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Detrimental role of donor-recipient HLA-DQ_5 and -DQ_6 disparities on cadaver kidney graft survival

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Abstract. Donor-recipient incompatibility (D + R −) for HLA-DQ_1, but not for -DQ_2 or -DQ_3, is associated with an adverse effect on cadaver kidney graft survival. Until now, however, DQ_1 recipients of DQ_1-negative kidneys (D − R +) have not been differentiated from DQ_1-identical donor–recipient pairs (D + R +) and splits of DQ_1, DQ_5 and DQ_6, have not been studied in that respect. From our data (480 transplantations performed from January 1980 to December 1990), three donor–recipient DQ combinations (D + R +, D − R +, D + R −) were formed for each of four DQ specificities (DQ_2, DQ_3, DQ_5, DQ_6). As DR–DQ linkage disequilibrium is well conserved in caucasoid individuals, DQ specificities were inferred from the associated DR specificities. Graft survival rate (%) was significantly lower for the DQ_5 D + R − and the DQ_6 D − R + combinations when compared with the other corresponding DQ combinations, whereas no significant difference was observed between the DQ_2 and DQ_3 combinations. In conclusion, if DQ_1 plays a prominent role in kidney graft survival, the effects of its splits appear dissociated: DQ_5 could be a marker of high antigenicity and DQ_6 a marker of high responsiveness.

Key words: Cadaver kidney graft survival – HLA-DQ histocompatibility

In previous retrospective [11] and prospective [12] studies from our centre, donor–recipient HLA-DR disparities characterized by the presence of the antigen in the donor but not in the recipient, or vice-versa, were shown to affect cadaver kidney graft survival differentially. Some of those disparities were beneficial (DR4, DR5 and DR7 in the donor; DR5 in the recipient) whereas others were detrimental (DR1 and DR2 in the donor; DR2, DRW6 and DR7 in the recipient) for graft survival when compared with the other HLA-DR disparities.

More recently, donor–recipient HLA-DQ_1-incompatible grafts have been shown to have a poorer 1-year survival (65%) than DQ_1-compatible grafts (89%), whereas DQ_2 and DQ_3 did not influence graft prognosis [7]. In this study, however, DQ_1 compatibility involved both identity (D + R +) and DQ_1 recipients of DQ_1-negative kidneys (D − R +); splits of DQ_1, DQ_5 and DQ_6 were not studied.

The present study was undertaken to investigate the effects of donor–recipient DQ combinations on graft survival, differentiating the D − R + from the D + R + combinations when compared with the incompatible (D + R −) combination, for each of four DQ specificities (DQ_2, DQ_3, DQ_5 and DQ_6).

Materials and methods

Patients

From the data collected on 480 cadaver kidney transplantations performed at our centre between January 1980 and December 1990, three groups of donor–recipient DQ combinations (D + R +, D − R +, D + R −) were formed for each of four DQ specificities (DQ_2, DQ_3, DQ_5 and DQ_6). As DR–DQ linkage disequilibrium is very well conserved in caucasoid individuals [6], DQ specificities were inferred from their associated DR specificities: DQ_2 with DR3 and DR7, DQ_3 with DR4 and DR5, DQ_5 with DR1 and DRW10, and DQ_6 with DR2 and DRW6. This DR–DQ linkage was checked in 114 blood specimens from organ donors in which DR and DQ specificities were simultaneously determined.

Immunosuppressive therapy consisted of cyclosporin, azathioprine and prednisolone as previously described [11]. Prophylactic OKT3 was administered to 193 recipients during the first 2 weeks after transplantation, while the other patients received the triple therapy from the first postoperative day onwards. Rejection episodes were treated with pulses of methylprednisolone in most circumstances and the few corticoresistant episodes with either antilymphocyte globulin or OKT3. All but four recipients had received at least one pretransplant blood transfusion.

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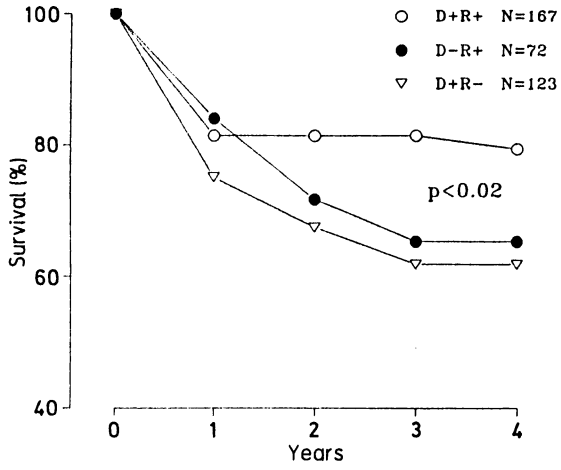

Fig. 1. Donor (D)/recipient (R) HLA-DQ_1 combinations and kidney graft survival. D + R +, D positive/R positive; D − R +, D negative/R positive; D + R −: D positive/R negative; NS, not significant; N, numbers of grafts

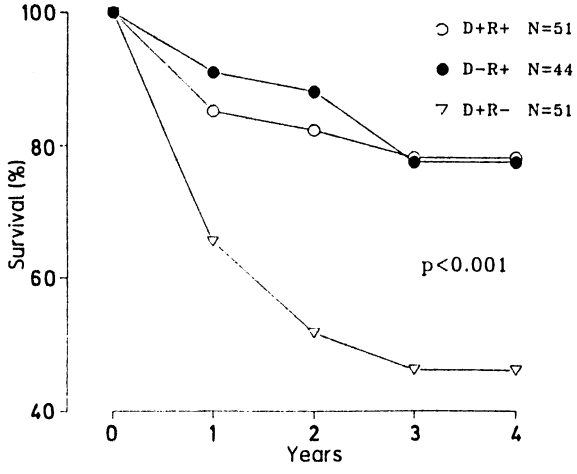

Fig. 2. Donor (D)/recipient (R) HLA-DQ_5 combinations and kidney graft survival

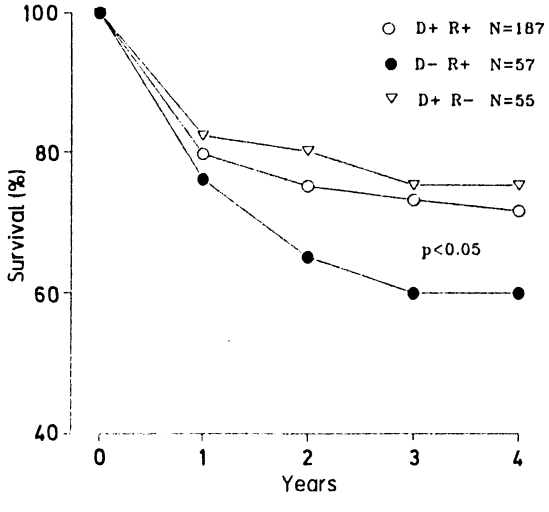

Fig. 3. Donor (D)/recipient (R) HLA-DQ_6 combinations and kidney graft survival

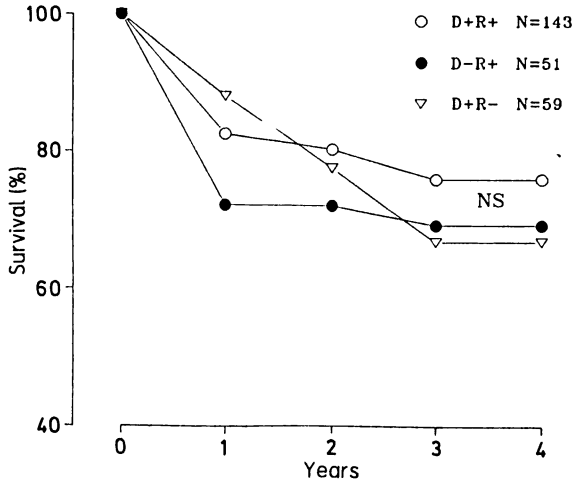

Fig. 4. Donor (D)/recipient (R) HLA-DQ_2 combinations and kidney graft survival

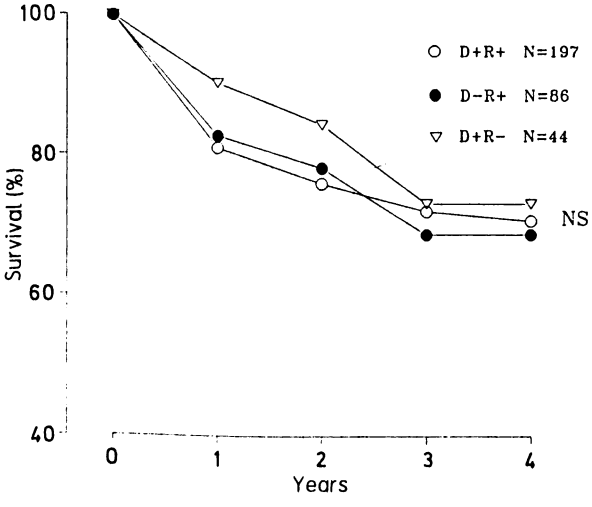

Fig. 5. Donor (D)/recipient (R) HLA-DQ_3 combinations and kidney graft survival

HLA typing

HLA-DR and -DQ typing was performed according to the standard NIH microcytotoxicity method [8], using sera obtained in our laboratory and those provided by Eurotransplant.

Statistical analysis

Graft survival was studied according to the actuarial life-table method [5], and differences between survival curves were assessed using the Lee–Desu statistic [4].

Results

The DR–DQ linkage disequilibrium was perfectly conserved between DQ_5 and DR1–DRW10 and between DQ_3 and DR4–DR5, but somewhat less well between DQ_6 and DR2–DRW6 and between DQ_2 and DR3–DR7 (Table 1). The overall concordance between the associated DR and DQ specificities was 89% (Table 2), validating the in-

Table 1. Linkage disequilibrium between HLA-DR and -DQ specificities

HLA-DR Specificities	No. of HLA-DQ specificities associated with HLA-DR				
	HLA-DQ_2	HLA-DQ_3	HLA-DQ_5	HLA-DQ_6	Total
1			10		10
2			5	25	30
3	24	1			25
4		23			23
5		43			43
W6		3	6	17	26
7	29	8			37
W10			6		6

Table 2. Concordance of associated HLA-DR and -DQ specificities

DQ_2 with DR3 and DR7	53/62	85%
DQ_3 with DR4 and DR5	66/66	100%
DQ_5 with DR1 and DRW10	16/16	100%
DQ_6 with DR2 and DRW6	42/56	75%
Overall DQ-DR	177/200	89%

ference of DQ from DR specificities for the total set of our data.

Graft survival was similar for HLA-DQ_1 in the D − R + and in the D + R − combinations; it was significantly lower than that observed in the D + R + combination (Fig. 1). When the splits of DQ_1 were separately considered, two donor–recipient combinations appeared significantly detrimental for the graft: DQ_5 D + R − (Fig. 2) and DQ_6 D − R + (Fig. 3). The graft outcome was not significantly different between the DQ_2 (Fig. 4) and DQ_3 (Fig. 5) donor–recipient combinations.

Discussion

Our results fully confirm the predominant role of DQ_1 in cadaver kidney graft survival, but the effects of its splits are dissociated. Whereas DQ_5 D + R − grafts behave poorly when compared with either the D − R + or the D + R + combination, survival for the DQ_6 D − R + combination is lower than that observed for either the D + R − or the D + R + combination.

The mechanisms underlying these results are still poorly understood as are those involved in alloreactivity. The demonstration of an influence of DQ molecules on kidney graft survival is surprising for, in vitro, the proliferative response observed in mixed lymphocyte reaction depends on DR and DP, but not on DQ molecules [9]. However, the recent demonstration of the prominent role of DQ as immune response molecules in diseases such as type I diabetes mellitus [10] opens the debate for a role of those antigens in transplantation, a hypothesis already put forward by Duquesnoy et al. [3] and more recently by Sengar et al. [7]. Assuming that the model proposed for class II molecules and applied for antigen presentation [2] is valid for alloreactivity, we are currently studying amino acid homologies on the top of the groove formed by the α_1 and β_1 chains of DQ molecules. Interestingly, only one amino acid of exon 2 of the DQ β_1 chain perfectly discriminates DQ_5 and DQ_6 from the other DQ alleles: glutamine characterizes DQ_5 and DQ_6 and leucine the other DQ alleles [6]. Whether this difference affects allodeterminant expression remains to be elucidated on a prospective basis.

Alternatively, HLA-DQ molecules produced by immune suppression (IS) genes could be involved in active suppression with respect to a specific antigen, as recently suggested by Altmann et al. [1]. Thus, according to the properties of their DQ molecules, recipients would be responders or nonresponders; DQ_6-positive recipients of DQ_6-negative kidneys would belong to the first category and recipients bearing other DQ molecules than DQ_6 to the second one. Here again, further studies are needed to establish a relationship between the presence of particular DQ molecules and the emergence of suppression mechanisms.

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