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Research Article

Treatment of new-onset type 1 diabetes with peptide DiaPep277® is safe and associated with preserved beta-cell function: extension of a randomized, double-blind, phase II trial

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KEYWORDS

type 1 diabetes • randomized controlled trial • C-peptide • HSP60 • DiaPep277

ABSTRACT

Background

Treatment with DiaPep277®, a peptide derived from HSP60, has been shown to preserve beta-cell function in non-obese diabetic mouse (NOD) mice and in a trial with newly diagnosed human patients with type 1 diabetes treated over a 10-month period. This article extends the clinical trial observations to a total of 20 months of treatment to determine the safety and the effects of repeated doses of DiaPep277 on endogenous insulin secretion, metabolic control, and exogenous insulin requirements.

Methods

Thirty-five male patients (aged 16-58) with a basal C-peptide greater than 0.1 nmol/L were assigned to periodic treatment with DiaPep277 (1 mg) or placebo for a 12-month treatment and 18-month observation protocol, later extended to an additional year of treatment. Stimulated C-peptide, HbA_{1c}, and an exogenous insulin dose were the clinical endpoints.

Results

At 18 months, stimulated C-peptide concentrations had fallen in the placebo group ($p = 0.0005$) but were maintained in the DiaPep277 group. The need for exogenous insulin was higher in the placebo group than in the DiaPep277 group. Mean HbA_{1c} concentrations were similar in both groups. After extension of the study, patients continuing treatment with DiaPep277 and those switched from placebo to DiaPep277 manifested a trend towards a greater preservation of beta-cell function compared to

patients maintained on or switched to placebo. The safety profile of DiaPep277 was similar between the treatment and placebo groups, and no drug-related adverse events occurred.

Conclusions

Periodic treatment of subjects with DiaPep277 over 2 years was safe and associated preservation of endogenous insulin secretion up to 18 months was observed. Copyright © 2007 John Wiley & Sons, Ltd.

ARTICLE TEXT

Introduction

Type 1 diabetes mellitus is caused by the progressive destruction of the insulin-producing beta cells through an autoimmune process [1]. Autoimmune destruction remains non-symptomatic and hence undetected until the number of beta cells is insufficient to produce the amount of insulin needed to maintain glucose homeostasis, at which point, diabetes becomes clinically apparent. To some degree, insulin replacement repairs the secondary endocrine disease but it cannot stop the autoimmune destruction of beta cells. Trials that used cyclosporine A or anti-CD3 antibodies to dampen or modulate the immune response have been reported to be successful [2-4] and islet transplantation followed by a degree of immunosuppression has also shown much promise [5], demonstrating that beta-cell destruction does not progress if the T-cell mediated autoimmune destruction is halted. However, blanket immunosuppression is not a viable prospect for otherwise healthy diabetic patients and the above trials demonstrated that the destruction of beta cells continues once the immunosuppression is lifted [6][7]. Primary cure of type 1 diabetes would require the timely arrest of the autoimmune process in a selective and long-term fashion without immunologically compromising the patient.

Despite species differences, the NOD mouse model has been very helpful in raising fundamental questions about human disease [8]. Autoimmune T cells in NOD mice and in humans with type 1 diabetes react spontaneously to many different self-antigens, one of which is the 60-kDa heat shock protein (HSP60) [9-11]. Treatment with DiaPep277, a peptide derived from human HSP60, has been shown to save residual beta-cell function in NOD mice even late in the course of autoimmune destruction, after the onset of clinical hyperglycemia [10][12].

We previously reported the interim results for the first 10 months of a placebo-controlled clinical trial in which patients were treated within 6 months of diagnosis with 1 mg DiaPep277 or placebo [13]. After 10 months, mean C-peptide concentrations had fallen in the placebo group (n = 16) but were maintained in the DiaPep277-treated group (n = 15; 0.26 [SD 0.11] *versus* 0.93 [SD 0.35] nmol/L; p = 0.039). Here, we report the extension to 18 months of follow-up and a fourth injection of peptide at the 12th month of the initial trial. Thereafter, an extension study continued the follow-up for a further 12 months and 4 doses of continued treatment or cross-over with DiaPep277 peptide or placebo.

Materials and methods

Study design

Treatment drug
DiaPep277 is a synthetic peptide of 24 amino acids having the sequence of the p277 peptide of human HSP60 (437-460), where two cysteine residues (442 and 447) are substituted by valines. The peptide has amino acid sequence:

Vlgggvallrvipaldsltpaned

It was synthesized according to the regulations of Good Manufacturing Practice by PolyPeptide Laboratories, Malmo, Sweden; sterile, freeze-dried manufacturing of the injected peptide with mannitol as excipient was done by TEVA Pharmaceutical Industries Ltd., Kefar Saba, Israel. For administration, the sterile peptide is dissolved in a 10% lipid emulsion (10% Lipofundin MCT/LCT, B Braun, Melsungen, Germany) and injected subcutaneously. The placebo consisted of freeze-dried sterile mannitol and lipid manufactured under the same conditions as DiaPep277.

Study organization

The studies were carried out at the Diabetic Clinic of the Hadassah University Hospital, Jerusalem, Israel, and were approved by the Institutional Review Board and by the National Committee for Human Trials of the Israel Ministry of Health. The number of patients in the different groups was designed to provide a basis for analysis of the results, but no formal power calculations were possible at the time the study was designed due to a lack of efficacy data in humans.

Patients

The patients were 16- to 58-year-old males with a diagnosis of type 1 diabetes within the previous 6 months. Inclusion criteria were as follows: presentation with acute hyperglycemia and ketonuria; diabetes of less than 6 months duration; residual beta-cell function detected by a fasting basal C-peptide serum level of more than 0.1 nmol/L; a BMI between 19 and 28; and compliance with diet and insulin treatment resulting in well-controlled diabetes for at least 2 weeks. The patients were free of other diseases and their informed consent was obtained, including the consent of the legal guardian for patients aged 16-18. Patients on corticosteroid medication within the previous 2 months or any immunosuppressant or cytostatic agent within the previous 6 months were excluded. Although toxicological reproductive studies showed that DiaPep277 is not teratogenic, only men were included in this trial. The randomization list was generated by the Contract Research Organization (CRO), who managed the study, using the computer program RANCODE version 3.6 (idv Datenanalyse und Versuchsplanung, Gauting/München, FRG, 1997). The software utilized the random number generator by G. Marsaglia and T.A. Bray (Mathematical Note No. 551, Mathematics Research Laboratory, Boeing Scientific Research Laboratories).

Endpoint assessment

The clinical investigators prescribed the amounts of insulin required to control each patient's blood glucose concentration according to accepted standards of care, and the amount of insulin per kilogram bodyweight was calculated from the patient's treatment diary. Percent HbA_{1c} and fasting plasma glucose were determined as a measure of glycemic control. In addition, standard blood chemistry and hematology were evaluated to monitor drug safety.

The key efficacy end point was glucagon-induced C-peptide secretion, reflecting endogenous insulin secretion, and the functional beta-cell mass. The glucagon-induced C-peptide secretion test was elicited in the morning, 10-12 h after the last insulin dose, and recorded as the fasting basal concentration and 2, 6, 10, and 20 min after the intravenous administration of glucagon (1 mg). The area under the curve (AUC) was calculated for the basal over a 20-min period.

HLA typing

The HLA haplotype was determined for all patients in the study. It was preferably performed at Visit 7, but could also be performed at any visit during the study. The assay was carried out at a central laboratory: Università Campus BioMedico, Policlinico Universitario, Via Longoni, 83, 00155 Rome, Italy [14].

Antibodies to DiaPep277

The level of antibodies in sera to DiaPep277, both before and after administration of DiaPep277 or placebo, was measured using a standard ELISA assay [15] with DiaPep277-coated ELISA plates.

Statistics

The intention to treat population was used for statistical calculations, which included all patients who received at least one dose of the study drug. One patient in the placebo group was considered to be an outlier. Analysis was performed with this value unless so noted in the text. Samples were compared using the paired Wilcoxon signed rank test for longitudinal comparisons and the Mann-Whitney test for comparison of the different treatment groups. Graph Pad Prism, version 4.00 for Windows, Graph Pad Software, San Diego, California, USA, was used to perform the analysis.

Protocol for the two stages of the study

Stage 1

The first stage of the study was a single-center, randomized, double-blind, single dose level (DiaPep277 1 mg) placebo-controlled parallel group trial carried out over 18 months of follow-up. Two treatment groups were given four injections of either DiaPep277 (1 mg) or placebo at months 0, 1, 6, and 12 (Figure 1). In all, 35 male patients were randomized, 17 to the DiaPep277 group and 18 to the placebo group.
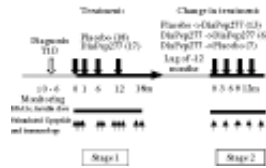

Figure 1. Scheme of DiaPep277® administration, dosing, and treatment arms
[Normal View 5K | Magnified View 12K]

Stage 2

The second stage was a 1-year extension of the original study. The extension was conducted on patients who had successfully completed stage 1 and had maintained fasting basal C-peptide values above 0.1 nmol/L. Patients received either DiaPep277 or placebo at months 0, 3, 6, and 9 (Figure 1). Since the extension study was designed and submitted for approval of the ethical committee after most of the patients had already completed the original 18-month study, and since the recruitment period extended for more than a year, by the time stage 2 was started some patients were already 12 months out of the original study. Thus, there was a lag of 0-12 months from the end of stage 1 to the re-initiation of treatment under the stage 2 protocol (Figure 1). While maintaining the blinding from stage 1, all patients who had previously received placebo were crossed over to receive DiaPep277 (13 patients), while the patients who had previously received DiaPep277 were re-randomized to receive either placebo or DiaPep277 in the second stage (seven and six patients respectively).

Results

Table 1 shows the baseline data as the median and interquartile range for patients entering the study. Of the 35 patients randomized, 14 (82.4%) in the peptide-treated group and 13 (72.2%) in the placebo group had completed 18 months of stage 1. No significant difference was observed between treatment groups with respect to the number and percent of patients who completed or were discontinued from the study. The safety profile of DiaPep277 treatment was comparable with that of the placebo group: over the whole 2-stage duration, there were four serious adverse reports, two suffered by patients on placebo treatment and two by DiaPep277-treated patients. No serious adverse event was judged by the clinical investigators to be drug-related. The frequency of all adverse experiences reported during the study was 82.4% and 77.8% for DiaPep277 and placebo respectively. Table 2 shows all the adverse events considered to be possibly related to the study drug. Except for one incidence of fever in a placebo-treated patient, adverse events were entirely local and involved either pain, reaction, or inflammation, all of which spontaneously resolved. Vital signs, blood chemistry, hematology, and urinalysis showed no safety concerns related to the treatment and no significant differences between the treatment groups.

Table 1. Clinical and metabolic parameters of patients with type 1 diabetes mellitus randomized into the study for the different treatment arms at baseline. Data is shown as median and interquartile range

	Placebo	1.0 mg DiaPep277™
Age (years)	20 (18-26)	25 (21-34)
Number (*n*) all male	18	17
BMI (*kg/m^2*)	22.5 (20-24)	20 (20-23)
GADA pos/neg	14/15	12/16

DiaPep277 antibodies pos/neg	13/18	15/17
Time from diagnosis (days)	104 (70-162)	117 (75-134)
HbA_{1c} (%)	6.4 (5.7-7.8)	6.7 (6.4-7.3)
Basal C-peptide (nmol/L min)	0.41 (0.26-0.59)	0.35 (0.24-0.49)
Induced C-peptide, AUC (nmol/L min)	12 (7.6-16)	7.35 (6-13.5)
Insulin dose (U/kg/day)	0.4 (0.15-0.48)	0.35 (0.25-0.44)
HLA-DR3,4 & 4,4 (*n*)	3	5
HLA-DR3/3 & 3/x & 4/x (*n*)	9	6
HLA-DRx, x (*n*)	5	6

Table 2. List of patients with adverse events possibly related to trial medication. Some patients reported more than one adverse event

	Stage 1		Stage 2		
Description	Placebo	DiaPep277	Placebo -> DiaPep277	DiaPep277 -> DiaPep277	DiaPep277 -> Placebo
(*n*)	18	17	13	6	7
Pain in injection site	3	4	4	1	-
Inflammation in injection site	1	1	-	-	-
Reaction in injection site	-	1	-	-	-
Fever	1	-	-	-	-
Total	4 (22%)	6 (35%)	3 (23%)	1 (17%)	0

At the first stage, patients treated with placebo manifested a significant loss of glucagon-stimulated C-peptide, decreasing from 15.6 nmol/L/min at baseline to 6.2 nmol/L/min at 18 months, shown as the individual and median C-peptide AUC for all placebo-treated patients (Figure 2(A), $p = 0.0005$) and as the change from baseline of average AUC (Figure 2(C)); these findings indicate a progressive, cumulative loss of beta-cell function with time. Indeed, the rapid loss of stimulated C-peptide supports the diagnosis of type 1 diabetes. In contrast to the placebo group, the group treated with DiaPep277 maintained their production of C-peptide: from 11.4 nmol/L/min at baseline to 10.9 nmol/L/min at 18 months. At the end of this treatment period, the DiaPep277-treated group showed essentially no loss of beta-cell function (13 months, Figure 2(B)) and a small but insignificant decrease at 18 months ($p = 0.83$). The changes in AUC from baseline of the DiaPep277 group compared to the placebo group were significant at all time points between 7 and 18 months of follow-up (Figure 2(C)).
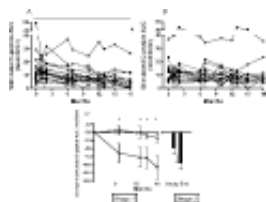

Figure 2. The effects of treatment on C-peptide. C-peptide was measured 0, 2, 6, 10 and 20 minutes after an i.v infusion of 1 mg glucagon and expressed as the AUC. (A) and (B) show individual results for the placebo and DiaPep277 treated groups, respectively in the lines and the median value for the relevant treatment group in the bars. Values in the placebo group decreased significantly over the course of the 18 months of study ($p = 0.0005$ by Wilcoxon signed rank test) while values in the treated group did not (Wilcoxon signed rank test, $p = 0.831$ or $p = 0.921$ if the high-value patient in the group is excluded). (C) On the left hand side shows the change in AUC from baseline, expressed as the mean and SEM for the placebo group (open circles) and the DiaPep277 treated group (black squares). The difference between the groups was significant at all the points shown. The bars on the right hand side show

the change in AUC at the end of the second stage extension protocol, calculated from the initial values at the start of stage 1 trial. The grey bar represents the group consistently receiving DiaPep277, the white block represents the group initially given DiaPep277 and then crossed over to placebo and the black block represents those patients that were in the placebo group in stage 1 and were given DiaPep277 in stage 2
[Normal View 17K | Magnified View 40K]

The effect of the second stage of the trial on beta-cell function was evaluated at the re-initiation of treatment and for 12 months thereafter, beginning 3 months after the last subject had received the last injection (Figure 1). Note, however, that the subjects had experienced a period of no treatment between the two stages that consisted of 6 months without treatment from stage 1 and up to 12 months before the beginning of stage 2. Thus, the overall period without treatment ranged from as long as 18 months, for the first patients to complete the first stage, to as short as 6 months, for the last patients. The beta-cell function decreased during this period without treatment in all the groups (Figure 2(C) Study End); this suggests that 6 months without treatment eventually resulted in the loss of the treatment effect and that the belated initiation of treatment was not very effective. Nevertheless, it should be noted that the group that was treated with DiaPep277 during both stages of the study showed the least drop in beta-cell function: those continuing DiaPep277 manifested a delta AUC of - 5.0 nmol/L/min compared to a delta AUC of - 9.6 nmol/L/min for those who were originally treated by placebo and only received DiaPep277 at stage 2 (Figure 2(C) Study End). Owing to the small size of the groups and the heterogeneity of the duration without treatment, this difference of almost two-fold was not statistically significant.

The average metabolic control seen over the first 18 months in both DiaPep277 and placebo groups was comparable; the average HbA_{1c} levels were approximately 7.5% throughout the study (Figure 3(A) and (B)). This HbA_{1c} value indicates that the subjects in both groups received similarly adequate treatment. Regarding the changes in HbA_{1c} values over time, the placebo-treated group was more diverse than the DiaPep277-treated group (Figure 3(A) and (B), interquartile range). At the second stage of the trial, all the groups showed an increase in the average level of HbA_{1c}, with the lowest increase in the group that had consistently received DiaPep277 at both stages (0.2 ± 0.41 as compared to 0.9 ± 0.81 in the group that crossed from DiaPep277 to placebo and 1.54 ± 0.79 in the group that initially had received placebo).
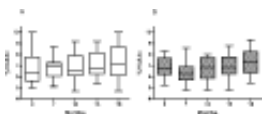

Figure 3. Metabolic control reflected by % HbA_{1c}. The values of individual patients are expressed as the median and interquartile range, with error bars for the total range, in the placebo group (A) and the DiaPep277 treated group (B)
[Normal View 8K | Magnified View 17K]

Figure 4 shows the insulin doses over time required by the subjects. The DiaPep277 group required less exogenous insulin to maintain adequate control than did the placebo group, as shown in Figures 4(A) and (B). The final doses of 0.49 U kg^{-1} day^{-1} ± 0.07 *versus*. 0.61 U kg^{-1} day^{-1} ± 0.08, respectively, at the end of the first stage of study are shown in Figure 4(C) (the difference is not significant). Although the groups were too small to demonstrate statistical significance, the group that had consistently received DiaPep277 maintained this trend toward a lesser need for insulin to the end of stage 2. This group required the lowest average insulin dose at the end of stage 2 (0.55 ± 0.13 U kg^{-1} day^{-1}), compared to 0.66 ± 0.09 U day^{-1} kg^{-1} in the DiaPep277-> Placebo group, and to 0.71 ± 0.12 U kg^{-1} day^{-1} in the Placebo-> DiaPep277 group.
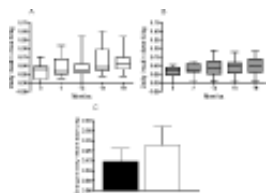

Figure 4. Daily insulin dose required. The values for individual patients expressed as the median and interquartile range with error bars for the total range, for insulin Units per kg body weight per day, for placebo patients (A) and DiaPep277 treated group (B). (C) Shows the daily insulin dose after the 18 months of follow up of stage 1 expressed as the mean and SEM for the DiaPep277 group (black bar) and placebo group (white bar)
[Normal View 11K | Magnified View 24K]

The amounts of serum antibody to DiaPep277 were variable, but most of the patients treated with DiaPep277 or with

placebo groups finished the follow-up period with the same amount of antibodies initially measured at baseline; 80% of the patients recruited to the study spontaneously presented with IgG binding to DiaPep277 prior to either DiaPep277 or placebo treatment. The presence of antibodies in patients with type 1 diabetes to HSP60 and DiaPep277 has been previously reported [15]. Only three patients in each of the two groups showed a decrease in the titre, and two patients in the placebo group (13.3%) showed an increase in titre. Therefore, there was no evidence for the induction of *de novo* antibodies to DiaPep277 or an increase in titre following repeated administration of DiaPep277.

Discussion

The results of these trials indicate that treatment with DiaPep277 (1 mg) is safe and well tolerated when given as repeated administrations over a period spanning up to 42 months. There were no drug-related findings of concern regarding safety, no increase in reported adverse events compared to the placebo-treated subjects, and no increase in adverse events focused on any specific body system or organ, with the exception of injection site sensitivity. Taken together with the lack of any treatment-related changes in standard immune responses (not shown) and no evidence of allergy or hypersensitivity responses, DiaPep277 administration appears to be free of concerns regarding safety till now.

The present results confirm and extend the efficacy described in our earlier report [13] regarding this group of patients after 10 months of stage 1. At the end of stage 1 - at 18 months - subjects treated with DiaPep277 manifested a significantly greater preservation of beta-cell function as measured by stimulated C-peptide than did the placebo-treated subjects. As has been proposed by opinion leaders [16], better preservation of beta-cell function is of paramount importance to T1D patients. It is reasonable to expect that maintaining even partial beta-cell function will enhance the ability of patients to attain better metabolic control, and the risk of complications characteristic of long-term diabetes will be reduced [17]. Since the DiaPep277-treated groups manifested a greater ability to produce endogenous insulin, the expectation is that these subjects would be less dependant on exogenous insulin. Indeed, the DiaPep277-treated group used 20% less insulin (per day per kg) on the average, while maintaining satisfactory glycemic control (average of approximately 7.5% HbA_{1c}). However, the degree of difference in insulin dose between the placebo and the DiaPep277 groups was not statistically significant, probably due to the small group size.

An important conclusion of this follow-up study is that DiaPep277 treatment must be continued to maintain the preservation of C-peptide. By the start of stage 2 of the study, the subjects in the DiaPep277 group at stage 1 had been without treatment for a period of 6 to 18 months and the results indicate that this treatment-free period is too long to successfully preserve beta-cell function. Even so, the group that consistently received DiaPep277, in both stages of the study, showed the smallest drop in C-peptide production and the lowest need for exogenous insulin to maintain adequate glycemic control. Despite the lack of statistical significance, the stage 2 extension suggests that stopping treatment with DiaPep277 results in a relapse, as shown by the patients who were switched from DiaPep277 to placebo in stage 2. Therefore, it appears that continued administration of DiaPep277 at intervals of at least 6 months is necessary for human patients. The observation that administration of p277 (the native sequence peptide of which DiaPep277 is an analogue) in the mouse models of diabetes could be stopped after one [10][12] or two administrations [18] suggests that the administration of DiaPep277 to humans also might be terminated eventually without losing the beneficial effect. The beneficial effects of treatment with DiaPep277 in our earlier report [13] and in the mouse studies [19] appear to be related to the induction of a shift in the cytokine phenotype of the autoimmune T-cell response from a pro-inflammatory to an anti-inflammatory phenotype. However, an extensive analysis of the immunological responses to treatment with DiaPep277 is outside the scope of the present article and will be described in full in a separate publication.

In summary, the results reported here support the safety and efficacy of continued treatment with DiaPep277 on beta-cell function in type 1 diabetes. In the light of these findings, a new clinical trial in a larger population is planned to be fully powered to test efficacy in continued treatment beyond 1 year.

REFERENCES

1   Bach J. Insulin-dependent diabetes mellitus as an autoimmune disease. *Endocr Rev* 1994; **15**(4): 516-542. Links

2   Bougneres PF, Landais P, Boisson C, *et al.* Limited duration of remission of insulin dependency in children with recent overt type I diabetes treated with low-dose cyclosporin. *Diabetes* 1990; **39**(10): 1264-1272. Links

3   Herold KC, Gitelman SE, Masharani U, *et al.* A single course of Anti-CD3 monoclonal antibody hOKT3γ1(Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. *Diabetes* 2005; **54**(6): 1763-1769. Links

4   Keymeulen B, Vandemeulebroucke E, Ziegler AG, *et al.* Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. *N Engl J Med* 2005; **352**(25): 2598-2608. Links

5   Jun HS, Yoon JW. Approaches for the cure of type 1 diabetes by cellular and gene therapy. *Curr Gene Ther* 2005; **5**(2): 249-262. Links

6   Bach J-F, Bendelac A, Brenner MB, *et al.* The role of innate immunity in autoimmunity. *J Exp Med* 2004; **200**(12): 1527-1531. Links

7   Roep BO. The role of T-cells in the pathogenesis of Type 1 diabetes: from cause to cure. *Diabetologia* 2003; **46**(3): 305-321. Links

8   Anderson MS, Bluestone JA. The NOD mouse: a model of immune dysregulation. *Annu Rev Immunol* 2005; **23**: 447-485. Links

9   Abulafia-Lapid R, Elias D, Raz I, *et al.* T cell proliferative responses of type 1 diabetes patients and healthy individuals to human hsp60 and its peptides. *J Autoimmun* 1999; **12**(2): 121-129. Links

10 Elias D, Cohen IR, Markovits D, *et al.* Peptide therapy for diabetes in NOD mice. Induction and therapy of autoimmune diabetes in the non-obese diabetic (NOD/Lt) mouse by a 65-kDa heat shock protein. *Lancet* 1994; **343**(8899): 704-706. Links

11 Horvath L, Cervenak L, Oroszlan M, *et al.* Antibodies against different epitopes of heat-shock protein 60 in children with type 1 diabetes mellitus. *Immunol Lett* 2002; **80**(3): 155-162. Links

12 Elias D, Cohen IR. Treatment of autoimmune diabetes and insulitis in NOD mice with heat shock protein 60 peptide p277. *Diabetes* 1995; **44**(9): 1132-1138. Links

13 Raz I, Elias D, Avron A, *et al.* Beta-cell function in new-onset type 1 diabetes and immunomodulation with a heat-shock protein peptide (DiaPep277): a randomised, double-blind, phase II trial. *Lancet* 2001; **358**(9295): 1749-1753. Links

14 Petrone A, Galgani A, Spoletini M, *et al.* Residual insulin secretion at diagnosis of type 1 diabetes is independently associated with both, age of onset and HLA genotype. *Diabetes Metab Res Rev* 2005; **21**(3): 271-275. Links

15 Abulafia-Lapid R, Gillis D, Yosef O, *et al.* T cells and autoantibodies to human HSP70 in type 1 diabetes in children. *J Autoimmun* 2003; **20**(4): 313-321. Links

16 Kolb H, Gale EA. Does partial preservation of residual beta-cell function justify immune intervention in recent onset Type I diabetes? *Diabetologia* 2001; **44**(10): 1349-1353. Links

17 Steffes MW, Sibley S, Jackson M, *et al.* Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. *Diabetes Care* 2003; **26**(3): 832-836. Links

18 Elias D, Cohen IR. The hsp60 peptide p277 arrests the autoimmune diabetes induced by the toxin streptozotocin. *Diabetes* 1996; **45**(9): 1168-1172. Links

19 Elias D, Meilin A, Ablamunits V, *et al.* Hsp60 peptide therapy of NOD mouse diabetes induces a Th2 cytokine burst and downregulates autoimmunity to various beta-cell antigens. *Diabetes* 1997; **46**(5): 758-764. Links