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Use of FK506 in pancreas transplantation

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Abstract Until recently, FK506 was used only for rescue therapy after pancreas transplantation. We report our initial experience with FK506 for 67 pancreas recipients (treated between 1 May 1993 and 30 April 1995). Of these recipients, 49 (73%) received FK506 for induction and maintenance therapy, 12 (18%) for rescue or antirejection therapy, and 6 (9%) for reasons other than rescue or antirejection therapy. In our induction and maintenance therapy group, 32 recipients (65%) underwent a simultaneous pancreas-kidney transplant (SPK), 8 (16%) a pancreas transplant alone (PTA), and 9 (19%) a pancreas after previous kidney transplant (PAK). Quadruple immunosuppression was used for induction; the median FK506 starting dose was 4 mg/day p.o. and target levels were 10–20 ng/ml. The most common side effects were nephrotoxicity (16%) and neurotoxicity (14%); transient episodes of hyperglycemia were also noted (12%), in particular in the presence of concurrent rejection and infection episodes. A matched-pair analysis was done to compare graft outcome with FK506 versus cyclosporin A (CsA). For SPK recipients, pancreas graft survival at 6 months was 79% with FK506 versus 65% with CsA ($P = 0.04$), for PTA, 100% versus 63% ($P > 0.35$), and for PAK, 88% versus 33% ($P > 0.01$). Pancreas graft loss due to rejection at 6 months posttransplant was lower with FK506 versus CsA. Two FK506 recipients died from B-cell lymphomas (Epstein-Barr virus positive) at 6 and 7 months posttransplant. In our rescue or antirejection group, 5 recipients underwent SPK, 3 PTA, and 4 PAK. The mean average FK506 dose was 10 mg/day p.o. and the mean average FK506 blood level was 11 ng/ml. The most common side effects were nephrotoxicity (33%) and neurotoxicity (16%). Two recipients developed hyperglycemic episodes, of whom 1 has remained on insulin with good exocrine pancreas graft function. Graft survival at 6 months after conversion was 75% for SPK, 67% for PTA, and 50% for PAK. Only one graft was lost due to chronic rejection. Our single-center experience shows that FK506 after pancreas transplantation is associated with: (1) a low rate of graft loss due to rejection when used for induction, in particular for solitary pancreas transplants, (2) a high rate of graft salvage when used for rescue, (3) a 1% rate of new-onset insulin-dependent diabetes mellitus, and (4) a 3% rate of posttransplant lymphoma. Further studies are necessary to analyze the long-term impact of FK506 on pancreas transplant outcome.

Key words Pancreas transplantation · FK506 · Tacrolimus

Introduction

The use of FK 506 (tacrolimus) for immunosuppression in abdominal solid organ transplantation has been extensively studied in human liver and kidney transplant recipients [5, 8]. But to our knowledge, no information has been published on its use for induction and maintenance therapy in human pancreas transplantation. Previous reports have focused only on rescue therapy in a small number of pancreas transplant recipients [7, 9].

The purpose of this single-center analysis was to study the efficacy and safety of FK 506 for induction and maintenance therapy, as well as for rescue and antirejection therapy, in pancreas transplantation. We studied three groups of FK 506 recipients: (1) those on FK 506 for induction and maintenance therapy, (2) those who convert to FK 506 for rescue or antirejection therapy, and (3) those who convert to FK 506 for reasons other than rescue or antirejection therapy.

Due to our short follow-up time, we report here our 6-month graft and patient survival rates. Matched-pair analysis was done to compare the effect of FK 506 versus cyclosporin A (CsA) for induction and maintenance therapy. An additional purpose of our study was to determine whether FK 506 decreases the incidence of rejection for solitary pancreas transplant recipients, thus improving graft survival. If so, application of this procedure could become more widespread for non-uremic patients with brittle diabetes mellitus.

Materials and methods

Between 1 May 1993 and 5 April 1995, FK 506 was given to 67 pancreas recipients. Of these, 49 (73 %) received FK 506 for induction and maintenance therapy, 12 (18 %) for rescue or antirejection therapy, and 6 (9 %) for reasons other than rescue or antirejection therapy. The three groups were analyzed separately.

1. FK 506 for induction and maintenance therapy

Of 49 recipients, 25 were male and 24 female. The median age was 36 years (range 23–52 years). Pancreas transplants were done in all three recipient categories: 32 patients (65 %) underwent a pancreas-kidney transplant (SPK), 8 (16 %) a pancreas transplant alone (PTA), and 9 (19 %) a pancreas after previous kidney transplant (PAK). The median HLA match was 2. Overall, recipients of solitary pancreas transplants (PTA, PAK) had better matched grafts than SPK recipients ($P = 0.001$).

For induction therapy, all but 1 recipient received antithymocyte globulin (ATG). The median duration of ATG administration was 10 days (range 5–14 days). All patients received FK 506, prednisone, and azathioprine for induction therapy. FK 506 was given p.o.: the median starting dose was 4 mg/day (range 2–40 mg/day). FK 506 was started in 43 (88 %) of 49 recipients within the first 3 posttransplant days. The median average FK 506 blood level was 12 ng/ml (range 5–30 ng/ml).

The most common side effects attributed to FK 506 were nephrotoxicity – defined as an increase in serum creatinine levels – in 8 (16 %) recipients, neurotoxicity in 7 (14 %) (tremors 7, confusion 1, muscle weakness 1), and gastrointestinal toxicity in 1 (2 %) (diarrhea).

Diabetogenicity – defined by transient hyperglycemia (fasting plasma glucose > 180 mg/dl) or temporary insulin administration – was reported in 6 (12 %) recipients. Hyperglycemic episodes occurred between 28 and 180 days posttransplant and the range of duration was 7–49 days. Of these 6 recipients, 4 experienced concurrent rejection or infection episodes and 1 required gastric tube feeding during treatment of malignancy. In 1 recipient, no cause other than FK 506 administration was held responsible. One recipient converted to CsA, but all 6 became normoglycemic again.

2. Conversion to FK 506 for rescue or antirejection therapy

In all, 12 pancreas recipients converted to FK 506 for rescue or antirejection therapy. Their transplants were done between 29 September 1988 and 19 September 1994. Of these 12 patients, 7 were female and 5 male. The median age at conversion to FK 506 was 37 years (range 11–51 years).

Recipients in all three pancreas transplant categories converted: 5 SPK, 3 PTA, and 4 PAK. There were eight primary transplants and four retransplants. The median HLA match was 2. Overall, recipients of solitary pancreas transplants (PTA, PAK) had better matched grafts than SPK recipients ($P = 0.001$).

With regard to previous rejection episodes, 6 recipients converted after a first, 3 after a second, 2 after a fourth, and 1 after an eighth rejection episode. Median time interval to FK 506 conversion was 324 days (range 28–2225 days) posttransplant. The median average FK 506 dose was 10 mg/day p.o. (range 2–34 mg/day), divided into two equal doses. The median average FK 506 blood level was 11 ng/ml (range 6–30 ng/ml).

The most common side effects attributed to FK 506 were nephrotoxicity in 4 recipients and neurotoxicity in 2 (tremor 2, headache 1). Diabetogenicity was noted in 2 recipients and both had concurrent rejection episodes. One had transient hyperglycemic episodes over a period of 120 days, remained on FK 506, but became normoglycemic again; the other has remained on insulin, after reversal of his rejection episode, with good exocrine pancreas graft function.

3. Conversion to FK 506 for reasons other than rescue or antirejection therapy

Six pancreas recipients converted to FK 506 for reasons other than rescue or antirejection therapy. Before conversion, all had been on CsA-based triple immunosuppression. The reasons for conversion were CsA side effects in 3 recipients (all neurotoxicity); of the other 3, 1 had memory loss, 1 had hearing loss, and 1 had deterioration of vision. There were 5 female and 1 male recipients and the median age at conversion was 37 years (range 29–48 years). By recipient category, 4 had undergone PTA, 1 SPK, and 1 PAK. The median FK 506 starting dose was 7 mg/day p.o. (range 4–16 mg/day p.o.) and the median average FK 506 level was 12 ng/ml. The most common side effects were nephrotoxicity in 4 recipients and neurotoxicity in 2. Diabetogenicity was not noted in this subgroup.

Statistical analysis

The Kaplan-Meier method was used to calculate patient and graft survival rates as well as the incidence of first reversible rejection episodes and first cytomegalovirus (CMV) infection episodes.

Two different analyses were done. The first analysis considered graft loss due to rejection, technical failure, and death with a functioning graft as graft failure. The second analysis considered only graft loss due to rejection as graft failure (death with a functioning graft and technical failure were censored). In the FK 506 induction and maintenance group, a matched-pair analysis was done to compare the outcome in FK 506 versus CsA recipients. Matching criteria included transplant category, transplant number, recipient and donor age, duct management technique, and HLA type. Outcome between these two subgroups was compared using the generalized Wilcoxon and the log-rank test.

Results

1. FK 506 for induction and maintenance therapy

Patient survival

Overall patient survival at 1, 3, and 6 months posttransplant was 100 %, 100 %, and 93 %. By recipient category, patient survival at 6 months was 89 % for SPK and 100 % for PAK and PTA recipients ($P = 0.8$). Of 49 recipients, 44 are alive. The five deaths were caused by posttransplant lymphoma in 2 recipients (SPK 1, PTA 1), infection in 2 (SPK 2), and hemorrhage in 1 (PTA).

The 2 recipients with posttransplant lymphoma died with functioning grafts at 6 and 7 months posttransplant, respectively. Both had B-cell lymphomas; in situ hybridization and immunoperoxidase stainings were positive for the Epstein-Barr virus (EBV). In both recipients, symptoms were very subtle beginning with diarrhea and a drop in the white blood cell count. Despite alpha-interferon therapy and discontinuation of immunosuppression, they died within several weeks of the diagnosis being made.

Graft survival

Overall pancreas graft survival at 1, 3, and 6 months posttransplant was 96 %, 96 %, and 85 %. For SPK recipients, graft survival at 3 and 6 months was 97 % and 79 %, for PTA recipients, 100 % and 100 %, and for PAK recipients, 100 % and 88 % (Fig. 1). The difference between the three groups was not significant ($P = 0.9$). Of 49 pancreas grafts, 41 are currently functioning and 5 recipients died with a functioning pancreas graft. The graft failed in 3 recipients, due to vascular thrombosis in 2 recipients (SPK 1, PAK 1) and bleeding in 1 (PAK).

Kidney graft survival for SPK recipients at 3 and 6 months posttransplant was 100 % and 89 %. Of 32 SPK grafts, 28 are functioning; 3 recipients died with a functioning kidney graft. The kidney graft failed in 1 recipient, due to infection.

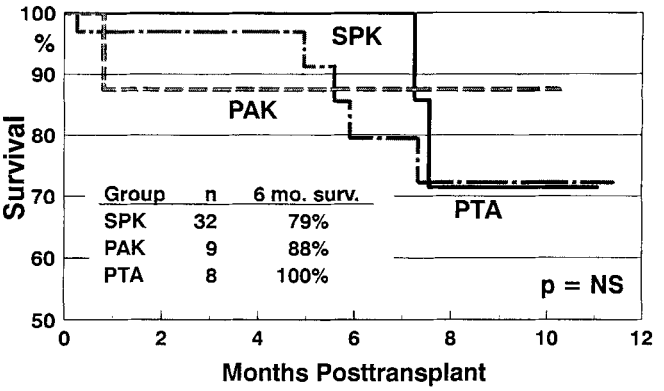

Fig. 1 FK 506 for induction/maintenance therapy. Pancreas graft survival by recipient category

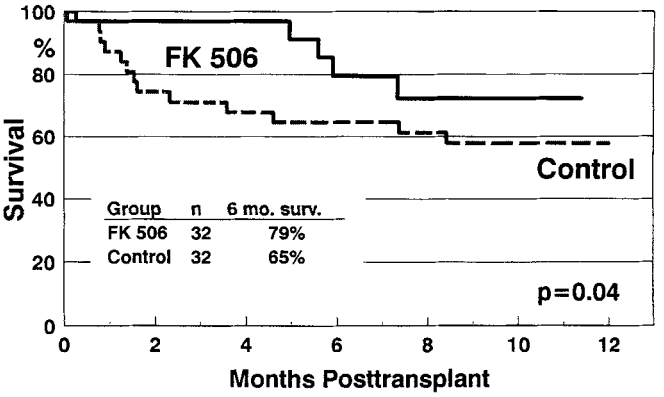

Fig. 2 SPK. Pancreas graft survival with FK 506 versus CsA (induction group)

Matched-pair analysis

For SPK recipients, pancreas graft survival at 3 and 6 months posttransplant was 97 % and 79 % with FK 506 versus 71 % and 65 % with CsA ($P = 0.04$, Wilcoxon test; $P = 0.08$, log-rank test) (Fig. 2). Kidney graft survival at 3 and 6 months posttransplant was 100 % and 89 % with FK 506 versus 78 % and 74 % ($P = 0.04$, Wilcoxon test; $P = 0.01$, log-rank test).

For PTA recipients, pancreas graft survival at 3 and 6 months posttransplant was 100 % and 100 % with FK 506 versus 63 % and 63 % with CsA ($P > 0.35$). When technical failures and deaths with a functioning graft were censored, pancreas graft survival was not statistically significant with FK 506 versus CsA.

For PAK recipients, pancreas graft survival at 3 and 6 months posttransplant was 100 % and 88 % with FK 506 versus 33 % and 33 % with CsA ($P > 0.01$). When technical failures and deaths with a functioning graft were censored, pancreas graft survival was not statistically significant between the FK 506- versus CsA-treated recipients.

Pancreas graft loss due to rejection in the SPK group at 6 months posttransplant was 0% with FK506 versus 5% with CsA ($P = 0.23$), for PTA recipients, 0% with FK506 versus 17% with CsA ($P = 0.19$) (Fig. 3), and for PAK recipients, 0% with FK506 versus 30% with CsA ($P = 0.12$) (Fig. 4).

Rejection episodes

The incidence of first reversible rejection episodes at 3 and 6 months posttransplant for SPK recipients was 29% and 39%, for PTA recipients, 25% and 25%, and for PAK recipients, 24% and 24%. The difference between the three groups was not significant ($P = 0.9$).

Infections

The incidence of first cytomegalovirus (CMV) infection episodes at 6 months posttransplant for SPK recipients was 14%, for PTA recipients, 0%, and for PAK recipients, 0% ($P = 0.7$). Overall, CMV infections were diagnosed in 4 recipients. Posttransplant, six intraabdominal infections and five wound infections developed. Urinary tract infections were noted in 26 recipients. Other types of infections were reported in 7 recipients.

Conversion to cyclosporine

Four recipients converted to cyclosporine: 2 for neurotoxicity, 1 for nephrotoxicity, and 1 for rescue therapy and transient hyperglycemia.

2. Conversion to FK506 for rescue or antirejection therapy

Patient survival

Overall patient survival at 3 and 6 months after conversion was 92% and 83%. For SPK recipients, patient survival at 3 and 6 months was 100% and 75%, for PTA recipients, 100% and 100%, and for PAK recipients, 100% and 75% ($P = 0.7$). Of the 12 recipients, 10 are alive, the two deaths being caused by infections.

Graft survival

Overall pancreas graft survival at 3 and 6 months after conversion was 83% and 65%. For SPK recipients, graft survival at 3 and 6 months was 100% and 75%, for PTA recipients, 67% and 67%, and for PAK recipients, 75% and 50% ($P = 0.8$) (Fig. 5). Graft loss from irreversible

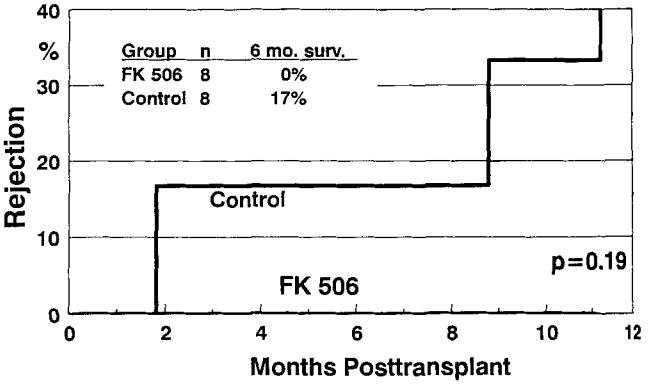

Fig. 3 PTA. Pancreas graft loss from rejection with FK506 versus CsA (induction group)

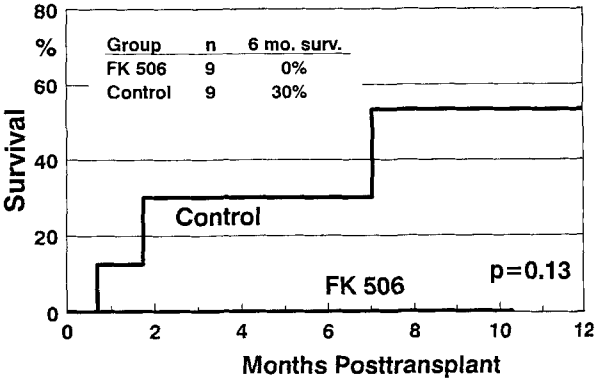

Fig. 4 PAK. Pancreas graft loss from rejection with FK506 versus CsA (induction group)

rejection for SPK recipients at 6 months after conversion (when technical failures and deaths with a functioning graft were censored) was 0%, for PTA recipients, 0%, and for PAK recipients, 33% ($P = 0.4$). Of 12 grafts, 8 are functioning. Two recipients died with a functioning graft; the pancreas graft failed in 2 recipients, 1 due to chronic rejection (PAK) and the other due to pancreatitis (PTA).

Rejection

The incidence of first reversible rejection episodes for SPK recipients at 3 and 6 months after conversion was 20% and 47%, for PTA recipients, 0% and 0%, and for PAK recipients, 25% and 50% ($P = 0.9$).

Infection

The incidence of first CMV infection episodes at 6 months after conversion for SPK recipients was 20%,

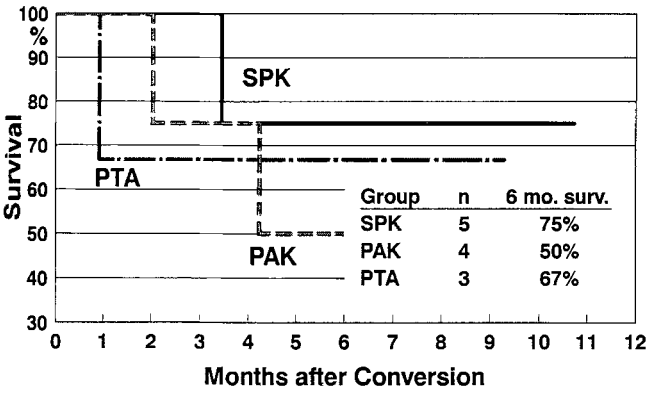

Fig. 5 FK 506 for rescue/antirejection therapy. Pancreas graft survival by recipient category

for PTA recipients, 33 %, and for PAK recipients, 0 % ($P = 0.5$). Overall, CMV infections were diagnosed in 2 recipients. After conversion, four intraabdominal infections and seven urinary tract infections developed. Other types of infections were reported in 7 recipients. No lymphomas occurred after conversion.

Reconversion to cyclosporine

Only 1 recipient converted from FK 506 to CsA for transient hyperglycemia. She has remained normoglycemic on CsA.

3. Conversion to FK 506 for reasons other than rescue or antirejection therapy

All 6 recipients who converted to FK 506 for other reasons are alive with functioning pancreas grafts. Two recipients reconverted to CsA 7 and 13 months after conversion to FK 506: 1 due to nephrotoxicity and the other due to neurotoxicity (tremor).

Discussion

Despite the introduction of CsA in the 1980s, rejection has remained a problem after pancreas transplantation. According to the International Pancreas Transplant Registry (IPTR), rejection is the second most common cause of pancreas graft failure in SPK recipients, accounting for 31 % of all their graft losses. It is the most common cause of pancreas graft failure in recipients of solitary pancreas transplants, accounting for 61 % of all graft losses in PTA recipients and 53 % in PAK recipients [2]. Thus, the outcome after pancreas transplantation could be further improved in all three recipient categories (SPK, PTA, and PAK) by decreasing the incidence of rejection as the cause of graft failure. This prospect motivated us to use FK 506 not only for rescue therapy, as previously reported [7, 9], but also for induction and maintenance therapy after pancreas transplantation.

Our single-center study produced encouraging results with the use of FK 506 to prevent rejection and to successfully treat rejection. In our 49 recipients who received FK 506 for induction and maintenance therapy, no pancreas graft was lost within the first 6 months posttransplant due to acute rejection. But eight grafts were lost due to rejection in the matched-pair, CsA group (SPK 2, PTA 3, PAK 3). FK 506 also decreased the incidence of first reversible rejection episodes. At 6 months, the rejection rates were 39 % for SPK, 25 % for PTA, and 24 % for PAK recipients with FK 506 versus 68 %, 85 %, and 65 % with CsA. The results are most striking in our solitary pancreas recipient groups (PTA, PAK), which has prompted us to more intensely promote pancreas transplantation alone for non-uremic patients with brittle diabetes.

The use of FK 506 for rescue or rejection therapy was similarly successful in our study. All 12 recipients who received FK 506 for these reasons had numerous previous rejection episodes (in one case as many as eight) before they converted from CsA to FK 506. Only one graft failed due to chronic rejection. The overall low rate of first reversible rejection episodes after conversion to FK 506 was likewise impressive: at 6 months, 47 % of SPK recipients, 0 % of PTA recipients, and 50 % of PAK recipients had experienced a first reversible rejection episode. Thus, the majority of these recipients, all at high risk for recurrent rejection, did not require additional antirejection therapy within the first 6 months after conversion.

The effect of FK 506 induction and maintenance therapy on pancreas transplant outcome has, to our knowledge, not been reported before. In two previous reports, FK 506 successfully treated relapsing rejection episodes, and was also used for rescue therapy [7, 9]. A third report focused on its successful use in an SPK recipient who developed hemolytic-uremic syndrome while on CsA; conversion to FK 506 normalized kidney function [4]. In all three of these reports, FK 506-induced new-onset diabetes mellitus was not mentioned; in contrast, one group noted normal oral glucose tolerance tests and C-peptide levels 8 months after conversion [7]. Nevertheless, in experimental studies on large and small animals, FK 506 has been shown to cause glucose intolerance, impaired insulin secretion, and decreased insulin release from beta cells [3]. In our study, diabetogenicity was defined by transient hyperglycemia (fasting plasma glucose > 180 mg/dl) or the need for insulin. In our induction and maintenance group, 6 (12 %) recipients seemingly met this definition and in our rescue group, 2 (17 %). However, of these 8 recipients, 6 had concurrent

rejection episodes (all reversed) and 1 recipient became hyperglycemic while on gastric tube feedings. All but 1 recipient became normoglycemic again; he converted to FK 506 for rescue therapy and now enjoys excellent exocrine graft function, but has remained on insulin. In addition, 2 recipients successfully converted to CsA without experiencing further hyperglycemic episodes. These findings suggest that impaired glucose metabolism might be associated with FK 506 therapy, particularly in the presence of concurrent rejection or infection episodes. Thus, in our study: (1) new-onset insulin dependent diabetes mellitus was not noted in recipients on FK 506 for induction and maintenance therapy and (2) transient hyperglycemia, if present, was frequently associated with concurrent rejection or infection episodes.

The spectrum of side effects of FK 506, including nephrotoxicity, neurotoxicity, and gastrointestinal toxicity, is similar to CsA. The incidence of nephrotoxicity was 16 % in our induction and maintenance group and 33 % in our rescue and antirejection therapy group. Increases in serum creatinine levels were only transient and controlled by a reduction in the FK 506 dose. The incidence of neurotoxicity was 14 % in our induction and maintenance therapy group and 17 % in our rescue and antirejection therapy group: the most common symptom was tremor, and severe neurologic symptoms were absent. Gastrointestinal toxicity (diarrhea) was noted in 1 recipient only. Most of these FK 506 side effects were dose related and subsided with dose reduction.

Target levels in both our induction and our rescue group were 10–20 ng/ml (median 12 ng/ml) and achieving as well as maintaining target levels with oral dosing was not difficult. FK 506 was given orally to all patients and conversions from CsA were easy to accomplish. Our study also demonstrates that recipients can successfully convert from FK 506 to CsA for rescue therapy or for treatment of transient hyperglycemia.

The spectrum of infectious complications in our FK 506 recipients has, in essence, not been different from our CsA recipients. The most common infections were urinary tract infections and wound infections (including intraabdominal infections in the induction and maintenance group). The incidence of first CMV infection episodes at 6 months posttransplant or after conversion was low, ranging between 0 % and 33 % in the three recipient groups.

Our overall positive impression of FK 506 is tarnished by the occurrence of two lymphomas in our induction group. Two recipients developed B-cell lymphomas, and in situ hybridization or immunoperoxidase stainings were positive for EBV. The diagnosis was made within the first 6 months posttransplant and initial symptoms were subtle. Despite discontinuation of immunosuppressive drugs and alpha-interferon treatment, both recipients died only several weeks after the disease was diagnosed. In contrast, none of the patients in our rescue and antirejection therapy group developed lymphoproliferative disease, even though some had undergone several courses of anti-T-cell therapy. Follow-up studies are necessary to determine whether the incidence of posttransplant lymphoma increases after FK 506 induction therapy and whether this subgroup is at high risk for lymphoma (as with bowel transplant recipients of all ages and liver transplant recipients < 5 years of age) [1, 6].

In conclusion, FK 506 was associated in our study with a low rate of graft loss due to rejection and a low incidence of first reversible rejection episodes in all three pancreas recipient categories. In our induction and maintenance therapy group, the results were better than for CsA recipients, as shown by our matched-pair analysis. In our rescue and antirejection group, only one pancreas graft was lost due to rejection, demonstrating the potent immunosuppressive activity of FK 506. New-onset insulin-dependent diabetes mellitus was not noted in our induction and maintenance group, but several recipients experienced transient hyperglycemia (particularly during the treatment of concurrent rejection or infection episodes). Although the overall rate and the spectrum of infections with FK 506 and CsA appear to be similar, 2 recipients in our FK 506 induction and maintenance group died from EBV-related B-cell lymphomas early posttransplant. FK 506 seems to be a very promising and highly effective drug in pancreas transplantation, but future studies are necessary to determine its optimal use in minimizing the broad spectrum of side effects (including posttransplant lymphomas).

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