Pathologic Observations In Human Allograft Recipients Treated With FK 506

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FK 506, a powerful new immunosuppressant, has proved to be an effective drug for the prevention and treatment of allograft rejection in animals.[1-8] In some respects, it was even shown to be superior to CyA, which revolutionized solid organ transplantation a decade earlier. However, during trials in experimental animals, serious questions were raised regarding its potential toxicity. Wide-spread arterial necrosis, induction of a diabetic state, and renal tubular and liver damage were among the most worrisome harmful effects attributed to this agent.[9-12] These reported toxicities varied with the animal species used. Rats could be given relatively large doses with seemingly little consequence,[13] while dogs given the same amounts on a per weight basis experienced vomiting and emaciation, and often died.[6] Evidence of a peculiar, non-inflammatory necrosis of the media and periadventitia of muscular arteries was found at the time of death in the canine subjects.[6,8,9-12] Nevertheless, our group[6,8] and Ochiai et al[14] noted the same lesions in animals who never received the drug, while some of the other reported side effects were not observed at all.[6,8,13] These findings eased some, but not all, of the concern surrounding the use of FK 506 in humans.

Encouraged by the promise of this agent and the inconclusive nature of the most serious potential side effects, clinical trials were cautiously undertaken in humans who had already received allografts, but whose organs were failing from rejection under conventional therapy, in which CyA was the mainstay immunosuppressant. In fact, many of these first patients had already lost one or more grafts to rejection. The following report is an account of the pathologic findings in the organ allografts and other tissues from the patients who were the first to be given this drug.

PATIENTS AND METHODS
Patient Groups

As mentioned previously, FK 506 was first given to patients in an attempt to prevent graft failure in those experiencing organ rejection despite optimal conventional CyA and steroid therapy. Henceforth, these will be referred as "rescue" patients, and further classified by the type of organ allograft. All of these patients underwent allograft biopsy evaluation within 1 week before the initiation of FK 506 therapy.

Reassured by the ability of FK 506 to halt the progression of rejection in a number of the rescue patients and the relative lack of any apparent serious toxicities, patients who were experiencing unmanageable side effects from CyA or whose graft function had seriously deteriorated from unapparent causes were also switched to FK 506. These patients will also be referred to as "rescues," but were separated from those described above.

The last group of patients were those in whom FK 506 was used from the outset; these will be referred to as "primary" and further categorized as to the type of allograft. All the primary patients underwent protocol biopsy evaluation at 7-10 days after transplantation regardless of the clinical or serologic profile. Additional biopsies were obtained at the onset of graft dysfunction. A summary of the various treatment groups is shown in Table 1. All patients listed have had at least 1 month (up to 7 months) of clinical follow-up at the time of this writing.

Analysis of Pathologic Findings

For comparison analysis of the rescue patients before and after FK 506 therapy, the following criteria were used. The severity of acute cellular rejection in the liver specimens was graded according to previously published criteria.[15] Since "chronic" rejection is difficult, if not impossible, to grade, specific histologic features were assessed and compared before and after the initiation of FK 506 therapy. The specific histologic features analyzed included the severity of portal inflammation (mild, inflammation without expansion of the triad; moderate, expansion of the triad; and severe, marked expansion with spillover into the lobule and/or bridging). Duct damage was based on the percentage of affected ducts (mild, <25%; moderate 25-75%; and severe, >75%) and duct loss was based on the percentage of portal tracts without ducts but containing arteries (mild, <40%; moderate, 40-75%; and severe, >75%) and the presence of centrilobular cholestasis, hepatocyte dropout, and hepatic venular sclerosis. Criteria for the grading of

Table 1. Summary of the Various FK 506 Treatment Groups

Treatment Group	Type of Allograft	No. of Patients
Rescue	Liver	38
Rescue*	Kidney	5
Rescue	Cluster	2
Rescue	Heart	0
Primary	Liver	20
Primary†	Kidney	3
Primary	Cluster	2
Primary	Heart	2

* Two of these patients were also liver allograft recipients, and varying degrees of rejection were seen in both grafts.

† Two of these patients were also kidney "rescue" patients who had a new kidney graft placed after being switched to FK 506.

acute cellular rejection of kidney and heart grafts were based on previously published criteria.[16,17]

A group of 20 historic controls matched for age, disease, and United Network Organ Sharing priority status who were treated with CyA and steroids were also analyzed for comparison with the primary FK 506 liver allograft recipients. All graft pathology specimens taken from this group within the first month after transplantation were subjected to the same scrutiny as the FK 506 patients listed above.

RESULTS
Observations in Allografts

Liver Rescues (Rejection). Seventeen of the 24 patients switched from CyA to FK 506 had liver biopsy findings which, in the author's experience, are harbingers of a progressive and largely irreversible form of rejection (Table 2), often called early "chronic" rejection or "vanishing bile duct syndrome." This rejection was characterized by a relatively mild mononuclear portal infiltrate, localized around and in the small bile ducts and associated with significant ductular epithelial cell damage. The duct cell damage took the form of paranuclear vacuolization and/or pyknosis, eosinophilic transformation of the cytoplasm, uneven spacing of the nuclei around the circumference of

the duct, and even focal duct loss. Clinically, these findings correlated well with the presence of marked elevations in the canalicular enzymes (alkaline phosphatase and gamma glutamyl transpeptidase) in the absence of any evidence of large duct obstruction.

Eleven of the 17 patients showed histologic evidence of amelioration of at least one and often more of the histologic parameters assessed after the switch from CyA to FK 506 (Table 2). An example of a liver rescue in a patient with "chronic" rejection is shown in Fig 1. Pathologically although the bile ducts had not completely returned to normal in follow-up biopsies in nine patients, marked decreases in liver injury tests were noted in six. Four others failed to respond pathologically on the most recent biopsy and two lost their grafts to chronic rejection; both of these patients had already lost most of their bile ducts before being switched. There has been clinical improvement in the remaining two patients who did not respond pathologically. No pathologic follow-up was available in three additional patients, although clinical improvement was noted.

Six of the 24 patients in this group had biopsy findings which were best classified as acute cellular rejection,

Table 2. Comparison of Histologic Findings In Liver Allograft Biopsies Before and After Treatment With FK 506 In Liver Rescues With Rejection at the Time of the Switch From CyA to FK 506

Patients	Pathology of Previous Failed Graft(s)	Pre-FK 506			Post-FK 506			Pathologic Follow-up (d)	Graft Status
		Portal Inflammation	Duct Damage	Duct Loss	Portal Inflammation	Duct Damage	Duct Loss		
R.F.	GX1,GX2: CR and hepatitis	Mild	Mild	None	None	None	None	69	Functioning
L.W.	GX1,3: arterial thrombus; GX2,4: CR	Mild	Moderate	Minimal	Minimal	None	None	98	Failed: arterial thrombus
Y.R.*	GX1: CR	Moderate	Mild	None	Mild	Mild	None	93	Functioning
D.S.†	None	Severe	Severe	None	None	None	Mild	51	Functioning
M.B.	None	Moderate	Severe	Mild	None	Mild	Mild	65	Functioning
W.D.	None	Mild	Mild	None	None	None	None	32	Functioning
D.W.	GX1: CR	Moderate	Severe	Moderate	Mild	Moderate	Moderate	30	Functioning
H.M.	None	Moderate	Severe	Moderate	Mild	Severe	Severe	36	Failed: CR
H.W.†	None	Severe	Severe	Minimal	Mild	Severe	Severe	27	Failed: CR
R.F.†	None	Moderate	Moderate	None	NA	NA	NA	—	Functioning
F.B.	GX1: ischemic injury	Mild	Moderate	Mild	Minimal	Mild	Minimal	9	Functioning
D.J.	None	Mild	Severe	Moderate	Minimal	Mild	Moderate	9	Functioning
M.S.	GX1: CR	Moderate	Moderate	Mild	NA	NA	NA	—	Functioning
C.C.	None	Moderate	Severe	Severe	Mild	Severe	Severe	11	Failed: CR
J.W.	None	Moderate	Severe	Mild	Minimal	Moderate	Minimal	8	Functioning
P.H.†	None	Moderate	Moderate	None	NA	NA	NA	—	Functioning
J.B.†	None	Minimal	Mild	Minimal	None	None	None	17	Functioning
L.S.†	None	Mild	Mild	None	AU	AU	AU	—	Died: sepsis
F.J.	None	Mild	Severe	Moderate	Mild	Moderate	Mild	39	Functioning
T.B.	None	Mild	Moderate	Minimal	Minimal	None	Mild	32	Functioning
R.U.	None	Mild	Mild	None	Mild	Mild	None	30	Functioning
L.K.	None	Mild	Moderate	Mild	NA	NA	NA	—	Functioning
R.S.	GX1: ischemic injury	Mild	Moderate	None	NA	NA	NA	—	Functioning
R.C.	None	Mild	Moderate	None	Mild	Moderate	Minimal	12	Functioning: steatosis

Abbreviations: GX, graft; CR, chronic rejection; NA, not available; AU, autopsy.
* Patient was a liver and kidney allograft recipient and was switched primarily because of the rejecting kidney.
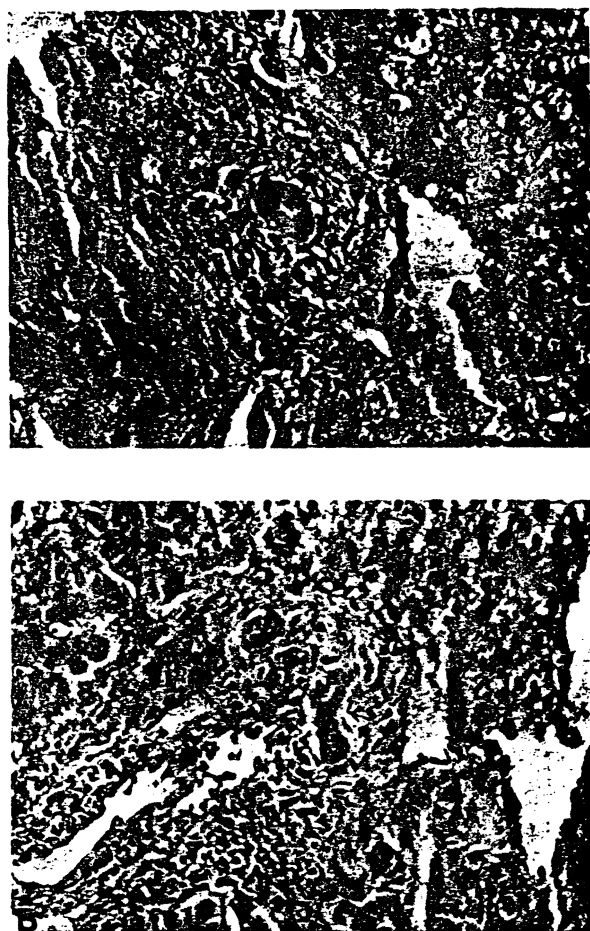† Patients with acute cellular rejection.

Fig 1. An example of a liver rescue with early chronic rejection. (A) The pre-FK 506 biopsy showed a mild portal mononuclear Infiltrate with marked bile duct distortion (arrow), and clinically, the gamma glutgamyl transpeptidase was in the 2,000 range. (B) Sixty-five days after the switch to FK 506, there was still a mild portal infiltrate, but the duct damage was less severe (arrow). The gamma glutamyl transpeptidase serum activity had decreased to the 500-600 range.

varying from histologically mild to severe, although clinically, all were experiencing significant graft dysfunction. One of the most dramatic examples of a rescue from severe acute cellular rejection is illustrated in Fig 2. Four of these patients have had histologic follow-up, and all improved with the exception of one who lost his graft to chronic rejection 27 days after the switch to FK 506.

One patient not included in Tables 1 and 2 was switched to FK 506, but was later withdrawn from therapy because of a mistaken diagnosis. The pre-FK 506 biopsy showed mild duct damage and little evidence of lobular disease activity other than marked centrilobular hepatocellular anisonucleosis. Since the patient's original disease was not hepatitis B, the diagnosis was not initially suspected, and B viral antigen stains were performed when the liver functions deteriorated after the switch to FK 506. Many cells were found to be infected with the B virus.

Other than the changes mentioned above, there were several other findings noted in some of the liver biopsy specimens after the switch to FK 506 which may or may not be attributable to the drug. These included mild hydropic cell swelling and thickening of the plates in zone 1 of the acinus and Kupffer cell hypertrophy. Only one of these patients developed cytomegalovirus (CMV) hepatitis. Another developed Kupffer cell granulomas, although no microorganisms or viral antigens could be detected by histochemical or immunohistochemical methods.

Liver Rescues (Renal Failure or Unexplained Graft Dysfunction). There were 13 patients who were switched to FK 506 from CyA for reasons other than pathologically severe acute or "chronic" rejection (Table 3), although four of them had a mild degree of acute cellular rejection on the pre-FK 506 biopsy. In five of the patients, the switch was made because of renal failure from CyA toxicity. One patient was switched because of steroid complications. Three other patients had lost prior grafts because of primary nonfunction, the causes of which were not apparent, and their second grafts were deteriorating due to unknown reasons. In the remaining patients, severe rejection was suspected clinically, but could not be verified histologically.

None of the post-FK 506 biopsies from this group of patients demonstrated rejection; the others showed repair of previous injury, and two of the patients died (see Autopsy Studies, below).

Kidney Rescues. There were five attempts to rescue rejecting kidney grafts. Four of the five had varying degrees of ongoing acute cellular rejection, chronic vascular changes, and interstitial fibrosis. One patient developed an acute humoral rejection after the switch to FK 506 and eventually lost the graft to this process. In total, four of the five rescue attempts were unsuccessful, and examination of the failed grafts revealed changes characteristic of "chronic" rejection, with marked obliterative arteriopathy, interstitial fibrosis, and tubular atrophy. A monoclonal (M, lambda) posttransplant lymphoproliferative disorder was also discovered in the hilum of one of these rejected allografts. This particular patient had been given several steroid recycles and OKT3 prior to the switch to FK 506 in an attempt to rescue his failing graft. Although no pathologic follow-up was available in the fifth patient, retransplantation was required and good results were obtained.

Shortly (within 2 weeks) after the switch from CyA to FK 506, three of these patients developed glomerular capillary loop and polar arteriolar thrombosis. In retrospect, these may have been due to the coadministration of CyA with FK 506. Proximal tubular vacuolization was also seen, but had been there prior to the switch.

"Cluster" Rescues. At the time of this writing, no pathologic follow-up was available in cluster allograft recipients who were switched to FK 506.

Liver Primaries. The pathologic diagnoses of the timed protocol liver samplings or biopsies obtained at the time of
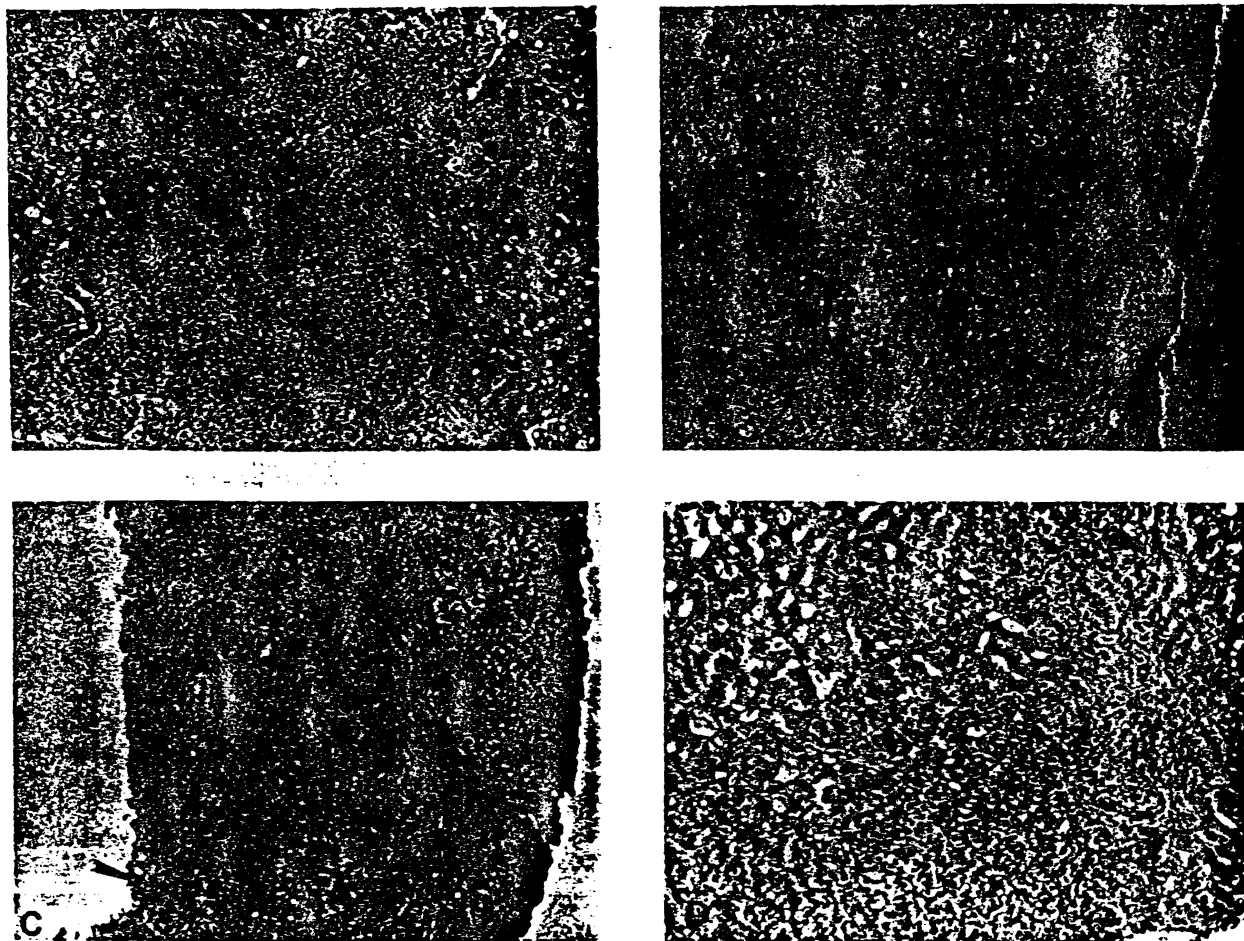
Fig 2. An example of a liver rescue with severe acute cellular rejection. (A) Severe acute cellular rejection 45 days posttransplant. This biopsy was taken after a steroid recycle. (B) The patient was then treated with a 10-day course of OKT3, and this biopsy was obtained at the completion of therapy. Although the portal infiltrate (pt = portal tract) has slightly decreased, there was centrilobular (arrow) dropout and portal-portal bridging and clinically, graft function deteriorated. (C) Fourteen days after the switch to FK 506, the portal infiltrate had largely subsided, but there was mild portal fibrosis (pt = portal tract). Remnants of centrilobular damage were still apparent (arrow). (D) One month later, the liver architecture was returning toward normal, including the centrilobular region (arrow) and no aberrations of liver function tests were present (pt = portal tract).

graft dysfunction in the primary liver allograft recipients and the historic CyA controls is shown in Table 4. Six of the 25 primary FK 506 liver allograft patients had findings in liver biopsy specimens that could be classified as acute cellular rejection and, in five of the six, the changes were mild. The sixth patient developed a more severe form of rejection which will be described in detail later.

Six other primary FK 506 liver recipients had minor histologic alterations in their biopsies that were categorized as "portal reactive change" (Fig 3). In these specimens, there were one to two dozen inflammatory cells located in the interstitia of the portal triads, comprised mostly of mononuclear cells, a few of which appeared as blastic lymphocytes. These cells were intermixed with fewer eosinophils and neutrophils. No subendothelial localization was appreciated, and little or no evidence of bile duct damage was apparent. However, many of the con-

nective tissue interstitial cell nuclei appeared hypertrophic. These findings were most often seen in the protocol samples when there was little or no clinical evidence of liver dysfunction. The only apparent aberration was mild elevations of the gamma glutamyl transpeptidase activity in the serum, which spontaneously resolved without additional immunosuppressive therapy.

Two patients had mild portal eosinophilia and five others had either nonspecific changes or mild "preservation" injury unassociated with significant liver malfunction. A biopsy was inadvertently omitted in one patient. The biopsy results in the FK 506-treated liver primaries and CyA historic controls are shown in Table 4.

Aside from the relatively mild nature of five of the six episodes of the "pathologic" acute cellular rejection, they appeared similar from a histologic perspective to those reported on conventional CyA therapy (Fig 4). Portal vein

Table 3. Pathology Findings in Liver Rescue Patients in Whom CyA or Steroid Toxicity Was the Reason for the Switch or in Whom Rejection Was Suspected by the Clinicians

Patient	Pathology of Previous Failed Grafts	Pre-FK 506 Biopsy Diagnosis	Post-FK 506 Biopsy Diagnosis	Graft Status
J.G.	None	Treated ACR, repair of harvesting	Chronic cholestasis	Functioning
J.B.	GX1; PNF; ischemic	Ischemic injury	Minimal cholestasis	Functioning
P.M.*	None	Mild ACR, sepsis	NA	Functioning
J.C.	GX1; PNF; ischemic	Mild ACR, preservation injury	NA	Functioning
J.M.	None	Severe preservation injury	Repair of preservation injury	Functioning
A.T.*	GX1; duct obstruction	Ischemic injury	NA	Functioning
F.G.	None	Severe preservation injury	Repair of preservation injury	Functioning
C.K.*	None	Mild ACR, reactive changes	Nonspecific changes	Functioning
T.R.	None	Nonspecific changes	Microgranulomas	Functioning
A.M.*	None	NA	NA	Functioning
J.S.*	None	Sepsis, ischemic injury	Repair of ischemic injury	Functioning
D.M.*	None	NA	Severe ischemic injury	Died
G.S.	GX 1; PNF; ischemic	Mild ACR, preservation injury	Cholangitis, sepsis	Died: sepsis ARDS

Abbreviations: PNF, primary nonfunction; GX, graft; ACR, acute cellular rejection; NA, not available; ARDS, adult respiratory distress syndrome.
* Patients switched to FK 506 because of renal failure (CyA toxicity) or steroid complications.

phlebitis and bile duct damage were the hallmark features. The exceptions were the presence of marked Kupffer cell hypertrophy and portal eosinophilia. Also, phlebitis of the portal and terminal hepatic veins was more noticeable in the FK 506 patients with definite rejection.

One patient developed a particularly severe form of rejection which deserves special attention because of its unique histologic characteristics (Fig 5). At day 6, this patient had findings typical and diagnostic of mild acute cellular rejection, although many eosinophils were noted.

By 13 days, liver function had worsened, but a kinked biliary stent was found and bacteria were cultured from the liver tissue. A pathologic diagnosis of ongoing cellular rejection and cholangitis was rendered. Despite treatment with antibiotics and removal of the stent, liver functions continued to deteriorate and a repeat biopsy showed changes of severe acute cellular rejection with arterial subendothelial inflammation, portal interstitial hemorrhage, and centrilobular hepatocellular dropout. The unique finding was the presence of an arteritis and marked

Table 4. Biopsy Pathology Diagnosis in Specimens Obtained During First Month From Patients Treated From the Outset With FK 506 Versus Historic Controls Treated With CyA

Primary FK 506		Controls	
Patient	Pathology Diagnosis (Days posttransplant)	Patient	Pathology Diagnosis (Days posttransplant)
A.D.	Mild focal ACR (11)	T.F.	Moderate ACR (4, 13)
C.A.	Portal reactive change (14)	G.K.	FG, arterial thrombosis (14)
D.B.	Portal reactive change (12)	L.K.	Mild ACR (10)
I.C.	Mild ACR (6); Moderate ACR, cholangitis (13); severe ACR (27)	L.K.	Mild ACR (9)
J.C.	Minimal portal eosinophilia (8)	H.S.	Moderate preservation injury (4)
D.F.	Portal reactive change (11)	B.Z.	Mild preservation injury (5)
G.G.	Portal reactive change (8)	J.H.	Mild ACR (11)
T.H.	Mild ACR (3), mild ongoing ACR (14)	W.E.	Moderate ACR (7)
N.H.	NSC (3, 11)	S.C.	NA
S.K.	Mild portal eosinophilia (10)	L.C.	NA
S.M.	Portal reactive change (8)	L.D.	Mild ACR (30)
S.M.	Mild ACR (10)	M.M.	NA
A.M.	Mild ACR (11)	Z.G.	Moderate ACR (9)
D.M.*	Portal reactive change (14)	H.I.	FG, arterial thrombosis, mild-moderate ACR (4)
S.R.	NSC (11)	C.K.	NA
D.R.	Mild preservation injury (6, 10)	D.H.	Moderate ACR (11)
J.S.	NA	J.G.	Mild ACR, partially treated (9)
H.S.	Mild ACR (7)	M.T.	Moderate ACR (10)
M.S.	Mild steatosis (13)	E.M.	Moderate ACR (20)
K.W.	Mild preservation injury (12)	B.E.	Severe preservation injury (12)

Abbreviations: ACR, acute cellular rejection; FG, failed graft; NA, not available; NSC, nonspecific changes.
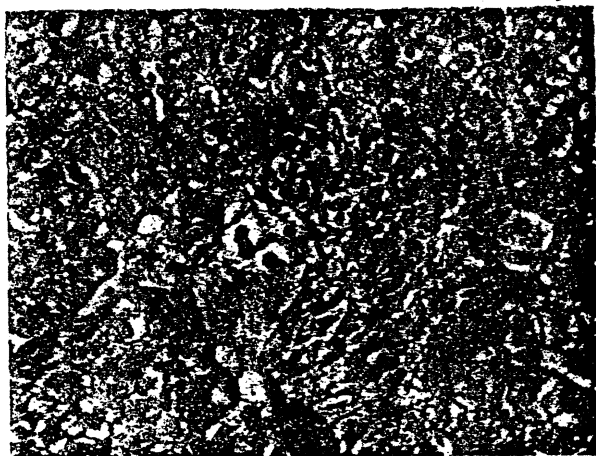* Patient died.

Fig 3. An example of portal reactive change. Although there is a mild portal infiltrate, no evidence of duct or venular endothelial damage is seen. Clinically, this change was associated with mild elevations of the canalicular enzymes that spontaneously resolved without additional therapy.

eosinophilia, constituting greater than 50% of the intense inflammatory infiltrate, findings which were uncommonly encountered in rejection under CyA.

Among the historic controls, 12 patients had histologically verified acute cellular rejection, which varied from mild (n = 6) to moderate (n = 6). A noticeable difference between the two groups was the severity of the portal infiltrate, which was less in the FK 506 patients when compared with the CyA-treated controls. Two patients in the control group lost grafts from hepatic arterial thrombosis, two had preservation injury, and no biopsies were available in four.

Other liver biopsy findings in the primary FK 506 patients included mild hepatocyte swelling and thickening of the plates in zone 1 of the acinus, Kupffer cell granulo-
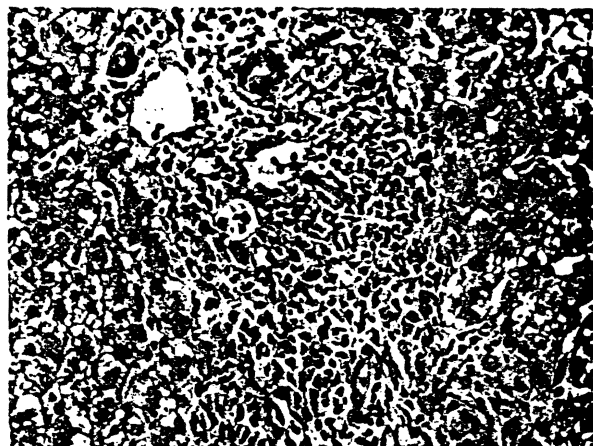

Fig 4. An example of mild acute cellular rejection in a primary liver recipient under FK 506 therapy. Focal bile duct damage and venous infiltration (arrows) are the characteristic features.

mas (n = 10) and sinusoidal cell hypertrophy (Fig 6). No fungi, acid-fast bacteria, CMV viral antigens, or viral inclusions could be identified in the small granulomas.

Kidney Primaries. There were three patients whose kidney grafts were placed under FK 506 therapy. All three had prior liver grafts and therefore had been on CyA. Two of these patients were also failed FK 506 kidney rescue attempts. One of these patients died from severe pneumonia and sepsis after hepatic retransplantation for B viral hepatitis. At autopsy, no rejection was seen in the kidney graft. The second patient lost her primary FK 506 renal graft from a mycotic (Candida) aneurysm and thrombosis at the arterial anastomosis. The renal parenchyma showed widespread polar arteriolar thrombosis, presumably from fungal seeding of the arterial blood. The last patient had a renal biopsy 42 days after placement of the new kidney; it showed moderate acute cellular rejection which responded to additional steroid therapy.

Multiorgan Primary. There was one patient who received separate liver, kidney, pancreas, and small intestinal grafts under FK 506. Biopsies of the liver at 6, 18, and 30 days were unremarkable. However, the pancreas graft was removed at 30 days because of arterial thrombosis. The graft had mild interstitial fibrosis, accompanied by a mild mononuclear infiltrate and areas of fat necrosis. There was also evidence of fat necrosis in the abdominal fat, including that attached to the intestines. Several small arteries in the pancreas and intestines, near areas of fat necrosis, showed focal mural necrosis.

Heart Primaries. Two patients have had pathologic follow-up after heart transplantation initiated under FK 506. At 1 week, there was no evidence of lymphocytic inflammation, but by 2 weeks there was a mild perivascular lymphocytic infiltrate, some of which was blastic. No myocyte necrosis was seen, but eosinophils were noted within the perivascular space and scattered elsewhere in the interstitium. As in the liver primaries, rebiopsy 1 week later showed no evidence of inflammation.

Autopsy Studies

There were six deaths in patients under FK 506 therapy, and five of the six autopsies were available for review at the time of this writing, except for neuropathology. The treatment groups, survival, duration of FK 506 therapy, and cause of death are listed in Table 5. Four of the six patients were liver rescues: one had acute cellular rejection, one lost a prior liver graft from primary nonfunction and his second graft was rapidly deteriorating, and a third had pancreatitis, which prompted the switch, in an attempt to lower the steroid therapy. The last rescue patient was the one withdrawn from FK 506 therapy because of mistaken diagnosis.

Five of the six patients suffered from multiple intraoperative or postoperative complications, which made evaluation of autopsy findings difficult. Rather than describe in detail the findings in each case, the pathologic changes in
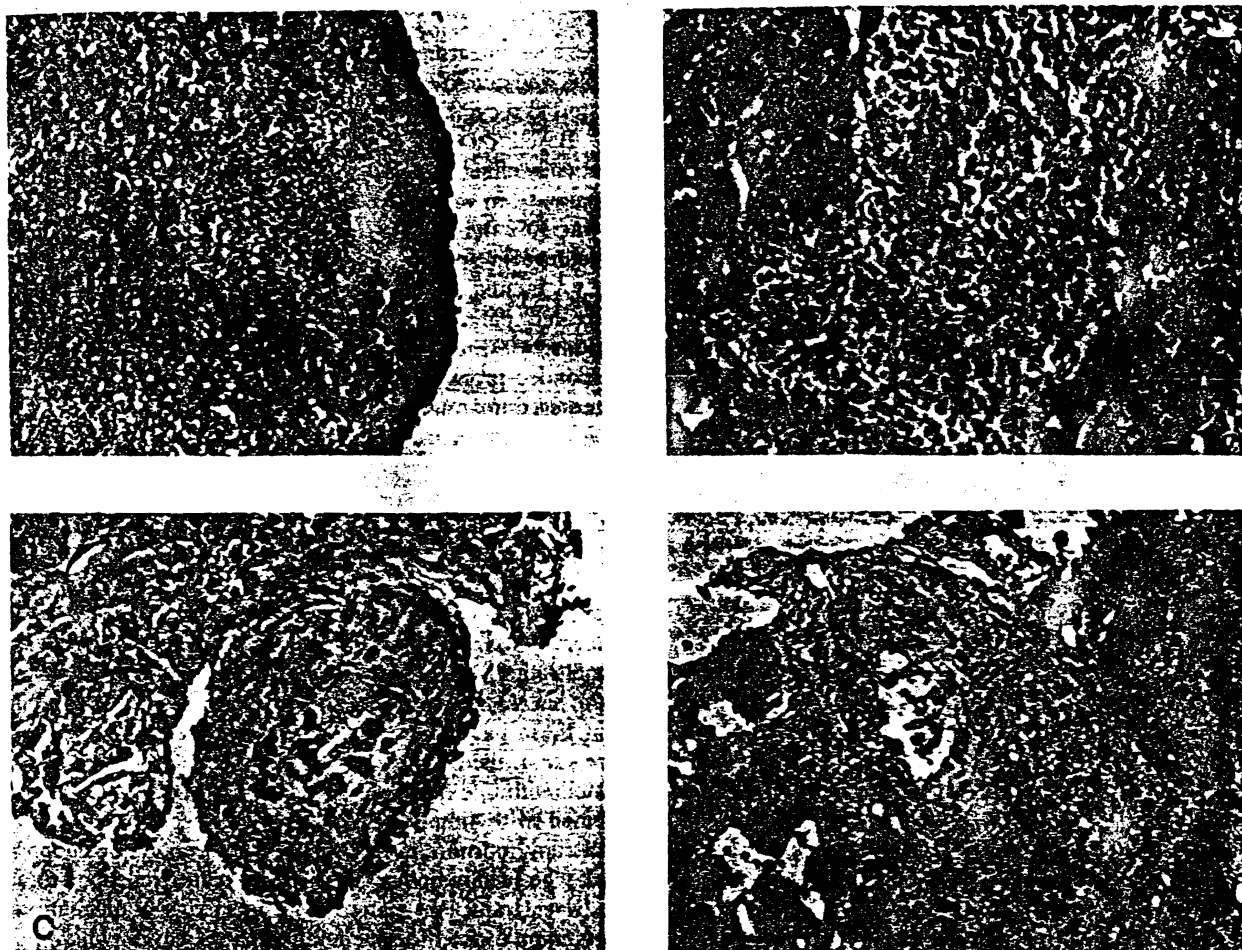
Fig 5. Severe rejection in a primary liver recipient under FK 506. (A) Six days after transplantation, a biopsy revealed changes characteristics of acute cellular rejection. (B) Two weeks later, the portal infiltrate had increased and bile duct damage was evident (arrow). (C) An inflammatory arteritis was also present in the same biopsy as shown in panel B, as was (D) marked phlebitis of the terminal hepatic venule.

organ systems which are potential sites of FK 506 toxicities are listed in Table 6. Most of the liver specimens showed centrilobular necrosis and/or congestion and hemorrhage, consistent with agonal hypotension. The kidneys showed varying degrees of tubular vacuolization, most noticeable in the proximal portions. Three of the patients had acute pancreatitis and focal necrosis of segments of the pancreatic arteries. There were multiple possible etiologies for the pancreatitis and in two patients, the pancreatitis was diagnosed clinically prior to the switch to FK 506. Focal necrosis of the media of small and medium-sized muscular arteries was seen in the same three patients and was limited to the pancreatic and peripancreatic intestinal fat vascular beds, which also showed evidence of fat necrosis. One patient had arterial necrosis in a vessel in the perirenal fat at the pelvic-ureter junction of the left kidney. The area was thought to have been traumatized while completing the lower venal caval anastomosis during the difficult transplant operation, when 60 U of blood were consumed.

DISCUSSION

The efficacy of FK 506 as an immunosuppressive agent was demonstrated in both the "rescues" and "primary" treatment groups. Since our experience with the extrahepatic organs is limited, the following comments are largely restricted to liver allograft recipients. The ability of FK 506 to slow or stop, and possibly reverse, the progression of the alterations associated with the early phases of "chronic" rejection in over 50% of the patients with this diagnosis was the most surprising finding. Although a longer period of follow-up is needed to confirm this observation, in our experience, any response in patients with elevated canalicular enzymes and severe bile duct damage on biopsy is unusual. Most of those who did not respond had already lost more than 50% of their bile ducts and had obliterative arteriopathy confirmed by examination of the allograft hepatectomy specimens.

FK 506 was also effective in the treatment of acute cellular rejection, when used in a manner similar to ste-
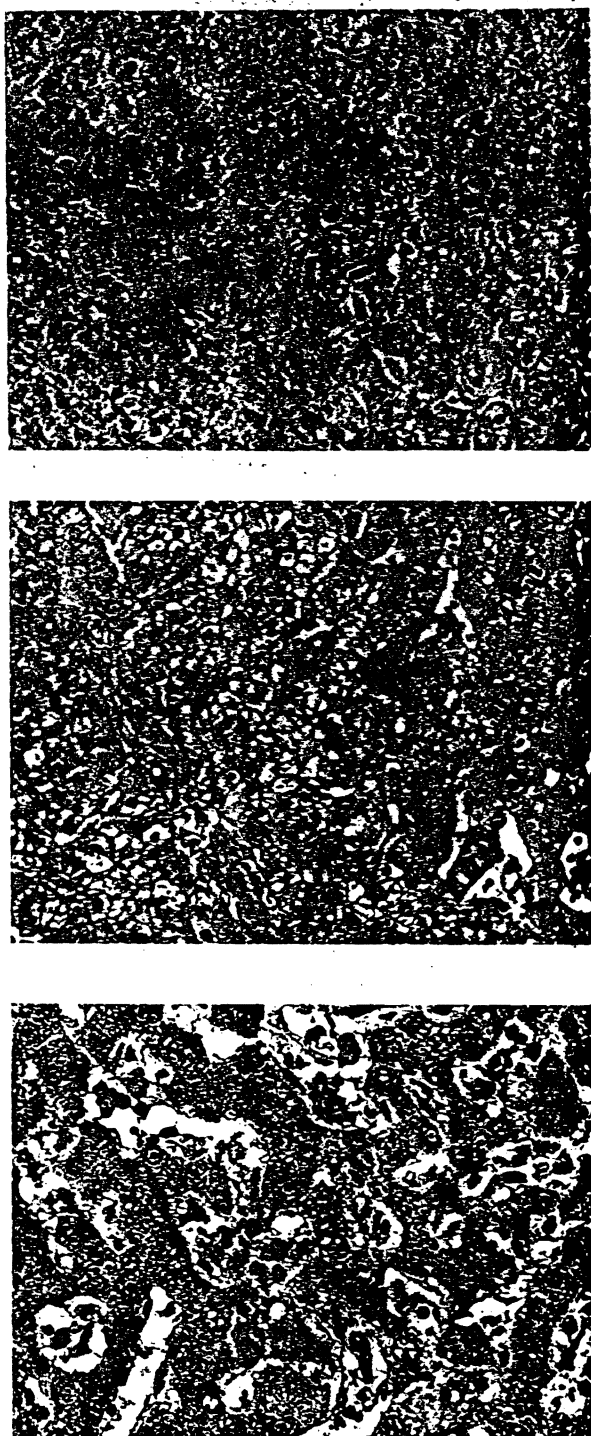
Fig 6. Other findings in liver biopsies from patients treated with FK 506 included (A) small Kupffer cell granulomas and microabscesses (arrows), although no microorganisms could be detected, (B) mild hydropic swelling of periportal hepatocytes (arrows), and (C) sinusoidal cell hypertrophy.

roids or OKT3, but was seemingly more potent. The reversal illustrated in Fig 2 was the most dramatic example, and occurred in a patient who had been resistant to a steroid recycle followed by OKT3.

Based on protocol biopsy evaluation, FK 506 was equally effective as preventive therapy in the primary liver patients, in whom the incidence of acute cellular rejection was 30% during the first postoperative month. This percentage is approximately half that seen in the historic CyA-treated controls (60%). A similar figure for CyA-treated patients has been reported at several institutions.[18,19] Furthermore, all but one of the episodes responded promptly to a steroid bolus, and no OKT3 was required in any patient.

The histologic appearance of acute cellular rejection of the liver under FK 506 therapy was similar to that seen in the CyA-treated patients. The characteristic features were a predominantly mononuclear portal tract infiltrate, combined with evidence of bile duct and venous endothelial infiltration and damage. However, eosinophils were quite prominent in several cases, marked sinusoidal cell hypertrophy was often a conspicuous finding, and the venous infiltration, when present, was more apparent. Although the histologic changes attributed to acute cellular rejection in these patients may raise the consideration of a drug reaction, the triad of mononuclear portal infiltrate associated with bile duct and venous endothelial damage, combined with timing of reaction and response to steroid therapy, is more characteristic of rejection. Eosinophils may be seen in both a rejection and a drug reaction but, in a liver transplant patient, the former is a much more common cause of tissue and peripheral eosinophilia.[20]

Based on the information to date, it was difficult to attribute any specific morphologic finding to FK 506 toxicity. Minor alterations that were seen in association with the agent were mild periportal hepatocellular swelling, Kupffer cell hypertrophy, and mild tubular vacuolization of the kidneys. The small Kupffer granulomas present in the primary patients were not as conspicuous in the rescue group. Although some of these morphologic alterations have been associated with hepatic toxicity of other macrolides[21] (FK 506 is a macrolide), others have not, and cholestasis was generally not prominent, as reported in nongrafted livers with erythromycin-associated liver injury. Nevertheless, neither organ was the site of any morphologic or functional alteration, which might cause the use of FK 506 in humans to be questioned.

The vascular necrosis and induction of a diabetic state in animals were the most worrisome changes that have been ascribed to FK 506 toxicity.[8-12] The vascular lesion observed in dogs was best described as focal medial necrosis and not true vasculitis, since an inflammatory component was rarely encountered. However, the nature of the lesion is puzzling because an indistinguishable lesion was found in control animals, by us[6,8] and by Ochiai et al,[14] with equal frequency and severity. Although the morphologic changes are far from specific, arterial necrosis can be seen

Table 5. Treatment Groups, Survival, Duration of Therapy, and Cause of Death In Patients Who Died While on FK 506 Therapy

Patient	Treatment Group	Survival (d)	Duration of FK 506 Therapy (d)	Cause of Death
D.M.	Liver primary	14	14	Cardiac arrest
M.S.*	Liver primary	10	10	Cerebellar hemorrhage
A.N.†	Liver rescue	152	5	Necrotizing pneumonia
G.S.	Liver rescue	28	13	Sepsis, ARDS, pancreatitis
L.S.	Liver rescue	17	6	Sepsis, ARDS, DIC
D.M.	Liver rescue	30	20	Sepsis

Abbreviations: ARDS, adult respiratory distress syndrome; DIC, disseminated intravascular coagulation.
* Patient not included in primary list reported in Table 4.
† Patient removed from FK 506 after liver failure from fulminant hepatitis B.

in rodents with the administration of dopaminergic agents,[22] which were received by most of the patients who died while on FK 506.

In humans under FK 506 therapy, arterial necrosis was seen in four patients; the arterial necrosis was limited to the pancreatic and peripancreatic intestinal tissue in three patients with acute pancreatitis. Although arterial necrosis as a consequence of pancreatitis in humans had been reported by Rich and Duff in 1938,[23] mention of this lesion has all but disappeared from the modern pathology literature. The only evidence of arterial damage outside this area was encountered in the perinephric fat near the pelvic-ureter junction of the left kidney, which serves as the operative bed for the lower venal caval anastomosis. To date, no arterial necrosis has been detected in the heart, kidney, liver, spleen, or other extraabdominal organ.

The pancreas has also been cited as a possible target for serious FK 506 toxicity.[9-14] Of the six patients who died, four had acute pancreatitis at autopsy; although in two the pancreatitis was present before the switch to FK 506. In those without pancreatitis, the islets were intact and no consistent morphologic alteration was noted. Further-

more, no specific pancreatic endocrine or exocrine functional defect has been noted in the patients maintained on this agent (D.H. Van Thiel, personal communication).

Finally, one is faced with the task of rendering an overall interpretation of the findings reported above. It seems fairly clear that FK 506 is a potent immunosuppressive agent capable of effectively treating established acute (and even the early phases of) chronic rejection. FK 506 is somewhat unique in that it can be used as preventive or primary therapy as well as a "rescue" agent and appears to be superior to all antirejection drugs in the present arsenal. To date, any potential acute toxicities have not been blatant or consistent enough to recognize a pattern of association with the drug. Although vascular necrosis was seen in several patients at autopsy, it was generally limited to the pancreatic and peripancreatic intestinal tissues, and associated with acute pancreatitis or vascular trauma. Using Irey's criteria[24] for analyzing possible adverse drug reactions, from a conservative perspective, we can say at this point that an association between these two complications is possible, but not likely. The encouraging results to date endorse continued clinical trials, from which more

Table 6. Histologic Findings In Organs That are Potential Sites of FK 506 Toxicity In Patients Who Died While on Therapy

Patient	Liver	Kidney	Pancreas	Blood Vessels	Other
D.M.	Microabscesses; no rejection	Mild arterial and arteriolonephrosclerosis; Fabray's heterozygote	None	Atherosclerosis of LAD; hypertensive pulmonary arteriopathy	Severe coronary artery atherosclerosis
M.S.	Focal infarcts and congestion; minimal rejection	Marked tubular vacuolization; congestion	None	Focal mural necrosis of arteries in perinephric fat of left renal pelvis	Cerebellar hemorrhage
A.N.*	Centrilobular congestion and hemorrhage	Mild tubular vacuolization; no rejection	Acute pancreatitis with acinar dilatation and focal arterial necrosis	Focal thrombosis and necrosis of pancreatic arteries	Severe necrotizing pneumonia (polymicrobial)
G.S.	Congestion and focal mild rejection	Minimal tubular vacuolization; changes of ATN	Autolysis with focal pancreatitis; mild interstitial fibrosis	Infarcted colonic epiploic with necrotic artery	Subhepatic abscess; organizing diffuse alveolar damage of lungs
L.S.	Congestion; mild focal rejection	Focal infarct; marked tubular vacuolization; occasional polar arteriolar thrombosis	Acute hemorrhagic pancreatitis with arterial necrosis and thrombosis	Intraluminal fibrin thrombi in pulmonary arteries, submucosal veins of colon and renal polar arterioles	Large pulmonary thromboembolus

Abbreviations: ATN, acute tubular necrosis; LAD, left anterior descending coronary artery.
* Patient was taken off FK 506 before death because of mistaken diagnosis of hepatitis B.

information on the effectiveness and long-term safety of FK 506 can be obtained.

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