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ACUTE REJECTION OF LIVER GRAFTS

G. Gubernatis, M.D., Ph.D.

Medizinische Hochschule Hannover
Hannover, Germany

R.G. LANDES COMPANY

909 Pine Street, Georgetown, TX 78626
or
P.O. Box 4858, Austin, TX 78765
Phone: 512/863-7762 • FAX: 512/863-0081

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CHAPTER 3

ACCELERATED REJECTION OF LIVER GRAFTS WITH PARTICULAR ATTENTION TO FK506

Ignazio Roberto Marino, Thomas E. Starzl, John J. Fung

INTRODUCTION

Vascularized organ transplants can be rejected by either humoral or cell mediated mechanisms that are not mutually exclusive. This is not unexpected given the relation of both arms of the immune system. Cell mediated rejection in naive recipients of allografts is a first set immune event, generally requiring days to development of cellular rejection. Yet, donor specific antibodies can be detected in allografts which are undergoing first set rejection. On the other hand, proliferative and cytotoxic donor specific T cell responses can be detected in vitro in animals which have been presensitized to donor antigens. Isolated reports of accelerated cell mediated rejection exist in sensitized recipients, (Eichwald et al 1985) but overall this is uncommon, and the focus of this chapter will be to discuss the role of antibodies in accelerated liver transplant rejection.

CHARACTERIZATION OF ANTIBODIES INVOLVED IN REJECTION

The phenomenon of hyperacute rejection was first recognized as being related to preformed antibodies in kidney allografts transplanted in ABO incompatible combinations. These findings were also noted in recipients bearing lymphocytotoxic antibodies, as a result of pregnancy, previous blood transfusions or failed grafts. The importance of avoiding transplantation of kidney allografts into recipients bearing preformed antidonor antibodies was noted in many early reports describing hyperacute rejection (Starzl 1964, Terasaki et al 1965, Kissmeyer-Nielsen et al 1966, Williams et al 1968, Starzl et al 1970). The impact of preformed antibodies in other vascularized organ allografts is variable, with the heart being susceptible to antibody rejection, (Rose 1991) while the liver is less vulnerable. (Starzl 1969, 1974, 1987, Garnier 1965, 1970, Cordier 1966, Calne 1967a, b, 1969, 1970a, Peacock 1967, Lempinen 1971, Mazzoni 1971, Iwatsuki 1981, 1984, Houssin 1985,

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1986, Orosz 1986, Gordon 1986a, Gubernatis 1987, Knechtle 1987a, b, Gugenheim 1988a, b, Demetris 1988, 1989, Davies 1989, Suminoto 1991, Furuya in press).

In xenotransplantation, preformed antibodies occur naturally, without prior exposure to antigens from other species of animals. These antibodies are capable of mediating a brisk hyperacute rejection (Perper 1966a, b, Calne 1970b, Giles 1970). It is thought that these naturally occurring antibodies are the results of exposure to common environmental antigens (Marino 1990, First 1992). These antibodies react with glycolipids and glycoproteins on the cell surface of the xenograft.

The class of immunoglobulins involved in hyperacute rejection depends on the antigenic determinants which the antibodies recognize. Lymphocytotoxic antibodies to MHC determinants, as a result of prior transfusion or failed allografts, are often of the IgG class. Both xenoantibodies and, to a great extent, ABO isoagglutinins are of the IgM class, but high titers of IgG can be induced by sensitization. The titer of preformed xenoantibodies and ease of inducing xenoantibodies was proposed to be able to provide an assessment of phylogenic diversity (Landsteiner 1962), hence the designation of discordant and concordant combinations (Calne 1970b).

In the discordant xenotransplant combination, IgM and IgG can be shown to exist in high titers, such as in the guinea pig-to-rat combination (Gambiez 1990), the pig-to-Rhesus monkey combination (Fischel 1990) and the pig-to-dog combination (Giles 1970, Makowka 1987). In concordant xenotransplant combinations IgM may exist, usually in low titers, such as in the hamster-to-rat combination (Valdivia 1987a), the fox-to-dog combination (Brendel 1977), and baboon-to-rhesus monkey combination (Marquet 1978). In both combinations, sensitization following transplantation generally results in an abrupt rise in the IgM titer followed shortly by an increase in the IgG titer. In a few models, other classes of immunoglobulins besides IgG and IgM, can cause hyperacute rejection. In some of our previous experimental studies, IgA and IgG were able to initiate hyperacute rejection in a kidney transplant model (Marino 1990, 1991).

PATHOPHYSIOLOGY OF ANTIBODY MEDIATED REJECTION

Independent of the nature of immunoglobulin class of preformed antibody involved in triggering antibody mediated rejection, the pathophysiology of the acute inflammatory response is similar. Preformed antibodies trigger rejection by their deposition on the endothelium of the vascularized graft. These antibodies in turn activate complement, which in turn activates a characteristic cascade of inflammatory, nonspecific mediators, such as recruitment of polymorphonuclear leukocytes, platelet adhesion and degranulation, followed by intravascular thrombosis (Starzl 1964, Kissmeyer-Nielsen 1966, Williams 1968, Giles 1970) (Figs. 1 and 2).

Complement activation can occur via the classical and alternative complement pathways. In the classical pathway, the C1q component of C1 is activated following binding to the Fc region of IgM and IgG. This in turn results in C1r and C1s activation and the generation of the C1qrs protease complex, in turn leading to C4 and C2 cleavage, producing the C3 convertase, C4b2a complex. C3 is then cleaved to produce the biologically active components, C3a and C3b. In the alternative pathway, complement can be activated via IgA, IgE and other nonimmunologic factors such as polysaccharides and bacteria. Activation of C3 occurs via nonspecific cleavage to generate C3b.

The common pathway of complement activation is via the C5 cleavage which generates C5b which in turn leads to the assembly of the C5b-C9 membrane attack complex. This membrane attack complex binds to the cell surface resulting in a porous membrane which is susceptible to osmotic pressure leading to either cell damage or cell death.

Cell damage also occurs by activation of other inflammatory pathways. Reactive oxygen metabolites, prostaglandins and cytokines can be generated by the degradation products of complement activation (Forbes 1982). Polymorphonuclear leukocytes and macrophages are attracted to the site of inflammation via the C5a fragment, which results in the release of lysosomal enzymes and resultant cell damage (Forbes 1984). C3b also enhances adhe-

sion of these cells to damage cells. C3b also promotes binding of platelets which may lead to degranulation and release of vasoactive substances, such as serotonin and histamine, both increasing vascular permeability.

Thrombosis of the microvasculature is enhanced by the loss of membrane associated heparin sulfate, from the endothelial cell. The release of tissue factors from injured cells also promotes thrombosis.

The importance of complement in the pathophysiology of antibody mediated rejection is shown in studies in which complement is depleted. Cobra venom inactivates the C3 component, resulting in paralysis of the complement system (Kemp 1982, Adachi 1987, Johnston 1992). Hasan and coworkers have been able to obtain long-term survival of xenografts during treatment with cobra venom factor (Hasan 1992).

SUSCEPTIBILITY OF THE LIVER TO ANTIBODY MEDICATED REJECTION

Transplanted livers have been reported to be relatively resistant to both cell mediated and antibody mediated rejection (Starzl 1969, 1974, 1987, Garnier 1965, 1970, Cordier 1966, Calne 1967a, b, 1969, 1970a, Peacock 1967, Lempinen 1971, Mazzoni 1971, Iwatsuki 1981, 1984, Houssin 1985, 1986, Gordon 1986a, Orosz 1986, Gubernatis 1987, Knechtle 1987a,b, Gugenheim 1988a,b, Demetris 1988, 1989, Davies 1989, Suminoto 1991, Furuya, in press). Liver allografts were shown to have prolonged survival when compared to organs and tissues, when immuno-

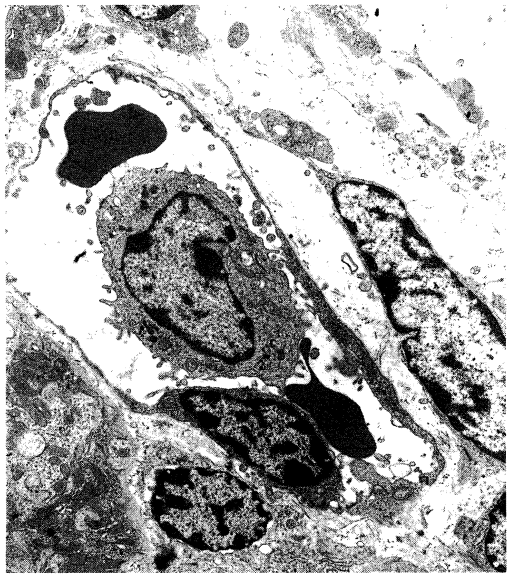

Fig. 1. Electron photomicrograph of a xenografted kidney (pig-to-rabbit) tissue sample obtained 15 minutes after reperfusion. In the peritubular capillary a monocyte, erythrocytes and platelets (showing some adherence to the endothelium) can be observed. The interstitium is edematous (x4600). (Reprinted from : Histopathological, immunofluorescent, and electron-microscopic features of hyperacute rejection in discordant renal xenotransplantation, by Marino IR et al, in Xenotransplantation, Cooper DKC, Kemp E, Reemtsma K, and White DJG eds., Springer-Verlag, Berlin, Chapter 12, Fig. 12.6, p.214, 1991).

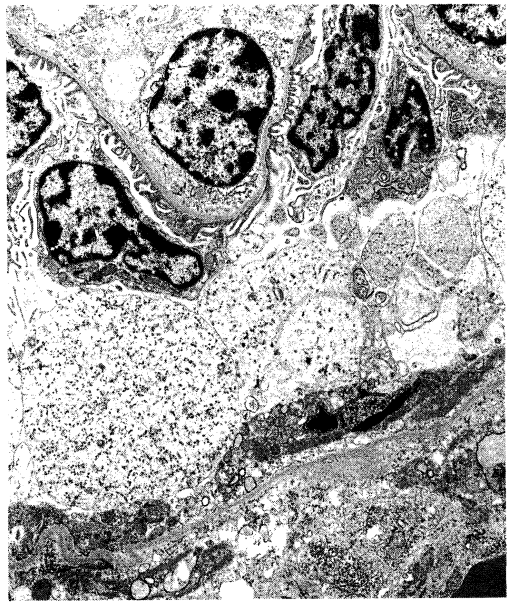

Fig. 2. Electron photomicrograph of a xenografted kidney (pig-to-rabbit) tissue sample obtained 120 minutes after reperfusion. The urinary space of the glomerulus is completely occupied by cell debris, and the epithelial cells of the Bowman's capsule are dramatically damaged (x4600). (Reprinted from: Histopathological, immunofluorescent, and electron-microscopic features of hyperacute rejection in discordant renal xenotransplantation, by Marino IR et al, in Xenotransplantation, Cooper DKC, Kemp E, Reemtsma K, and White DJG eds., Springer-Verlag, Berlin, Chapter 12, Fig. 12.15, p.223, 1991).

suppression is not given. In fact, several groups have demonstrated spontaneous liver allograft survival in the porcine model, without immunosuppression (Calne 1967a, b, Peacock 1967, Lempinen 1971, Mazzoni 1971).

A number of observations on the effect of the presensitized state on liver transplant survival suggests that the liver is less susceptible to antibody mediated rejection. Starzl and coworkers have noted resistance of human liver allografts to humoral rejection (Starzl 1974, Iwatsuki 1981, 1984). This resistance is sufficient to allow transplantation under conditions which would be unacceptable for kidneys. It has been evident that hyperacute rejection of the liver does not commonly occur with lymphocytotoxic presensitized states, while occurring more frequently with ABO-incompatible liver transplants. While a penalty accrues to those patients receiving ABO-incompatible liver allografts, there were a surprisingly large number of such grafts that were successful (Starzl 1974, 1987, Iwatsuki 1981, 1984, Gordon 1986a, Demetris 1988, 1989, 1992, Rego 1987, Gugenheim 1989, 1990, Fischel 1989). The pathology of the ABO-mismatched livers which failed revealed evidence of humoral rejection, with hemorrhagic necrosis and intraparenchymal coagulation (Demetris 1988, 1989). The long-term complication of ABO-incompatibility may also manifest with biliary tract complications (Starzl 1987, Demetris 1989, Sanchez-Urdazpal 1991). This pattern of rejection is rarely seen in liver allografts in which a positive lymphocytotoxic crossmatch occurs. As would be predicted, the pattern of xenoantibody rejection of the liver is much more similar to that of ABO-incompatibility than for MHC specific sensitization. In animals receiving a discordant liver transplant, IgM and IgG deposition on the vascular endothelium and sinusoids is also accompanied by complement activation. Vascular thrombosis due to platelet aggregation leads to hemorrhagic necrosis, with little or no cellular infiltrates.

The relative resistance of the liver allograft to antibody mediated rejection appears to confer some protection systemically, presumably by neutralizing or reducing the titer of lymphocytotoxic antibodies. One of the possible explanations for this unique capacity of the liver to withstand antibody attack is the observation that the liver is a source of soluble MHC Class I antigens (Davies 1989, Suminoto 1991). These soluble MHC antigens may neutralize the circulating anti-donor antibody (Houssin 1985, 1986, Orosz 1986, Gugenheim 1988a, b). In addition, the liver serves as a rich reticuloendothelial organ, removing circulating immune complexes by actions of the Kupffer cell which lines a nonendothelial vascular network which is less susceptible to vasoactive substances than end-organ vessels such as seen with the heart and kidney.

Extracorporeal donor-specific liver hemoperfusion can reduce the level of cytotoxic antibodies in hypersensitized rats (Orosz 1986, Gugenheim 1985, 1988, Kamada 1988). This finding was the premise to utilize the liver allograft to protect the subsequent kidney allograft in patients with preformed donor-specific antibodies (Fung 1988, Flye 1990). The lymphocytotoxic crossmatch in patients with preformed antibodies will often convert from positive to negative following liver transplantation. When this occurs, placement of a kidney allograft from the same donor will often result in prevention of hyperacute rejection of the kidney (Fung 1988, Flye 1990). It should be noted that this protection is not universal, and cases of rejection of the kidney following liver transplantation have been reported (Starzl 1989).

In spite of the unique immunologic properties of the liver, reports of accelerated rejection of the liver have been published (Hanto 1987, Bird 1989, Starzl 1989, Karuppan 1991). Knechtle and coworkers noted that the resistance of liver allografts to rejection could be overridden by presensitization with skin grafts (Knechtle 1987a,b). In 9 of 10 presensitized rat recipients, hyperacute rejection was noted, and immunofluorescence could detect IgG and complement in the sinusoids and perivascular tissues. Murase and coworkers also noted antibody mediated rejection in an arterialized rat liver transplant model if

the recipients had received at least four skin grafts from the donor, and if the transplant was performed within nine weeks (Furuya in press). In a porcine model of acceptance of liver allografts, the liver allograft could be induced to be uniformly rejected when the recipient pigs were presensitized, either by prior skin grafting or kidney transplantation (Calne 1969). In a primate study, Gubernatis and coworkers demonstrated that hyperacute or accelerated rejection of the liver could be observed (Gubernatis 1987).

The first report of hemorrhagic necrosis following human liver transplantation was by Williams and Hume, more than 25 years ago (Hume 1969). In 1987, Hanto and coworkers published a case report of hyperacute rejection in a strongly positive T cell crossmatched recipient (Hanto 1987). The pattern of rejection in this patient was notable for a lack of antibody and complement in the sinusoids or portal vessels. The adverse effect of lymphocytotoxic antibodies in liver allograft survival in human liver transplantation may have been masked by the immunosuppression which has been utilized in most immunosuppressive regimens. In contrast to the early reports on the relative lack of effect of a positive crossmatch on liver allograft survival (Iwatsuki 1981, 1984), Takaya and coworkers noted that there was an increased graft loss in these patients (Takaya 1992a). The principle difference in the two populations was the utilization of high dose steroids in the former group, while low dose steroids (20 mg/day) were utilized in the latter group. In fact, when the steroid doses were increased in subsequent positive crossmatch liver recipients, the incidence of graft loss decreased.

TREATMENT OF THE PREFORMED ANTIBODY STATE

Since 1956 a number of treatments have been proposed as methods to reduce preformed antibodies, or to minimize the damage which would be antibody mediated (Clark 1964, 1966, Gerwurz 1966, Rosenberg 1969, 1971a, b, Shons 1970, 1973, 1974a, b, Bier 1970, Moberg 1971, Hawkins 1971, Kux 1971, Merkel 1971, Baldamus 1973, Winn 1973, Kemp 1982, 1976, 1977, 1987a, b, Shapiro 1990a). These include: antibody depletion (including specific and nonspecific antibody removal), interruption of the clotting cascade, and interruption of the complement cascade.

Several antibody depletion techniques have been utilized in the past 30 years. The first report of thoracic duct drainage (TDD) was in 1964 (Franksson 1964, 1967, 1976). A number of series of patients treated with TDD in the pre-cyclosporine era, undergoing kidney transplantation, have been reported (Sonoda 1966, Murray 1968, Tilney 1968, 1970, Archimbaud 1969, Martelli 1970, Sarles 1970, Estevam 1974, Walker 1977, Johnson 1977, Starzl 1979a, b, Koep 1980, Ono 1987, Ohshima 1981, 1987, 1988, 1989c, d). In these series, it was noted that the level of lymphocytotoxic antibodies fell during the course of TDD. However, with the advent of cyclosporine, the cumbersome use of TDD has been largely abandoned.

Plasmapheresis has also been utilized to lower preformed antibody levels. This technique has also been combined with cyclophosphamide, an antiproliferative agent (Marino 1993), in highly sensitized patients receiving kidney transplants (Taube 1984a, b). Its use in the posttransplant period to reverse established antibody rejection has met with varying success (Cardella 1977, Naik 1979, Rifle 1979, Kirubakaran 1981, Power 1981). The cost and variable efficacy has also led to abandonment of this procedure.

A relatively newly described method to lower antibody levels is the ability of the *Staphylococcus aureus* Protein A to bind to the Fc receptor of IgG (Forsgren 1966). The application of this principle to column technology has allowed Protein A to be bound covalently to cyanogen bromide activated Sepharose B, creating a solid phase immunoabsorbant. It has been possible to deplete serum IgG levels by 75-90% with a single treatment (Shapiro 1990a). Few clinical trials have been performed both in Europe and in the United States, and the results have also been variable (Palmer 1987, 1989, Gjorstrup 1988, Shapiro 1990b.)

The use of antigen-specific antibody depletion has centered on the pre-perfusion of a donor vascularized organ prior to transplan-

tation. Reports by Starzl and coworkers with pre-perfusion of liver, kidneys and spleen by heterotopic ex vivo perfusion of the recipient, was shown to immediately decrease the levels of preformed antibodies (Giles 1970). This allowed prolonged graft survival in situations which normally would lead to rejection.

Other techniques to control the damage mediated by preformed antibodies have focused on abrogating the inflammatory mediator response (Makowka 1987), interrupting the clotting cascade (Giles 1970, 1971, Kux 1971, Moberg 1971, Kemp 1976, 1977, 1982), or preventing complement activation (Moberg 1971, Kemp 1982, Adachi 1987, Johnston 1992, Hasan 1992). Unfortunately, none of these techniques have resulted in clinical applications. Inhibition of soluble mediators with antiplatelet activating factors have provided encouraging laboratory results, especially if combined with prostaglandins, but generally at the expense of an hemorrhagic diathesis. Kux and coworkers described the use of a calcium chelating agent, sodium citrate, over 20 years ago (Kux 1971). Citrate theoretically functions by virtue of its anticoagulation ability, but also secondarily by inhibition of complement activation, which is also calcium dependent. In this model, citrate was perfused intra-arterially into the vascularized organ. Unfortunately, the doses of citrate which are required, soon led to citrate intoxication.

Prevention of complement activation is a strategy which is attractive for future development. Cobra venom, which was described over 20 years ago for its ability to prevent complement activation, is also a potent anticoagulant. It has been effective in prolonging the hyperacute rejection of guinea pig hearts in a discordant xenograft model using rats as recipients (Johnston 1992).

USE OF FK506 IN PRESENSITIZED STATES

Nonspecific immunosuppression has been utilized to decrease the immune responsiveness in preformed antibody states. Many of these agents have required "cocktail" therapy, including agents which act on different limbs of the immune response (Murase 1993, in press). Cyclosporine has not been very effective in the xenograft models (Adachi 1987, Valdivia 1987b, Gambiez 1990). On the other hand, another T cell specific immunosuppressive agent, FK506, has some effect in xenograft models, in which the level of preformed antibodies is low (Valdivia 1987a).

FK506 is a newly described macrolide antibiotic, with potent suppression of both cell mediated and T cell dependent antibody responses (Kino 1987, Starzl 1991).

The large experience accumulated in the last four years with the clinical use of FK506 showed very encouraging results (Starzl 1991) when compared with the other drugs presently used. However, limited information is available on the effect of FK506 on the humoral response, both experimentally and clinically. In 1988, Woo et al (Woo 1988), demonstrated profound suppression of the production of splenic IgM-secreting plasma cells and antibody levels in rats immunized with sheep red blood cells. IgM-producing splenic plasma cells underwent a 93% reduction in the group of animals treated with FK506 in association with cyclosporine, and a 98% reduction in the group treated with FK506 alone. Inamura et al (Inamura 1988), that same year, and Takagishi et al (Takagishi 1989), the following year, showed that when FK506 treatment was begun on the same day as type II collagen immunization, FK506 inhibited the development of arthritis and suppressed and immunological response to type II collagen in rats. These findings, along with the fact that experimental arthritis can be induced in congenitally athymic nude rats by humoral mechanism alone (Takagishi 1985), can be explained as a result of the inhibition of anticollagen antibody production by FK506.

Our group has reported in the past (Iwatsuki 1981, 1984, Gordon 1986b) that one and two year liver graft survivals were not adversely affected by the lymphocytotoxic antibody and that a positive crossmatch was not a contraindication for liver transplantation. However, the fact that many of the crossmatch positive patients were highly sensitized and that specific alloimmunization of platelets to class I antigens is a major cause of bleeding

and platelet transfusion refractoriness in liver transplant candidates was documented shortly thereafter (Marino 1988). These facts, along with the knowledge that crossmatch-positive liver grafts have been lost for unclear reasons (Hanto 1987, Bird 1989, Starzl 1989, Karuppan 1991) in different centers motivated us to reanalyze the effect of antidonor lymphocytotoxic antibody upon graft survival. Takaya et al demonstrated, for the first time and in the largest patient series available, that antidonor lymphocytotoxic antibody (positive crossmatch) adversely affects the survival of primary liver transplantation during the first 12 months after surgery (Fig. 3) (Takaya 1991, 1992a). These studies showed an increased incidence of graft failure from rejection, and of vascular and biliary complications in this population. The adverse impact of using positive cytotoxic crossmatch donors was evident both under cyclosporine or FK506 as primary immunosuppressant (Takaya 1991, 1992a). There was no difference in the one-year graft survival between 25 positive crossmatch patients in the FK506 era (56%), when compared to 22 positive crossmatch patients in the cyclosporine era (59%) (Takaya 1991, 1992a). Similar results in a series of liver transplant patients have been also reported by Karuppan et al in Sweden (Karuppan 1991). None of the grafts in this Swedish series were hyperacutely rejected, and graft survival was significantly lower in the group of patients that had cytotoxic antibodies reactive with donor splenic T and/or B cells. Nakamura et al (Nakamura 1991) conducted a clinicopathologic analysis of 26 liver transplant recipients harboring preformed dithiothreitol (DTT) resistant (Iwaki 1988) lymphocytotoxic antibodies. These 26 patients were identified among adult patients who received primary liver allografts under FK506 immunosuppression at the University of Pittsburgh. Similar to the smaller Swedish series, none of the grafts of this Pittsburgh series underwent "hyperacute" rejection. On the

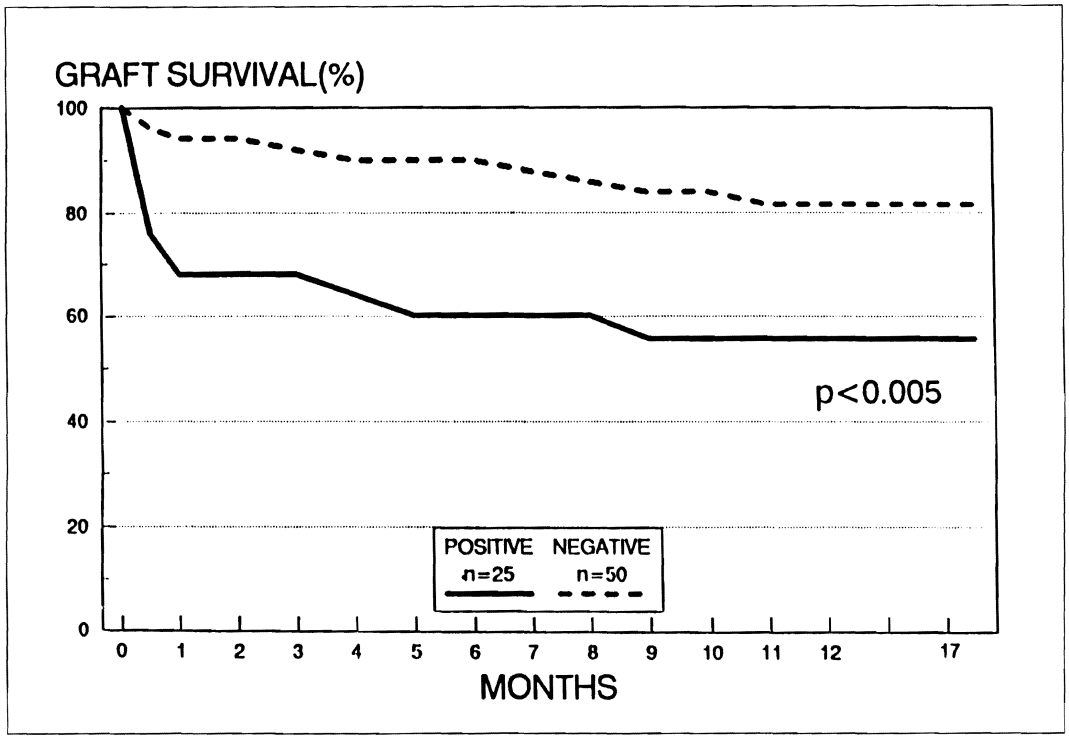

Fig. 3. The actuarial graft survival rates in 25 adult liver transplant positive-crossmatch patients and 50 negative-crossmatch patients (Reprinted from: The adverse impact on liver transplantation of using positive cytotoxic crossmatch donors, by Takaya S. et al, in Transplantation 53(2):p.401, Fig.1, 1992).

other hand, when compared to crossmatch negative control patients, the crossmatch positive recipients had prolonged early graft dysfunction, a significantly larger number of clinically indicated biopsies, and of biopsy proven early acute cellular rejection within the first 10 post transplant days. There was also a higher incidence of graft failure within the first two months. Furthermore, pathologic specimens from these positive crossmatch patients showed early platelet margination in central veins and sinusoids, neutrophilic portal venulitis followed by cholangiolar proliferation, acute cholangiolitis, centrilobular hepatocyte swelling (mimicking "preservation" injury), relapsing episodes of acute cellular rejection and endothelial activation of arteries with medial changes. A significant clinical difference in the course of these patients is represented by the fact that the centrilobular hepatocyte swelling mimicking a "preservation" injury often do not resolve (as generally happens in the "true" preservation injury) but rather tend to persist or worsen in the posttransplant weeks. All these pathologic events indicated that transplant recipients harboring preformed DTT-resistant lymphocytotoxic antibodies have a worse early posttransplantation graft function and survival, even though in these FK506-treated recipients hyperacute or accelerated rejection was not seen. These clinicopathologic results were actually very similar to the experimental observations by Houssin et al (Houssin 1985, 1986), and Furuya et al (Furuya in press). In fact, the seven (27%) failed allografts from crossmatch positive patients in the Pittsburgh series showed significant changes in the arteries and in the peribiliary vascular plexus (Nakamura 1991). The medium-sized muscular arteries presented changes suggestive of arterial spasm (Nakamura 1991), resembling the changes observed in sensitized rats (Furuya in press). Also, medial thickening was common and an analysis of the arterial wall thickness/diameter ratio resulted in a significant difference between the crossmatch positive patients and the controls. Immunofluorescence revealed venous and sinusoidal IgG, C1q, and C3 deposition only in biopsies performed 6-24 hours after liver reperfusion (Iwaki 1988). No significant immune deposits were detectable later in biopsy specimens. This was the only important dissimilarity between the clinical (Nakamura 1991) and the experimental (Furuya in press) pathologic findings.

Differing from renal grafts, where humoral rejection does not respond to immunosuppression, there is clinical evidence that sensitized liver allograft recipients may resist an antibody-mediated rejection if an FK506 based immune suppression regimen is used (Woodle 1991, Takaya 1992b). Woodle et al (Woodle 1991) reported a case of biopsy proven liver humoral rejection, where an ABO-incompatible donor organ was used (A to O), that promptly resolved after switching the patient to FK506 immunosuppression. Initial posttransplant liver biopsies showed several features of humoral rejection, including arteriolar hyaline necrosis, disrupted endothelium, intraluminal fibrin deposition, and IgM and complement endothelial deposition. All these findings regressed four days after FK506 treatment was started and disappeared in eight days. Even though plasmapheresis and OKT3 were used perioperatively the clinicopathologic picture dramatically improved only when FK506 therapy was initiated, unequivocally supporting the use of this drug in a similar condition.

More recently, Takaya et al (Takaya 1992b) reported their experience in positive cytotoxic crossmatch liver transplant patients using FK506 in conjunction with high dose steroids and prostaglandin E_1 (PGE_1) (Quagliata 1972, Mundy 1980, Rappaport 1982, Strom 1983, Shaw 1985, Makowka 1987, Starzl 1993, Marino 1993). Using this immunosuppressive strategy it was possible to convert the prognosis of recipients harboring preformed cytotoxic antibodies to essentially the same as that of the conventionally treated crossmatch negative recipients. In fact, the six-month graft survival rate in the positive crossmatch patients treated with low dose steroids was only 60.7%, while the six-month graft survival rate in the group treated with high dose steroids and PGE_1 was 92.9% ($P=0.03$). This Pittsburgh study, along with the experience reported by Woodle et al (Woodle 1991) indicates that it is possible under FK506 treatment to transplant a liver

into a sensitized recipient with a reasonable expectation of avoiding accelerated or hyperacute rejection. However, long-term results are needed before it can be concluded that the strengthened immuno- suppression can ameliorate the effects of preformed antibodies to the point that this should not be considered an issue. A longer clinicopathologic follow-up should clarify if the better short-term results are not subsequently diminished by biliary or vascular complications like biliary sludge, bile duct necrosis or small bile duct loss. These could appear later and nevertheless be the result of an initial antibody mediated damage. If the long-term follow-up does not show an increased incidence of any of these complications a positive crossmatch or an ABO-incompatibility would not be considered an absolute contraindication to liver transplantation in the FK506 era. Especially considering the observation of "mutual natural immunosuppression" that is established between the donor and the recipient by the donor-recipient cell traffic starting immediately after reperfusion (Iwaki 1991). Recently, Starzl and Demetris (Starzl submitted) stated, on the basis of the Pittsburgh investigations on mixed allogeneic microchimerism that "if the initial storm can be weathered, as has been increasingly possible with modern immunosuppression, the anticipated typing effect dwindles". Most probably FK506, along with "old" immunosuppressive drugs (steroids, PGE_1, cyclophosphamide) (Marino 1993, Starzl 1993) and possible manipulation of immune cells effecting the microchimeric state (Monaco 1970, Caridis 1973, Slavin 1977, Thomas 1983, Ildstad 1985, Barber 1991, Starzl submitted) will allow the antibody barrier in allo- and xenotransplantations to be routinely overcome.

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