Combination of Nicotinamide and Steroid Versus Nicotinamide in Recent-Onset IDDM

The IMDIAB II Study

P. Pozzilli
N. Visalli
M.L. Boccuni
M.G. Baroni
R. Buzzetti
E. Fioriti
A. Signore
M.G. Cavallo
D. Andreani
L. Lucentini
M.C. Matteoli
A. Crinò
C.A. Cicconetti
C. Teodonio
R. Amoretti
L. Pisano
M.G. Pennafina
G. Santopadre
G. Marozzi
G. Multari
L. Campea
M.A. Suppa
G.C. De Mattia
M. Cassone Faldetta
G. Marietti
F. Perrone
A. V. Greco
G. Ghirlanda

OBJECTIVE — The aim of this study was to compare the effect of nicotinamide (NCT) alone or in combination with a cortisone-like substance, deflazacort (DFL), on the integrated parameters of metabolic control in patients with the recent-onset of insulin-dependent diabetes mellitus (IDDM).

RESEARCH DESIGN AND METHODS — Thirty-six patients who were diagnosed with diabetes between 5 and 35 years of age entered a randomized, double-blind, 1-year prospective study. Group A ($n = 18$) received NCT for 1 year (25 mg · kg^{-1} · day^{-1}) plus DFL for 3 months (0.6 mg · kg^{-1} · day^{-1} in the first month, 0.3 mg · kg^{-1} · day^{-1} in the other 2 months). Group B ($n = 18$) received NCT for 1 year (25 mg · kg^{-1} · day^{-1}) plus placebo for the first 3 months. All patients were treated with intensified insulin therapy.

RESULTS — At 3 months after diagnosis, the insulin dose was significantly higher in group A compared with group B ($P < 0.03$) with similar HbA_1 levels. Basal and stimulated C-peptide levels in group A of both adults and children were significantly higher compared with patients of group B ($P < 0.05$ and $P < 0.03$, respectively). At the end of a 1-year follow-up, basal C-peptide did not differ between the two groups, although stimulated C-peptide was still significantly higher in patients of group A compared with group B ($P < 0.05$). Finally, insulin requirement did not differ between the two groups.

CONCLUSIONS — A short-term course of DFL therapy at diagnosis in addition to NCT slightly increases glucagon-stimulated but not basal β-cell function after 1 year.

From Endocrinologia (I), Istituto di Clinica Medica II, Universita di Roma "La Sapienza," Rome, Italy.
Address correspondence and reprint requests to Paolo Pozzilli, MD, Endocrinologia (I), II Clinica Medica, Policlinico Umberto I, 00161 Rome, Italy.
Received for publication 20 August 1993 and accepted in revised form 24 March 1994.
IDDM, insulin-dependent diabetes mellitus; NCT, nicotinamide; DFL, deflazacort; BMI, body mass index.

Insulin-dependent diabetes mellitus (IDDM) is the consequence of an autoimmune process directed toward β-cells (1), thus explaining why immunosuppressive therapy has been introduced in patients with recent-onset diabetes to protect residual β-cells from complete destruction (2). IDDM usually results in permanent loss of β-cell function; however, those few patients who still secrete insulin 24 months after clinical onset of the disease may continue to do so indefinitely (3). The ability to produce even a small amount of insulin seems to have a favorable influence on diabetic control and in delaying the onset of vascular complications. Because several other autoimmune diseases including IDDM are favorably influenced by a course of corticosteroids, it seemed reasonable to investigate whether steroids alone or in combination with other drugs improve residual β-cell function in recent-onset IDDM (4–7). Thus, steroids have been used in the early phase of IDDM to preserve residual β-cell function (8–9). However, conflicting data have been reported, and to date, conclusive results are missing. Among agents that can be used in the early phase of IDDM, nicotinamide (NCT) is of particular interest. In recent-onset IDDM patients (particularly with adult patients), NCT augments the frequency of clinical remissions and appears to preserve residual β-cell function (10–12), although this was not confirmed (13,14).

This study was designed to test whether a combination of NCT with an anti-inflammatory steroid, deflazacort (DFL), compared with NCT alone could produce a synergistic effect in improving metabolic control and possibly favoring clinical remission.

RESEARCH DESIGN AND METHODS

Selection of patients

Newly diagnosed IDDM patients were selected to take part in this study if they

Table 1—*Clinical characteristics of patients*

	Adults		Children	
	DFL + NCT	Placebo + NCT	DFL + NCT	Placebo + NCT
n	8	7	7	11
Age (years) (range 5–35)	25.1 ± 5.7	23.2 ± 4.8	11.1 ± 1.5	11.0 ± 1.7
Sex (M/F)	5/3	5/2	4/3	4/7
Blood glucose at diagnosis (mg/dl)	445 ± 143	301 ± 174	420 ± 201	367 ± 145
BMI	20.7 ± 1.3	21.9 ± 1.9	16.1 ± 1.8	18 ± 2.9

Data are means ± SD.

fulfilled the following criteria: *1*) diagnosis of the disease according to World Health Organization criteria; 2) diagnosis between 5 and 35 years of age; and *3*) duration of clinical disease <4 weeks.

Investigations and follow-up

Patients were started on a 55% carbohydrate diet and received short- and intermediate-acting human insulin three times daily. Self-determined capillary glucose was recorded daily, fasting in the morning and twice before and after meals, and insulin dosage was adjusted to obtain near-normal blood glucose levels. Patients were examined weekly for the first month of therapy and then monthly by the same team of physicians in each participating center. Drug toxicity was evaluated at follow-up visits that included liver and renal function tests and total blood count. HbA_1 was measured every 3 months by a column assay (Bio-Rad, Milan, Italy), and C-peptide secretion (basal and after 1 mg of intravenous glucagon) was evaluated after hyperglycemia was normalized before entry into the trial and at 3-month intervals for 1 year thereafter. The stimulatory test was performed at fasting in the morning with blood glucose <180 mg/dl. C-peptide was evaluated using a commercially available radioimmunoassay kit (Bio-Rad). The normal range of fasting C-peptide established in 150 healthy subjects 5–40 years of age is 2–5 ng/ml.

Treatment protocol

After informed consent was obtained and participation in baseline studies was completed, patients were assigned in a randomized, double-blind manner for DFL administration to the two treatment regimes. Eighteen patients (group A) were treated with DFL at 0.6 mg/kg body weight and NCT at 25 mg/kg of body weight. After 1 month, the DFL dose was reduced to 0.3 mg/kg of body weight daily for 2 months. Eighteen patients (group B) received placebo for 3 months and NCT at the same dose as above. For comparison, a standard dose of DFL (5.7–6.6 mg is equivalent to 5 mg prednisone) was given. Patients of both groups remained on NCT therapy up to 1 year. Intensive insulin treatment was adopted to optimize metabolic control.

Sample size and statistical analysis

The number of patients to be included in the study was calculated from analysis of the results of trials published in the past in patients receiving NCT or steroids, based on the assumption of improved parameters of metabolic control 1 year after diagnosis in half of the treated patients compared with the control group. Setting α (probability of type 1 error) = 0.05 and β (probability of a type II error) = 90%, the required sample size was 15 for a two-sided test. Allowing for dropouts, 18 patients were allocated per group. Differences were analyzed by analysis of variance.

Table 2—*Basal and stimulated (1 mg glucagon) C-peptide levels at diagnosis and at 3-month follow-ups*

	n	Diagnosis	3 months	6 months	9 months	12 months
Basal						
DFL + NCT	15	0.5 ± 0.3	1.4 ± 0.3*	1.1 ± 0.3	0.7 ± 0.3	0.8 ± 0.3
Placebo + NCT	16	0.6 ± 0.3	0.8 ± 0.3	0.7 ± 0.4	0.6 ± 0.3	0.6 ± 0.3
Stimulated						
DFL + NCT	15	1.3 ± 0.5	2.9 ± 0.7†	2.2 ± 0.6	1.6 ± 0.5	1.4 ± 0.4‡
Placebo + NCT	16	1.4 ± 0.4	1.8 ± 0.7	1.7 ± 0.7	1.2 ± 0.5	0.9 ± 0.4

Data are means ng/ml ± SD. *$P < 0.05$ vs. basal placebo group at 3 months. †$P < 0.03$ vs. stimulated placebo group at 3 months. ‡$P < 0.05$ vs. stimulated placebo group at 12 months.

Table 3—Insulin dose and HbA_1 levels at diagnosis and at 3-month follow-ups

	n	Diagnosis	3 months	6 months	9 months	12 months
Insulin dose (IU/kg of body weight)						
DFL + NCT	15	0.8 ± 0.3	0.6 ± 0.3*	0.4 ± 0.3	0.6 ± 0.3	0.6 ± 0.3
Placebo + NCT	16	0.6 ± 0.3	0.4 ± 0.2	0.4 ± 0.3	0.5 ± 0.3	0.5 ± 0.3
HbA_1 (%)						
DFL + NCT	15	10.3 ± 1.7	6.4 ± 1.3	6.2 ± 1.1	6.5 ± 1.3	7.3 ± 1.3
Placebo + NCT	16	9.3 ± 1.7	6.5 ± 1.2	6.6 ± 1.2	6.8 ± 1.3	7.6 ± 1.3

Data are means ± SD. $P < 0.03$ vs. placebo group at 3 months.

RESULTS — No significant differences were observed between DFL plus NCT– and placebo plus NCT–treated patients for baseline clinical characteristics and metabolic control at the time of entry into the study (Table 1). Overall, there were three dropouts in patients receiving DFL plus NCT during the first 6 months of therapy. In all three cases, patients were unable to follow physician's recommendations and therefore were excluded. Addition of DFL did not make diabetes more difficult to control.

Metabolic outcomes during follow-up

Intensive insulin therapy resulted in near-normal mean HbA_1 levels in all patients throughout the period of observation. Integrated parameters of metabolic control are shown in Tables 2 (C-peptide) and 3 (HbA_1 and insulin dose). Basal and stimulated C-peptide levels were significantly raised at 3 months in patients of group A (both adults and children) compared with group B. This difference disappeared after DFL suspension, and 12 months after diagnosis, basal C-peptide did not differ between the two groups, whereas only stimulated C-peptide was still significantly higher in those patients who received DFL compared with group B (Table 2).

To keep HbA_1 levels as near to normal values as possible, patients of group A required a significantly higher insulin dose at 3 months compared with patients of group B (Table 3). However, after DFL suspension, comparable insulin requirements were needed in groups A and B throughout the remaining period of observation. At the end of the follow-up, HbA_1 levels were also similar between groups. Two patients experienced full clinical remission for a period of <1 month and were both treated with DFL plus NCT. In one patient of group B, flush was detected at the first administration of NCT.

CONCLUSIONS — We have demonstrated that in patients with recent-onset IDDM, the addition of DFL to NCT for 3 months may improve only stimulated β-cell function detectable 1 year after clinical onset compared with patients treated with NCT alone. The increase in C-peptide at 3 months reflects purely DFL-induced insulin resistance. The long-term effect of DFL at 1 year may reflect its anti-inflammatory property efficacious at the time of diagnosis when the cytotoxic β-cell process is still active. Combined with NCT, this steroid may favor the action of NCT on β-cell protection that has been recently suggested (15). Furthermore, DFL has been shown not to substantially increase blood glucose levels in prediabetic subjects as other steroids may do (16), which is an advantage in diabetic patients. Recent data suggest that DFL possesses interesting properties in protecting animals from developing diabetes (17) by inhibiting macrophage-derived interleukin-1 secretion and blocking the production of many other cytokines that directly or indirectly are important mediators of β-cell damage. Our study is the first that considers the adoption of a combination of a steroid such as DFL and NCT in the early phases of IDDM. The slight effect of DFL in increasing only stimulated β-cell function compared with patients receiving NCT alone appears similar in children and adults. The marginal discrepancy between our data and those of Mistura et al. (9), who concluded that a short-term prednisone therapy at diagnosis does not modify the natural history of the disease during the first year, could be due to the characteristics of their patients and the time when IDDM was diagnosed. Thus, all patients in their study were ketonuric, and higher insulin doses were required, suggesting that diagnosis was made later in the process of β-cell destruction compared with patients selected in our study. Moreover, the addition of NCT in our study might have had an additional effect in protecting β-cells. Based on the present-day diagnosis of the disease, which was made earlier than a few years ago (18), the combination of an anti-inflammatory agent with NCT may be considered at the time of the first presentation of diabetic symptoms. Thus, a low incidence of microvascular complications has been reported in IDDM patients with some residual β-cell function (19), including protection from proliferative retinopathy in those who still maintain β-cell function (20). This encourages adoption of some sort of adjunct therapy to insulin at diagnosis of IDDM (21).

Acknowledgments— We thank the staff members and nurses of participating centers.

References

1. Muir A, Schatz DA, Maclaren NK: The pathogenesis, prediction, and prevention of insulin-dependent diabetes mellitus. *Endocrinol Metab Clin North Am* 21:199–219, 1992
2. Andreani D, Kolb H, Pozzilli P (Eds.): *Immunotherapy of Type 1 Diabetes*. Chichester, Wiley, 1989
3. Marks JB, Skyler JS: Clinical review: immunotherapy of type I diabetes mellitus. *J Clin Endocrinol Metab* 72:3–9, 1991
4. Elliott RB, Crossley JR, Berryman CC, James AG: Partial preservation of pancreatic β-cell function in children with diabetes. *Lancet* 2:1–4, 631–632, 1981
5. Ludvigsson J, Heding L, Lernmark A, Lieden G: An attempt to break the autoimmune process at the onset of IDDM by the use of plasmapheresis and high doses of prednisone. *Bull Int Study Group Diab Child Adolesc* 6:11–12, 1982
6. Eisenbarth GS, Srikanta S, Jackson R, Rabinowe S, Dolinar R, Aoki T, Morris MA: Anti-thymocyte globulin and prednisone immunotherapy of recent onset type I diabetes mellitus. *Diabetes Res* 2:271–276, 1985
7. Secchi A, Pontiroli AE, Falqui L, Pastore MR, Scorza R, Carenini A, Meroni PL, Pozza G: Prednisone, indomethacin, or theophylline administration and the remission phase in recent-onset type I insulin dependent diabetic patients. *Transplant Proc* 18:1540–1542, 1986
8. Elliott RB, Pilcher CC, Edgar BW: Long-term outcome of children with insulin-dependent diabetes mellitus treated ab initio with prednisone. *Pediatr Adolesc Endocrinol* 15:345–349, 1986
9. Mistura L, Beccaria L, Meschi A, D'arcais AF, Pellini C, Puzzovio BS, Chiumello G: Prednisone treatment in newly diagnosed type I diabetic children: 1-Yr follow-up. *Diabetes Care* 10:39–43, 1987
10. Vague P, Picq R, Bernal MT, Lassman Vague V, Vialettes B: Effect of nicotinamide treatment on the residual insulin secretion in type 1 (insulin-dependent) diabetic patients. *Diabetologia* 32:316–321, 1989
11. Pozzilli P, Visalli N, Ghirlanda G, Manna R, Andreani D: Nicotinamide increases C-peptide secretion in patients with recent-onset type 1 diabetes. *Diabetic Med* 6:568–572, 1989
12. Pozzilli P, the IMDIAB Study Group: Randomized trial comparing nicotinamide and nicotinamide plus cyclosporin in recent-onset insulin-dependent diabetes. *Diabetic Med* 11:98–104, 1994
13. Chase HP, Butler-Simon N, Garg S, McDuffee M, Hoops SL, O'Brien D: A trial for nicotinamide in newly diagnosed patients with type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 33:444–446, 1990
14. Lewis CM, Canafax DM, Sprafka JM, Barbosa JJ: Double-blind randomized trial of nicotinamide on early onset diabetes. *Diabetes Care* 15:121–123, 1992
15. Pociot F, Reimers JI, Andersen HU: Nicotinamide: biological actions and therapeutic potential in diabetes prevention. *Diabetologia* 36:574–576, 1993
16. Pagano G, Lombardi A, Ferraris GM: Acute effect of prednisone and deflazacort on glucose tolerance in prediabetic subjects. *Eur J Clin Pharmacol* 22:469–471, 1982
17. Rabinovitch A, Suarez WL, Power RF: Combination therapy with an antioxidant and corticosteroid prevents autoimmune diabetes in NOD mice. *Life Sci* 51:1937–1943, 1992
18. Pozzilli P, Andreani D: Type 1 diabetes at presentation: the scene changes. *Diabetic Med* 7:762–763, 1990
19. Sjoberg G, Gunnarsson R, Gjotterberg M, Lefvort AK, Porccon A, Ostman J: Residual insulin-production glycemic control and prevelance of microvascular lesions and polyneurophathy in long-term type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 30:208–211, 1987
20. Klein R, Klein BEK, Moss SE, Davis MD, DeMels DL: Epidemiologic study of diabetic retinopathy. IX. Four-year incidence and progression of diabetic retinopathy when age at diagnosis is less than 30 years. *Arch Ophthalmol* 107:237–243, 1989
21. Pozzilli P, Maclaren NK: Immunotherapy at clinical diagnosis of insulin-dependent diabetes: an approach still worth considering. *Trends Endocrinol Metab* 4:101–105, 1993