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AN OVERVIEW ON CLINICAL ORGAN TRANSPLANTATION UNDER FK 506

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INTRODUCTION

FK 506 was discovered in 1984 in Japan and the first reports on its in vitro and in vivo immunosuppressive properties were published in 1987 (1-6). The clinical use of FK 506 in solid organ transplantation began in March 1989, when a clinical trial in liver transplantation was started at the University of Pittsburgh. Initially, the new drug was used to "rescue" rejecting liver allografts under cyclosporine based immunosuppression (7,8). A few months later the use of FK 506 was extended to primary immunosuppressive treatment for transplantation of the liver and subsequently of the kidneys and the thoracic organs (9,10).

We will summarize here the results previously reported on the initial clinical experience and the properties of FK 506.

PHARMACOKINETIC PROPERTIES OF FK 506

FK 506 is a macrolide antibiotic which is many times more potent than cyclosporine on a weight basis. The molecular structure of FK 506 is unrelated to that of cyclosporine and the two drugs have different cytosolic binding sites (11,12). However both drugs inhibits T-lymphocyte activation and suppress the synthesis and expression of multiple cytokines such as interleukin 2 and gamma-interferon (1,3,6).

FK 506 is incompletely absorbed after oral administration and its distribution in the body is extensive. The time required to reach peak concentration

varies from 1 to 4 hours. FK 506 is a high clearance drug, which is completely metabolized by the liver so that less than 1% of the dose is excreted unmetabolized in the urine. The mean half-life is 8.7 hours (13).

Changes in FK 506 dosage do not seem to be necessary in patients with kidney failure or in patients on dialysis. However, with hepatic dysfunction accumulation of FK 506 may be rapid unless dose reductions are made promptly (14,15).

LIVER TRANSPLANTATION: "RESCUE"

A group of 121 liver allograft recipients with cyclosporine related complications (resistant cellular rejection, nephrotoxicity, hypertension, excessive steroid toxicity) was converted to FK 506 immunosuppression (8,16). In the majority of these patients, the oral FK 506 treatment was started (0.3 mg/Kg/day divided in two doses) 12-24 hours after cyclosporine treatment had been stopped. In a smaller group of patients, the initial doses of FK 506 were given intravenously (0.15 mg/kg/day) in order to treat a severe acute cellular rejection resistant to the conventional therapy.

After a follow-up period ranging from 1 to 12 months (median time 95 days), 101 patients were alive with normal liver function, 6 patients required retransplantation because of progressive liver dysfunction and 14 died. Sepsis represented the primary cause of death (7 cases). However, 6 of these patients were septic at the time of the conversion. The other patients died because of primary non-function of the liver allograft (2), fulminant B virus hepatitis (1), metastatic hepatoma (1), liver failure-chronic rejection (1), rupture of splenic artery aneurysm (1) or intraoperative death (1).

Liver function improved in most patients: the median total bilirubin was 3.8 mg/dl at the time of conversion and fell to 1.4 mg/dl 1 month and later after the initiation of FK 506. Similar findings were noted with the median SGOT, which improved from 291 IU/l to 96 IU/l in the same period

of time.

The benefit of FK 506 conversion was surprising in a highly selected group of patients, with end stage liver disease (defined by a serum bilirubin >2.5 mg/dl) and with chronic rejection documented by histology. In this group the median time of FK 506 conversion was 17 months following transplantation. Six patients required retransplantation for persistent liver failure, while the remaining 13 had both histological and clinical improvement.

Steroid doses were eliminated or reduced in over 50% of FK 506 converted patients, allowing reversal of the steroid morbidity.

PRIMARY LIVER TRANSPLANTATION

Of the 120 patients enrolled in this group, 105 were adults and 15 were children (9). Non-alcoholic and alcoholic cirrhosis accounted for two thirds of the adult indications. Primary biliary cirrhosis and sclerosing cholangitis were the indications in only 27% of the patients. In 8 of the 15 pediatric patients, biliary atresia was the indication for the transplant, followed by cirrhosis (4), tumor (2) and fulminant failure (1).

The immunosuppression with FK 506 was started in the operating room with an intravenous dose of 0.075 mg/kg infused over 4 hours and repeated every 12 hours until the oral intake was began. We now believe that this induction dose should be 0.10 mg/kg in the first day, given as a constant infusion over the 24 hour span instead of in boluses. An oral dose of 0.15 mg/kg every 12 hours was started when the patient could eat. Dose adjustments were dictated by plasma trough levels, quality of the graft function, toxicity symptoms.

All of the patients were given steroids. The first 50% received 1 g. intravenous methylprednisolone after graft reperfusion followed by a rapid daily taper from 200 mg to 20 mg. over 5 days. In the second half of the series, the intraoperative bolus and subsequent steroid cycle were

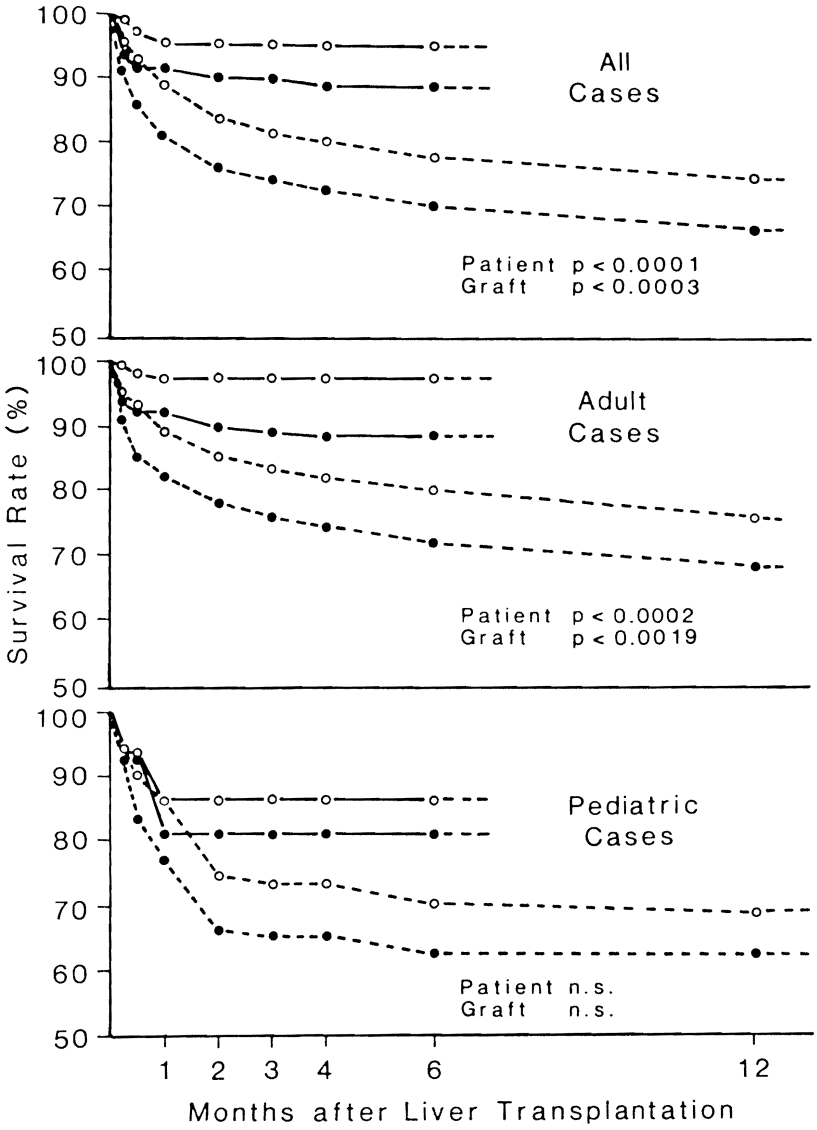

Figure 1 --- Life survival curves for primary liver transplant recipients given FK 506 and cyclosporine. The upper curve is for 125 liver transplant patients, the middle curve is for the 110 adult patients, while the bottom curve is the for the 15 pediatric patients, under the age of 18. Adapted from Todo et al, Ann Surg 212:295-305, 1990.

omitted, using 20 mg/day from the outset. The pediatric doses of steroids were adjusted downwards according to patient size.

After a follow-up period of 2 to 7.5 months, 112 of the 120 patients (93.3%) were alive (fig.1). Only 7 patients required retransplantation (5.8%) and the only graft lost for rejection was in a highly sensitized patient with positive antidonor cytotoxic cross-matches. Sepsis was the primary cause of death (4 cases); 3 patients died of technical complications and one child with fulminant hepatic failure died of coma after the liver transplant.

The function of the grafts in the surviving patients was good. The median bilirubin was 0.5 mg/dl and only one patient with recently repaired duct obstruction had a bilirubin over 2 mg/dl. The median SGOT and alkaline phosphatase were in a normal range: 50 IU/L and 153 IU/L respectively. The median creatinine was 1.4 mg%.

The requirement of steroids was low. A rapid dose reduction of steroids was attempted during the first month so that by the second and the third month the daily average doses were less then 5 mg/d. When compared to a historical control group of 400 patients treated with cyclosporine based immunosuppression, the use of additional immunosuppression for the treatment of rejection in the FK 506 patients was significantly less. The absolute rate of clinical rejection was less ($p<0.01$) and the episodes were much easier to reverse (9). FK 506 treated patients required only 43% of the steroid boluses used in the cyclosporine controls, 7% of the steroid recycles, 4% azathioprine use, and 23% of the OKT3 courses used to treat rejection.

While the infectious disease profiles were similar when compared to the historical control, the incidence of bacterial and fungal infections have been reduced. The most common viral infection was cytomegalovirus (17). Two patients developed symptomatic EBV infection which was confirmed histologically and were associated to a polyclonal lymphoproliferative disease.

The principal adverse reactions seen were nephrotoxicity, neurotoxic symptoms (tremors, paresthesias, insomnia, mood changes) and diabetogenity. The incidence of a new onset diabetes requiring insulin was 8.9% (9). Two patients developed transient expressive aphasia in the early postoperative period (18).

KIDNEY AND THORACIC ORGANS

A detailed report of the kidney cases has been reported elsewhere (10). In summary, 36 renal transplant recipients were treated with FK 506 immunosuppression. This group of patients represented a high risk population because their high sensitization and other risk factors including prior liver transplantation (29%), previous kidney transplantation (29%) and degree of illness. With a follow-up of 4 to 13 months, all but 2 of the 36 patients were alive, 29 (81%) were dialysis-free and most had good renal function. The low steroid doses, a relatively freedom from hypertension and low serum cholesterol levels were noteworthy in these patients. Only one kidney was lost to cellular rejection and a high rate of irreversible humoral rejection occurred in patients with antidonor cytotoxic antibodies in current or historical serum samples (3 of 9 patients).

The 11 heart recipient were all alive and in good clinical condition after a follow-up of 2 to 6 months (9,19). These patients had a striking freedom from hypertension that was common in historical controls and most of them had normal serum cholesterol levels. The two double-lung and the heart-lung recipients never received maintenance steroid therapy and they were alive and in good conditions respectively after 130, 165, and 173 days.

DISCUSSION

The advent of cyclosporine had a fundamental impact in Nevertheless the development of rejection remained the most frequent complication, often requiring high doses of steroids and other drugs (azathioprine, monoclonal antibody, antilymphocyte globulin) to prevent or to treat rejection.

As a consequence of this, other complications, primarily infectious, can occur.

The advent of FK 506 may represent an important advance in immunosuppression for two reasons. First, this drug offers an option for patients already transplanted with failing grafts under cyclosporine therapy. The second reason is the efficacy and flexibility with which FK 506 can be used as primary therapy. In transplant patients treated with FK 506 there was a decreased incidence of rejection and of bacterial or fungal infections without an increased risk of lymphoproliferative disease or irreversible toxicity (9).

The response of a special group of patients with chronic rejection was surprising, namely those with the "vanishing bile duct syndrome", has been considered a progressive and largely irreversible form of rejection. Most of the patients who did not respond had lost more than 50% of their bile ducts and had obliterative arteriopathy confirmed by histology. The hepatotrophic properties of FK 506, demonstrated in experimental studies (20) might help explain FK 506 ability to reverse the histological damage of chronic rejection.

When FK 506 was the primary treatment in liver transplantation, it usually could be used as monotherapy after perioperative induction with an FK 506-steroid combination. In the kidney and thoracic organs, the results also are encouraging, even if the number of patients is still small. Prospective, randomized trials comparing FK 506 therapy with cyclosporine based immunosuppression are currently underway in liver and kidney transplantation.

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