Editorials

Immunosuppression in IDDM

Rationale, Risks, Benefits, and Strategies

Lipton et al. (this issue, p. 776) in their article "Cyclosporin Therapy for Prevention and Cure of IDDM: Epidemiological Perspective of Benefits and Risks" discuss the definitive assessment of immunotherapy in preclinical and overt IDDM. They focus on the effects of cyclosporin A (CsA) in insulin-requiring patients with recent onset of the disease. The authors contend that an epidemiological approach is necessary in determining the eventual role of immunointervention in IDDM, that such trials must fully assess long-term adverse and beneficial effects, and that further studies with CsA are not justifiable. Their discussion raises important points concerning the need for experience with an experimental drug in preparation for a definitive study of clinical benefit, including the problem of risks that are identifiable but rare. We argue that continuing assessment of the therapeutic value of immunosuppressive agents, including CsA, in relatively short-term studies is warranted.

RECOGNITION OF BENEFIT AND ASSESSMENT OF RISK

The difficulties inherent in establishing a therapeutic role for a new intervention in a disease with acute and chronic manifestations are exemplified by immunosuppression with CsA in IDDM. The experiments were justified by the potential for clinical benefit and their importance to the understanding of the disease. In the first step, the capacity to induce clinical remission defined in terms of the insulin-treatment status in recent-onset IDDM was demonstrated in short-term studies (1–4). It was also found that, although remissions to a non–insulin-receiving state were not maintained (3,4), β-cell function was improved and stabilized through the year in a high proportion of CsA-treated patients (4). Thus, the case for study of the risks and benefits in the longer term could be considered. However, current knowledge of the relationship of the dosage with CsA or other immunomodulatory agents to their potential beneficial and adverse effects is not adequate for their use in long-term trials. Thus, accepting the rationale, additional studies of limited duration would be necessary for graduation to definitive trials.

Although a randomized clinical trial is the most rigorous method to assess all known risks, it may not be feasible. Lipton et al. calculate that in the case of CsA-associated neoplasia, an extremely large sample would be necessary to ascertain a clinically significant difference with acceptable power. This is a feature of clinical trials in which rare adverse effects may arise. The possible occurrence of a specific rare and even mortal event attributable to the intervention may be inescapable, and the judgment must be made whether the risk is outweighed by the potential for net clinical benefit. In the assessment of its capacity to detect an effect on overall mortality, any study of an experimental treatment in IDDM would depend on data derived from the clinical setting. On this basis, it has been estimated that 3% of patients with IDDM will die of all causes over the first 10 yr of disease (5). With the use of the standard formula for sample-size determination with dichotomous outcome and an α-error of 5% (1-tailed) and power of 80%,

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a total of >20,000 subjects would be required to detect a 20% increase in all-cause mortality from the experimental therapy (6). If the study was designed to assess effects on cause-specific mortality, even larger numbers of patients would be required. For example, accepting an estimate that 4% of deaths in IDDM may be due to hypoglycemia (7), with the same overall mortality, >30,000 subjects would be required to detect as large an adverse effect as a doubling of such events. For these reasons, recent large-scale clinical trials have usually addressed effects on common features of a disease relevent to processes underlying its morbidity and ultimate mortality. With this rationale it was possible in the Diabetes Control and Complications Trial (DCCT) to select a sample of 1400 subjects with the expectation that the potential effect of intensive insulin therapy on retinopathy, beneficial or adverse, and not all known risks of the experimental treatment, would be detectable within a period of observation of 7 yr (8). Thus, in the less than ideal world, attribution of rare but important adverse outcomes to an intervention has depended on observational rather than experimental techniques and will probably continue to do so.

In the case of CsA-associated nephrotoxicity, the situation is different because this adverse effect is more likely to arise than neoplasia. As Lipton et al. indicate, nephrotoxicity must be incorporated into the primary outcome measures of a clinical trial of treatment with CsA in IDDM that addresses long-term risk and benefit. The sample size should be calculated with this in mind. However, their estimate of the incidence of nephrotoxicity in such patients is based on experience with dosages of CsA that are higher than those used more recently. These lower-dosage schedules may not be associated with permanent morphological changes of clinical significance (9,10), but their capacity to modify the process of β-cell damage in IDDM awaits confirmation in a controlled trial. Possible future studies of longer duration with low doses of CsA would assess the reversibility of effects on kidney function if present and the risk of morphological damage.

In future studies, benefit must be defined precisely. This may call for controlled trials of CsA or other agents that may not address long-term effects. Thus, clinical benefit may be associated with preservation of β-cell function at levels not sufficient to maintain glycemic control without insulin therapy. Several large observational studies suggest that patients with residual β-cell function exhibit relatively good glycemic control (11–14). Two randomized control trials suggest that this depends on a cause and effect relationship (5,15). In addition, two studies have shown an inverse association between residual β-cell function and the frequency of microvasculopathic complications (16,17). Other studies have not shown such an association as Lipton et al. note (18), but all these data are limited in that they are cross-sectionally derived and concern patients with IDDM who are severely insulinopenic. Hence, it remains plausible that the preservation of β-cell function attainable with immunosuppression may be sufficient to impact on long-term complications, although not necessarily permitting sustained insulin independence.

FEASIBILITY OF PREVENTIVE THERAPY

With respect to preventive intervention, it should be questioned whether the potential for clinical benefit from this approach differs substantially between patients in the remission phase of IDDM and those in the period shortly preceding overt disease according to the Joslin model (19). This is because the insulin secretory response to intravenous glucose in patients in non–insulin-receiving remission appears to be comparable to that defined by the model in prediabetes (20). Furthermore, as Lipton et al. suggest, if the model does not approach 100% specificity in its prediction of IDDM, the use of active agents in prediabetes is more problematical than in subjects with frank IDDM. Furthermore, the preventive approach is not yet feasible in sporadic disease in non–first-degree relatives. Thus, although it appears that tests of the effects of immunomodulatory interventions on β-cell function can be undertaken in preclinical or overt IDDM, studies in overt diabetes have the advantage of avoidance of exposure to risk of prediabetic patients identified by procedures that are still under assessment and that require the presence of severe β-cell damage to be highly specific. Such studies should yield information important to the development of therapy for the prediabetic patient.

FUTURE DIRECTIONS: PROGRESSION TO DEFINITIVE CLINICAL TRIALS

It is concluded that further controlled studies are necessary to determine whether acceptable safe immunotherapy can preserve levels of β-cell function that impact favorably on metabolic control in patients with overt IDDM. For this purpose, it would be appropriate to adopt normalization of glycosylated hemoglobin levels as the target of glycemic control, with or without administration of insulin. The duration of such studies should encompass the period through which residual β-cell function is lost in most patients receiving insulin alone, an interval of ~5 yr, by which time even intensive insulin therapy fails to normalize the glycosylated hemoglobin level in most patients (11,21). If the treatment was effective in improvement of metabolic control, the hypothesis that it could ameliorate long-term clinical outcomes in IDDM would have to be tested by means of a randomized control trial. This question would need to be answered without regard to the outcome of the DCCT, which addresses the question of effects of different levels of glycemic control in patients with complete or nearly complete β-cell failure. Similar strategic considerations would apply in a range of ap-

proaches that might be considered as preventive or therapeutic interventions in IDDM.

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Southerly Migration

The July issue of *Diabetes Care* marks an important change in both the personality and geography of the journal. The editorial offices have been moved from Vermont and are now located at the Medlantic Research Foundation in Washington, DC. Like a faithful pet, *Diabetes Care* followed me on sabbatical leave to the laboratories of Drs. Ngoc Anh-Le, Barbara Howard, and Virgil Brown.

It is a great pleasure to welcome Drs. Richard Eastman, Maureen Harris, Barbara Howard, Jim Howard, and Bob Silverman as associate editors. These individuals are well known for their work in the areas of atherosclerosis, lipoprotein metabolism, substrate metabolism, clinical diabetes, clinical trials, and epidemiology. They bring new areas of expertise and a change in personality to the editorial committee.

I leave behind and will miss the four Vermont-based friends and associate editors and the energetic and scin-