Is It Time to Draw the Curtain on Immune Intervention Trials in Newly Diagnosed Patients With IDDM?

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Appearing in this issue of *Diabetes Care* is an article by Rakotoambinina et al. (1) documenting the absence of an effect of therapy with cyclosporin A in the progression of β-cell destruction in a group of seven young adults with biochemically unequivocal, but clinically asymptomatic, diabetes. The study was neither placebo-controlled nor randomized, although there were seven similar subjects who remained untreated. All 14 subjects progressed to overt diabetes under observation.

Earlier studies with cyclosporin documented that when given at the time of diagnosis, cyclosporin was associated with an increased frequency and duration of clinical remission (2–5). However, invariably, this β-cell protective effect was lost, and complete insulin deficiency soon followed. The development of renal complications provided additional evidence that this approach was ill-advised.

Many investigators have concluded that at the time of clinical diagnosis of insulin-dependent diabetes mellitus (IDDM), β-cell damage is so extensive that no intervention strategies are likely to be successful. This observation has moved the investigative spotlight to much earlier in the time course of immune destruction. The present study is an intermediate step back in the immune process. The seven patients were asymptomatic but clearly diabetic by diagnostic standards. Cyclosporin therapy had no detectable effect on the progressive course of β-cell destruction. The report of Rakotoambinina et al. (1) adds further evidence that immune intervention at the time of diagnosis of diabetes has little chance of success.

In 1990, Lipton et al. (6) critiqued the five then-active cyclosporin trials and raised serious concerns about the inadequacy of study design, power calculation, patient numbers, and documentation of complications, both short- and long-term. Those admonitions have gone largely unnoticed.

Traditionally, medical research advances have been the product of the individual investigator-initiated proposals. The development of institutional review boards or human rights committees has resulted because of the need to ensure patient protection as well as quality and appropriateness of investigation. These individual hospital or institutional boards vary enormously in expertise, experience, decision-making capability, and knowledge of the big picture in issues such as the pharmacological approaches to the delay or prevention of IDDM.

In a recent editorial (7), Pozzilli reviewed a series of new interventions directed toward the newly diagnosed patient with IDDM. Adequate details are not provided to assess study design or other critical features of these studies. However, over the past decade, numerous single investigator-initiated intervention trials have come and gone. These "fishing expeditions" were rarely randomized or placebo-controlled, nor did they have adequate patient numbers to achieve statistical significance. Such studies should never have been initiated or approved by the local institutions.

Several large multicentered intervention trials directed toward individuals who are at high risk for the eventual development of IDDM but who are metabolically normal are now underway. These are carefully designed studies with adequate numbers to answer the specific questions regarding delay in onset or prevention of disease. Harrison (8), in a recent position paper, reviews the immunology of diabetes and these new immunologic interventions. Harrison makes a strong case for more basic studies in animals and raises a number of penetrating questions regarding the proposed therapies.

In view of these ongoing major trials and recognizing the failure of previous small-scale uncontrolled studies to provide answers, it is critical that future investigations be appropriately designed and powered. Asymptomatic individuals should not be exposed to any potentially harmful interventions without at least a

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IDDM, insulin-dependent diabetes mellitus.

reasonable chance that definitive conclusions can be drawn. Such an approach should ensure that we gain the maximum benefit with minimum risk.

References

1. Rakotoambinina B, Timsit J, Deschamps I, Laborde K, Jos J, Boitard C, Assan R, Robert JJ: Cyclosporin A does not delay insulin dependency in asymptomatic IDDM patients. *Diabetes Care* 18:1487–1490, 1995
2. Stiller CR, Dupre J, Gent M, Jenner MR, Keown PA, Laupacis A, Martell R, Rodger NW, von Graffenried B, Wolfe BMJ: Effects of cyclosporin immunosuppression in insulin-dependent diabetes of recent onset. *Science* 223:1362–1367, 1984
3. Dupre J, Stiller CR, Gent M, Donner A, von Graffenried B, Murphy G, Heinriches D, Jenner MR, Keown PA, Laupacis A, Mahon J, Martell R, Rodger NW, Wolfe BW: Effects of immunosuppression with cyclosporin in insulin-dependent diabetes mellitus of recent onset: the Canadian open study at 44 months. *Transplant Proc* 20 (Suppl. 4):184–192, 1988
4. Assan R, Feutren G, Sirmai J: Cyclosporin trials in diabetes: updated results of the French experience. *Transplant Proc* 20 (Suppl. 4):178–183, 1988
5. Bougneres PF, Carel JC, Castano L, Boitard C, Gardin JP, Landais P, Hors J, Mihatsch MJ, Paillard M, Chaussain JL, Bach JF: Factors associated with early remission of type I diabetes in children treated with cyclosporin. *N Engl J Med* 318:633–670, 1988
6. Lipton R, LaPorte RE, Becker DJ, Dorman JS, Orchard TJ, Atchison J, Drash AD: Cyclosporin therapy for prevention and cure of IDDM. *Diabetes Care* 13:776–784, 1990
7. Pozzilli P: Intervention therapy for type I diabetes. *Diabetes Rev Int* 4:1–2, 1995
8. Harrison LC: Antigen-specific therapy for autoimmune disease: prospects for the prevention of insulin-dependent diabetes mellitus. *Mol Med.* In press

Authors' Response

The editorial by Dr. Allan Drash has raised very important issues on immune intervention trials. We wish to comment on the time and type of interventions and the design of such studies.

We fully agree that interventions—whatever the agents used—have until now been started very late, after the patient has become dependent on insulin. However, studies in the NOD mouse model have clearly shown that even when started at the stage of overt diabetes, some types of immune intervention can restore normoglycemia and even induce immune tolerance (1,2). These results raise the question of whether β-cell destruction is actually as far advanced at the onset of clinical diabetes as it is usually considered to be. They also suggest that provided efficient and well-tolerated agents are available, intervention at the stage of recent-onset diabetes may still deserve consideration. The question is not simply one of the time of intervention but also of the type and mechanism of action of the agent used.

It must be pointed out that at the time when our study was initiated, cyclosporin A was the only agent with a consistent efficacy in randomized placebo-controlled trials. In patients with insulin dependency, cyclosporin A did preserve partial insulin secretion for up to 4 years. The long-term benefit of this effect remains to be determined (3). Nephrotoxicity is one concern raised by the use of cyclosporin A, but its occurrence can be minimized by careful monitoring (4). Long-term follow-up (10 years) has shown that no clinical toxicity was detected in the treated patients (5; R.A., unpublished observation).

Another important issue is the design of intervention/prevention studies. We certainly agree that only carefully designed randomized studies involving sufficient numbers of subjects will draw reliable information. At best, these studies should also be placebo-controlled. However, it seems very reasonable to assess the feasibility and the potential efficacy of new interventions in pilot studies before engaging hundreds of subjects in demanding trials that will last several years. This is exactly what has been done with the two agents, nicotinamide and insulin, that are currently tested in prediabetes (6,7). In the same respect, documenting efficacy, even partial, in patients with overt diabetes can be a preliminary step before intervening in prediabetic subjects.

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References

1. Maki T, Ichikawa T, Blanco R, Porter J: Long-term abrogation of autoimmune diabetes in nonobese diabetic mice by immunotherapy with anti-lymphocyte serum. *Proc Natl Acad Sci USA* 89:3434–3438, 1992
2. Chatenoud L, Thervet E, Primo J, Bach JF: Anti-CD3 antibody induces long-term remission of overt autoimmunity in nonobese diabetic mice. *Proc Natl Acad Sci USA* 91:123–127, 1993
3. De Filippo G, Carel JC, Landais P, Bach JF, Boitard C, Bougnères PF: Long-term results of early cyclosporin therapy in juvenile type I insulin-dependent diabetes. *Diabetes.* In press
4. Feutren G, Mihatsch MF: Risk factors for cyclosporine-induced nephropathy in patients with autoimmune diseases. *N Engl J*