Letters to the editor

Effect of Cyclosporin A on B-cell loss in Type 1 (insulin-dependent) diabetes mellitus

Dear Sir,

In patients with newly diagnosed Type 1 (insulin-dependent) diabetes mellitus, a treatment by cyclosporin A increases the frequency and duration of remission [1–3] by blocking the autoimmune process. However the process underlying relapse when treatment is discontinued is not precisely described.

In the French cyclosporin trial [2] which we took part in, double-blind treatment with cyclosporin $7.5 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ or placebo was discontinued at six months if remission was not achieved, and continued at least until the twelfth at decreasing doses if remission was achieved. For ethical reasons, our group chose not to continue treatment beyond the twelfth month. Since all the patients who participated in this study are still being attended by the same team and follow-up is now as long as three years in all cases, it is possible to analyse the evolution of residual insulin secretion after discontinuation of cyclosporin treatment.

In our department 28 newly diagnosed Type 1 diabetic patients between the ages of 15 and 40 years met the inclusion criteria of the French trial and entered the study. Fifteen of these patients (mean age: 26.1 years, HLA DR 3 and/or 4 12/15) received cyclosporin for 6 to 12 months (mean = 9.7) and 13 (mean age: 23.2 years, HLA DR 3

and/or 410/13) the placebo. As in the overall French series, these two groups were comparable and no serious adverse effects were observed.

Table 1 shows that the cyclosporin treated group differs from the placebo group by higher levels of fasting and stimulated (5 min after 1 mg glucagon injected i.v.) C-peptide throughout the follow-up. These data show that a pause had occurred in the destructive autoimmune process during the treatment period. This phenomenon has a clinical relevance because in the overall group of 28 patients a significant negative correlation was found between the daily insulin dose and the plasma C-peptide peak at months 12, 24 and 36 ($r = -0.43$, -0.41 and -0.38 respectively, $p < 0.05$).

After cessation of the immunosuppressive treatment the decrease in plasma C-peptide peak occurred at the same apparent rate (around $0.12 \text{ nmol} \cdot \text{l}^{-1} \cdot \text{year}^{-1}$) than in the non-treated group. This point shows that while a pause in the autoimmune process did occur it was followed by neither a slowing down nor by a rebound after cessation of treatment. Therefore, if the objective is to block the immune process, treatment would have to be maintained for a long time if not indefinitely, an attitude which may be considered as unethical on account of the drug's nephrotoxicity and the susceptibility of Type 1 diabetic patients to develop late renal failure.

However, cyclosporin treatment has allowed the maintenance for some months of a higher degree of insulin secretion, the beneficial effect of which is known [4] and this delay may be helpful while other forms of treatment can be assessed.

Yours sincerely,

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Table 1. Daily insulin dose, metabolic control, fasting and stimulated C-peptide of the Type 1 (insulin-dependent) diabetic patients treated either by cyclosporin for 6 to 12 months (mean = 9.7) or placebo

	At entry	At 12 months	At 24 months	At 36 months
Cyclosporin (<i>n</i> = 15)				
Insulin dose (IU/day)	38 ± 5	16 ± 3^a	27 ± 2	35 ± 3
HbA _{1c} (%)	10.8 ± 0.8	7.7 ± 0.5	8 ± 0.05	7.3 ± 0.06
Fasting C-peptide (nmol/l)	0.17 ± 0.02	0.35 ± 0.04^a	0.24 ± 0.02^a	0.17 ± 0.02
Stimulated C-peptide (nmol/l)	0.31 ± 0.04	0.48 ± 0.05^a	0.36 ± 0.06^a	0.24 ± 0.05^a
Placebo (<i>n</i> = 13)				
Insulin dose (IU/day)	41 ± 6	27 ± 4	34 ± 4	41 ± 3
HbA _{1c} (%)	11.2 ± 0.7	8.8 ± 0.4	8.7 ± 0.5	9.6 ± 0.6
Fasting C-peptide (nmol/l)	0.16 ± 0.02	0.29 ± 0.04	0.12 ± 0.02	0.10 ± 0.02
Stimulated C-peptide (nmol/l)	0.27 ± 0.05	0.31 ± 0.06	0.16 ± 0.04	0.11 ± 0.02

^a denotes statistically significant difference ($p < 0.05$) between cyclosporin and placebo treated groups (two tailed non-parametric Mann Whitney test)

Values are shown as mean $\pm$ SEM

References

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