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INDUCTION OF REMISSION OF INSULIN-DEPENDENT DIABETES BY CYCLOSPORIN

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It is now generally admitted that the vast majority of cases of insulin-dependent diabetes mellitus (IDDM) have a immunologic origin. More precisely, arguments have been collected in the animal models of the BB rat and the NOD mouse to indicate that T cells are predominantly involved: the disease is prevented by T cell depletion and is transferred by low amounts of purified T cells. It was thus logical to attempt preventing the disease by immunosuppressive agents, particularly those acting selectively on T cells as cyclosporin does.

Justification of the use of ciclosporin in insulin-dependent diabetes mellitus (IDDM) — The answer to this question derives from new hypotheses concerning the etiopathogenesis of IDDM. It is generally accepted that in most, and perhaps nearly all cases, IDDM is caused by aggression toward the pancreatic B cells that produce insulin by autoimmune, cellular and humoral reactions (Eisenbarth, 1986; Boitard et al., 1985).

The blood of diabetics whose disease is of recent onset contains both anti-islet cell antibodies (detectable by a number of techniques) and T cells capable of inhibiting insulin secretion by cultured islet cells stimulated by glucose. Like other autoimmune diseases IDDM is very often observed in subjects having a particular HLA phenotype (DR3 and/or DR4 in the case of IDDM). Moreover, the spontaneous IDDM of BB rats and NOD mice, which is highly similar to human IDDM, can be prevented by the administration of immunosuppressive agents and can be transferred to healthy animals by purified T lymphocyte preparations. All these arguments suggest using immunosuppressive agents at a very early stage of the disease, before a majority of B cells has been irreparably destroyed. Preparations which act on T cells are used for two reasons: first, because T cells comprise most of the mononuclear cells infiltrating the islet cells of diabetic patients, and second because, as seen above, T cells can transfer the disease in experimental models. Therefore, ciclosporin is the treatment of choice because it is the most powerful and the most T-cell specific of all immunosuppressive agents now in clinical use (Bach & Strom, 1985).

Efficacy of ciclosporin in IDDM — The first pilot studies in Canada (Stiller et al., 1984) and Paris (Assan et al., 1985) were encouraging but not conclusive, for spontaneous remissions (called "the honeymoon") are not rare during the first weeks of insulin treatment. However, the recent largescale randomized study including six major French diabetes units as well as the modthodology team led by E. Eschwege, established incontestably that ciclosporin induces prolonged remission of IDDM (Feutren et al., 1986). When sufficient doses are givem to maintain total blood levels of ciclosporin above 300 ng/ml, from 3 to 6 weeks after the beginning of insulin treatment, approximately 1/3 of patients have complete remission (no further insulin requirement), 1/3 have partial remission (clearly lowered insulin requirement) and 1/3 are treatment failures. When only patients at the very beginning of the disease are considered, the percentage of remissions is higher, over 60% complete remissions and 90% complete plus partial remissions (unpublished results). These data have recently been confirmed in other randomized trials performed in Canada and Europe. Thus, there is no longer any doubt that ciclosporin does induce remission in IDDM.

Some of these patients still have no insulin requirement after more than three years, and no sign of imminent relapse (Bach et al., 1987). In other less favorable cases, relapse has been observed within 6 months to 2 years. Virtually all these relapses occurred in patients who had stopped ciclosporin treatment. It appears, in fact, that when ciclosporin is stopped within the first two years of treatment, most patients relapse, although remission can be prolonged in a few cases. On the contrary, when ciclopsorin is continued, even at low doses (total blood levels around 200 ng/ml), most remissions are prolonged. In other words, as long as moderate immunosuppression is continued, it is reasonable to hope that ciclosporin-induced remissions will last several years. It follows that such patients would get significant benefits, including inter-

ruption of the need for insulin injections, and above all, the prevention of the progression of degenerative complications. The severe morbidity involved in IDDM treated by insulin justifies intensive research into alternative treatments which would afford better control of blood sugar levels than can be provided by injection of insulin at fixed times.

As we have just seen, it is difficult to stop ciclosporin administration during the first two years risking relapse, which then appears to lead to definitive diabetes. Does this indicate that such treatment must be uninterrupted in order to maintain prolonged remission? Three lines of reasoning suggest not. First, it is hoped that ciclosporin can be replaced by other agents, in particular by immunomodulators, which do not have the toxicity of ciclosporin. Secondly, it is hoped that, like other autoimmune diseases, anti-islet cell autoimmunity may evolve by bursts separated by prolonged remissions not requiring immunosuppression. The fact that some siblings of diabetics produce anti-islet antibodies and then spontaneously stop production without developing IDDM (Botazzo, G.) favors this hypothesis. Lastly, it may be that it will be possible to give intermittent immunosuppression as soon as immunological or metabolic tests can detect relapses early enough to stop renewed islet cell aggression before irreversible lesions occcur.

Side effects. The problem of nephrotoxicity — No opportunistic infections, tumors or lymphomas have been observed in over 400 diabetics thus far treated by ciclosporin, for periods of over one year in 2/3 or them. This is a hopeful sign since in organ transplant recipients receiving ciclosporin, infectious or tumoral complications are usually observed within the first year of treatment (Pen, 1986). The difference is probably due to the lower doses given to diabetics as well as to the absence of associated corticosteroid treatment. However, the occurrence of such side effects cannot be excluded, although they fortunately can often be controlled (even lymphomas when recognized early enough — Starzl et al., 1984). This possibility suggests that both treatment and follow-up must be pursued very carefully.

The only toxic effect of ciclosporin that has proven to be a clinical problem is nephrotoxicity. The problem became more acute with the recent publication of severe and partially irreversible renal involvement in heart transplant recipients (Myers et al., 1984) and patients suffering from uveitis (Palestine et al., 1986) who received high doses of ciclosporin. In fact, nearly half the patients in the randomized trial cited above had raised blood creatinine. However, these levels did not exceed values considered as the upper limit of normal (110 μmol/l) in 90% of the cases. In addition, renal biopsy studies in 17 patients in remission after 12 to 20 months of treatment showed no severe lesions, and only moderate lesions in 30 patients and minimal or no lesions in the 14 others (it is in fact difficult to define precisely and to predict the course of the "minimal" lesions that are also observed in some normal kidneys). This morphological data was supported by renal function tests, which were normal in virtually all the patients studied between 12 and 24 months, even those who had transiently raised blood creatinine levels.

These results are reassuring, particularly since they are corroborated by the more recent observations cited above, where children had remission from diabetes with moderate doses of ciclosporin without raised blood creatinine or histological renal lesions. However, one should remain cautious with regard to the long-term prognosis of ciclosporin nephrotoxicity. Severe and sometimes irreversible lesions have been observed in the above described non diabetes patients who were treated by high doses of the drug. Although they should not be confused with diabetics who receive much lower doses, it cannot be excluded that renal lesions may occur in some of these diabetic patients, nor can the possible course of such lesions be precisely evaluated, particularly in view of possible associated diabetic renal involvement. All these considerations suggest strict control and follow-up when using this product to assure that total trough blood levels never exceed 500 ng/ml. In such conditions, there is no objetive reason to fear a major risk of chronic toxic nephropathy. It should be stressed again that the lesions cited above occurred in patients having received distinctly higher doses than those given to diabetic patients in our trials. In support of such measured optimism are recent results in kidney transplantation, where nephrotoxicity is not observed at moderate doses of ciclosporin.

Perspectives — Two lines of research must be followed. The first is to determine the optimum effective dosage that is low enough to avoid side effects due to immunosuppression (i.e., infections and tumors) or to ciclosporin itself (nephrotoxicity). The margin between effective and toxic doses is small but is clinically acces-

sible with good pharamacologic and immunologic monitoring. The second line of research is the treatment of patients in earlier stages of the disease. We have set up a screening program to detect IDDM at the very beginning of hyperglycemia. This screening is based on genetic criteria (HLA), immunologic criteria (anti-islet cell antibodies, activated T cells) and metabolic criteria (reduction of early insulin production after glucose overloading). Eventually, it should be possible to treat diabetics before reduction of their B cell population (the first lesions are probably reversible). At that time, ideal conditions will have been established for eradication of the disease. There is a long way to go before this goal is reached. Numerous diabetologists and immunologists have already taken up the challenge.

At the present time, the persisting uncertainties limit the immunosuppressivw treatment of IDDM to specialized centers making controlled trials. The most recent results are hopeful. However, several years will certainly be necessary before diabetes is recognized early enough and before the best immunomodulator treatment for inducing and maintaining remission is found. When the two converge, prevention and evetually eradication of the disease will possible.

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