

The antibody crossmatch in liver transplantation

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Six hundred sixty-seven first, second, and third orthotopic liver allografts in 520 patients were reviewed to determine the effect of recipient panel-reactive antibody (PRA) and donor-recipient antibody crossmatch on 2-year patient and liver allograft survival rates. Neither a high panel-reactive antibody nor a positive crossmatch for donor-specific preformed antibody was associated with decreased patient or liver allograft survival for primary grafts or retransplants. Two patients have been given kidney transplants immediately after a liver allograft from a donor with whom each patient had an initial strongly positive donor-specific antibody crossmatch. The liver apparently removed or neutralized circulating anti-donor antibody, since the renal allografts functioned promptly and did not experience hyperacute rejection.

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TRANSPLANTATION OF RENAL allografts in the presence of preformed antibody to human leukocyte (HLA)-antigens on donor lymphocytes is associated with a high incidence of hyperacute allograft rejection.¹⁻⁴ Furthermore, transplantation of a renal allograft from a crossmatch-negative donor into a recipient with a high percentage of panel-reactive antibody (PRA) at the time of transplantation is associated with decreased graft survival.⁵

We have previously reported that transplantation of the liver in the presence of preformed antidonor antibody is associated with neither hyperacute rejection of the liver nor with decreased graft survival.^{6,7} Our last report was based on an analysis of 1-year graft survival rates for 134 recipients of 174 liver transplants. We now have accumulated experience with 520 recipients of 667 grafts. In this article, the relationship between antibody crossmatch and recipient PRA at the time of transplantation and 2-year graft survival rates are examined once more.

MATERIAL AND METHODS

Case material. Six hundred sixty-seven liver grafts in 520 patients performed between March 1, 1980 and Dec. 31, 1985 with cyclosporine-prednisone are included in this study. Three primary grafts done before March 1, 1980 with azathioprine and steroids are not included. One surviving patient has received a fourth transplant that is also not included. Thus this review is based on 517 primary grafts, 123 second grafts, and 27 third grafts.

All patients have been followed through Jan. 31, 1986. Actuarial patient and graft survival were calculated by the life table method.^{8,9} The age range of the patients was 4 months to 67 years (mean 25.3 ± 18.1 , SD years) including 310 adults given 385 grafts and 210 children given 282 grafts.

All patients were treated with cyclosporine-prednisone.¹⁰ Since December 1984, OKT3 monoclonal antibody (Ortho Pharmaceuticals, Raritan, N.J.) has been given for brief periods (10 to 21 days) to about 75 patients for treatment of acute cellular rejection or during periods of reduced cyclosporine coverage.¹¹

The most common primary indications for liver replacement are cirrhosis (25.6%) biliary atresia (20.6%), primary biliary cirrhosis (17.2%), inborn errors of metabolism (13.0%), sclerosing cholangitis (8.1%), and primary liver tumors (3.9%).

Donor-recipient matching. Recipients were selected on the basis of medical need, estimated liver size and

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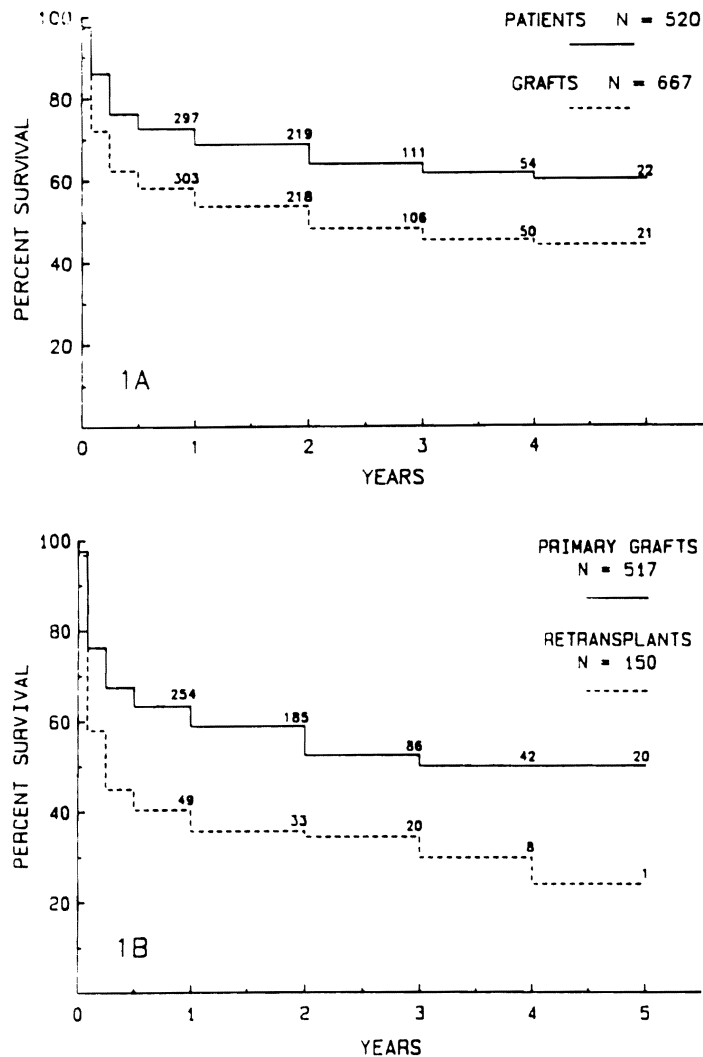


Fig. 1. A, The actuarial survival rate for 520 patients and 667 first, second, and third liver allografts. B, Actuarial graft survival rate for 517 primary grafts and 150 retransplants. The primary graft survival rate is significantly better than the survival rate for retransplanted grafts ($p < 0.001$).

body weight, and ABO blood group. HLA typing and lymphocytotoxic crossmatching were done retrospectively and played no role in recipient selection. The lymphocytotoxic antibody crossmatch was done by the trypan blue dye exclusion method with recipient serum and unfractionated donor lymphocytes at 37° C. Antibodies in the recipient serum were detected with the same techniques, using a panel of lymphocytes obtained from 60 normal volunteers. PRA was derived from the results. If antibodies were present against 30 of the 60 donors, the PRA was 50%; if the reactivity was against 15 of the 60, the PRA was 25%, etc.

RESULTS

Patient and graft survival. The actuarial survival rate is 63.8% for the 520 patients at 2 years and 48.2% for all 667 grafts at 2 years (Fig. 1, A). The actuarial survival rate of primary grafts versus retransplants is shown in Fig. 1, B. Two hundred ninety-eight (57.6%) primary grafts and 53 (35.3%) retransplants are functioning. The 2-year actuarial survival rate for primary grafts is 52.3% and 34.4% for retransplants. Primary graft survival is significantly better than survival of retransplants ($p < 0.001$).

Graft survival and PRA. The actuarial survival

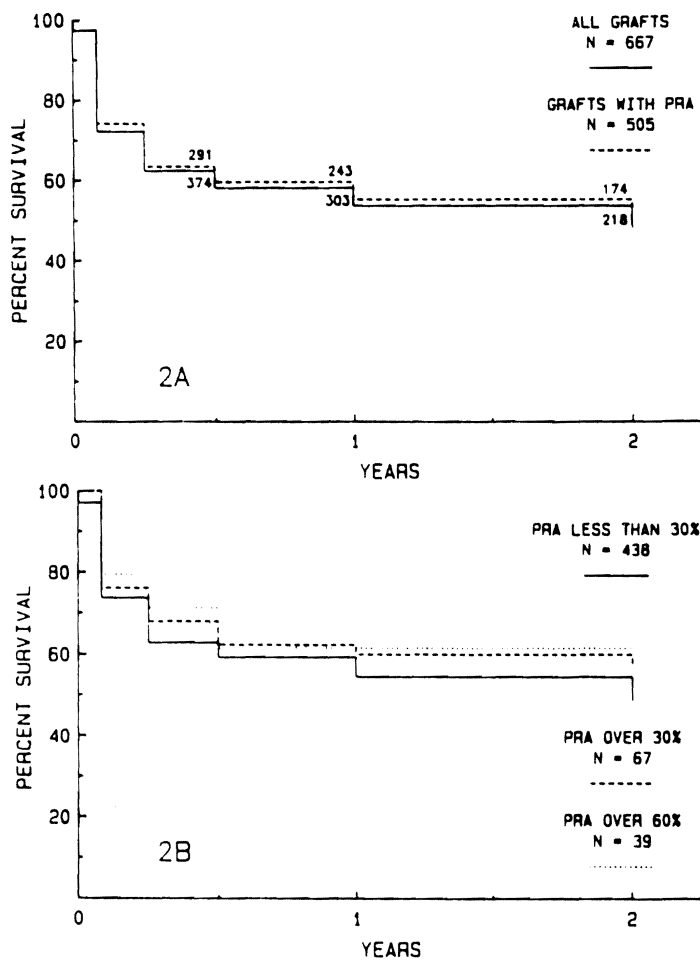


Fig. 2. A, The actuarial survival rate for 505 grafts for which PRA data are available is compared with the survival rate for the entire series of 667 transplants. There is no significant difference. B, The actuarial survival rate for 67 grafts in patients with a PRA greater than 30%, including 39 grafts in patients with a PRA greater than 60%, compared with 438 grafts in patients with a PRA less than 30%. There are no significant differences in graft survival rates.

rates for 505 grafts (75.7%) for which PRA analysis is available are shown Fig. 2, A and are the same as survival rate for the entire series of 667 transplants. Sixty-seven patients had a PRA of 30% or more at transplantation including 39 patients with a PRA greater than 60%. The 2-year graft survival rate in patients with a PRA under 30% is 48.9%, with a PRA of more than 30% is 51.4%, and with a PRA greater than 60% is 61.5% (Fig. 2, B). These survival rates are not significantly different.

PRA data are available for 417 (80.7%) of the 517 primary grafts and 88 (58.7%) of the 150 retransplants. Fig. 3, A and C shows no difference in graft survival rates for the primary grafts or retransplants for which

PRA data are available and the entire series of 517 primary grafts and 150 retransplants. PRA was greater than 30% for transplantation of 48 primary grafts, including 31 patients with a PRA of more than 60%. PRA was greater than 30% for 19 patients with retransplants, including eight patients with retransplants with PRA greater than 60%. There are no significant differences in graft survival rates for primary grafts (Fig. 3, B) or retransplants (Fig. 3, D) with high or low PRA.

Graft survival and antibody crossmatch. Antibody crossmatch data are available for 433 (64.9%) grafts that show no difference in survival from the complete series of 667 grafts (Fig. 4, A). The 2-year

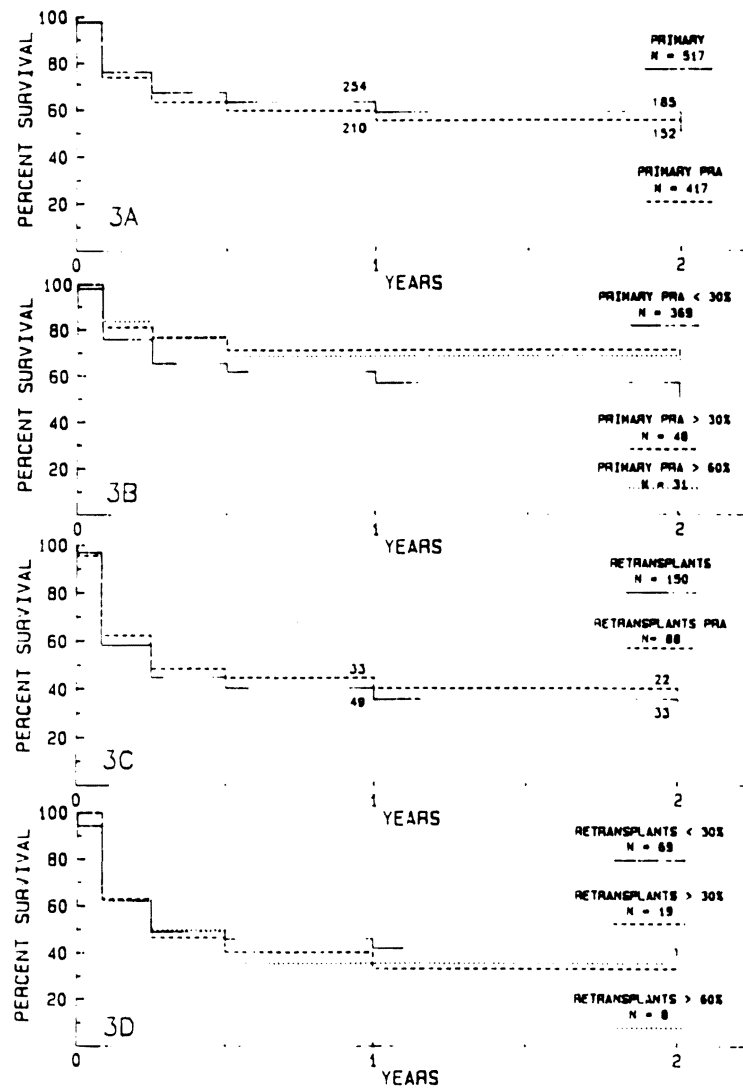


Fig. 3. There are no significant differences in actuarial survival rates for 417 primary grafts (A) and 88 retransplants (C) for which PRA data are available compared with all 517 primary grafts (A) and all 150 retransplants (C). There are no significant differences in graft survival rates for 48 primary grafts in patients with a PRA greater than 30% (B), including 31 grafts in patients with a PRA greater than 60%, compared with 369 primary grafts in patients with a PRA under 30% (B) or for survival of 51 retransplants with a PRA greater than 30% (D), including eight retransplants in patients with a PRA greater than 60%, compared with 69 retransplants in patients with a PRA less than 30% (D).

survival rate for 62 grafts transplanted with a positive crossmatch is 55.8% and 49.8% for 371 grafts with a negative crossmatch (Fig. 4, B). There is no statistical difference in graft survival rates for patients with positive and negative crossmatches at transplantation.

There are no differences in graft survival rates for the 337 (65.2%) primary grafts (Fig. 5, A) or 96 (64.0%) retransplants (Fig. 5, C) for which crossmatches are available and the entire series of 517 primary grafts and 150 retransplants. Antibody cross-

match was positive for 38 (11.3%) of the 337 cross-matched primary grafts and for 24 (25.0%) of the 96 cross-matched retransplants. There is no significant difference in graft survival between positive and negative crossmatched primary grafts (Fig. 5, B) or between positive and negative crossmatched retransplants (Fig. 5, D).

Among the 667 grafts were 382 (57.3%) grafts for which both antibody crossmatch and PRA data are available. Fig. 6, A shows no significant difference in

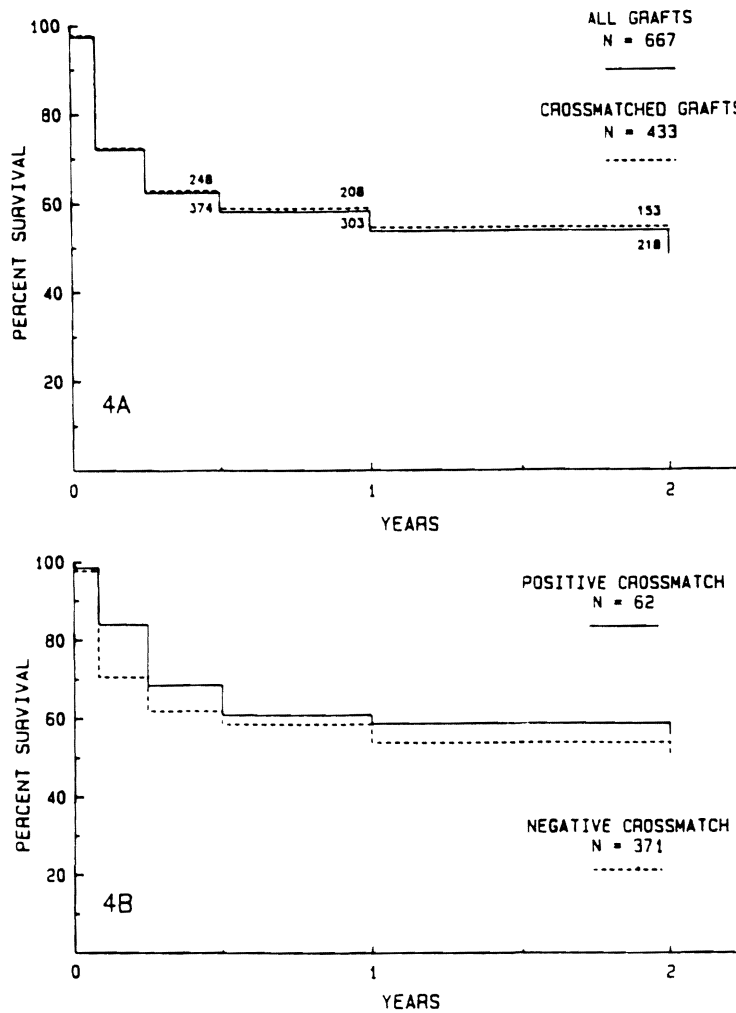


Fig. 4. A, The actuarial survival rate for 433 grafts for which antibody crossmatch data are available compared with the survival rate for the entire series of 667 transplants. There is no significant difference. B, Actuarial survival for 62 grafts in patients with a positive crossmatch compared with 371 grafts in patients with a negative crossmatch. There are no significant differences in graft survival rates.

graft survival for these 382 grafts compared with the entire series of 667 transplants. Twenty-eight transplants were done in recipients with a positive donor antibody crossmatch and a current PRA of more than 30%, including 20 patients with a PRA greater than 60%. There is no difference in graft survival rates for these high antibody, positive crossmatch transplants and 305 grafts done with a negative crossmatch and PRA less than 30% (Fig. 6, B).

Incidence of rejection and retransplantation. Antibody crossmatches were done in 53 of 78 patients in whom a graft was lost and retransplantation was done because of allograft rejection. The incidence of retransplantation for rejection of a graft with a positive crossmatch was seven of 62 grafts (11.3%) and with a negative crossmatch 46 (12.4%) of 371 grafts. There is

no significant difference between these rates of retransplantation for rejection of crossmatch-positive and crossmatch-negative grafts.

Renal transplantation after liver transplantation with a positive crossmatch. Five patients with chronic liver and kidney failure have been given a renal allograft immediately after a liver transplant from the same donor. In two cases, the antidonor lymphocyte crossmatch was strongly positive immediately before liver transplantation. However, within a few hours after implantation of the liver, repeat crossmatches could no longer detect significant levels of circulating preformed antidonor antibody. Renal allografts then implanted in these two patients functioned promptly and did not undergo hyperacute rejection. The postoperative course of one of these patients is shown in Fig.

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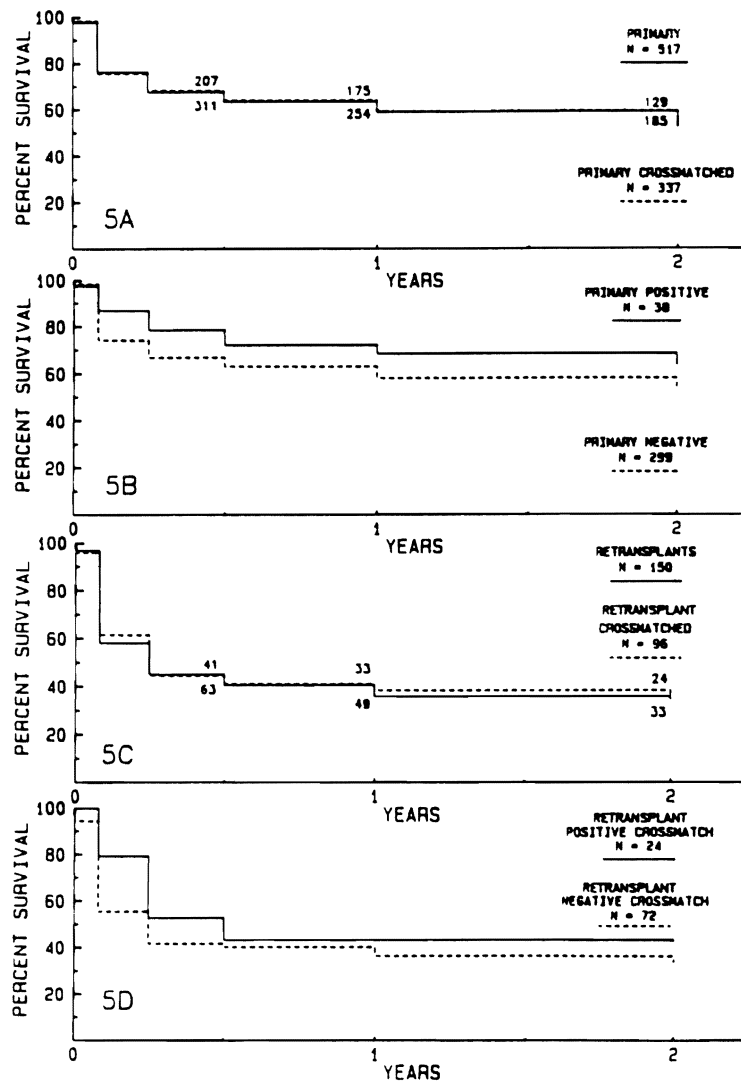


Fig. 5. There are no significant differences in actuarial survival rates for 337 primary grafts (*A*) and 96 retransplants (*C*) for which crossmatch data are available compared with all 517 primary grafts (*A*) and all 150 retransplants (*C*). There are no significant differences in graft survival rates for 38 primary grafts in patients with a positive crossmatch (*B*) compared with 299 primary grafts in patients with a negative crossmatch (*B*) or for survival of 24 retransplants with a positive crossmatch (*D*) compared with 72 retransplants in patients with a negative crossmatch (*D*).

7. All five patients continue to survive with functioning liver and renal allografts 2 weeks to 18 months after transplantation.

DISCUSSION

In a previous report on the results of liver transplantation in 36 patients with a positive cytotoxic crossmatch,⁷ we used current recipient sera with fractionated donor T-lymphocytes assayed at 37° C. The results in the current series are based on crossmatches done with sera collected just before transplantation and

unfractionated donor lymphocytes at 37° C by means of the trypan blue dye exclusion technique. In our laboratory's experience the results for this method correlate strongly with the assay using fractionated T-lymphocytes at 37° C if kill of cells is complete. Therefore it is reasonable to believe that the positive crossmatches reported here represent mostly preformed antibody to HLA antigens expressed on donor T-lymphocytes.

This study again confirms our previous observation that the liver allograft is not subject to hyperacute

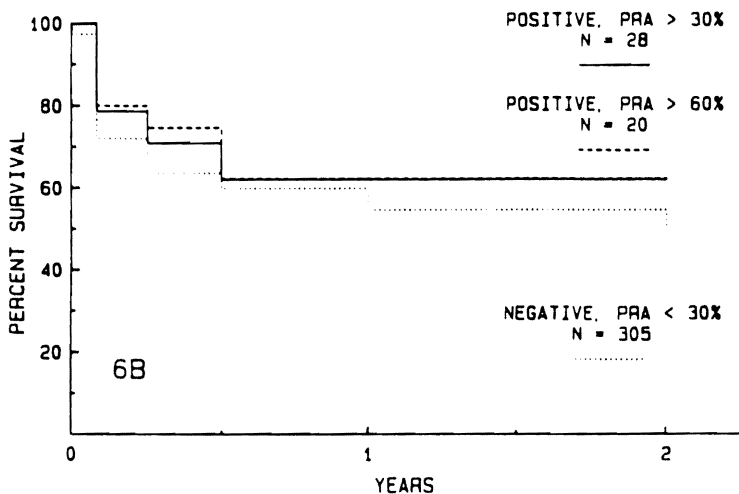
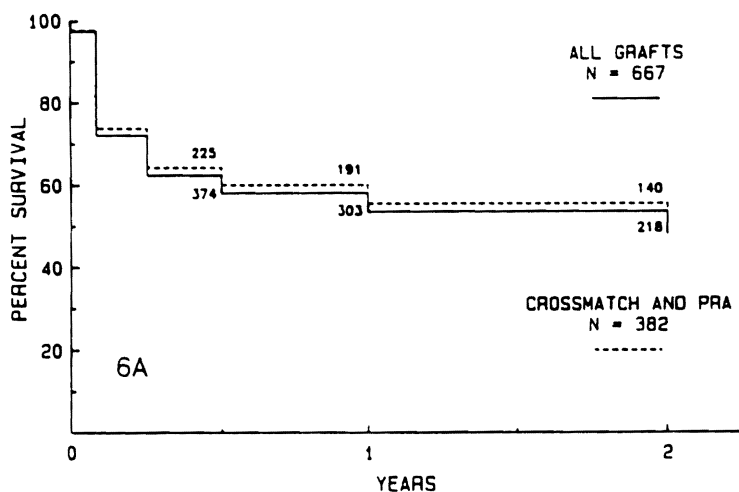


Fig. 6. A, The actuarial survival rate for 382 grafts for which both antibody crossmatch and PRA data are available is compared with survival rate for the entire series of 667 transplants. There is no significant difference. B, The actuarial survival rate for 282 grafts in patients with a positive crossmatch and a PRA greater than 30% (including 20 patients with a PRA more than 60%) is compared with survival rate for 305 grafts in patients with a negative crossmatch and PRA less than 30%. There are no significant differences in graft survival rates.

rejection in the presence of preformed antidonor antibody and also shows that liver allograft survival as long as 2 years is not adversely affected by a positive antibody crossmatch for primary grafts or retransplants. In further contrast to events in renal transplantation, a high panel-reactive antibody at the time of liver transplantation is also not associated with decreased graft survival.

The hyperacute rejection of renal allografts in patients who receive kidneys in the presence of preformed antidonor antibodies has been well described.¹⁻⁴ Such grafts do not sustain an effective renal blood flow

and angiography shows that the small vessels of the excised kidneys can be closed. Histopathologically, the arterioles and capillaries are plugged with formed blood elements, particularly erythrocytes and platelets. Our experience with combined liver-kidney transplantation in two patients with a positive antibody crossmatch suggests that a liver allograft is able to clear or neutralize quickly sufficient circulating preformed antidonor antibody to permit transplantation of a renal allograft from the same donor without hyperacute rejection. Elucidation of the mechanism by which the liver allograft is able to inactivate or eliminate pre-

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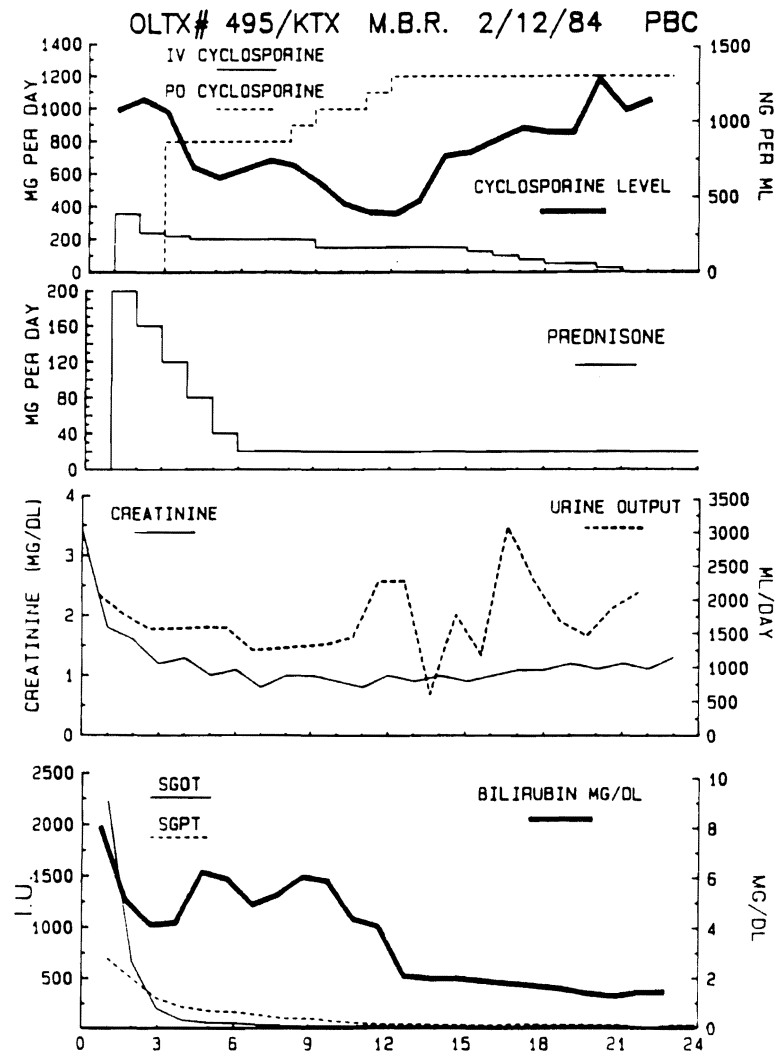


Fig. 7. A 43-year-old woman with chronic liver and renal failure from end-stage primary biliary cirrhosis received a liver transplant from a cadaver donor with whom she had a positive antibody crossmatch. A kidney was implanted from the same donor immediately after completion of the liver transplant. The postoperative course, including immunosuppression with cyclosporine and prednisone, renal function, and liver function, is shown. Hyperacute rejection of either graft did not occur and both grafts continue to function well 18 months after transplantation.

formed antibody may be important in developing clinical methods for the prevention or abrogation of hyperacute rejection in renal transplantation.

The clinical circumstances of liver allograft loss are often complicated and the causes of graft loss are often multifactorial. Therefore it is difficult in the large and complex series of patients reported here to assess the relationship between antibody crossmatch and the incidence of graft loss from rejection. The best data are available for patients having retransplantation for rejection, since thorough examination of the removed graft is possible. We found that the incidence of

retransplantation for rejection of a prior transplant with a negative or a positive crossmatch was not significantly different.

In nearly every group of patients analyzed, survival was slightly better for grafts in patients with a positive antibody crossmatch or a high PRA at transplantation. However, this advantage in graft survival was not statistically significant in any case. Nevertheless, even in this large series of cases, less than 10% of the grafts were performed with a positive antibody crossmatch, and just 10% of the grafts involved recipients with a current PRA greater than 30%. It will require an even

larger experience to determine if preformed antibody has a significant protective or tolerogenic effect in liver transplantation.

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DISCUSSION

Dr. Folkert O. Belzer (Madison, Wis.). I had the opportunity to review this manuscript a short time ago, and as usual I stand in awe of the enormous experience of the Pittsburgh group, 660 transplants in 520 patients. From what I hear they are going to be adding another 500 this year.

When one listens to this paper or reads the manuscript, it sounds as though this group is actually violating a basic immunologic process, namely, successful transplantation against a positive cytotoxic T cell crossmatch and yet there must be an explanation.

I always thought a positive crossmatch could be caused by nonspecific antibodies and not always by human leukocyte antigen (HLA) antibodies. All of these antibodies are toxic to

the organ, but the nonHLA antibodies will not produce an anamnestic response with the formation of more antibodies.

Many years ago our Recorder, Dr. Turcotte, presented a series of kidney transplants that were performed against a positive crossmatch, and although many of those kidneys had early poor function, many survived. The explanation given was that these were probably B warm and not T warm antibodies. At that time we did not differentiate between B and T warm, but perhaps they were nonspecific antibodies.

Our Canadian colleagues have recently emphasized the importance of having a recent negative T cell crossmatch and that the historical positive crossmatch was unimportant. If all of these antibodies were HLA antibodies, even a positive historical crossmatch should have been important.

Thus have you looked at those retransplants in which you could identify a specific HLA antibody such as an anti-HLA-2 and then have transplanted that patient with a second liver from a donor who had the HLA-2 antigen? What has happened to those livers? Have you also studied this in the laboratory where you could take a dog and transplant the kidney from another dog and allow the kidney to reject and then take the liver from the same donor and transplant it into the recipient dog? Did those livers function?

Dr. Ronald M. Ferguson (Columbus, Ohio). Everyone in the transplant business is in awe of 660 liver transplants done in 4-years. Certainly for that the authors should be congratulated. Just reviewing that amount of data to make the presentation is an enormous effort.

I think what the authors have done is to reconfirm and reaffirm existing policies in most centers. Because the logistics of donor procurement, donor-recipient matching with a prospective crossmatch is rather difficult in liver transplantation, so most centers are not prospectively doing it. As Dr. Belzer mentioned, I think most of us feel much more comfortable with this size of experience reaffirming our current policy.

I have several specific questions about crossmatch policies at Pittsburgh and several theoretic questions. First, were these really all recent sera, immediately pretransplant sera, that the crossmatches were done on in those 62 positive patients, or were these sera from 2 weeks or a month before transplant? Second, were these T cell crossmatches, or were they on whole lymphocyte preparations from either the spleen or the lymph nodes? It makes a big difference, because clearly a positive warm B cell crossmatch has very little influence on the outcome of solid organ transplantation. The disastrous effects of hyperacute rejection are generally directed at antigens present on T cells and not on B cells.

Third, do these patients with positive crossmatches have a more "stormy" clinical course? Is there a higher incidence of acute aggressive rejection early after transplant in these patients?

Those are three clinical questions—now to some theoretic ones. First, why would the vascular bed of the liver be so different from that of the kidney? If you had preformed

cytotoxic complement-fixing antibody working against donor antigens, they would bind to the endothelial bed of the liver, fix complement, activate the coagulation cascade, and cause immediate loss of function and clotting of that graft, but that does not happen in the liver. Does this have something to do with clearance of antibody binding to certain cell types in the liver? Is there something about the fixed reticuloendothelial function of the liver that can eliminate this? What are your group's thoughts about this?

Second, a theoretic question that I believe is most intriguing is that the best way to obtain a brisk antibody response is to perform plasmapheresis on a patient who has preexisting antibody to an antigen, present the antigen, and get an anamnestic response. So if the liver is acting as a sieve to acutely absorb a preexisting antibody, if it absorbs it out, there should be a strong anamnestic response once you present antigen in the form of the liver.

You then might say that we are placing these patients on immunosuppression therapy. Certainly people have repeatedly tried with plasmapheresis and all types of immunosuppressants to eliminate positive crossmatches before kidney transplantation and have been unsuccessful. You use cyclosporine and prednisone. Of all the immunologic effects of cyclosporine, the one that does least well is blocking a secondary antibody response; in fact, experimentally it has hardly any effect on secondary antibody responses, so why once you acutely absorb antibody aren't these patients coming back strongly 7 days later with a brisk response of antibody and rejecting their liver?

Third, in those patients with past positive crossmatches, the presence of anti-idiotypic antibody to the anti-HLA antibody that is formed in these individuals might be terribly important in downregulating the antibody response to that particular set of alloantigens on the donor graft. Have you looked back at the presence of idiotypic antibody in these patients, for instance, like the group at Columbia is doing, and does this play a role in modifying the adaptive immune response to these grafts?

Dr. Jeremiah G. Turcotte (Ann Arbor, Mich.). Dr. Gordon and the group from Pittsburgh are once again to be complimented on a very impressive clinical series. Six hundred sixty-seven liver transplants within 5½-year period is a remarkable achievement.

In both the presentation and the manuscript, strong evidence is presented that the presence or absence of a positive donor-recipient crossmatch does not have a major influence on the outcome of liver transplantation. However, a word of caution must be interjected before these results are interpreted to indicate that a positive crossmatch or a high panel-reactive antibody makes no difference in the outcome of liver transplantation. With kidney transplantation, it was initially thought that ABO incompatibility, HLA matching, or the presence of a positive donor-recipient crossmatch made little difference. Although it quickly became apparent that ABO incompatibility and the donor-recipient crossmatch had a major impact on outcome, it took many years to demon-

strate that HLA typing had a 5% to 15% influence on long-term results. This is because so many variables may influence survival of the graft or the patient; it will require hundreds of patients to demonstrate differences in the range of 5% to 15%. The problem could probably be best studied in the laboratory where most of the variables can be controlled. Nevertheless, the data presented is the best available and indicates that there is little or perhaps even no influence of the crossmatch or the presence of preformed antibody.

Not only have the antibody data been presented, but this paper represents an update of the clinical results with liver transplantation at Pittsburgh, which is by far the largest experience in the world.

Dr. Peter J. Fabri (Columbus, Ohio). The liver is a very large organ in relative terms, and we are aware that it requires at least 95% destruction before we see many of the abnormalities that we call liver dysfunction.

Although no one would argue that death is a very specific marker of liver dysfunction, it is not a very sensitive one, and I wonder whether the authors have initiated any prospective evaluation of liver dysfunction so that they might be able to tell us whether there is a difference in these patients, even though they are still alive.

Dr. Gordon (closing). Dr. Belzer has raised the question of the relevance of HLA matching in liver transplantation. During the past year we have reviewed the results for more than 500 consecutive liver transplant recipients treated with cyclosporine and prednisone to determine the relevance, if any, of ABO blood group matching, antibody crossmatch, and HLA matching to graft outcome.

We recently reported to the Society of University Surgeons that ABO matching has a small but significant effect on primary graft survival. ABO-matched donor-recipient grafts fared better than ABO compatible but nonidentical or ABO incompatible grafts. We continue to recommend the use of ABO-matched grafts when practical.

We have reported here that preformed antidonor antibody has no significant effect on graft outcome. We are still in the process of analyzing the results for HLA matching so I do not yet know what our findings will be. Once our analysis of the HLA data is available, we will be in a position to reassess the question raised by Dr. Belzer about whether preformed antibodies to particular HLA specificities are relevant.

Dr. Ferguson, the results we have reported today are essentially warm T cell crossmatches. Several years ago Dr. Iwatsuki reported similar results for our first 174 grafts using nylon wool-fractionated donor lymphocytes assayed with recipient serum at 37° C. Our laboratory staff is quite confident that the results of this extended series, based on assays using unfractionated donor lymphocytes at 37° C, are essentially the same as that achieved with fractionated cells. We have routinely collected sera from all liver recipients just before transplantation for both transplantation antibody studies and viral serology and cultures.

Dr. Ferguson has asked why the kidney is different from the liver in its vulnerability to preformed antibody. I do not

have the answer, but some obvious differences come to mind. The kidney is designed to filter the blood and is mainly a capillary organ. Its microcirculation is vulnerable to clogging by platelets, products of coagulation, and other blood elements including antibody-coated erythrocytes. The liver is more complex in function, is mainly sinusoidal in architecture, and is also a reticuloendothelial organ well equipped to clear potentially damaging elements from the circulation.

It was also asked whether we have observed any difference in early or late graft function in these patients that might be related to preformed antibody. Early after transplantation, this is difficult to assess because of the complex clinical setting in which liver transplantation is performed. Variable degrees of liver dysfunction can be related to preservation injury, medical risk factors, technical problems with surgery, drugs, sepsis, or rejection. It is my impression, however, that patients with a positive antibody crossmatch do not have a

stormier clinical course. Beyond 6 months after surgery, graft function, as assessed by traditional laboratory profiles, is remarkably stable in most patients. Subtle differences in graft function would require special testing and probably are of no real significance. However, graft loss is an easily identified end point and has the greatest significance to the patient.

The data presented here suggest the possibility that preformed antibody may actually be protective of the liver allograft. Does antibody coat antigen presenting cells in the liver and inhibit antigen processing? Why is there no rebound phenomenon such as Dr. Ferguson has suggested? An even larger series of patients will be needed to determine if, in fact, preformed antibody is protective in clinical liver transplantation. As each of the discussants has suggested, laboratory investigation is necessary to unravel mechanisms.

La compatibilidad de anticuerpos en el transplante de hígado

Se revisaron 667 primero, segundo, y tercer aloinjertos en 520 pacientes con el objeto de determinar el efecto del anticuerpo reactivo "panel" del receptor (PRA) y compatibilidad cruzada de anticuerpos donador-receptor en un estudio a dos años de supervivencia de pacientes e injertos hepáticos. No se encontró asociación con disminución de la supervivencia de pacientes o de injertos hepáticos en los injertos primarios o secundarios (retransplantes) ni relación con compatibilidad cruzada positiva para anticuerpo donador específico preformado, ni para anticuerpo reactivo. Dos pacientes han recibido trasplantes renales después de un injerto hepático de un donador con el cual cada paciente tenía una prueba de compatibilidad cruzada de anticuerpos donador específico fuertemente positiva. El hígado, aparentemente eliminó o neutralizó los anticuerpos anti-donador puesto que los aloinjertos renales empezaron a funcionar de inmediato y no sufrieron rechazo hiperagudo.

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