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# Is repeated mismatching at regrafting deleterious?

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**Abstract.** We reviewed our clinical experience of allowing kidney regrafting with a repeated HLA mismatch. We also permitted a weakly positive B-cell cross-match. All patients who received a second or subsequent renal graft ($n = 92$) between January 1985 and June 1990 were analysed for graft survival. The overall 1-year graft survival was 70%. A repeated mismatch occurred in 29 of the patients at at least one HLA locus and their 1-year graft survival was 66%. The balance of the regrafts (63) were performed without a repeated mismatch, and their 1-year graft survival was 70%. Even a weakly positive B-cell cross-match was deleterious; when a grafting with a repeated mismatch was performed only one out of five grafts survived. Our results indicate that retransplantation of renal grafts with a repeated mismatch in the HLA A or B locus can be performed without a negative influence on transplant outcome provided that both the T- and B-cell cross-matches are negative.

**Key words:** Regrafting – HLA mismatching – B-cell cross-match

In our clinic we had observed an accumulation of patients waiting for regrafting, a phenomenon observed also in many other institutions. Because of this, we decided in January 1985 to give priority to regrafting. Also, we questioned the previous belief that patients previously exposed to HLA antigens should not be grafted with tissue containing the same antigens (repeated mismatch). Contributing to our questioning were two clinical findings: (A) The first Scandinavian multicentre study failed to detect any beneficial effect of DR matching when cyclosporine was used as the main immunosuppressant despite the previously observed beneficial effect of DR matching on graft survival [5]; (B) Taube et al. suggested that it was possible to remove panel reactive antibodies by means of plasmapheresis and maintain a low level by the use of immunosuppression prior to transplantation and thereafter perform successful grafting [7].

We therefore decided to allow regrafting also with repeated mismatch on locus A, B or DR and perform kidney transplantations against a weakly positive B-cell cross-match. The only mandatory requirement for accepting a regraft was a negative T-cell cross-match.

This paper describes some features of such a policy carried out at a single institution. We have analysed the graft survival of all regrafts performed from January 1985 to June 1990 with regard to graft survival, waiting time, influence of repeated mismatches at any locus and the influence of a current positive B-cell cross-match.

## Materials and methods

### *Patients*

All patients who received a second or subsequent renal graft ($n = 92$) between January 1985 and June 1990 were analysed. This patient group represented 23% of the total number of renal graft recipients during the same time period.

### *Immunosuppression*

Base line immunosuppression for these patients generally consisted of conventional triple therapy and in about 50% of the cases ATG (Fresenius AG, Bad Homburg, FRG) or ALG (Horse ALG, Merieux Lyon, France) were given prophylactic ly. Anti-rejection therapy consisted of either methylprednisolone, ATG or ALG or OKT-3 (Ortho Pharmaceuticals, Raritan, New Jersey, USA).

### *Postoperative management*

The patients were monitored by daily laboratory parameters. In addition the grafts were frequently biopsied, as described elsewhere [8], as all regrafts were suspected to be of high immunological risk.

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*Pretransplant immunosuppression*

Patients who reacted to more than 50% of a random blood donor panel were also treated with pretransplant plasmapheresis or pretransplant immunoabsorption according to protocols described elsewhere [1, 2]. Nine out of the 29 patients with a repeated mismatch, and 11 out of the 63 patients without a repeated mismatch, received such a treatment.

*Cross-match technique*

A current cross-match was always performed prior to transplantation. These were carried out using the NIH technique [6] or using the dynal bead technique [9].

*Data presentation*

The actual results of the procedure were evaluated in terms of 1-year graft survival. The data are expressed as percentage survival of eligible grafts.

## Results

The results of this retrospctive study are summarized in Table 1. The overall 1-year graft survival was 70%. The median time on the waiting list was 4.5 months (0–31 months). A repeated mismatch occurred in 29 of the patients at at least one HLA locus and the 1-year graft survival in these patients was 66%. Their median time on the waiting list was 3 months (range 0–19 months). The balance of the regrafts (63) were performed without a repeated mismatch, and their 1-year graft survival was 70%. Their median waiting time was 6 months (0–31 months).

The 29 patients who had a repeated mismatch could be subdivided according to the locus for which they were mismatched. Three of these patients had mismatches in more than one locus and are therefore included more than once in the following discussion, (two of these three patients were doing well at the time of writing). Of 11 patients with a repeated mismatch at the A locus, 82% had a functioning graft after 1 year. Of 15 patients with a repeated mismatch at the B locus, only 60% had a functioning graft 1 year later. Amongst these patients, only 11 had a negative B-cell cross-match. The number of patients with repeated DR mismatches was low ($n = 6$), and the graft survival at 1 year was 50%. Only 25% of the grafts (1/4) with a repeated mismatch and a positive B-cell cross-match survived for 1 year.

**Table 1.** Percentage 1-year graft survival and median time on waiting list (range) for regrafts performed at our institution. Influence of repeated mismatch

| Regraft group | *n* | Survival (%) | Waiting time (months) |
|---|---|---|---|
| All | 92 | 70 | 4.5 (0–31) |
| With repeated mismatch | 29 | 66 | 3 (0–19) |
| Without repeated mismatch | 63 | 71 | 6 (0–31) |
| Repeated mismatches | | | |
| HLA-A | 11 | 82 | |
| HLA-B | 15 | 60 | |
| HLA-B with negative B-cell cross-match | 11 | 73 | |
| HLA-B with positive B-cell cross-match | 4 | 25 | |
| HLA-DR | 6 | 50 | |

## Discussion

We have shown that regrafts can be performed with a repeated mismatch with approximately the same graft survival as in patients without a repeated mismatch. The advantage of allowing repeated mismatches is that patients waiting for regraft are not unnecessarily denied an otherwise suitable graft. Subanalyses of such a policy shows good graft survival if there is a repeated mismatch at the A or B locus provided that the current B- and T-cell cross-match is negative. In our small experience, even a weakly positive B-cell cross-match should be regarded as a contraindication. The number of observations are too small to allow any firm conclusions regarding DR mismatch. Furthermore, because of a sometimes incomplete DR typing with close to a 20% blank registration of DR genes in the Scandinavian population, that analysis becomes even less meaningful.

Subanalyses of the cause of graft loss of any of the previous grafts as contributing to the outcome of the next graft was not possible in this small patient group. However, theoretically antigen presentation and sensitization may occur within 10 min after revascularization of a graft [4], and therefore the reason for a previous graft loss may only be of academic interest. A somewhat surprisingly good (about 80%) graft survival of repeated mismatched grafts in A and B loci was achieved at 1 year provided that the cross-matches were negative. This could even perhaps suggest that patients without circulating antibodies, despite previous graft exposure, may be tolerant to these antigens.

The ethical implications of our findings for organ allocation seem to fit well into a proposal for future organ allocation within the United States [3] where it was proposed to allocate at least one-quarter of the available kidneys presented to a local harvesting organization to high-risk patients.

In summary, our results indicate that retransplantation of grafts with repeated mismatch in HLA A or B loci can be done without a negative influence on transplant outcome, provided that both the T- and B-cell cross-matches are negative. This procedure makes it more likely for previously grafted patients to receive a graft within a reasonable time.

## References

1. Backman U, Fellström B, Frödin L, Sjöberg O, Tufveson G, Wikström B (1989) Successful transplantation in sensitized patients. Transplant Proc 21: 762–763
2. Danielson BG, Wikström B, Backman U, Fellström B, Tufveson G, Sjöberg O (1990) Pretransplant immunoabsorbtion plasma

treatment of HLA-immunized patients – preliminary report. Artif Organs 14 [Suppl 2] 231–232
3. Halasz NA (1991) Medicine and ethics, how to allocate transplantable organs. Transplantation 52: 43–46
4. Haltunen J, Häyry P (1987) Mobile blood-derived components in renal allograft contain significant immunogenic potential. Scand J Immunol 25: 121–126
5. Lundgren G, Groth CG, Albrektsen H, Brynger H, Flatmark A, Frödin L, Gäbel H, Husberg B, Klintmalm G, Maarer W, Persson H, Thorsby E (1986) HLA matching and pretransplant blood transfusions in cadaveric renal transplantation – a changing picture with cyclosporine A. Lancet II: 66–69
6. NIH lymphocyte microcytotoxicity technique (1916) In: Ray JG Jr, Hare DB, Pedersen PD, Mullally DI. NIAID manual of tissue typing techniques 1976–1977. (DHEW publication no. (NIH) 76-545) Government Printing Office, Washington, D. C., pp 22–24
7. Taube DH, Cameron IS, Ogg CS, Welsh KI, Williams DG, Bewick M, Rudge CJ, Kennedy LA, Thick MG (1984) Renal transplantation after removal and prevention of resynthesis of HLA-antibodies. Lancet I: 824–826
8. Tufveson G, Hanås E, Lindgren PG, Larsson E, Andersson T, Fellström B, Wahlberg J, Tötterman T (1989) A review of the Uppsala experience of Biopty-Cut renal transplant biopsies. Transplant Proc 21: 3581–3582
9. Vartdal F, Gaudernack G, Funderud S, Bratlie A, Lea T, Ugelstad J, Thorsby E (1986) HLA class I and II typing using cells positively selected from blood by immunomagnetic isolation – a fast and reliable technique. Tissue Antigens 28: 301–312