Published in final edited form as:
Transplant Proc. 1991 December ; 23(6): 3105–3108.

Adverse Effects Associated With the Use of FK 506

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Cyclosporine (CyA)-based immunosuppression significantly enhanced both patient and graft survival in all solid organ transplants. when compared to the era of azathioprine and steroids. The widespread use of CyA has spawned a growing body of experience delineating the side effects of CyA use, which was apparent in the first reports on human patients.[1] Prior to the utilization of monitoring techniques, renal dysfunction was often used as a guideline to effective CyA dosing.2 More recently, monitoring of CyA trough levels has been used to guide CyA dosing,3 although some patients manifest toxicity at “therapeutic levels.” while others do not manifest any side effects at levels considered “excessive”.4 This has held true, regardless of the development of a number of different assay systems monitoring either parent CyA drug or its metabolites.

Nephrotoxicity remains the principle limiting side effect of CyA, and has been reported to occur in more than 50% of patients. Unfortunately, the mechanism(s) of CyA nephrotoxicity have not been clearly defined. Hypertension (40% to 60%), hyperkalemia, hirsutism (60% to 80%), gingival hypertrophy, hepatotoxicity (40% to 60%), and tremors are relatively common side effects of CyA (reviewed by Thiru5).

Malignant complications include a higher incidence of posttransplant lymphoproliferative disease (PTLD), as well as a variety of skin cancers, including Kaposi’s sarcoma. PTLD is an abnormality of lymphocyte proliferation in a setting of an immunosuppressed patient. The spectrum of PTLD can range from a benign lymphoid proliferation, such as a mononucleosis syndrome, to a frankly malignant lymphoid tumor. PTLD has been associated with all types of immunosuppressive therapy. The incidence of PTLD in the CyA era is generally estimated between 2% and 4%.[7] Most (90% to 95%) of PTLD are B cell in origin, and most are associated with integration of Epstein-Barr virus (EBV) DNA into the genome of the B cell. A smaller number of PTLD are T cell in origin.

Because of the relatively high percentages of patients developing rejection on CyA therapy (estimated at 50% to 70%), multiple drug combinations have been utilized to prevent rejection, while minimizing toxicities. The sequelae of overimmunosuppression in attempts to treat rejection, such as use of excessive steroids, antilymphocyte preparations, are fraught with a high incidence of infectious complications and metabolic sequelae, such as diabetogenesis and ulcerogenesis. In addition, each component of the “cocktail”, has its inherent limitations. It stands to reason that a baseline immunosuppressive agent which allows for less incidence of rejection, and easier treatment of rejection, would decrease both graft and patient loss.

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FK 506 is a recent addition to the armamentarium of immunosuppressive agents. FK 506 shares some pharmacologic similarities with CyA, such as bioavailability, lipophilicity, and hepatic metabolism.[8] Both drugs bind to proteins having a peptidyl-prolyl *cis-trans* isomerase activity, although the binding proteins for CyA and FK 506 are unique.[9] A wealth of animal data[1–12] and human experience[13–16] suggest that FK 506 is effective in both the prevention and treatment of rejection. FK 506 appears to not only decrease the absolute incidence of rejection episodes, and allows for marked reduction in steroid doses, but makes the treatment of rejection much simpler. Nevertheless, a delineation of the side effects of FK 506 therapy is important in the comparison of two effective immunosuppressive agents. FK 506 and CyA share some of the same side effects, although they differ significantly in other important aspects. The purpose of this study was to examine the adverse effects associated with FK 506 therapy.

Adverse reactions requiring treatment or adjustment of FK 506 doses can be categorized into four primary areas: (1) alterations in kidney function; (2) alterations in glucose metabolism; (3) neurotoxicity; and (4) susceptibility to infection or malignancy.

STUDY SOURCES

Since the introduction of FK 506 to clinical trials in February 1989, and December 31, 1990, a total of 1057 patients have been enrolled, for both primary therapy and rescue therapy. The vast majority of patients studied have been patients who have received liver transplants. Therefore, most of the data regarding the toxicity of FK 506 were compiled from a series of 370 consecutive primary liver transplant patients transplanted between August 1989 and December 1990. A smaller series of 41 patients were randomized to receive FK 506 in a trial comparing FK 506 and CyA in low-risk liver transplant patients.[17] Reference to 208 kidney transplant recipients[18] and 52 heart transplant patients[19] will also be made.

In the group of 370 primary liver transplant patients, the median follow-up was 377 days. Fifty-four patients died (mortality was 14.6%). The 1-year patient survival was 86%. No deaths were directly attributed to FK 506 therapy.

In the randomized study, a total of 41 patients received FK 506. The median follow-up was 343 days. The overall mortality in the FK 506 limb was 7%, and the 1-year patient survival was 93%.

NEPHROTOXICITY

Alterations in kidney function are manifested by electrolyte abnormalities and changes in glomerular filtration, as evidenced by changes in serum creatinine. Significant hyperkalemia, following administration of FK 506, was defined as a serum potassium greater than 5.1 mEq/L, which required treatment. Treatment of hyperkalemia was generally with potassium-binding resins or potassium-restricted diets. Because many of these patients have a relative hyporenin-hypoaldosterone status, addition of a synthetic mineralocorticoid, Florinef, relieves the hyperkalemia by increasing potassium excretion by the kidney. Approximately 50% of liver transplant patients on FK 506 require treatment for hyperkalemia. The incidence in other organ transplant systems is less; for heart transplant recipients, Florinef is utilized in less than 20% of patients.

Decrements in renal blood flow following liver transplantation has been documented by nuclear medicine studies. The filtration fraction generally remains the same. Causes of altered renal function in transplant patients are multifactorial and include: perioperative hypotension, severely altered hepatic function, use of nephrotoxic antibiotics, degree of preexisting renal dysfunction, and high levels of FK 506. In fact, liver transplant patients have been shown to have a mean decrease in estimated renal blood flow of 32% prior to transplantation.[20]

In the liver transplant patients, renal dysfunction was classified as “acute” if elevation of serum creatinine (SCr) to >3.0 mg/dL occurred within the first 30 days following transplantation in patients whose pretransplant SCr was ≤2.0 mg/dL. Excluding 21 patients who were on hemodialysis prior to liver transplantation and an additional 8 patients with SCr >2.0 mg/dL, the overall incidence of renal dysfunction in the first month was 36.2% (134 patients). A careful analysis of “contributing factors” (use of nephrotoxic antibiotics, primary nonfunction of the liver, and the requirement for retransplantation) revealed that 64 of the 134 patients had one or more of these complicating factors. The mortality of the contributing factor group was 29 of 64 (45%), verifying the impact of these factors on patient surviVal. Pure FK 506 nephrotoxicity was found in the other 70 patients, and only one patient died in this group. The peak SCr was similar in both groups (4.34 ± 1.46 mg/dL for the FK 506 toxicity 4.59 ± 1.29 mg/dL for the contributing factors). Of significance was the difference in the FK 506 level at the time of the peak SCr. In the FK 506 toxicity group, the FK 506 level was 4.06 ± 3.1 ng/mL, occurring a median of 6 days following transplantation. In the other group, the FK 506 level was 7.03 ± 10.47 ng/mL at 5 days posttransplantation. A total of 81 (23.2%) patients required hemodialysis following transplantation (does not include the 21 patients on hemodialysis prior to transplantation). Only 30 of the 81 patients were in the FK 506 toxicity group, while the rest were in the contributing factor group. Improvement of renal function was the rule (94%) in both groups if the patients survived, although recovery took twice as long (16 days) in the contributing factors group when compared to the FK 506 toxicity group (8.5 days).

Chronic nephrotoxicity was defined as a SCr >2.0 mg/dL occurring after the first 30 days following transplantation. In the series of 370 patients, a total of 115 patients (31.1%) with a SCr ≤2.0 mg/dL prior to transplantation, had a rise to over this value after 30 days. Forty of these 115 patients recovered a SCr ≤2.0 mg/dL following changes in FK 506 dosing, requiring a mean of 154 days to accomplish this.

In the 41 patients who were in the randomized group, hemodialysis was required in 4 patients (10%) during the posttransplant period. Long-term hemodialysis was required in one patient (3%). The mean SCr was determined during various intervals following transplant. The SCr at 1, 2, 3, 4, and 6 months following transplantation were: 1.54, 1.70, 1.71, 1.61, and 1.75 mgl/dL, respectively. In this study, the incidence of nephrotoxicity was somewhat less than that for the CyA group. Thirty-three percent of the randomized FK 506 patients in the randomized trial had a SCR >2.0 mg/dL at 6 months posttransplant. The progression of chronic renal failure to dialysis requiring renal failure is not known.

No patient has required maintenance hemodialysis following heart transplantation. Renal dysfunction in this group of patients was manifested by a peak SCr of 2.25 mg/dL within the first 30 days posttransplant. Chronic nephrotoxicity appeared to be more prevalent in the heart transplant patients, with 60% of patients having an elevated SCr >2.0 mg/dL at 6 months posttransplant. Only one nontransplant patient, with a diagnosis of T-cell lymphoma (Sezary syndrome) required hemodialysis, but in a setting of having received high doses of aminoglycosides to control recurrent sepsis.

Hypertension, in previously normotensive patients, may be a result of excessive water volume, intrinsic renal damage, or increased vasomotor tone. Concomitant usage of glucocorticoids or mineralocorticoids may lead to retension of excessive water. Liver failure patients manifest a low peripheral resistance prior to transplant, which may mask essential hypertension until the transplant is completed. The incidence of newly diagnosed cases in the 370 primary liver transplant patients was 42.4% (157 patients). A total of 38 of these patients were able to be successfully taken off of antihypertensive medications, as the fluid status of the recipients normalized. The randomized liver patients had an incidence of hypertension at 3 and 12 months

of 27% and 33%, respectively. A low incidence of hypertension (20%) was also seen in heart transplant patients.

DIABETOGENESIS

Alterations in glucose metabolism are the result of changes in peripheral sensitivity to insulin and/or changes in the response of the islet cells to hyperglycemia. Factors which affect perioperative glucose metabolism are: high glucose administration in hyperalimentation, steroid administration., and excessive catabolic states such as sepsis.

The overall incidence of hyperglycemia requiring insulin during the posttransplant period was 35.5% (151 patients out of 370 liver transplant recipients). The timing following transplantation suggests that perioperative events were more likely to lead to insulin requirement than the use of FK 506, since the median time to initiation of insulin therapy was only 2 days. Recovery was noted in 106 of these recipients, so that the incidence of long-term insulin requirement was 12.1%.

The incidence of new onset diabetes was approximately 10% in FK 506 kidney transplant patients. This is the same incidence as was seen in the early heart transplant trials (10%). The incidence of new-onset diabetes in other immunosuppressive regimens, incorporating CyA or azathioprine, is approximately 20%. The long-term consequence of insulin requirement in transplant patients toward the development of diabetic complications is not known.

NEUROTOXICITY

Liver transplant patients are particularly prone to the development of perioperative neurologic events. The susceptibility of liver transplant patients to changes in serum electrolytes has been previously reported. For the purposes of this discussion, mild neurotoxicity is manifested by insomnia, mild tremors, headaches, photophobia, and hyperesthesias. Significant, severe neurotoxicity is defined as confusion requiring investigation, new onset of seizures, persistent coma, or dysarthria (expressive aphasia). The overall incidence was 8.4% (31 patients), and was broken down into: confusion (12 patients), seizures (10 patients), dysarthria (5 patients), and persistent coma (4 patients).

INFECTIOUS AND MALIGNANT COMPLICATIONS

A total of 16 patients have developed de novo PTLD lesions while on FK 506 therapy, both primary and rescue therapy. Seven of these patients died, although PTLD was associated with death in only five cases. The remaining 9 patients had relatively mild forms of PTLD, 3 of these had a mononucleosis syndrome with presentation of sore throat and tonsillar enlargement. Treatment with lowering immunosuppression and IV acyclovir proved to cure all of them. In the remaining 6 patients, 3 required operative procedures (2 small bowel resections, 1 liver resection) which were directly related to PTLD, while the other 3 were treated by reduction of immunosuppression only. The incidence of de novo PTLD following initiation of FK 506 therapy was 1.4%. All of the cases of PTLD occurred within the first year following initiation of FK 506, with the median time from FK 506 therapy to onset of disease being 4 months. FK 506 shows no evidence of any increase in the risk of developing or succumbing to PTLD when compared to previously quoted figures on the incidence of PTLD (based on other immunosuppressive regimens). No patients treated with FK 506 for nontransplanted indications have developed any malignancies.

Cytomegalovirus (CMV) infections are considered the most common opportunistic infection in the transplant patient. Several factors determine the severity and development of CMV infections. The seronegativity and use of intensive immunosuppression are considered major

contributing factors. The incidence of CMV infections in the FK 506-treated transplant patients is approximately 20%. This figure is similar to that seen in transplanted patients on CyA. No patient treated with FK 506 for nontransplant indications has developed CMV infection.

DISCUSSION

Since both FK 506 and CyA appear to act, in part, by inhibition of a family of isomerase enzymes, it is reasonable to expect that some of the side effects are similar. However, one of the major benefits of FK 506 appears to be a relative lack of some of the side effects of CyA. Some of these are cosmetic, such as hirsutism and gingival hyperplasia, which has not been seen with FK 506. Other more significant side effects, such as hypertension, appear to be less in the FK 506 patients than for those on CyA. Hypertension, which is seen in 60% to 70% of all CyA-treated patients, may result in complications such as hypertensive stroke, cardiomyopathy, and augment renal failure. The incidence of hypertension in FK 506-treated patients appears to be at least 50% less. The ability to use less steroids in patients with FK 506, when compared to CyA, may result in less complications ascribed to chronic steroid use, such as: osteoporosis. Cushinoid habitus, stunted growth, ulcerogenesis, and diabetes.

A clearer profile of adverse reactions and side effects of the drug has been accumulated. In humans, the primary side effects of FK 506, in order of decreasing frequency, are: insomnia, tremors, headaches, tingling sensations, muscle achiness, itching, fatigue, visual sensitivity to light, and GI symptoms. In a prospective, randomized study, the side effects of FK 506 were compared to that of CyA. The only differences between the two drugs were an increased incidence of headaches and insomnia in the FK 506 group, while those on CyA had an increased incidence of hair growth.

The treatment for the four areas of toxicity varies, to a large extent, on the degree of toxicity. Generally, toxicity improves with lowering the doses of FK 506. Some reactions, such as the development of dysarthrias, may be idiosyncratic or require multiple factors in order to become apparent and, therefore, may not respond to decreased doses of FK 506. Specific therapy or supportive measures are indicated until the toxicity resolves. The requirement for hemodialysis in liver transplant patients is one such example. Renal dysfunction in these cases is generally reversible.

While it has taken over 10 years to elucidate the limitation of CyA therapy, we believe that the profile of adverse effects of FK 506 has been determined. Schemes to minimize these effects will increase the safety of this agent for immunosuppression.

Acknowledgments

Supported by Research Grant No. DK 29961 from the National Institutes of Health, Bethesda, Maryland, and the Veterans Administration.

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