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The clinical significance of conversion of complement-dependent cytotoxic T cell crossmatch test after renal transplantation

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Abstract The purpose of this study was to investigate the clinical relevance of conversion of post-transplant T cell crossmatch between kidney donor and recipient. This study comprises 892 cadaveric renal transplantations performed on 874 adult patients between August 1991 and December 1997. Recipient selection was based on a negative complement-dependent cytotoxic T cell crossmatch test with current (≤ 2 months old) serum. For this study, on day 0 and day 14 after transplantation, serum samples were collected for later crossmatching. On day 14 after transplantation, the crossmatch had converted to positive in 76 transplantations (8.5 %). Acute rejection occurred in 50 % of the converters and 22 % of the non-converters ($P < 0.005$), and graft survival was significantly poorer ($P < 0.025$), being 85 vs 94 % at 1 and 68 vs 83 % at 5 years, respectively. In patients with delayed graft function, 1-year graft survival was 77 % in the converters and 91 % in the non-converters ($P < 0.05$). Conversion of T cell crossmatch, especially in connection with delayed graft function, identifies a subgroup of patients at high risk of severe rejection and poor graft survival.

Key words Kidney transplantation · Graft rejection · Crossmatching

Introduction

With the growing availability of new immunosuppressive drugs, the transplant clinicians are able to use a more aggressive and individualized immunosuppression on those renal allograft recipients who are at an increased risk of early allograft rejection.

A clinician needs to know how to identify the high-risk recipients who might benefit from an individually-tailored immunosuppression. Patients having previously lost a kidney graft due to immunological reasons are known to be high-risk candidates for retransplantation. A severe vascular rejection, however, can be encountered by recipients of a first graft and also by patients without any previous history of immunization.

It is generally accepted that mild rejections responding to treatment do not jeopardize the long-term survival of the grafts, and our own experience has shown that an early acute rejection as such is not a bad prognostic sign [8]. On the other hand, it is known that an early rejection not responding properly to antirejection therapy, or a rejection not treated adequately, leads to deleterious changes in the graft and accelerates graft loss [2, 22]. Furthermore, van Saase et al. showed that early vascular rejection is the most important variable in predicting both early and late graft loss [18]. Such rejection episodes naturally eliminate the grafts from long-term survival analyses, such as the determination of transplant half-life, which only include grafts surviving the first post-transplant year. Matas et al. [13] demonstrated how even a single episode of acute rejection influences the half-life of primary renal grafts.

In our experience, a negative cytotoxic T cell crossmatch test against the donor sometimes converts to positive in association with a severe allograft rejection. A similar finding, made in patients with repeated or re-

fractory rejection, was also reported by Greger et al. in 1989 [5]. It is not known, however, whether the post-transplant conversion of the crossmatch was brought about by the ongoing rejection process, or whether it already occurred during the early post-transplant period before any clinical signs of rejection developed, or even whether it occurred without any rejection process at all.

The purpose of this study was to evaluate the relevance of post-transplant crossmatch conversion as a predictor of success of transplantation. We screened our recipients of cadaveric renal allografts who underwent transplantation between August 1991 and December 1997 by means of the complement-dependent cytotoxic T cell crossmatch test on day 0 and day 14 after transplantation. The results of these tests were correlated with relevant clinical outcome parameters in these 892 kidney transplantations.

Patients and methods

Patients

From August 1991 to December 1997, all adult patients who underwent cadaveric kidney transplantations at our center were enrolled in this study. For this study, serum samples were collected prospectively just before transplantation and 14 days thereafter. Eight cases in which the patient died or the graft was removed before day 14, and 69 cases in which blood samples were not taken on day 14, mainly because of early discharge from the transplant unit, were excluded from the analysis. The results of the remaining 892 transplantations are reported herein.

Our normal procedure for accepting patients to the waiting list requires the patient to be on maintenance dialysis and have had 3 units of random, leukocyte-poor, packed red cell transfusions unless having been pregnant or having received transfusions previously. The selection criteria for patients for transplantation comprise ABO blood group compatibility, in general a sharing of ≥ 2 HLA-AB and ≥ 1 HLA-DR antigens as well as a negative complement-dependent cytotoxic T cell crossmatch test. Repeated HLA-class I antigen mismatch transplantations are not allowed. Lymphocytotoxic panel-reactive antibodies were screened using a randomly picked T cell panel of 30 blood donors every 2 months, and the latest PRA level was used in this analysis.

All kidney grafts were retrieved from heart-beating donors (553 from male and 339 from female donors). The mean age of donors was 39.3 years (ranging from 1 to 66 years).

Of the transplantations, 748 were first, 114 second, 28 third, and 2 fourth kidney transplantations. The cause of uraemia and other characteristics are described in Table 1.

Table 1 Characteristics of 892 cadaveric renal transplantations in adult patients 1991–1997 (*TX* transplantation)

Cause of uraemia, *n* (%)			
Glomerulonephritis		358	40.1%
Diabetes		223	25.0%
Polycystic disease		140	15.7%
Other		171	19.2%
Mean age, years (range)		45	(15–72)
Gender, M/F (% females)		536/356	(39.9%)
Mean time on dialysis, months (range)	1st TX	16.4	(1–181)
	2nd TX	26.5	(1–171)
	3rd TX	42.2	(3–215)
Mean cold ischaemia time, hours (range)		25.1	(12–43)

Crossmatch

Our standard complement-dependent cytotoxic crossmatch for recipient selection is performed on donor spleen T cells using the Amos technique [1] with sensitizing washing step. The patients' sera are each tested in four wells: undiluted, in 1:10 dilution, in serum excess, and in complement excess. If any of these wells has more dead cells than the negative control, the test is considered positive. The test is performed both at room temperature and at + 37 °C to eliminate autoantibodies, and if the test is positive at both temperatures, it is considered positive. From each patient selected for crossmatching, at least one serum (≤ 2 months old), together with all available (≤ 6 months old), is used for the pretransplant crossmatch test. The fine specificity is not analyzed.

For this study, the follow-up crossmatch tests on sera obtained on day 0 and day 14 were performed with the same technique, and the pretransplant serum (≤ 2 months old) was always included as a reference. The results of the crossmatch tests of the study were not used for clinical purposes, as the samples were analyzed later. The study sera of the converters who had rejection episodes ($n = 38$) were retested against the donor T cells using flow-cytometry together with anti-IgM- and anti-IgG-antibodies (DAKO, Glostrup, Denmark). The target molecule for the antibody binding to donor T cells was not analyzed.

Immunosuppression

The induction immunosuppression normally consisted of triple therapy: methylprednisolone, 1 mg/kg in divided doses, tapered within 2 weeks to 0.2 mg/kg in one dose; azathioprine, 50 mg thrice daily, and from 2 weeks on 25 mg thrice daily; and cyclosporine, started preoperatively, initially 5 mg/kg twice daily and adjusted to a trough level of 200–300 μmol/l. In patients undergoing retransplantation with high preoperative antibody titers, additional induction treatment with ATG (Fresenius, Munich, Germany) was instituted.

The first-line antirejection treatment consisted of peroral methylprednisolone, 3 mg/kg in divided doses for 5 days. Patients with steroid resistant rejection (SRR) were treated with OKT3 (Orthoclone OKT3, Ortho Pharmaceutical Corp., Raritan, N.J.) or ATG. If the histology showed signs of acute vascular rejection (AVR), a course of plasma exchanges was instituted.

Clinical outcome parameters

Acute rejections within the first 100 days were recorded. A clinical suspicion of rejection was investigated further with ultrasound and Doppler flowmetry and confirmed with fine needle aspiration or histological biopsies. The histological findings were scored according to the Banff classification [20]. Histological biopsies were taken in cases of SRR and also to reveal symptomless rejection in grafts with prolonged primary nonfunction.

The concept of delayed graft function (DGF) was used as described by Halloran et al. [6]: plasma creatinine levels of greater

Table 2 Comparison of characteristics in the Converters and Non-Converters

	Converters	Non-converters	
n	76	816	
Gender, M/F (% females)	37/39 (51.3)	499/317 (38.8)	N.S.
Mean age, years (range)	43.3 (19–66)	45.2 (15–72)	N.S.
Retransplantations, *n* (%)	31 (40.8)	113 (13.8)	$P < 0.005$
Time on dialysis, months (range)	29.8 (1–215)	17.5 (1–171)	$P < 0.00001$
Panel reactive antibodies, *n* (%)			
0%–29%	60 (78.9%)	755 (92.5%)	
30%–79%	11 (14.5%)	49 (6.0%)	$P < 0.005$
80%–100%	5 (6.6%)	12 (1.5%)	
Cold ischaemia time, hours (range)	24.8 (14–43)	25.0 (12–42)	N.S.
Delayed graft function, *n* (%)	40 (52.6%)	247 (30.3%)	$P < 0.005$

than 500 μmol/l throughout the 1st week after transplantation, the requirement of more than one dialysis within the 1st week, or the delay of more than 2 days in reaching a urine output of more than 1 l/24 h.

The time of graft failure was defined as the day after transplantation at which the patient returned to permanent dialysis. Patient death with functioning graft was classed as graft failure.

Statistics

The chi-squared test was used with contingency tables and when actual 1-year survival data were evaluated. The survival curves were calculated with an actuarial life-table analysis using the product-limit method for censored data. Comparisons between survival curves were made using a log-rank analysis. Graft half-life was calculated by fitting an exponential curve to 1- to 6-year survival data by the least-squares method. Multiple regression analysis was used in evaluating the effect of different parameters on rejection incidence.

Results

In these 892 adult cadaveric kidney transplantations, the overall 1-year patient survival, graft survival (GS), and graft survival in connection with deaths with functioning graft censored were 96.7, 93.6, and 95.9%, and the 3-year survival figures 94.9, 88.9, and 92.6%, respectively. The onset of graft function was delayed in 287 transplantations (32.2%). In 11 transplantations (1.2%) the graft never started to function. An acute rejection episode within 100 days after transplantation occurred in 220 cases (24.7%).

Crossmatch conversion

In 76 transplantations (8.5%) the crossmatch had converted to positive by day 14 (converters), and in 816 (91.5%) it had remained negative (non-converters). In all of them, the day 0 crossmatch test was negative. The crossmatch from those converters who had rejections was repeated using flow-cytometry. In all of these cases the pretransplant sera remained negative, whereas the day 14 sera showed donor-specific IgG antibodies. The characteristics of the converters and non-converters are given in Table 2. Retransplantations were significantly more frequent with the converters who also had a longer time on dialysis before transplantation. Among the converters, there were also more patients with moderately elevated (>30%) or high levels (>80%) of panel-reactive antibodies (PRA). The cold ischaemia time (CIT) was very similar in the two groups. Despite this, there were significantly more transplantations with DGF among the converters. In the whole study population, the mean CIT in transplantations with DGF was 26.8 h and in transplantations with early function it was 24.2 h.

The converters had significantly less DR-compatible (13 vs 30%) transplantations and significantly more transplantations with two DR mismatches (18 vs 7%) than the non-converters ($P < 0.001$).

Acute rejections within 100 days after transplantation

Acute rejections occurred more frequently among the converters than among the non-converters (50.0 vs 22.3%, $P < 0.005$). Furthermore, the proportion of more severe types of acute rejections, SRR and AVR, was greatly increased as shown in Fig. 1 ($P < 0.005$). The frequency of rejection was somewhat higher in grafts with DGF than in grafts with early function in both converters (57.5 vs 41.7%) and non-converters (25.9 vs 20.7%). The frequency of rejection showed no correlation with PRA-levels within the groups. In a multiple regression analysis with HLA-DR mismatches, first/retransplantations and crossmatch conversion, conversion ($\beta = 0.200$, $P = 0.000000$) and DR mismatches ($\beta = 0.164$, $P = 0.000001$) correlated independently with rejection frequency.

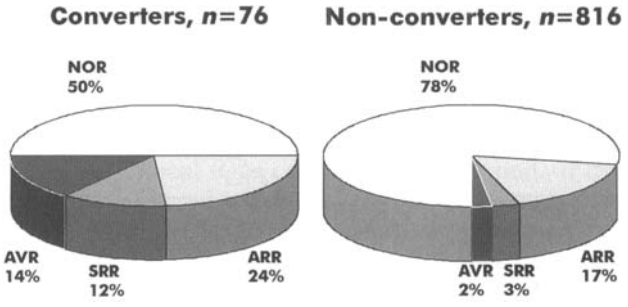

Fig. 1 Frequency and type of acute rejections in 892 cadaveric transplantations in Converters and Non-Converters (*NOR* no rejection, *ARR* acute reversible rejection, *SRR* steroid-resistant rejection, *AVR* acute vascular rejection)

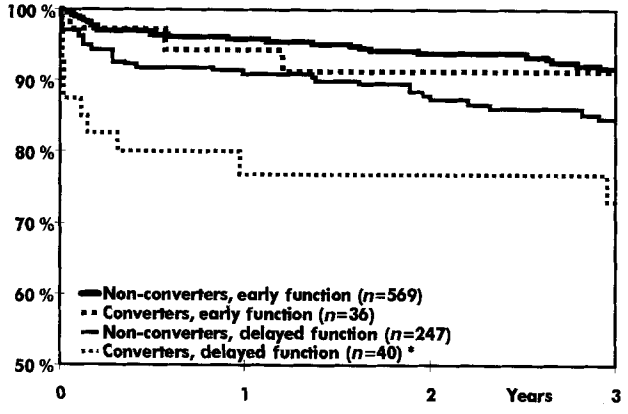

Fig. 2 Graft survival in Converters and Non-Converters by onset of graft function * $P < 0.05$

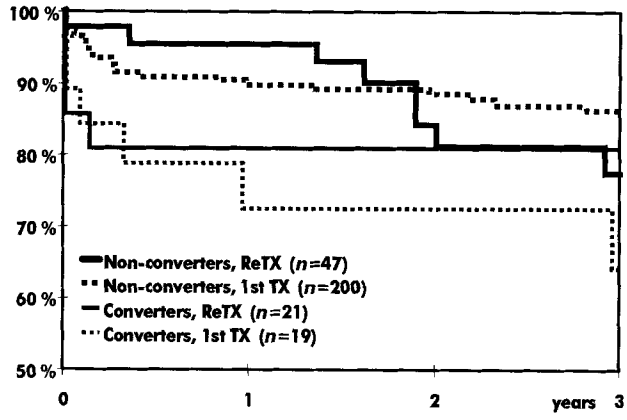

Fig. 3 Graft survival in Converters and Non-Converters with delayed graft function, by transplant number. The difference in first transplantations was statistically significant ($P < 0.01$) (*TX* transplantation)

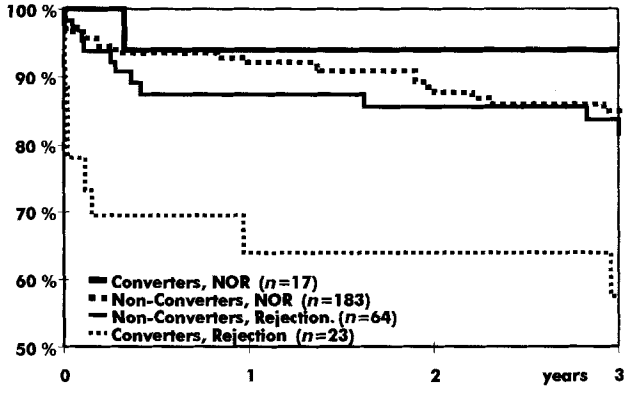

Fig. 4 Graft survival in Converters and Non-Converters with delayed graft function, by occurrence of acute rejection. The difference in the Converters with rejection was significantly worse than in Non-Converters with rejection ($P < 0.05$) (*NOR* no rejection)

Graft survival

Graft survival was significantly poorer among the converters than among the non-converters with a 1-year GS of 85.2 vs 94.1% ($P < 0.025$). In transplantations with GS of over 1 year, the mean serum creatinine value at 1 year was 141 μmol/l in the converters and 129 mol/l in the non-converters (NS).

No significant differences between converters and non-converters were noted with respect to GS in transplantations with an early onset of graft function (1-year GS: 94.3 vs 95.9%). However, in the case of DGF, the converters showed significantly worse GS than the non-converters (1-year GS: 76.8 vs 90.9%) (Fig. 2).

Graft survival in the case of DGF

We analyzed GS in the subgroup with DGF according to graft number. In first transplantations, GS was worse among the converters than with the non-converters (1-year GS: 72.4 vs 89.8%, $P < 0.01$). The same trend was apparent for retransplantations (1-year GS: 81.0 vs 95.6%, NS) (Fig. 3). When GS was analyzed according to the occurrence of rejection, we found no difference between the groups in transplantations without rejection, whereas in transplantations with acute rejection the converters showed significantly worse GS than the non-converters (1-year GS: 63.8 vs 87.5%. $P < 0.05$) (Fig. 4).

The calculation of kidney graft half-life after 1 year of survival showed that converters ($n = 66$) had a *T1/2* of 14.7 (95% confidence interval (CI): 12.5–17.6) years and non-converters ($n = 717$) a *T1/2* of 21.7 (95% CI: 21.6–21.8) years.

To check for possible bias caused by the exclusions, we analyzed the 69 transplantations for which cross-match data were not available and found that their

5-year graft survival was 82.0% compared to 82.3% among patients in the study, and the rejection frequency was 26.1% compared to 24.7% in the study.

Discussion

Our aim was to find out if conversion of our standard crossmatch with the same method as used for patient selection for transplantation could be a relevant indicator of success of transplantation, and if so, whether it could be used as a marker for a need of an individually-tailored intensified immunosuppressive regimen.

Day 14 after transplantation was chosen as the day of testing so that it could be performed before the first acute rejection while being late enough for an immunocompromised individual to respond to the transplanted organ.

In the present study of 892 transplantations of cadaveric renal allografts, the complement-dependent cytotoxic T cell crossmatch test converted to positive in 8.5% when measured on day 14 after transplantation. There are reports on crossmatch conversion after transplantation demonstrating the correlation with acute rejection and prognosis [3, 5, 7, 12, 16]. However, no data are available on the natural post-transplant course of the crossmatch test between the kidney donor and recipient, and the possible conversion of the test in rejection-free patients.

In our study, the number of acute rejections was higher among the converters, than among the non-converters, which is consistent with earlier reports [3, 5, 12]. The distribution of rejection episodes according to the severity of rejection was different in the two groups, having the same association of severe rejections and crossmatch conversion than in O'Malley et al. [16]. Thus it is not surprising that the 1-year graft survival of the converters was significantly lower and the mean serum creatinine concentration at 1 year after transplantation higher than in the non-converters.

The key issue in the present study seems to be the subgroup analysis according to the onset of graft function. The conversion of crossmatch as such was not detrimental, as one half of the converters were doing well. When conversion occurred in patients with DGF, it appeared to be a bad prognostic sign, not only in the case of retransplantation, but in particular for recipients of first grafts.

The consequences of DGF and the initial quality of graft function on long-term GS have been studied extensively [7, 11, 15, 21]. Pfaff et al. [17] demonstrated a strong association of DGF with reduced GS, but failed to demonstrate any between GS and such factors which are known to associate with DGF. In our study, the subgroup to which the post-transplant conversion of crossmatch best applies as a predictor of GS is the one of patients with DGF. This pronounced effect is not explained by CIT, which was very similar in all groups.

There is experimental evidence [19] that at least part of the factors leading to ischaemic injury of the graft and DGF may be of immunological origin. One explanation would be that these patients are immunized towards the donor prior to transplantation. Kimball et al. [9] showed that cytotoxic crossmatch-negative primary transplant recipients may be donor-specific pretransplant crossmatch-positive when tested by flow-cytometry, and this finding correlated with SRRs.

The number of PRA-positive patients in our study and of transplantations with a suboptimal HLA match, although within our strict requirements for HLA-matching, was somewhat higher in the converters, but the levels of PRA did not explain differences in rejection frequency between converters and non-converters. Furthermore, the effect of conversion was more pronounced in the case of first transplantations than with retransplantations. Pre-existing low level immunity against the donor cannot be excluded as a cause of crossmatch conversion. However, donor-specific antibodies, which have been missed at the time of transplantation like non-complement-fixing antibodies, are not the probable explanation. After repeating the crossmatches with flow-cytometry, which picks up non-complement-fixing antibodies as well, no antibodies could be shown prior to transplantation.

Costa et al. [4] found that the rise of PRA after transplantation correlated with rejections not responding to standard therapy, which is in accordance with the results of the present study. Similar results were published by Monteiro et al. [14], who monitored pre- and post-transplant PRA levels by ELISA. They showed that the rise of PRA after transplantation was a deleterious sign and suggested that these patients were immunologically high responders. Anti-donor-specific HLA antibodies were not found by panel screening. However, direct crossmatch with donor cells was not performed.

Our converters may represent a subpopulation of high responders. As they had more HLA mismatches, they were exposed to a broader spectrum of HLA antigens in their grafts than the non-converters. This high responsiveness, however, was not caused by their own HLA allele repertory. The frequency of alleles was the same in all subgroups.

Whatever the mechanism behind the conversion of crossmatch at post-transplant day 14 is, together with DGF it indicates a subpopulation of patients producing potentially harmful antibodies. The target of these antibodies remains to be determined.

It has been postulated that antibodies against a graft may allow natural killer cells to infiltrate the graft and mediate the process of chronic rejection by antibody-dependent cell-mediated cytotoxicity [10]. In our study, the converters had a worse graft half-life than the non-converters, which may suggest that antibodies causing conversion may be involved in chronic rejection too.

Our results show that post-transplant crossmatch test conversion identifies renal transplant recipients with a poorer prognosis and alerts the clinician to the risk of insidious rejection and poor long-term survival especially with respect to patients with delayed graft function.

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