

Donor specific transfusions

Date written: June 2007

Final submission:

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GUIDELINES

- a. The best designed Randomised controlled trial demonstrates no advantage of donor-specific transfusions in graft survival (2 years) or incidence of acute rejection (Level II evidence)
- b. There is randomised controlled trial evidence (in a small trial) for a beneficial effect of donor-specific transfusions in cyclosporin-treated recipients of 1 haplotype mismatch living related donations in terms of less acute rejection and lower serum creatinine in the short term. Benefit on 1-year graft survival was not seen. (Level II evidence)

SUGGESTIONS FOR CLINICAL CARE

(Include information and suggestions based on Level III and IV evidence)

- The high risk of sensitization does not justify the routine use of donor-specific transfusions (Level III evidence)
- There is Level III evidence to suggest that a single pretransplant donor specific transfusion (DST) is as effective as multiple DSTs. (Level III evidence)
- The potential benefit of DST needs to be weighed against the risk of sensitization (~30%) and infection.
- There is insufficient evidence on the use of DSTs to assist deletion of donor-specific antibodies pretransplant to support their use.

Background

Maximising graft survival from living donors is a major goal in transplantation given the mismatch between the number of available donors and the ever-increasing number of recipients. Blood transfusion from living donors to the recipient prior to kidney transplantation was introduced several decades ago with the aim of improving graft outcome. However with reduced acute rejection rates with newer immunosuppressive agents and recombinant erythropoietin use, DST is rarely practiced. Modulating the immune response to the donor and inducing ‘pseudo-tolerance’ without having to rely heavily on immunosuppression however continues

to be a goal of transplantation medicine. When reviewing the evidence it needs to be recognized that there may be fundamental differences in the DST of today as red blood cells are now washed and essentially free of white blood cells which may have been the important mediator of the effect seen. Furthermore more recent literature suggests that the beneficial effect of tolerance develops only if the blood donor and recipient have 1 HLA haplotype or at least one HLA-B and one HLA-DR antigen in common (van Twuyer E). Many of the studies reviewed below do not specify these details.

Search strategy

Databases searched:

Databases searched: MeSH terms and text words for kidney transplantation and living donor were combined with MeSH terms and text words for blood transfusion. The search was carried out in Medline (1966 – September Week 2 2006). The Cochrane Renal Group Trials Register was also searched for trials not indexed in Medline.

Date of search: 26 September 2006

What is the evidence?

(Summary descriptions of trials – highlight key findings)

Level II evidence

The beneficial effect of donor specific transfusions (DST) in 1 haplotype mismatch living related donors was first suggested by Salvatierra et al, 1987. Since then 2 prospective randomized trials have been reported (Alexander JW et al 1999 and Sharma RK in 1997).

Alexander JW et al compared DST (24 hours prior to transplant and 7-10 days post) in 115 patients to 97 patients who did not receive DST. Immunosuppression was routine triple immunosuppression commenced post transplant. All patients were -HLA non-identical (>50% had more than 2 Class I mismatches and more than 1 Class II mismatch). There was a similar distribution of HLA mismatch between the 2 groups. More biopsy proven rejection episodes were seen in the DST group (81 vs 54 in non-DST) although this did not make statistical significance. There was however a significantly higher creatinine seen in the DST group at 7 and 14 days. This did not translate into a difference in 1 or 2 year graft survival. One of the primary outcomes of the study was the ability to withdraw steroid treatment with no significant difference seen between the 2 groups. There was no difference in adverse events between the 2 groups. The inclusion of a diverse degree of HLA matches and too small a sample size to adequately study the effect of DST for the different HLA matches may have flawed this study.

Sharma et al in a smaller prospective trial randomized living related recipients n=15 to receive DST (1 transfusion 24 hours prior to transplant) or no DST, n=15. All patients received cyclosporin 3 days prior to transplant and continued routine triple therapy post transplant. In addition all patients received 3rd party transfusions 2-3 weeks prior to transplantation to correct anaemia. They found a significantly greater

incidence of acute rejection in the non-DST group (1.1 per patient vs 0.26, $p < 0.01$). A significantly lower creatinine was also seen in the DST group from 3 months to 12 months post transplant (at 12 months 1.12 vs 2.02 mg/dl, $p < 0.05$) however there was no difference in graft survival in the short term (1 year). It is difficult to extrapolate results from this study to current practice because the degree of HLA match was not specified and patients in both groups received 3rd party transfusions to correct anaemia (prior to standard erythropoietin usage).

Bordes-Aznar et al reported a small randomized trial comparing the outcome of DST to cyclosporine and prednisone, followed by azathioprine in living related recipients who were haploidentical but had highly reactive mixed lymphocyte cultures (MLC). This group traditionally has a lower graft survival and is considered high risk. There was no difference in patient or graft survival at 1 year between the 2 groups (70% graft survival in both). 30% of potential donors were not able to be used because of sensitization. Immunosuppression was not given during the transfusion periods. Sample size immunosuppression was not clearly stated and the randomization method was not explained.

Level III evidence

In 2006, Marti et al reported a prospective study of 61 potential allograft recipients (adults >16 yrs) both living related and unrelated who received DST's and compared them to carefully selected matched controls from the CTS (Collaborative Transplant Study Group). The controls were matched for age, sex, related vs unrelated, original disease, cold ischemia time, number of transplant, year of transplant, time on dialysis and HLA match. All patients were on cyclosporine and prednisone with 31/55 also receiving either azathioprine or mycophenolate. There was not significant difference in induction therapy between the DST and matched control group. Although there was a trend to better allograft survival in the DST group (98% vs 82%) this failed to reach statistical significance and when examined on an intention to treat basis, the 6 year graft survival of the DST group was 88.5%. There was no statistically significant difference in 1 year serum creatinine, or treated acute rejection rate between the 2 groups. Of concern was that fact that 10% (n=6) patients in the DST group developed positive T cell crossmatches following the transfusions and living donation did not proceed. This study was underpowered to look at graft survival differences and historical controls were used. There were more pre-emptive transplants in the DST group (although time on dialysis was similar).

Sonoda et al retrospectively analyzed patients in the Japanese transplant registry. 1292, one HLA haplotype mismatch LRD patients were analyzed in subgroups according to immunosuppression (cyclosporin n=315; or no cyclosporin n=977) and DST transfusion (97 of the 315 cyclosporin; 298/977 without cyclosporin). In the cyclosporin groups the graft survival rate at 4 years for those with DST was 93.5% vs 76.2% for those with 3rd party transfusion (not DST) and 62.7% for those without transfusion. This improvement in graft survival was not seen in the non-cyclosporin group where the 4 year graft survival for DST was 73.3%, 73.2% for 3rd party and 69% for those with no transfusion.

Davies et al prospectively (not randomized) compared 3 different protocols for DST:

1. Multiple DST with azathioprine during the period and oral cyclosporin post transplant (n=34)
2. Multiple DST with azathioprine during this period and oral cyclosporin 1 day pre-transplant.
3. Single pretransplant DST 24 hours prior to transplant with pretransplant intravenous cyclosporin. All patients were LRD recipients with a 1 haplotype mismatch. There was no significant difference in recipient age, panel reactive antibodies (PRA) or the number of 3rd party transfusions between the 3 groups. There was no significant difference in the acute rejection rate or in 1 year patient or graft survival between the 3 groups. There was however a significantly higher incidence of CMV infection in Group 2 vs the other groups (16% vs 0% and 0%).

Satoh et al retrospectively examined long term (3-13 years) graft survival in 52 one-haploidentical living related first renal transplants and compared them with historical controls (n=12, 38 respectively) Recipients received 3 DST's without immunosuppression. Historical controls were not extensively matched as in the study by Marti et al and the DST group had significantly lower donor age. All patients received prednisone, azathioprine and cyclosporine. There was no significant difference in acute rejection or long term graft survival rates between the 2 groups. 16.7 % (N=2) of the DST group developed donor specific antibodies which were subsequently removed by plasmapheresis and T and B cell crossmatches became negative. ;This study was important in demonstrating that longer term graft survival was not different as one of the hypotheses regarding use of DST's was that it may reduce chronic rejection and therefore alter long term outcome.

Otsuka et al retrospectively analysed 40 potential recipients of DST and cyclosporin and compared them to a historical control who received a one haplotype matched living related kidney but no DST during the same period (n=13). All patients received a calcineurin inhibitor. Cyclosporin was administered at the time of DST. There was no significant difference in graft survival rate and 5 and 10 years between the 2 groups and no difference in acute rejection rates within 3 months after transplant. The sensitization rate was 7.5% and 1 patient of the 3 who developed positive crossmatches could not proceed with living donation. One patient developed CMV infection as a consequence of the DST.

Lezaic et al retrospectively compared living related transplant recipients who had received DST (with azathioprine cover) n=19 to 15 untransfused patients and 25 random polyinfused patients. Post transplant immunosuppression consisted of azathioprine, cyclosporine and prednisone. Serum creatinine was significantly higher at 1 and 3 years in the non-transfused group compared to the DST and the randomly transfused group despite the fact that there were no differences in the incidence of acute rejection or early graft function. There was also no difference in HLA mismatch, MLC reactivity and panel reactivity. There is little detail however on the patients in this report and how the groups compared were selected. Numbers included are small. 15.7% developed cross-reactivity with their donors in the DST group.

Flye et al examined the effect of 3 200mL aliquots of donor specific transfusions given biweekly with azathioprine cover in 163 living related or living unrelated potential renal transplant recipients. The number of mismatches ranged from 1-2.

Following transplantation only prednisone and azathioprine were given and their outcome was compared to a group of HLA identical living recipients (n=53) and a group of 1-2 mismatched living donor recipients (n=54) treated with triple immunosuppression and induction therapy. Permanent T cell crossmatch sensitization occurred in 11 of the 163 patients (7%). Actual 1 and 5 year graft survivals were 94%, 100%, 100% and 72%, 85% and 71% respectively for the DST treated groups. This was comparable to the HLA identical group. No lymphoproliferative or CMV disease was seen in the DST group.

In a retrospective paediatric study (Leone et al), results of DST with post transplant immunosuppression of prednisone and azathioprine was compared to a routine triple immunosuppression group. All received haploidentical grafts. 3 of 24 treated with DST had circulating cytotoxic AB to the donor. There was no difference in graft or patient survival at 1 year or mean rejection episodes. However there was less hospitalization and less severe rejection in the first 3 months in the cyclosporine (non-DST) group. Given the equivalent graft survival and the risk of recipient sensitization they concluded that routine triple immunosuppression was preferable.

Summary of the evidence

Please refer to the enclosed evidence tables

What do the other guidelines say?

Kidney Disease Outcomes Quality Initiative: There is some evidence that donor-specific transfusion with living donor transplantation improves survival, but the decision to perform donor-specific transfusion must still be made on a case-by-case basis. Blood transfusions can induce antibodies to histocompatibility leukocyte antigens that can reduce the success of kidney transplantation; thus, transfusions generally should be avoided in patients awaiting a renal transplant.

UK Renal Association: No recommendation.

Canadian Society of Nephrology: No recommendation.

European Best Practice Guidelines: No recommendation.

INTERNATIONAL GUIDELINES:

Implementation and audit

No recommendation.

Suggestions for future research

No recommendation.

References

Alexander JW, Light JA, Donaldson LA et al. Evaluation of pre- and posttransplant donor-specific transfusion/ cyclosporine A in non-HLA identical living donor kidney transplant recipients. Cooperative Clinical Trials in Transplantation Research Group. *Transplantation* 1999; 68: 1117 – 1124.

Bordes-Anznar J, Odor A, Dib-Kuri F et al. Randomized clinical trial of cyclosporine or donor specific transfusion in high risk living related donor transplantation. *Transplantation Proc* 1987; 19: 2276 – 77.

Davies CB, Alexander JW, Cofer BR et al. Efficacy of a single pretransplant donor-specific transfusion and cyclosporin A administered 24 to 48 hours before one-haplotype-mismatched living related donor kidney transplant. *Ann Surg* 1992; 215: 618 – 625.

Mardi H, Henschkowski J, Laux et al. Effect of donor-specific transfusion on the outcome of renal allografts in the cyclosporine era *Transplant International* 2006; 19: 19 – 26.

Otsuka M, Yuzawa K, Takada Y et al. Long term results of donor-specific blood transfusion with cyclosporine in living related transplantation. *Nephron* 2001; 88: 144 – 148.

Salvatierra O Jr, Vincenti F, Amend W et al. Deliberate donor-specific blood transfusions prior to living related renal transplantation. A new approach. *Ann Surg* 1980; 192: 534 - 52.

Satoh S, Sugimura J, Omori S et al. Long-term graft survival with or without donor-specific transfusion in cyclosporine era in one haplo-identical living related renal transplant recipients beyond the first year: a 19 year experience. *Tohoku J Exp Med* 2002; 197: 201 – 207.

Sharma RK, Rai PK, Kular A et al. Role of preoperative donor-specific transfusion and cyclosporine in haplo-identical living related renal transplant recipients. *Nephron* 1997; 75: 20 – 24.

Sonoda T, Ishibashi M. Donor-specific transfusion: a report of the Japanese Renal Transplant Registry. *Clin Transpl* 1987; 257 – 60

Appendices

Table 1 – Characteristics of included studies

• Study ID (author, year)	N	Study Design	Setting	Participants	Intervention (experimental group)	Intervention (control group)	Follow up (months)	Main conclusions	Comments
Alexander et al 1999	212	Randomised controlled clinical trial	8 centres, US	Non-HLA identical living kidney transplant recipients	Donor-specific transfusion	No intervention	21 months	DST had no practical effect on patient or graft survival for up to 2 yrs, donor-specific responsiveness was more frequent in transfused patients.	
Sharma et al 1997	30	Randomised controlled clinical trial	India	Haplotype-matched living related renal transplant recipients	Donor-specific transfusion	No intervention	13 to 18 months	DST and cyclosporine administered 24h before Tx is effective in improving graft function and reducing acute rejection.	

Table 2 – Quality of randomised trials

Study ID (author, year)	Method of allocation concealment *	Blinding			Intention-to-treat analysis †	Loss to follow up (%)	Quality Score
		(participants)	(investigators)	(outcome assessors)			
Alexander et al 1999	Central	No	No	No	No	5.8%	
Sharma et al 1997	Computer generated	No	No	No	Not stated	0.0%	

* Choose between: central; third party (e.g. pharmacy); sequentially labelled opaque sealed envelopes; alternation; not specified.

† Choose between: yes; no; unclear.

Quality score: Very well (+), okay (Ø). Poorly (-)

Table 3 – Results for dichotomous outcomes

Study ID (author, year)	Outcomes	Intervention group (number of patients with events/number of patients exposed)	Control group (number of patients with events/number of patients not exposed)	Relative risk (RR) [95% CI]	Risk difference (RD) [95% CI]
Alexander et al 1999	Immunological hyporesponsiveness	1/37	9/49	0.15 (95%CI: 0.03, 1.11)	-0.16 (95%CI:-0.28, -0.04)
	Mortality at 2 years	4/115	2/97	13.69 (95%CI: 0.32, 9.01)	0.01 (95%CI:-0.03, 0.06)
	At least one rejection	60/115	44/97	1.15 (95%CI: 0.87, 1.52)	0.07 (95%CI:-0.07, 0.20)
Sharma et al 1997	Severe SSR	2/15	3/15	0.67 (95%CI:0.13, 3.44)	-0.07 (95%CI:-0.33, 0.20)
	Mortality	1/15	2/15	0.50 (95%CI:0.05, 4.94)	-0.07 (95%CI:-0.28, 0.15)
	Graft loss	2/15	3/15	0.67 (95%CI:0.13, 3.44)	-0.07 (95%CI:-0.33, 0.20)

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