Pre-formed Donor-Specific HLA-Antibodies in Living and Deceased Donor Transplantation

A Multicenter Study

Malte Ziemann, Wolfgang Altermann, Katharina Angert, Wolfgang Arns, Anette Bachmann, Tamam Bakchoul, Bernhard Banas, Anette von Borstel, Klemens Budde, Vanessa Ditt, Gunilla Einecke, Ute Eisenberger, Thorsten Feldkamp, Siegfried Görg, Martina Guthoff, Antje Habicht, Michael Hallensleben, Falko M. Heinemann, Nicole Hessler, Christian Hugo, Matthias Kaufmann, Teresa Kauke, Martina Koch, Inke R. König, Christine Kurschat, Claudia Lehmann, Matthias Marget, Anja Mühlfeld, Martin Nitschke, Luiza Pego da Silva, Carmen Quick, Axel Rahmel, Thomas Rath, Petra Reinke, Lutz Renders, Florian Sommer, Bernd Spriewald, Oliver Staeck, Dirk Stippel, Caner Süsal, Bernhard Thiele, Daniel Zecher, Nils Lachmann

Supplemental material

Supplemental Table 1: Multivariable Cox regression models for graft survival differentiating for DSA strength.

A: Total overall graft survival for living donors (n=1189, 135 observations deleted due to missing data)

	Hazard ratio (95% CI)	*p*-value
Pretransplant donor-specific HLA antibodies (DSA)		
DSA < 3000 MFI	**2.16 (1.06 - 4.40)**	**0.03**
DSA ≥ 3000 MFI	**2.97 (1.51 - 5.84)**	**0.002**
Pretransplant desensitization		
ABO-incompatible transplantation	**2.16 (1.06 - 4.40)**	**0.001**
Desensitization in ABO-compatible transplantation	2.97 (1.51 - 5.84)	0.22
Time on dialysis, per year	**1.15 (1.04 - 1.27)**	**0.004**
Number of HLA-A/B/DR-mismatches, per mismatch	**1.19 (1.03 - 1.37)**	**0.02**

B: 3-month overall graft survival for deceased donors (n=2322, 486 observations deleted due to missing data)

	Hazard ratio (95% CI)	*p*-value
Pretransplant donor-specific HLA antibodies (DSA)		
DSA < 3000 MFI	1.70 (1.29 - 2.23)	0.05
DSA ≥ 3000 MFI	1.04 (0.69 - 1.58)	0.92
Patient age, per year	0.99 (0.98 – 1.00)	0.13
Kidney donor risk index (KDRI, Rao et al.[1])	**2.48 (2.13 - 2.89)**	**<0.001**

C: Late overall graft survival for deceased donors (n=2142, 450 observations deleted due to missing data)

	Hazard ratio (95% CI)	*p*-value
Pretransplant donor-specific HLA antibodies (DSA)		
DSA < 3000 MFI	1.57 (1.23 - 2.01)	**0.07**
DSA ≥ 3000 MFI	**1.90 (1.49 - 2.43)**	**0.009**
Patient age, per year	**1.05 (1.04 - 1.05)**	**<0.001**
Kidney donor risk index (KDRI, Rao et al.)	**1.51 (1.34 - 1.71)**	**<0.001**

95% CI: 95% interval of confidence, MFI: medium fluorescence intensity.

Supplemental Table 2: Multivariable Cox regression models with center as random effect.

A: Overall graft survival for living donors (n=1189, 135 observations deleted due to missing data)

	Hazard ratio (95% CI)	*p*-value
Pretransplant donor specific antibodies	**2.47 (1.43 - 4.28)**	**<0.001**
Pretransplant desensitization		
ABO-incompatible transplantation	**2.10 (1.33 - 3.34)**	**0.001**
Desensitization in ABO-compatible transplantation	1.76 (0.79 - 3.92)	0.16
Time on dialysis, per year	**1.16 (1.05 - 1.28)**	**0.004**
Number of HLA-A/B/DR-mismatches, per mismatch	**1.18 (1.02 - 1.37)**	**0.02**

B: Overall graft survival for deceased donors (n=2322, 486 observations deleted due to missing data)

	Hazard ratio (95% CI)	*p*-value
Pretransplant donor specific antibodies	**1,59 (1,20 - 2,12)**	**0.001**
Patient age, per year	**1,02 (1,01 - 1,03)**	**<0.001**
Kidney donor risk index (KDRI, Rao et al.)	**1,85 (1,53 - 2,23)**	**<0.001**

95% CI: 95% interval of confidence.

Supplemental Table 3: Multivariable Cox regression models for death-censored graft survival.

A: Death-censored graft survival for living donors (n=1322, 2 observations deleted due to missing data)

	Hazard ratio (95% CI)	*p*-value
Pretransplant donor-specific HLA antibodies	**3.78 (2.12 – 6.74)**	**<0.001**
Pretransplant desensitization		
ABO-incompatible transplantation	**2.46 (1.46 - 4.12)**	**<0.001**
Desensitization in ABO-compatible transplantation	**2.30 (1.03 - 5.13)**	**0.04**
Time on dialysis, per year	**1.18 (1.05 - 1.32)**	**0.004**

B: Death-censored graft survival for deceased donors (n=2119, 689 observations deleted due to missing data)

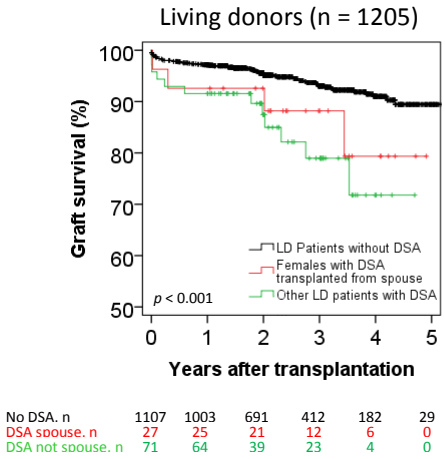
	Hazard ratio (95% CI)	*p*-value
Pretransplant donor-specific HLA antibodies	**1.57 (1.11 - 2.22)**	**0.01**
Initial immunosuppression		
Tac/MMF/steroids	Reference	
CsA/MMF/steroids	**0.72 (0.54 - 0.97)**	**0.03**
other	0.88 (0.60 - 1.28)	0.50
Retransplantation	**1.49 (1.02 - 2.17)**	**0.04**
Kidney donor risk index (KDRI, Rao et al.[1])	**2.40 (2.00 - 2.89)**	**<0.001**

95% CI: 95% interval of confidence, CsA: Cyclosporine A, MMF: Mycophenolate-mofetil, Tac: tacrolimus.

The increased risk of graft failure in patients receiving a desensitization treatment prior to ABO-compatible transplantation has to interpreted with caution, because it just reached the predefined level of significance ($p<0.05$) and was not found for overall graft survival. Nevertheless, the association could be due to reverse causation: Desensitization was performed more often in patients deemed to be at high risk for rejection due to information not available in this study (e. g. early loss of previous transplants due to rejection). As these patients also have decreased graft survival, an association between desensitization treatment and worse graft survival is observed.

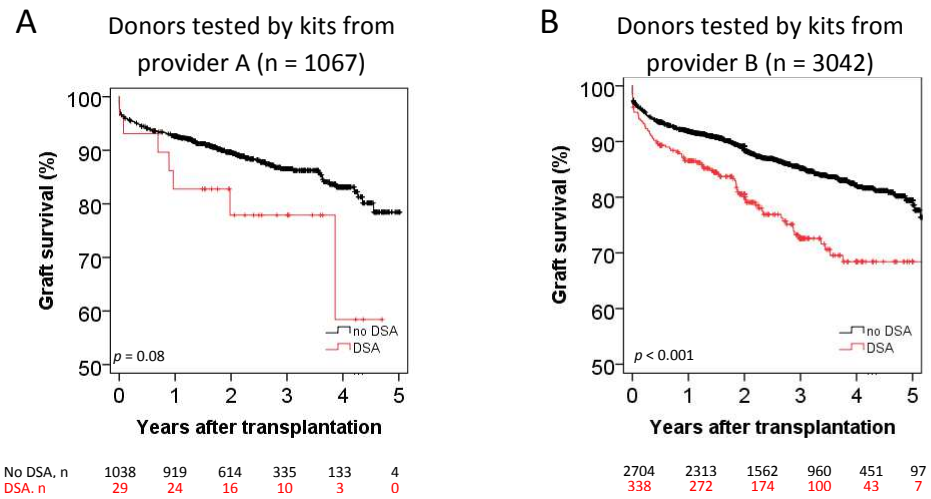
The same phenomenon of reverse causation might have caused the association between Ciclosporin A and decreased risk of graft failure, because Ciclosporin A was thought to be less suitable for patients at high risk for allograft rejection.[2] A recent metaanalysis of randomized trials, however, showed only marginal differences between CNI-based regimens and mTOR-inhibitors.[3]

Supplemental Figure 1: Overall graft survival of females transplanted from their spouse.



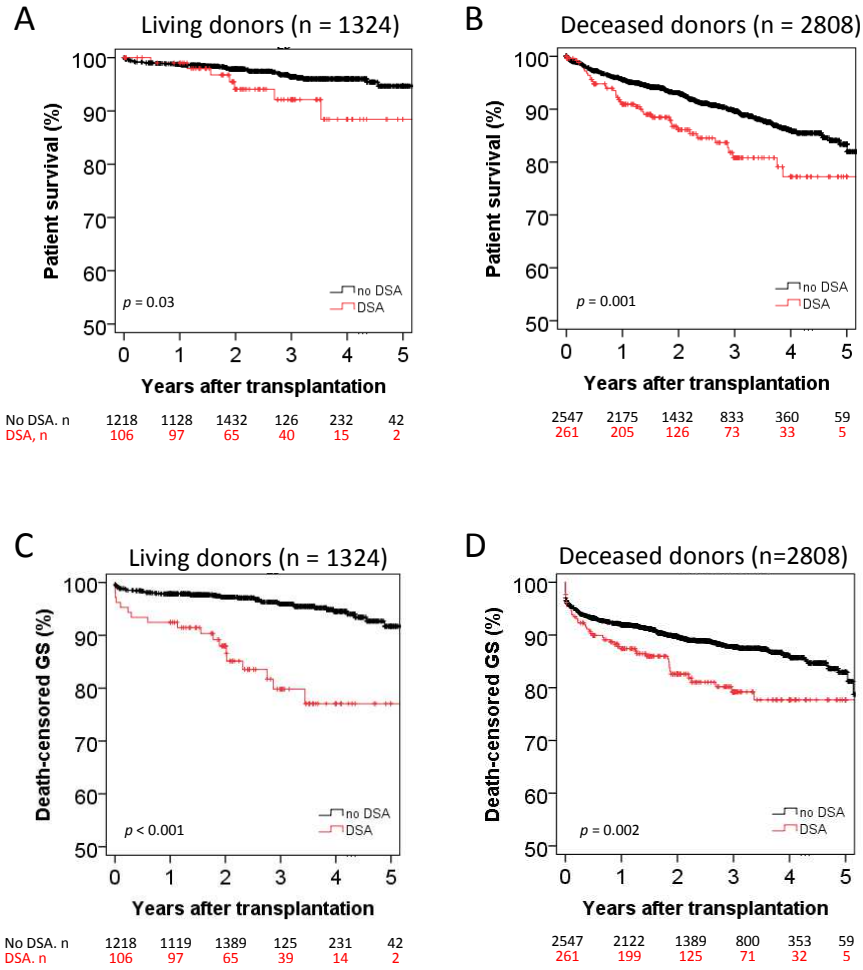
Overall graft survival is shown for female patients with pretransplant donor-specific HLA antibodies (DSA) transplanted with a kidney from their spouse, other patients with DSA prior to living transplantation, and living donor recipients without DSA. Patients with DSA had decreased graft survival, but there is no visible difference between female patients with DSA transplanted with a kidney from their spouse and other patients with DSA prior to living transplantation. 119 patients were excluded from this comparison because no information about the relationship between donor and recipient was available.

Supplemental Figure 2: Overall graft survival according to test method.



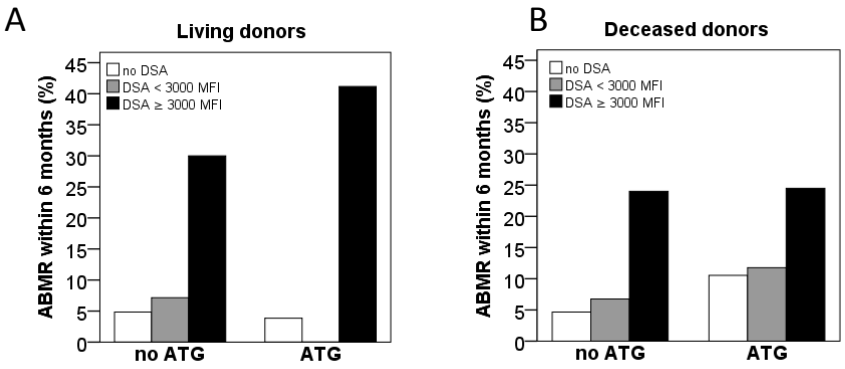
Overall graft survival according to the presence of pretransplant donor-specific HLA antibodies (DSA) is depicted for (A) patients tested by kits from provider A, and (B) patients tested by kits from provider B.

Supplemental Figure 3: Patient survival and death-censored graft survival.



According to the presence of pretransplant donor-specific HLA antibodies (DSA) are depicted: (A) patient survival for living donors, (B) patient survival for deceased donors, (C) death-censored graft survival (GS) for living donors, and (D) death-censored graft survival for deceased donors.

Supplemental Figure 4: Induction treatment with ATG and antibody-mediated rejections.



Induction treatment with ATG showed no association with a lower incidence of antibody-mediated rejection.

References

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