of the immunomodulating effects of 20 µg Diamyd™ is warranted. Two more clinical trials are therefore now under way in Sweden using Diamyd™. The first of these is a double-blind trial in a greater number of patients in order to confirm efficacy in LADA patients, and the second is to investigate therapeutic efficacy in newly diagnosed type 1 diabetic patients. The outcome from these trials will be critical to future Phase III clinical trials for efficacy.

Background

- Autoimmune destruction of pancreatic β-cells is the major cause of Type 1 diabetes.
- Presence of GADA, IA2A, or IAA predict Type 1 diabetes.
- These antibodies, especially GADA, may occur in up to 10% of LADA patients.
- Studies in the NOD mouse have shown that destruction of islet β-cells was associated with T cells recognizing GAD65.
- GAD65 effectively prevent autoimmune β-cell destruction and reduce and delay the development of spontaneous diabetes.

Purpose

The purpose of this study was to evaluate if alum-formulated recombinant GAD65 (Diamyd™) is safe and does not comprise beta cell function in GAD65-autoantibody positive type 2 diabetes patients.

Reference

Agardh C-D, Cilio CM, Lethagen ÅL, Lynch K, Leslie RDG, Palmér M, Harris RA, Robertson JA, Lernmark, Å (2005) Clinical evidence for the safety of GAD65 immunomodulation in adult-onset autoimmune diabetes J Diabetes Complications 19:238-246

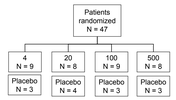
Methods

Trial design

A phase II randomized, double blind, placebo controlled trial in LADA patients

Following a screening phase, 47 LADA patients were randomized into four dose groups:

4, 20, 100, 500 µg
Injected twice – subcutanuosly – four weeks apart



Inclusion Criteria

- Diabetic patients of both sexes aged 30-70 years
- Diagnosed with Type 2 diabetes within 5 years
- Presence of GADA
- Diabetes treatment with diet and/or oral agents
- Females of non child-bearing potential

Test substances

The unmodified recombinant form of human GAD65 (Diamyd™ Bulk Drug) was formulated with Alhydrogel® (aluminium hydroxide). The bulk drug was manufactured using baculovirus/insect cell expression of the cDNA for rhGAD65. Both manufacture of the Diamyd™ Bulk Drug and Diamyd™ was performed under strict conditions of current Good Manufacturing Practice. Each vial contained a sterile formulation of either 4, 20, 100, or 500 µg of Diamyd™ Bulk Drug in a constant amount of Alhydrogel®. Coded vials containing an identical amount of Alhydrogel® alone were used as placebo.

Markers of diabetes in placebo and treatment dose groups at baseline

Diabetes markers	Placebo (13)	4ug (9)	20ug (8)	100ug (9)	500ug (8)
Age (years)	56 (37-66)	58 (39-66)	57 (48-67)	57 (30-69)	53 (39-62)
Males (*n*)	12	7	6	6	8
BMI (kg/m^2)	26 (23-32)	27 (20-35)	28 (23-33)	27 (20-39)	26 (21-33)
HbA1c (%)	5.9 (0.7)	6.9 (1.6)	6.5 (1.6)	6.0 (0.8)	6.3 (0.9)
High risk HLA DQB1*0302	5 (38)	3 (33)	4 (50)	5 (56)	4 (50)
Auto-antibodies					
GAD65	13 (100	9 (100)	8 (100)	9 (100)	8 (100)
IA-2	1 (8)	1 (11)	2 (25)	1 (11)	1 (13)
IAA	1 (8)	0 (0)	0 (0)	1 (11)	0 (0)
ICA	10 (77)	8 (89)	7 (88)	6 (67)	3 (38)
S-Albumin (g/L)	39 (36 – 47)	38 (34 – 41)	38 (35 – 43)	40 (36 – 46)	43 (36 – 46)
S-C-reactive Protein (mg/L)	9 (5 – 12)	9 (9 – 10)	9 (9-9)	9 (5- 15)	5 (5 – 9)
S-LDL (mmol/L)	3.5 (2.5 – 4.5)	2.8 (2.4 – 4.4)	2.7 (2.3 – 4.4)	3.1 (2.5 – 3.7)	3.5 (2.7 – 4.3)
S-HDL (mmol/L)	1.3 (0.7 – 1.5)	1.1 (0.7 – 1.6)	1.0 (0.9 – 1.6)	1.3 (0.9 – 1.9)	1.2 (0.7 – 2.0)
S-Triglycerides (mmol/L)	1.1 (0.4 – 10.0)	0.8 (0.4 – 2.6)	1.3 (0.5 – 2.5)	1.1 (0.7 – 2.5)	1.1 (0.6 – 3.5)

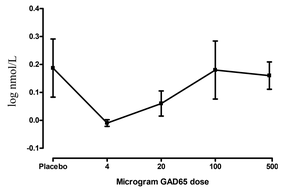
Variables summarized as median(range) or count (percentage)

Results

Baseline GADA and fasting C-peptide in patients who started insulin within 24 months and in patients who did not

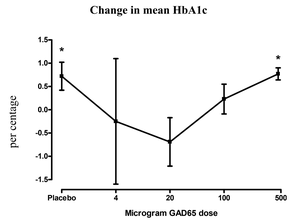
Group	*Started insulin (months)*	*n*	*GADA (U/ml)*	*f-C-peptide (nmol/l)*
Placebo	**5-14**	**3**	**4221 (52-595917)**	**0.66 (0.30-0.77)**
	no	**9**	**96 (26 – 816)**	**0.68 (0.50 – 1.70)**
4 µg	**7-12**	**4**	**879 (50-12419)**	**0.39 (0.31 – 0.43)**
	no	**4**	**501 (60 – 1696)**	**0.89 (0.55 – 1.55)****
20 µg	**8**	**1**	**1416**	**0.51**
	no	**7**	**55 (32 – 120)**	**0.74 (0.48 – 1.37)**
100 µg	**3**	**1**	**273**	**0.33**
	no	**7**	**33 (29 – 2335)**	**0.72 (0.58 – 1.50)**
500 µg	**4-14**	**4**	**226 (102-1851)**	**0.39 (0.27 – 0.70)**
	no	**4**	**36 (28 – 117)***	**1.00 (0.54 – 1.80)***

Change in mean GADA



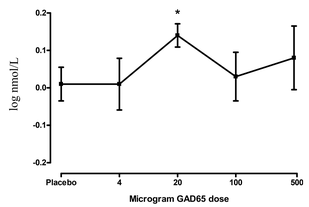
Change in log-GADA levels between dose groups was minor and did not differ between groups.

Change in mean HbA1c

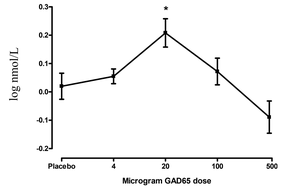


The two-year follow-up analysis showed that HbA1c in the placebo group increased by +0.72 (0.04 – 1.41) percentage (mean, 95%CI) (p=0.04) compared to baseline. HbA1c also increased in the 500-ug-dose group by 0.77 (0.19 – 1.34) percentage (p=0.03)

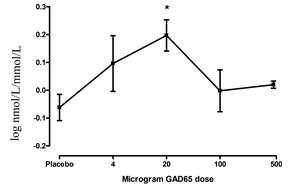
Change in mean fasting c-peptide



Change in mean stimulated c-peptide

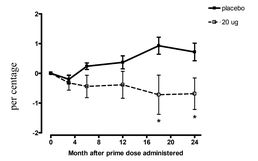


Change in mean fasting c-peptide / glucose



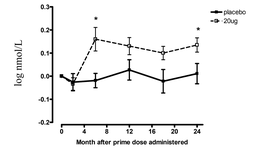
In the 20 ug dose group, fasting c-peptide increased by +0.14 (0.06 – 0.21) log nmol/L, p<0.005), stimulated c-peptide by +0.19 (0.06 – 0.31) log nmol/L (p=0.01), as well as fasting c-peptide/glucose by +0.20 (0.06 – 0.33) log nmol/L/mmol/L (p=0.01) compared to baseline.

Change in HbA1c

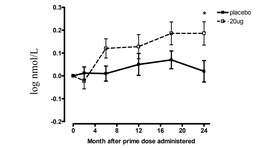


Over time, HbA1c in the 20 ug dose group declined gradually compared to the placebo group and differing significantly after two years (p=0.03).

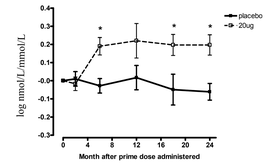
Change in fasting c-peptide



Change in stimulated c-peptide



Change in fasting c-peptide/glucose



The 20-ug-dose group showed an increase compared to the placebo group in fasting c-peptide (p=0.05), stimulated c-peptide (p=0.03) and fasting c-peptide/glucose (p<0.005).