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ANALYSIS OF IMMUNOLOGICAL RISK FACTORS OF T-CELL AND ANTIBODY-MEDIATED REJECTION AFTER ORGAN TRANSPLANTATION

Komise pro obhajoby doktorských disertací v oboru: Imunologie

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1. INTRODUCTION AND STATE OF THE ART

Organ transplantation is the treatment of choice for chronic end-stage kidney disease (ESRD) (1) and is a life-saving procedure for heart, lung and liver organ failure (2) (3) (4). A serious complication, despite the remarkable progress in immunosuppressive regimens in recent years, is the development of acute allograft rejection. T-cell mediated rejection (TCMR) remains an independent-risk factor for graft loss (5), while antibody-mediated rejection (AMR) is currently considered to be the most important immunological reason of allograft failure (6) (7). Previously it was believed that acute AMR develops in about 10-15% of all kidney graft-rejection episodes, however now, it is accepted that its incidence is higher due to the fact that a number of cases might have been previously misdiagnosed (8). It is well-documented that AMR and TCMR often occur simultaneously, furthermore, pathological signs like tubulointerstitial inflammation and injury are common both in TCMR and chronic AMR (9). The immune reaction to the organ allograft involves components of the adaptive (specific) immunity, i.e., T-, B- lymphocytes, antibodies (10), and innate (non-specific) immunity – NK cells, macrophages, neutrophils, the complement system, etc. (11). The adaptive alloimmune response includes cellular cytotoxicity, the antibody response, and delayed type hypersensitivity (DTH) reaction (12). T cells are represented by Th1, Th2, Th17 and regulatory T cells (Tregs). Th1 and Th17 cells secrete proinflammatory cytokines (such as IFN-gamma/TNF-alpha and IL-17, respectively), while Th2 cells release anti-inflammatory cytokines such as IL-10 and IL-4 (13) (10).

Assessing the immunological risk of transplant rejection (patient risk stratification) is of vital importance, because low immunosuppression may lead to acute rejection and irreversible damage of the allograft, while on the other hand, too strong immunosuppressive therapy has serious side effects, like tumor growth and severe (opportunistic) infections (14) (15) (16). Currently, various tests provide information about the state of cellular and humoral immunity before and after organ transplantation (17) (18) (19). Techniques assessing cellular immunity include the mixed lymphocyte reaction (MLR), the Enzyme-linked Immunosorbent Spot (ELISpot) assay, flow cytometry detection of cellular activation markers and etc. In the transplant situation, the ELISpot assay is generally used to determine cytokine-producing (IFN-gamma, IL-2, etc.) memory/effector T cells (17) (20). On the other hand, the wide application of solid phase tests for detection of HLA-specific antibodies led to substantial improvement of the diagnosis of AMR (21) (22). In certain cases, antibodies to non-HLA antigens - the MHC Class I chain-related molecules – MICA, MICB, the Angiotensin II Type 1 Receptor (ATR1), tubulin, vimentin, etc. may cause AMR, even accelerated AMR (hyperacute graft rejection) (23) (24). These antibodies may be detected by the Luminex and ELISA methods (25) (26), (ATR1) (27), or by tests based on the isolation of endothelial cells and subsequent analysis by flow cytometry (XM-One Kit) (28).

2. AIMS

The aim of this doctoral thesis was to study immunological risk factors for the development of T-cell and antibody-mediated rejection and their relevance for survival of the kidney, heart and liver organ transplants. For this purpose, our efforts were aimed to:

2.1 Assess the significance of measurement of frequencies of donor-specific IFN-γ-producing cells to predict acute cellular (TCMR) and antibody mediated rejection (AMR) after kidney transplantation from living donors. The numbers of pre-transplant IFN-γ-secreting cells were correlated with the incidence of TCMR and AMR, HLA mismatches and with other selected risk factors for rejection.

2.2 Analyze the efficacy and safety of administration of Bortezomib and Rituximab for the treatment of refractory (resistant) AMR in a cohort of high-risk patients from our transplantation center.

2.3 Evaluate the feasibility of implementing a European kidney exchange program with the objective to facilitate transplantation of immunologically high-risk patients with a low chance for transplantation with a donor from their own country.

2.4 Assess the clinical relevance of preformed, persistent and de novo-produced complement-binding donor-specific antibodies (DSA), as defined by solid-phase techniques for prediction of antibody-mediated rejection after liver transplantation.

2.5 Compare the levels of B-Cell Activating Factor (BAFF) between kidney transplant patients with diagnosed AMR and a control group of recipients without rejection, with the aim to test the hypothesis that BAFF concentrations may be helpful as a diagnostic marker of AMR.

2.6 Evaluate the relationship between HLA and MICA-specific antibodies detected before transplantation and the incidence of rejection in heart transplant recipients. Another aim of this study was to assess the pathogenicity of these DSA and their complement-binding capacity.

2.7 In a cohort of patients with failed kidney allografts, determine whether de novo produced donor-specific HLA antibodies are associated with kidney graft loss.

3. ACHIEVED RESULTS

3.1 Pre-transplant donor-specific Interferon-gamma-producing cells and acute rejection of the kidney allograft. Slavcev A, Rybakova K, Svobodova E, Slatinska J, Honsova E, Skibova J, Viklicky O, Striz I. Transpl Immunol 2015; 33(2): 63-8. doi: 10.1016/j.trim.2015.07.007

Our retrospective study included a cohort of 47 patients who underwent living donor kidney transplantation. The pre-transplant frequencies of donor-specific Interferon-gamma (IFN-γ) producing cells were defined by ELISpot assay and correlated with the incidence of acute cellular (TCMR), antibody-mediated rejection (AMR) and kidney graft survival up to one year after transplantation. An important observation of our study was the significant correlation between pre-transplant frequencies of IFN-γ-producing cells and HLA mismatches (HLA–A, –B, and simultaneously HLA–A, –B, and –DR) between recipients and their respective donors. The correlation between the frequencies of IFN-γ-secreting cells and the incidence of TCMR within 1 year after transplantation did not reach statistical significance. Nevertheless, after both allogeneic and autologous stimulation, patients with TCMR grade II had higher frequencies of IFN-γ-secreting cells compared with patients without rejection. Given that 58% of all cellular rejection episodes during the first month after transplantation were defined as TCMR grade II, the ELISpot assay may thus provide important information indicating increased risk of the more severe type of cellular rejection. Interestingly, patients with both acute TCMR and AMR had higher frequency of activated cells than patients with cellular rejection only.

3.2 Efficacy and safety of Bortezomib treatment for refractory acute antibody-mediated rejection - a pilot study. Slatinska J, Slavcev A, Honsova E, Hruba P, Kratochvilova I, Rohal T, Viklicky O. HLA. 2018; 92, Suppl 2:47-50. doi: 10.1111/tan.13387.

The aim of our study was to analyze the efficacy and safety of administration of Bortezomib and Rituximab in the treatment of refractory (resistant) AMR. Resistant AMR was defined by persisting deterioration of graft function in spite of depletion of DSA by plasmapheresis and application of intravenous immunoglobulins (IVIG) and Rituximab. Bortezomib is a proteasome inhibitor, an anticancer drug, originally applied to treat multiple myeloma and other malignancies. After Bortezomib treatment, we found a significant decrease of DSA to HLA-B and HLA-DR, but not to HLA-A and HLA-DQ antigens. Graft survival after therapy of resistant AMR in our cohort was comparable with that after re-transplantation. Statistical significance was observed between the 3-year graft survival of recipients after first transplantation and those with refractory AMR and also between first

and retransplant patients. The toxicity profile of this treatment regimen suggests that an exposure to higher doses of Bortezomib may be further studied.

3.3 A Europe wide acceptable mismatch program will enable transplantation of long waiting highly sensitised patients with a compatible donor. Mumford L, Fuggle SV, Martorell J, Slavcev A, Iniotaki A, Haasnoot GW, Heidt S, Claas FHJ. Transpl Immunol. 2021; 64: 101354. doi: 10.1016/j.trim.2020.101354.

The main objective of the EUROSTAM project (Europe-wide Strategy to enhance Transplantation of highly sensitized patients on the basis of Acceptable HLA Mismatches) was to compare the chance of transplanting highly sensitized patients in different European populations with donors outside their own donor pool. Information on the HLA type, AB0 group and the acceptable mismatches of long waiting highly sensitized patients were obtained from Eurotransplant (ET), UK, Barcelona, Prague (IKEM) and Athens. Out of more than three hundred hypersensitized patients identified in UK, the computer simulations revealed that 27% patients would benefit from being registered in a different European transplant waiting list. In the 23 long-waiting patients identified in IKEM, it was found that 4 patients would profit from being registered in another transplant waiting list. In the waiting list of Eurotransplant, it came out that 27 hypersensitized patients would have advantage from being registered outside Eurotransplant. Totally, 27% of all long-waiting patients from each partner organization included into this multinational study would have an increased probability to find a compatible kidney graft in a different donor pool. This simulation study provides evidence for the utility of starting of a Europe-wide program to facilitate transplantation of highly sensitized patients who have very low chance to be transplanted with donors derived from the local donor pool. The next phase should focus on the logistics of such an effort, which may also include the introduction of international kidney paired exchange programs for highly sensitized patients with an incompatible living donor.

3.4 De novo HLA Class II antibodies are associated with the development of chronic but not acute antibody-mediated rejection after liver transplantation - a retrospective study. Kovandova B, Slavcev A, Honsova E, Erhartova D, Skibova J, Viklicky O, Trunecka P. Transpl Int. 2020; 33(12): 1799-1806. doi: 10.1111/tri.13763

We included in our study a cohort of 120 liver allograft recipients, who were transplanted in our center between the years 2015 and 2017. No effect of preformed HLA-specific antibodies (both DSA and non-

DSA) on the incidence of acute AMR after transplantation was found. In contrast, liver recipients with preformed complement binding HLA Class I antibodies (C1q + and C3d+), both DSA and non-DSA, developed more frequently AMR than patients without HLA Class I complement-binding antibodies. In contrast with another report, we found no correlation between AMR and pretransplant HLA-specific complement-non-binding DSA. On the other hand, preformed complement-binding DSA directed to HLA Class I antigens came up as a clear predictor for the development of acute AMR. An important observation in our study was that de novo HLA antibodies to Class II antigens (including non-DSA were strongly associated with the incidence of chronic AMR. The reason why non-DSA to HLA Class II antigens predicted an increased risk for the development of chronic AMR is unclear. A probable explanation could be that DSA (both HLA Class I and Class II antibodies) might be bound to HLA antigens in the graft and extracted from the recipient blood circulation.

3.5 Soluble BAFF cytokine levels and antibody-mediated rejection of the kidney allograft. Slavcev A, Brozova J, Slatinska J, Sekerkova Z, Honsova E, Skibova J, Striz I, Viklicky O. Arch Immunol Ther Exp (Warsz). 2016; 64(Suppl 1): 47-53. doi: 10.1007/s00005-016-0428-4.

The B-cell activating factor (BAFF) is a cytokine belonging to the TNF superfamily and supports survival, maturation, and activation of B lymphocytes. It has been reported that the BAFF cytokine might facilitate the production of DSA. The aim of our study was thus to compare BAFF levels between high-risk patients with diagnosed AMR and a control group of patients without rejection, i.e., to test the hypothesis whether BAFF concentrations might be useful as a diagnostic marker of AMR. In AMR patients, BAFF levels were defined before transplantation and during rejection. In the control patient group, BAFF was determined before transplantation and 3 months after transplantation. The measured values of the BAFF cytokine before transplantation did not show significant differences between the patient groups with and without rejection. When analyzed separately (patients with AMR only and patients with simultaneous AMR and ACR), the group of patients with AMR had a trend of lower concentrations of BAFF in comparison with the control group. In contrast, patients with simultaneous AMR and ACR had significantly lower concentrations of BAFF vs. patients without rejection. No correlation was found between BAFF levels in patients with AMR and the production of DSA. Our results suggest that soluble BAFF measurements might be helpful as a marker of ongoing AMR and especially of simultaneous antibody-mediated and cellular rejection after kidney transplantation.

3.6 Novel insights into pretransplant allosensitization in heart transplant recipients in the contemporary era of immunosuppression and rejection surveillance. Svobodova E, Gazdic T, Kubanek M, Vymetalova J, Voska L, Kment M, Lanska V, Kolesar L, Urban M, Netuka I, Pirk J, Melenovsky V, Kautzner J, Slavcev A, Malek I. Transpl Int. 2016; 29(1):63-72. doi: 10.1111/tri.12684.

In this study, we analyzed the relevance of the standard complement-dependent (CDC) assay and the solid-phase tests, including the C1q-binding method, to predict rejection and graft survival in heart transplant recipients. We found association between preformed DSA to HLA and the development of AMR, especially early onset AMR. In agreement with other reports, we did not detect correlation between pretransplant allosensitization and impaired graft survival. Pretransplant MICA antibodies were not related to adverse clinical events, in addition, the C1q-binding assay did not provide additional predictive value to the standard single-antigen (solid phase) antibody testing. An intriguing finding was that the increasing number of DSA and cumulative mean fluorescence intensity of DSA were associated with stronger pathogenic effect of DSA. An important finding of our study is the additional value of elevated maximal (historical peak) PRA as defined by the standard CDC method to predict AMR. De novo production of DSA has been associated both with AMR and decreased survival in heart transplant recipients; however, this was not evaluated in our study. In conclusion, identification of preformed DSA by solid-phase methods, in addition to PRA monitoring by the complement-dependent (CDC) test, are helpful predictors of the development of AMR after heart transplantation.

3.7 Süsal C, Wettstein D, Döhler B, Morath C, Ruhenstroth A, Scherer S, Tran TH, Gombos P, Schemmer P, Wagner E, Fehr T, Živčić-Ćosić S, Balen S, Weimer R, Slavcev A, Bösmüller C, Norman DJ, Zeier M, Opelz G. Association of kidney graft loss with de novo produced donor-specific and non-donor-specific HLA Antibodies detected by single antigen testing. Transplantation 2015; 99: 1976–1980

A cohort of 83 patients with failed kidney grafts was studied with the goal to assess whether de novo produced DSA specific to HLA antigens as detected by the solid phase - single antigen bead (SAB) assay are associated with graft loss. Recipients with failed kidney grafts had pre-transplant sera and post-transplant serum samples obtained before graft failure. The control group with functioning grafts was matched for the most important confounding factors. The production of weak de novo DSA or non-DSA with MFI of ≥ 500 was higher in the graft loss cohort than in the non-rejector group. An important finding of our study was that 43% of patients with post-transplant DSA (de novo or persistent) in the graft failure cohort had C1q-binding antibodies (DSA and/or non-DSA) before graft loss, whereas none

of the patients in the control group showed C1q positivity. This finding suggests that the presence of C1q-reactive complement-binding HLA antibodies after transplantation may indicate an ongoing graft injury. Altogether, our findings indicate that pre- and posttransplant HLA antibody determinations provide prognostic information with respect to the identification of patients who are at increased risk of graft loss. The development of weak de novo HLA antibodies, even if not directed against mismatched HLA alleles of the donor, should be judged with caution due to the possibility of ongoing antibody-mediated rejection.

4. CONCLUSIONS

4.1 Kidney recipients with TCMR grade II had higher frequencies of IFN-γ-producing cells compared to patients without rejection. The ELISpot assay may thus provide important information indicating the increased risk of the more severe type of cellular rejection. Pre-transplant determination of the number of donor-specific IFN-γ-producing cells is helpful in the assessment of the status of patient T cell immunity before kidney transplantation from living donors.

4.2 In our patient cohort with resistant AMR, treatment with Bortezomib was generally well tolerated. In line with the results of other centers, we found a significant depletion of DSA to HLA-B and HLA-DR antigens, but not to HLA-A and HLA-DQ antigens.

4.3 International collaboration between European countries in sharing kidneys (kidney exchange programs) and eventually other organs (hearts, lungs, etc.) would be of help in finding acceptable donors and transplanting highly-sensitized patients.

4.4 Liver transplant recipients with preformed complement-binding HLA Class I antibodies, both DSA and non-DSA, developed more frequently AMR than patients without HLA Class I complement-binding antibodies. De novo HLA antibodies to Class II antigens (including non-DSA) were strongly associated with the incidence of chronic AMR.

4.5 The levels of the BAFF cytokine were significantly lower in patients with concurrent acute AMR and TCMR compared with patients free of rejection. Thus, soluble BAFF concentrations might be helpful as a marker of ongoing AMR and especially of simultaneous antibody-mediated and cellular rejection after kidney transplantation.

4.6 An association was found between preformed DSA and the development of AMR, especially early onset AMR after transplantation in heart transplant recipients. Identification of preformed DSA, in addition to panel-reactive antibody measurement, are helpful for predicting the development of AMR after heart transplantation.

4.7 HLA antibody determination pre-and posttransplant provides clinically significant information with respect to the identification of patients who are at increased risk of graft loss. The development of weak de novo HLA antibodies should be interpreted with caution due to suspected ongoing antibody-mediated rejection.

6. PUBLICATIONS INCLUDED INTO THE DISSERTATION THESIS

6.1 Pre-transplant donor-specific Interferon-gamma-producing cells and acute rejection of the kidney allograft. Slavcev A, Rybakova K, Svobodova E, Slatinska J, Honsova E, Skibova J, Viklicky O, Striz I. Transpl Immunol 2015; 33(2): 63-8. doi: 10.1016/j.trim.2015.07.007.

6.2 Efficacy and safety of Bortezomib treatment for refractory acute antibody-mediated rejection - a pilot study. Slatinska J, Slavcev A, Honsova E, Hruba P, Kratochvilova I, Rohal T, Viklicky O. HLA 2018; 92 Suppl 2:47-50. doi: 10.1111/tan.13387.

6.3 A Europe wide acceptable mismatch program will enable transplantation of long waiting highly sensitised patients with a compatible donor. Mumford L, Fuggle SV, Martorell J, Slavcev A, Iniotaki A, Haasnoot GW, Heidt S, Claas FHJ. Transpl Immunol 2021; 64:101354. doi: 10.1016/j.trim.2020.101354.

6.4 De novo HLA Class II antibodies are associated with the development of chronic but not acute antibody-mediated rejection after liver transplantation - a retrospective study. Kovandova B, Slavcev A, Honsova E, Erhartova D, Skibova J, Viklicky O, Trunecka P. Transpl Int 2020; 33(12): 1799-1806. doi: 10.1111/tri.13763.

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6.6 Novel insights into pretransplant allosensitization in heart transplant recipients in the contemporary era of immunosuppression and rejection surveillance. Svobodova E, Gazdic T, Kubanek M, Vymetalova J, Voska L, Kment M, Lanska V, Kolesar L, Urban M, Netuka I, Pirk J, Melenovsky V, Kautzner J, Slavcev A, Malek I. Transpl Int 2016; 29(1): 63-72. doi: 10.1111/tri.12684.

6.7 Süsal C, Wettstein D, Döhler B, Morath C, Ruhenstroth A, Scherer S, Tran TH, Gombos P, Schemmer P, Wagner E, Fehr T, Živčić-Ćosić S, Balen S, Weimer R, Slavcev A, Bösmüller C, Norman DJ, Zeier M, Opelz G. Association of kidney graft loss with de novo produced donor-specific and non-donor-specific HLA Antibodies detected by Single Antigen testing. Transplantation 2015; 99: 1976–1980

7. REFERENCES

1. Garcia GG, Harden P, Chapman J. The global role of kidney transplantation. Curr Opin Organ Transplant. 2012;17(4):362-7.
2. Awad MA, Shah A, Griffith BP. Current status and outcomes in heart transplantation: a narrative review. Rev Cardiovasc Med. 2022;23(1):11.
3. Bos S, Vos R, Van Raemdonck DE, Verleden GM. Survival in adult lung transplantation: where are we in 2020? Curr Opin Organ Transplant. 2020;25(3):268-73.
4. Zarrinpar A, Busuttil RW. Liver transplantation: past, present and future. Nat Rev Gastroenterol Hepatol. 2013;10(7):434-40.
5. Randhawa P. T-cell-mediated rejection of the kidney in the era of donor-specific antibodies: diagnostic challenges and clinical significance. Curr Opin Organ Transplant. 2015;20(3):325-32.
6. Cornell LD. Histopathologic Features of Antibody Mediated Rejection: The Banff Classification and Beyond. Front Immunol. 2021;12:718122.
7. Rodriguez-Ramirez S, Al Jurdi A, Konvalinka A, Riella LV. Antibody-mediated rejection: prevention, monitoring and treatment dilemmas. Curr Opin Organ Transplant. 2022;27(5):405-14.
8. Nankivell BJ, P'Ng CH, Shingde M. Glomerular C4d Immunoperoxidase in Chronic Antibody-Mediated Rejection and Transplant Glomerulopathy. Kidney Int Rep. 2022;7(7):1594-607.
9. Hara S. Cell mediated rejection revisited: Past, current, and future directions. Nephrology (Carlton). 2018;23 Suppl 2:45-51.
10. Cozzi E, Colpo A, De Silvestro G. The mechanisms of rejection in solid organ transplantation. Transfus Apher Sci. 2017;56(4):498-505.
11. Murphy SP, Porrett PM, Turka LA. Innate immunity in transplant tolerance and rejection. Immunol Rev. 2011;241(1):39-48.
12. Phillips BL, Callaghan C. The immunology of organ transplantation. Surgery (Oxford). 2017;35(7):333-40.
13. Alegre ML, Florquin S, Goldman M. Cellular mechanisms underlying acute graft rejection: time for reassessment. Curr Opin Immunol. 2007;19(5):563-8.
14. Srinivas TR, Meier-Kriesche HU. Minimizing immunosuppression, an alternative approach to reducing side effects: objectives and interim result. Clin J Am Soc Nephrol. 2008;3 Suppl 2(Suppl 2):S101-16.
15. Fishman JA. Opportunistic infections--coming to the limits of immunosuppression? Cold Spring Harb Perspect Med. 2013;3(10):a015669.

16. Bestard O, Thaunat O, Bellini MI, Böhmig GA, Budde K, Claas F, et al. Alloimmune Risk Stratification for Kidney Transplant Rejection. Transpl Int. 2022;35:10138.

17. Crespo E, Bestard O. Biomarkers to assess donor-reactive T-cell responses in kidney transplant patients. Clin Biochem. 2016;49(4-5):329-37.

18. Bestard O, Cravedi P. Monitoring alloimmune response in kidney transplantation. J Nephrol. 2017;30(2):187-200.

19. Eikmans M, Gielis EM, Ledeganck KJ, Yang J, Abramowicz D, Claas FFJ. Non-invasive Biomarkers of Acute Rejection in Kidney Transplantation: Novel Targets and Strategies. Front Med (Lausanne). 2018;5:358.

20. Girmanova E, Hruba P, Viklicky O, Slavcev A. ELISpot assay and prediction of organ transplant rejection. Int J Immunogenet. 2022;49(1):39-45.

21. Lobashevsky AL. Methodological aspects of anti-human leukocyte antigen antibody analysis in solid organ transplantation. World J Transplant. 2014;4(3):153-67.

22. Tait BD. Detection of HLA Antibodies in Organ Transplant Recipients - Triumphs and Challenges of the Solid Phase Bead Assay. Front Immunol. 2016;7:570.

23. Sumitran-Karuppan S, Tyden G, Reinholt F, Berg U, Moller E. Hyperacute rejections of two consecutive renal allografts and early loss of the third transplant caused by non-HLA antibodies specific for endothelial cells. Transpl Immunol. 1997;5(4):321-7.

24. Villa C, Mesa K, Cristy Smith M, Mooney DM, Coletti A, Klohe E. Hyperacute graft dysfunction in an orthotopic heart transplant in the presence of non-HLA antibodies. Am J Transplant. 2020;20(2):593-9.

25. Kamburova EG, Kardol-Hoefnagel T, Wisse BW, Joosten I, Allebes WA, van der Meer A, et al. Development and Validation of a Multiplex Non-HLA Antibody Assay for the Screening of Kidney Transplant Recipients. Front Immunol. 2018;9:3002.

26. Senev A, Ray B, Lerut E, Hariharan J, Heylen C, Kuypers D, et al. The Pre-Transplant Non-HLA Antibody Burden Associates With the Development of Histology of Antibody-Mediated Rejection After Kidney Transplantation. Front Immunol. 2022;13:809059.

27. Dragun D, Catar R, Kusch A, Heidecke H, Philippe A. Non-HLA-antibodies targeting Angiotensin type 1 receptor and antibody mediated rejection. Hum Immunol. 2012;73(12):1282-6.

28. Breimer ME, Rydberg L, Jackson AM, Lucas DP, Zachary AA, Melancon JK, et al. Multicenter evaluation of a novel endothelial cell crossmatch test in kidney transplantation. Transplantation. 2009;87(4):549-56.