Tacrolimus (FK506) Alone or in Combination With Methotrexate or Methylprednisolone for the Prevention of Acute Graft-Versus-Host Disease After Marrow Transplantation From HLA-Matched Siblings: A Single-Center Study


The pharmacokinetics, safety, and efficacy in marrow transplantation of FK506-based immunosuppression for graft-versus-host disease (GVHD) prophylaxis was evaluated in an open label pilot study of 18 patients. Patients more than 12 years of age (median, 35 years; range, 15 to 50 years) with advanced hematologic malignancies receiving HLA-matched sibling marrow grafts were randomized to receive FK506 alone, FK506 and methotrexate (MTX), or FK506 and methylprednisolone. Of 17 evaluable patients, all had evidence of sustained marrow engraftment. The median time to an absolute neutrophil count of greater than 500/μL was 15 days for patients receiving FK506 alone or FK506 plus methylprednisolone and 23 days for FK506 plus short MTX. Pharmacokinetic studies did not show any significant difference in clearance of FK506 when administered alone or in combination with methylprednisolone or MTX. The mean bioavailability after oral administration in these same three groups was 0.49 ± 0.1, 0.27 ± 0.12, and 0.16 ± 0.08, respectively (P = .003). The decrease in bioavailability may have resulted from an exacerbation of radiation-induced gastroenteritis by MTX. The most significant adverse effect associated with the administration of FK506 was nephrotoxicity, which occurred in 14 of 18 patients (78%). The mean glomerular filtration rate, determined by clearance of (99m)Tc-DTPA, decreased to 56% (±18%) of the pretransplant baseline level by week 8 (P = .002). Eight of 18 patients (44%) developed grades II-IV acute GVHD, predominantly of the skin and gastrointestinal tract. The actuarial probability of transplant-related mortality during the first 100 days was 24%. The actuarial probability of 1-year disease-free survival was 39%. In conclusion, although bioavailability of FK506 may be affected in patients receiving MTX, this study suggests that FK506 may have a role in the management of patients after allogeneic marrow transplantation.

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ACUTE GRAFT-VERSUS-HOST disease (GVHD) contributes significantly to the morbidity and mortality associated with allogeneic marrow transplantation. Previous studies have shown that the combination of cyclosporine (CSP) and four doses of methotrexate (MTX) is more effective than either agent alone in prevention of acute GVHD. Prednisone is an effective agent for therapy of acute GVHD and has been studied in combination with CSP for prophylaxis. In more recent studies, the combination of CSP, MTX, and prednisone was more effective in preventing acute GVHD than the combination of CSP and prednisone, but was not more effective than the combination of CSP and MTX. Although the combination of immunosuppressive agents has reduced the incidence of GVHD, the use of new agents (possibly in combination with MTX and prednisone) may permit a further reduction in the incidence or severity of acute GVHD and may avoid the toxicities associated with previously established regimens.

The macrolide FK506 produced by Streptomyces tsukubaensis inhibits T-cell activation by forming a complex with the FK binding protein-12 that blocks the serine-threonine phosphatase activity of calcineurin. This prevents interleukin-2 (IL-2) transcription mediated by NF-AT on the IL-2 gene promoter. FK506 inhibits certain pathways of T-cell activation such as those mediated by the T-cell receptor CD3 complex and by CD2 but did not affect the T-cell proliferation induced by CD28-specific monoclonal antibodies in the presence of phorbol 12-myristate 13-acetate. Clinical studies with FK506 were first performed in liver transplantation. In this setting, FK506 is effective for prevention of graft rejection and has also been effective as salvage therapy to control episodes of graft rejection. Preclinical studies of FK506 after marrow transplantation in a rat model that was fully major histocompatibility complex (MHC) and non-MHC disparate showed that GVHD could be prevented or treated successfully. In a model established to study GVHD, dogs were grafted with unrelated MHC-nonidentical marrow after 920 cGy total body irradiation (TBI). In the group of dogs that received FK506 in combination with MTX, survival was prolonged when compared with controls receiving no immunosuppression or FK506 alone. Based on these studies of immunosuppressive activity and because there were no previous reports of the use of FK506 with MTX or prednisone for acute GVHD prophylaxis, a pilot study was conducted in patients with advanced hematologic malignancies to investigate drug interactions and safety.

MATERIALS AND METHODS

Patients. From July 1992 to August 1993, 18 patients were registered on this protocol. Patient characteristics are shown in Table 1.
The protocol and consent forms were approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. The risks and benefits of the treatment regimens were explained to each patient in detail before hospital admission. Patients were sequentially randomized to one of the three regimens of GVHD prophylaxis: FK506 alone, FK506 and MTX, or FK506 and methylprednisolone. In this small group of patients, a randomized selection of patients to each GVHD prophylaxis group allowed a comparison of the pharmacokinetic data.

**Conditioning regimens.** Before marrow transplantation, patients with lymphoid malignancies (acute leukemia or lymphoma) received intravenous cyclophosphamide (60 mg/kg body weight) on each of 2 successive days followed by 2.25 Gy to TBI on each of 7 successive days (1,575 cGy). Patients with myeloid malignancies (acute leukemia, chronic myeloid leukemia [CML] in blast crisis, or myelodysplasia) received oral busulfan (7 mg/kg over 4 days) and cyclophosphamide (50 mg/kg/day over 2 days), followed by 200 cGy of TBI on each of 6 successive days (1,200 cGy). One patient received a chemotherapy regimen consisting of BCNU, cyclophosphamide, and VP-16 because of a past history of radiation to the mediastinum. The radiation was delivered by two opposing 60Co sources at a rate of 6.5 cGy/min. Within 4 hours of the last dose of TBI or 36 hours after the last dose of cyclophosphamide, donor marrow was infused intravenously. The day of marrow infusion was designated as day 0. Engraftment was defined as the first day a neutrophil count was greater than 500 $\times$ 10^3/L and was sustained for 2 days. Eight patients with lymphoid malignancies were treated with recombinant $\alpha$-interferon (IFN) when neutrophil counts were sustained greater than 200 $\times$ 10^3/L for 3 days as part of an investigational protocol evaluating the risk of relapse after marrow transplantation.

**GVHD prophylaxis, assessment, and treatment.** Postgrafting immunosuppression in all study patients included FK506 alone or in combination with methylprednisolone or MTX. FK506 was begun on the day before marrow infusion. In this pilot study, the intravenous dose was 0.03 mg/kg/d as a continuous intravenous infusion, which was maintained until the patients had recovered from regimen-related gastrointestinal toxicity, when oral FK506 (0.15 mg/kg/d in 2 divided doses) was substituted. After the seventh patient on study, the oral dose was reduced to 0.12 mg/kg/d. The MTX dose was 15 mg/m^2 on day 1 and then 10 mg/m^2 on days 3, 6, and 11 after marrow transplantation. Methylprednisolone was started at 0.5 mg/kg on day 7 and was increased to 1 mg/kg from day 15 through day 28 and then tapered through day 72. The full dose of FK506 was administered until day 60 unless adverse effects or acute GVHD developed. Generally, if the serum creatinine doubled above baseline values or increased above 2 mg/dL, the FK506 dose was reduced or temporarily withheld. After day 60, if the patients had no evidence of GVHD, the FK506 dose was tapered until the drug was discontinued by day 180. If patients relapsed, FK506 was stopped. FK506 steady-state levels during continuous intravenous infusion or trough levels during oral treatment were determined by enzyme-linked immunosorbent assay (ELISA). An attempt was made to maintain FK506 whole blood levels between 2 and 60 ng/mL.

Donors and recipients were genotypically HLA-identical as determined by serologic histocompatibility typing for HLA-A and B and the results of HLA-DRB1 DNA analysis based on allelic typing by polymerase chain reaction (PCR)/sequence-specific oligonucleotide probe hybridization (SSOP). Assessment, grading, and treatment of acute GVHD has been previously reported. The time period after stopping FK506 was not evaluated for GVHD if patients had relapsed or elected to withdraw from the study with no GVHD or FK506-related toxicity. Acute GVHD was treated with methylprednisolone at 2 mg/kg/d for at least 14 days and then tapered over 8 weeks if tolerated. Alternatively, patients were enrolled in an investigational protocol with oral nonabsorbable beclomethasone if GVHD was isolated to the upper gastrointestinal tract. Before discharge home, patients were evaluated for chronic GVHD. Treatment of cGVHD was with FK506 0.12 mg/kg/d in two doses 12 hours apart and every other day with prednisone at 1 mg/kg. This regimen is similar to that previously reported with CSP except that FK506 was administered daily instead of every other day.

**Pharmacokinetics.** Whole blood levels of FK506 were determined by a previously described ELISA. Plasma methylprednisolone and cortisol were measured using the high performance liquid chromatography (HPLC) method of Ebling et al. Plasma prednisone, prednisolone, and cortisol were measured using the modified HPLC method of Rose and Jusko. Least-squares regression calculations related to standard curves were performed using the variance stabilizing transformation method. The area under the curve (AUC) for individual corticosteroid profiles from zero to infinity was calculated using a spline computer program.

In 17 patients, serial blood samples were obtained during continuous intravenous infusion of FK506 on day 11 after the administration of MTX and methylprednisolone for determination of the clearance of FK506 and methylprednisolone pharmacokinetics. Whole blood samples were drawn before the morning dose of MTX or methylprednisolone and then at 0.5, 1, 2, 4, 6, 8, and 12 hours after MTX or methylprednisolone dosing. In the group of patients who received neither MTX nor methylprednisolone, whole blood samples were drawn at similar time points in the morning to make them comparable. In 14 patients, a 12-hour pharmacokinetic profile of FK506 was obtained between weeks 4 and 8 after oral administration of a constant dose for 4 consecutive days. Whole blood samples (3 mL) were drawn before the morning dose of FK506 and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, and 12 hours after the dose. These data and the clearance of FK506 calculated from the pharmacokinetic profile obtained on day 11 were used to assess bioavailability. MTX concentrations were measured only at 24 hours after the dose. If the 24-hour MTX level was greater than 0.04 $\mu$g/mL, rescue with Leucovorin was started.

**Assessment of renal function and toxicities.** To assess the effects on renal function, the glomerular filtration rate (GFR) was determined by calculating the creatinine clearance (CLCR) from the plasma creatinine and creatinine production rate (CPR) measured before the morning dose of FK506 and at 0.5, 1, 2, 4, 6, 8, and 12 hours after the dose. If a patient developed renal insufficiency, FK506 was reduced to 0.12 mg/kg/d or temporarily withheld. After day 60, if the patients had no evidence of GVHD, the FK506 dose was tapered until the drug was discontinued by day 180. If patients relapsed, FK506 was stopped. FK506 steady-state levels during continuous intravenous infusion or trough levels during oral treatment were determined by enzyme-linked immunosorbent assay (ELISA). An attempt was made to maintain FK506 whole blood levels between 2 and 60 ng/mL.

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**Assessment of renal function and toxicities.** To assess the effects on renal function, the glomerular filtration rate (GFR) was deter-
minded before and during week 8 after marrow transplantation. The GFR was determined by clearance of technetium-99m (99m-Tc)-diethylenetriamine-pentaacetic acid (DTPA) from protein-free ultrafiltered plasma. The DTPA was injected and blood levels of DTPA measured at 1 hour. The GFR was calculated from this result.33

Nephrotoxicity was defined as a doubling of serum creatinine greater than baseline or a serum creatinine greater than 2 mg/dL. This degree of renal dysfunction was defined as significant because doses of nephrotoxic agents such as FK506 were adjusted at this point. Veno-occlusive disease (VOD) has been previously described and defined.32 Hypertension was defined as a diastolic blood pressure greater than 90 mm Hg or a systolic blood pressure greater than 140 mm Hg sustained for more than 3 consecutive days and requiring treatment. Hyperglycemia was defined as a serum glucose level greater than 140 mg/dL and requiring treatment. Hyperlipidemia was defined as a serum total cholesterol concentration ≥ 240 mg/dL.

Statistics. Cumulative incidence curves and corresponding statistical tests were used to describe acute GVHD and nephrotoxicity.33,34 Kaplan-Meier curves were used to describe transplant-related mortality and disease-free survival. The Wilcoxon signed rank test for matched pairs was used to compare GFR values before and after transplant. An analysis of variance was used to compare bioavailability and clearance of FK506 among the three different groups of FK506 alone, FK506 and methylprednisolone, and FK506 and MTX.35

RESULTS

Engraftment. Seventeen of the 18 patients in the FK506 group showed hematopoietic engraftment. The mean time to recovery of 500 neutrophils per microliter was 15.2 days (range, 8 to 23 days) in those patients who had received FK506 alone or FK506 and methylprednisolone, and 21.7 days (range, 15 to 28 days) in patients who received FK506 and MTX. One patient who received FK506 plus MTX died on day 23 after marrow transplantation with a granulocyte count of 423/μL.

Pharmacokinetics. The mean clearance rates of FK506 on day 11 were similar for patients treated with FK506 by continuous intravenous infusion, alone or combined with methylprednisolone or MTX (P = .61) (0.075 ± 0.048 [5 patients], 0.055 ± 0.023 [7 patients], and 0.063 ± 0.032 L/hr/kg [5 patients], respectively; Fig 1A). The bioavailability of oral FK506 between weeks 4 and 8 was significantly different among the same three groups (P = .003) and was the lowest in the group that received MTX (0.49 ± 0.1 [5 patients], 0.27 ± 0.12 [6 patients], and 0.16 ± 0.08 [3 patients], respectively [value of 1 = 100% bioavailability]; Fig 1B). None of the four patients tested had an elevated level of MTX 24 hours after the dose requiring rescue with folinic acid. The mean clearance of methylprednisolone (0.5 mg/kg) on day 11, in 7 patients tested, was 0.27 (±0.11) L/min/kg. Peak concentrations during the first hour after intravenous administration of methylprednisolone ranged from 166 to 278 ng/mL. Methylprednisolone concentrations then followed a typically linear decline. Cortisol was suppressed (<10 ng/mL) in all patients except one. On oral prednisone, between week 3 and 8, conversion to methylprednisolone was rapid. Prednisolone concentrations peaked at 183 to 676 ng/mL (mean, 379 ± 169) between 1 to 4 hours after the oral dose of prednisone, and cortisol was usually fully suppressed. The mean clearance of prednisolone was 0.105 ± 0.044 L/hr/kg.

Adverse effects. Nephrotoxicity (increase of serum creatinine to 2× baseline or greater than 2 mg/dL) was the major adverse effect associated with GVHD prophylaxis with FK506-based immunosuppression. The cumulative incidence of nephrotoxicity during the first 100 days was 78% (Fig 2). Dialysis was required for four patients (22%). In three of these patients, dialysis occurred during preterminal acute events, including idiopathic pneumonitis, sepsis, or systemic Aspergillus infection. The fourth patient had a baseline GFR of 66 mL/min and had an increase in FK506 levels to 62 mg/mL during the first 7 days after marrow transplantation, temporally associated with the onset of VOD of the liver. To further assess renal function in patients on FK506-based immunosuppression, GFR measurements were made before and during week 8 after marrow transplantation. All patients had GFR studies performed before transplant and 13 patients had GFR studies performed during week 8. All patients except one had a reduction in GFR (Fig 3). The mean GFR after at least 8 weeks of FK506 was reduced to 56% (P = .002 Wilcoxon sign rank test) of the baseline. Although nephrotoxicity was the most significant adverse effect, those nephrotoxic events not requiring dialysis, in
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Fig 2. The cumulative incidence of nephrotoxicity in patients receiving FK506 alone or in combination with MTX or prednisone was 78%. A patient was defined as developing nephrotoxicity if there was a doubling of serum creatinine over baseline or an increase over 2 mg/dL at any time in the first 100 days after marrow transplantation (n = 18).

Fig 3. Glomerular filtration rates for patients on FK506 before (○) and 8 weeks (●) after marrow transplantation. Thirteen patients were evaluable after marrow transplantation. The mean GFR was reduced to 56% of the pretransplant values (P = .002).

Fig 4. The cumulative incidence of acute GVHD (grades II-IV) in patients receiving FK506 alone or in combination with MTX or prednisone was 44% at 100 days (n = 18).

general, occurred later in the period after transplantation, appeared more directly related to the toxic effects of FK506, and improved on dose reduction in all cases.

Seven patients (39%) developed VOD as previously defined by McDonald et al. One patient had mild-moderate VOD with complete resolution of signs and symptoms. One patient with pre-existing mild liver disease before marrow transplantation developed severe VOD associated with significant ascites and a coagulopathy. Two patients who died before day 28 had clinical evidence of mild-moderate VOD but pulmonary complications secondary to systemic Aspergillus or toxicity from the conditioning regimen were found at autopsy. No association was observed between changes in bilirubin levels with FK506 dose adjustment. Other adverse effects were hypertension and hyperglycemia in nine and 10 patients, respectively. Six patients had hypercholesterolemia. All six patients developed hypercholesterolemia while on glucocorticoids and FK506 for prophylaxis or treatment of GVHD. One of these also had hyperkalemia and required treatment with both fludrocortisone acetate and gemfibrozil. These problems resolved after FK506 and prednisone were tapered. Neurologic adverse effects were noted in one patient who experienced delirium at the time FK506 whole blood levels were between 20 and 30 ng/mL. This resolved when the FK506 was held and other drugs were reduced in dose or discontinued. A burning discomfort in the extremities (hands and feet) or severe headaches during intravenous infusion occurred in 11 patients but improved or resolved after reducing the rate of the intravenous infusion or changing to oral FK506. Two patients required additional narcotic analgesia to control this discomfort.

GVHD. The cumulative incidence of grades II-IV acute GVHD was 44% (8/18; Fig 4). Skin GVHD occurred in six patients. In addition, six patients had GVHD of the gastrointestinal tract. Two patients were considered to have GVHD of the liver, but both of these patients also had moderate-severe hepatic VOD. Four of six patients receiving FK506 alone, one of seven patients receiving FK506 plus methylprednisolone, and three of five patients receiving FK506 plus MTX developed overall grades II-IV GVHD. Six of the eight patients were treated with 2 mg/kg of methylprednisolone for 2 to 3 weeks and then received tapered doses. Four of these patients had a complete response. Two of the eight patients had biopsy-proven GVHD of the upper GI tract only, manifested by anorexia and vomiting. One patient was treated with prednisone at 1 mg/kg and the other with oral nonabsorbable beclomethasone (investigational drug). Both patients had responses and did not require second-line therapy. Only one patient received second-line treatment with ATG for an increasing serum bilirubin after FK506 had been discontinued. However, this patient also had VOD with ascites and a gram-negative bacteremia that likely contributed to the changes that led to this intervention. Three of the eight patients who developed grades II-IV GVHD were receiving IFN at the time of onset but there was no obvious correlation of administration of IFN to the development of acute GVHD. Nine patients in hematologic remission were evaluable for chronic GVHD (cGVHD). One patient was treated for subclinical cGVHD (positive lip and skin biopsies with an abnormal Schirmer's test) with FK506 and prednisone. Two
other patients developed cGVHD after successfully tapering off FKS06 at day 180 and were therefore treated with CSP and prednisone as previously described.26

Survival. The actuarial probability of transplant-related mortality during the first 100 days was 24% (Fig 5). Only 1 of 16 patients in the study (without myelodysplastic syndrome [MDS]) were in remission at the time of transplant. Seven patients relapsed during the first year after transplant. The actuarial probability of disease-free survival was 39% at 1 year after transplant.

DISCUSSION

Patients with advanced hematologic malignancies were selected for this study of acute GVHD prevention because the efficacy and safety of FKS06 as an immunosuppressive agent after marrow transplantation was unknown. If these patients with a high risk of relapse had a higher incidence of acute GVHD as a result of using this new agent than what otherwise might have been expected, the overall survival of the group might not have been affected because of the graft-versus-leukemia effect.36,57 During this period, patients with advanced hematologic malignancies received more intensive conditioning regimens at this center, either with higher doses of TBI (1,575 cGy) or intensified chemotherapy (combination of busulfan and cyclophosphamide with TBI). More intensified conditioning regimens, especially with intensified TBI, have been associated with an increased incidence of acute GVHD.38,39 This may occur because of a potentiating effect of TBI on acute GVHD. Another reason for the increased incidence of acute GVHD might be an inability to administer effective doses of immunosuppressive agents because of the increased regimen-related toxicity. The incidence of acute GVHD reported in this study is comparable to what has been reported in previous studies of patients receiving conditioning regimens of higher intensity.38,39 In this study, an increased risk of acute GVHD was not observed with IPN administration.40

FKS06 is a highly lipophilic macrolide with a large volume of distribution. The drug is primarily eliminated by hepatic metabolism (P-450 3A), with less than 1% of an intravenous or oral dose appearing in the urine. Marrow transplant patients can develop liver and gastrointestinal tract complications, all of which possibly could affect clearance or bioavailability. Drug interactions might also affect these parameters. Prednisolone inhibits FK506 metabolism and another agent, such as FKS06, which is a substrate of cytochrome P-450 3A, cyclosporine A, can decrease the metabolism of prednisolone.41-44 Delays in MTX elimination have been observed during the concomitant administration of ketoprofen and a macrolide-like antibiotic, Pristinamycin.45,46 Clearance of FKS06 was similar in all three groups. The differences observed in bioavailability among the three groups might have resulted from the exacerbation of the radiation-induced gastroenteritis by MTX. The range of values for both clearance and bioavailability of FKS06 in our study were similar to results obtained after liver and small bowel transplantation. All studies have shown large interindividual variability.47-49 Because the number of patients studied here were small, the differences observed in the bioavailability of FKS06 among the three groups will need to be confirmed. No major effect of FKS06 on clearance of methylprednisolone or prednisolone was found, although the clearance of methylprednisolone and prednisolone may have been slightly decreased compared with results reported for healthy individuals.50,51 There was no apparent effect of FKS06 in delaying the elimination of MTX, as determined by serum levels 24 hours after dosing. During this pilot study of FKS06, we were attempting to maintain whole blood levels between 2 and 60 ng/mL. More recently, for other studies, we have reduced the upper limit and increased the lower limit of this range of whole blood FKS06 levels. These pharmacokinetic results confirm that (1) although the association between whole blood FKS06 levels and toxicity or acute GVHD is currently unclear, the high degree of interindividual variability in clearance and bioavailability resulting from multiple factors, requires routine monitoring and adjustments of dose; and (2) FKS06 does not have any significant interactions on other important immunosuppressive agents now used after marrow transplantation.

The major adverse effect associated with the administration of FKS06 was nephrotoxicity. Renal tubular cell damage and glomerular thrombosis have been associated with FKS06 nephrotoxicity.52 FKS06 has been reported to be cytotoxic for tubular cells in vitro, inducing ultrastructural changes and delayed regeneration. Moreover, release of endothelin from renal tubular cells may perturb renal hemodynamics, decreasing GFR and renal plasma flow and increasing renal vascular resistance.53,54 Sodium depletion in an experimental rat model potentiates FKS06 nephrotoxicity.55 The incidence of severe nephrotoxicity requiring hemodialysis was similar to what has been previously reported after marrow transplantation with CSP-based regimens of GVHD prophylaxis.56 In the four patients of this study of FKS06 who required hemodialysis, nephrotoxicity was associated with hepatic VOD or serious infections. Although it is likely that FKS06 was contributory, the limited observations in this study would confirm what has been previously reported with CSP, that in patients early after marrow transplantation, other complications such as VOD, sepsis, hypotension, and the use of Amphotericin B more closely correlate with the devel-
opment of acute renal failure requiring hemodialysis. After liver transplantation, nephrotoxicity observed in the FK506 group was also described as the major adverse effect, occurring in 37% to 54% of patients, similar to the incidence observed in patients treated with CSP. Because both the immunosuppressive and nephrotoxic effects of FK506 may be linked to the ability of the FK506-binding protein-12 complex to inhibit the phosphatase activity of calcineurin, a degree of nephrotoxicity may be unavoidable to achieve adequate immunosuppression. The incidence of VOD has previously been determined to be 54% and severe VOD was seen in 15% of patients after marrow transplantation. The incidence of VOD in this study of FK506 in patients who were at higher risk of developing this complication because of the higher-dose regimen of cytoreductive therapy is comparable to the previous experience.

Hypertension and hyperglycemia were common but manageable adverse effects. After marrow transplantation with CSP for GVHD prophylaxis, a 60% incidence of hypertension was reported, similar to what was obtained in this study of FK506. In a prospective randomized trial comparing FK506 to CSP after liver transplantation, hypertension was less frequent in the group receiving FK506. Hyperglycemia has been observed in 17% to 20% of patients treated with FK506 after liver and kidney transplantation. Preclinical studies in rats, dogs, and primates have indicated that one of the mechanisms for the development of hyperglycemia was a reduction in insulin secretion during treatment. Seizures, delirium, dysarthria, or coma occurred in 8.4% of liver transplant patients treated with FK506. These complications were associated with toxic FK506 levels and responded to dose reduction in all but one case. The spectrum of FK506-related complications observed after marrow transplantation is similar to that observed after solid organ transplantation.

FK506-based immunosuppression after marrow transplantation has an acceptable safety profile and has immunosuppressive activity that appears to be effective for prophylaxis of acute GVHD. No significant interactions were observed between FK506, MTX, or prednisone that affected clearance, although because bioavailability of oral FK506 in patients receiving MTX may be reduced, blood levels should be carefully monitored. In another recent phase II study of FK506 alone for GVHD prophylaxis after marrow transplantation from HLA-matched siblings, the incidence of grades II-IV acute GVHD in 27 patients was 41%. Based on phase II clinical studies in marrow transplantation and on the preclinical study of GVHD in dogs showing that FK506 in combination with MTX significantly decreased the incidence of acute GVHD compared with FK506 alone, further studies are indicated to compare FK506 and MTX with CSP and MTX in patients receiving marrow grafts from HLA-matched siblings.

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Tacrolimus (FK506) alone or in combination with methotrexate or methylprednisolone for the prevention of acute graft-versus-host disease after marrow transplantation from HLA-matched siblings: a single-center study

RA Nash, R Etzioni, R Storb, T Furlong, T Gooley, C Anasetti, FR Appelbaum, K Doney, P Martin and J Slattery

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