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The Use of FK 506 in New-Onset Type I Diabetes in Man

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"INSULITIS" was recognized as a feature of type I diabetes mellitus early in the clinical descriptions, accompanied by pathological examination.[1] Thus, an etiologic role for inflammation and immunity in this condition was raised quite early. It is now appreciated that the disease may present abruptly, but studies of patients with new onset diabetes and their family members[2–5] have clarified that the destruction of B cells proceeds over months to years. As a direct result of these studies, the current view of the pathogenesis of diabetes is that it features a protracted prodromal phase that occurs after an unknown factor that initiates the autoimmune attack against the B cells.[6] During the prodromal period, there is evidence of immune response directed against the B cell and/or its secretory products,[7–10] loss of first-phase insulin release, and onset of clinical symptoms when sufficient B-cell destruction occurs. Based on the hypothesis that type I diabetes is, in most instances, an autoimmune disease, clinical trials have been undertaken with immunomodulatory and immunosuppressive treatments. Few studies showed an impact to alter the natural course of the disease, although some agents appeared to prolong and preserve endogenous insulin secretion.[11–19] The definitive studies that finally clarified the autoimmune nature of type I diabetes mellitus, and showed an effect of immunosuppression to induce remissions (noninsulin requiring state) in significant numbers of patients and alter the natural course of this disease, were the pilot and randomized trials employing cyclosporine (CyA).[20–22] The long-term outcome of patients who initially achieved a remission has been disappointing, with many patients evolving insulin resistance or showing metabolic deterioration after more than 1 year on immunosuppression.[23] Additionally, the studies indicated that the autoimmune process was not permanently interrupted by immunosuppression in that patients who discontinued cyclosporine came out of remission.[24] Nevertheless, results of these trials led to the hypothesis that earlier intervention might be more effective in prevention or cure.

FK 506 is a powerful new immunosuppressive drug currently under investigation in the field of organ transplantation. It is approximately 100 times more potent an immunosuppressive agent than CyA on a weight basis.[25] There is some clinical evidence that it may be useful in the treatment of autoimmune disease in man.[26,27] In addition, in vitro studies suggest a favorable profile on islet function,[28–30] and it allowed for the first long-term successful outcomes in the field of islet cell transplantation.[31] Moreover, FK 506 prevents the onset of diabetes in well-established animal models of type I diabetes mellitus.[32,33] Based on the wealth of clinical information available from the cyclosporine trials, as well as these preliminary encouraging results in animal models, a pilot trial to test the efficacy and safety of this agent in new onset diabetes has recently been undertaken.

AIMS

Our aim was to determine if intervention with FK 506 will allow for sustained complete remissions of new-onset diabetes in a significant number of patients enrolled early in an immune intervention trial with this agent.

METHODS

The trial design is randomized and placebo controlled. Patients are currently enrolled based on assignment by a computer random-number generator. Neither patients nor their referring physicians know which treatment limb the patient is assigned to. Physicians must be willing to suspend insulin use if clinically indicated and to work closely with the study team. The approved age group for the study is 13 to 45 years. Exclusion criteria include >7 days of insulin treatment, >10% loss of premorbid body weight, obesity, alcohol or drug abuse, pancreatic disease, kidney disease, malignancy, pregnancy, refusal to use an effective birth control method, multiple first-degree relatives with type II diabetes, serious infection at time of onset, serious underlying medical illness, use of medications that may influence glucose tolerance, and psychiatric illness or compliance problems.

Criteria for Remission

Complete remission is indicated by HbA1c, within 2 SD of normal, fasting glucose <140 mg/dL, 2-hour postprandial glucose <150 mg/dL, and off insulin with a nondiabetic oral glucose tolerance test. A *partial remission* is indicated by one who achieves these goals, but on oral agents, or a person who fulfills all other criteria, yet has a diabetic oral glucose tolerance test. Patients who fulfill these criteria but remain on low-dose insulin will not be considered to be in remission, even if they sustain C-peptide secretion over time.

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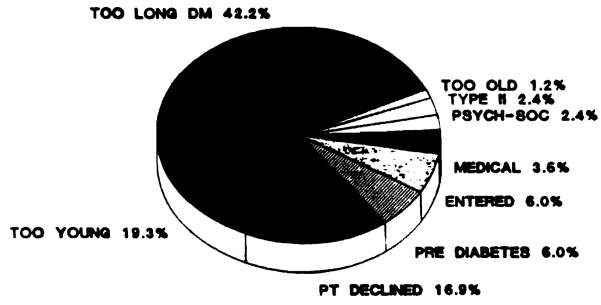

Fig 1. Primary reasons for patient exclusion from the FK 506 trial (83 patients screened).

Treatment

FK 506, or a look-alike placebo, is given orally 0.15 mg/kg BID, initially with subsequent adjustments made based on the patient's symptoms, trough levels, and/or toxicity profile. A 6-cal/kg oral liquid mixed meal (Sustacal) is used to assess endogenous insulin secretory capacity. The protocol calls for an oral glucose tolerance test 6 to 8 weeks after stopping insulin if criteria for remission are met.

RESULTS

To date, 83 patient referrals have been made (Fig 1). Of these, 35 (42%) were primarily rejected because they were referred too late, 16 (19%) were too young, 1 (1%) were too old, 5 (6%) were prediabetic, 3 (4%) had serious infections or histories of malignancy, 2 (2%) were excluded for strong suspicion of type II diabetes, and 2 (2%) for psychosocial reasons. Fourteen patients (17%), who were otherwise eligible, rejected the study for fear of potential toxicity or for concerns about the placebo nature of the trial. Thus far, five patients, aged 17 to 43, have been entered into the trial. One patient was accepted past the 7-day limit. At least one patient has been entered into each limb. The characteristics of patients entered into the trial are shown in Table 1. Thus far, two patients have recently suspended the use of insulin. The treatment groups these patients are in are not reported herein to preserve the blind nature of the trial.

Side Effects

Reported side effects have included headache, fine tremor, flushing sensation, heat and cold insensitivity and arthralgias. There have been two infections treated with antibiotics, one in each group: one sinusitis and one strep throat. A dose-related acute rise in baseline creatinine has been observed in some patients as has been elevation of serum potassium. No patient has discontinued the use of the drug for toxicity reasons.

Table 1. Characteristics of Patients in the FK 506 New-Onset Diabetes Trial

Patient	Age	Sex	Insulin Rx (Days)	HBA1c (%) (nL:3–5.9)	Fasting/Stim C-Peptide (0.46–1.59 pmol/mL)	Status
1	17	M	4	11.8	0.30/0.59	On insulin
2	22	F	1	6.7	0.67/1.3	On insulin
3	43	M	18	9.9	1.20/2.2	Off insulin
4	38	M	3	10.6	0.16/0.48	Off insulin
5	17	M	7	14.4	0.29/0.38	On insulin

CONCLUSIONS

A clinical trial has begun to assess: (1) if early entry into a trial with the potent new immunosuppressant, FK 506, can induce complete or significant partial remission in new-onset diabetes; and (2) if remissions can be sustained over time. The initial response has been encouraging, but recruitment this early is difficult, and early referrals will be critical to answer this question. The question of whether a cure is still possible at clinical onset of the disease is an important one, since type I diabetes appears to be increasing in our population. Current methods of screening for prediabetes are not 100% sensitive and specific, and would not be cost-effective to be applied to the low-risk general population, where most cases of diabetes will continue to occur. Thus, development of safe and effective methods of single agents, or combinations that could induce sustained remissions in patients with new onset diabetes, will continue to be of clinical benefit.

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REFERENCES

1. von Meyenburg H: Schweiz Med Wocheschr 70:247, 1940
2. Gorusch AN, Spencer KM, Lister J, et al: Lancet ii:1363, 1981
3. Srikanta S, Ganda OP, Eisenbarth GS, et al: N Engl J Med 308:322, 1983
4. Srikanta S, Ganda OP, Rabizadeh A, et al: N Engl J Med 313:461, 1985
5. Riley WJ, Maclaren NK, Krischer J, et al: N Engl J Med 323:1167, 1990
6. Eisenbarth G: N Engl J Med 314:1360, 1986
7. Irvine WJ, Gray RS, McCallum CJ: Lancet ii:1097, 1976
8. Palmer JP, Asplin CM, Clemons P, et al: Science 222:1337, 1983
9. Soeldner JS, Tuttleman M, Srinkanta S, et al: N Engl J Med 313:893, 1985
10. Baekkeskov S, Landin M, Dristensen JK, et al: J Clin Invest 79:926, 1987
11. Elliot RB, Crosbey JR, Berryman CC, et al: Lancet 2:1, 1981
12. Cobb WE, Molitch M, Reichlin S: N Engl J Med 303:1065, 1980
13. Ludviggson J, Heding L, Lieden G, et al: Brit Med J 286:176, 1983
14. Koivisto VA, Aro A, Chantell K, et al: Diabetologia 27:193, 1984
15. Jackson RA, Rabinowe SL, Dolinar R, et al: Diabetes Res 2:271, 1985

16. Harrison LC, Colman PG, Dean B, et al: Diabetes 34:1306, 1985

17. Heinze E, Thon A, Vetter U, et al: Acta Paetr Scand 74:605, 1985

18. Silverstein J, Maclaren N, Riley W: N Engl J Med 319:599, 1988

19. Hogan M, Beyer J, Stuermer W, et al: Arzneim-Forsch Drug Res 38:1185, 1988

20. Stiller CR, Dupre J, Gent M, et al: Science 223:1362, 1984

21. Feutren G, Assan R, Karsenty G, et al: Lancet ii:119, 1986

22. The Canadian European Randomized Control Trial Group; Diabetes 37:1574, 1988

23. Bougneres P-F, Landais P, Boisson C, et al: Diabetes 39:1264, 1990

24. Martin S, Schernthaner G, Nerup J, et al: Diabetologia 34:429, 1991

25. Kino T, Hatanaka H, Miyata S, et al: J Antibiot 40:1256, 1987

26. McCauley J, Tzakis AG, Fung JJ, et al: Lancet i:674, 1990

27. Jegasothy BV, Ackerman CD, Todo S, et al: JAMA (in press)

28. Leonard DK, Landry AS, Sollinger HW, et al: Diabetes 38:172, 1989

29. Tze WJ, Tai J, Cheung S, Transplantation 49:1172, 1990

30. Carroll PB, Boschero AC, Li MY, et al: Transplantation 51:275, 1991

31. Tzakis A, Ricordi C, Alejandro R, et al: Lancet 336:402, 1990

32. Murase N, Lieberman I, Nalesnik M, et al: Diabetes 39:1584, 1990

33. Miyagawa J, Yamamoto K, Hanafusa T, et al: Diabetologia 33:503, 1990