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Overview of the Poster Presentations at the International Symposium “Chronic Rejection in Experimental and Clinical Transplantation: New Strategies in Research and Therapy”

Tatiana V. Lebedeva, Detlef Meyer, and Ana Maria Waaga

Great progress has been made in the prevention of chronic rejection in organ transplantation over the past 2 decades. However, it still remains the limiting factor in transplanted organ survival. Two poster sessions reflected the variety of approaches being developed to resolve this problem.

The 1st session was devoted to the experimental studies of chronic rejection. Different strategies aimed at suppression of allogeneic response studied in animal models were presented. Dr. Otto (Würzburg, Germany) presented a study on immunomodulation of the allogeneic response with peptides derived from the β -chain hypervariable domain of major histocompatibility complex (MHC) class II molecules. The peptides were used with or without low-dose cyclosporin A (CsA) treatment. One of the peptides, RT1.B2, inhibited alloresponse and prolonged allograft survival time 2-fold. Interestingly, no RT1.B2-reactive T cells were detected in the immunized animals on day 40 after immunization. Although it remains unclear whether the observed inhibition of alloresponse was due to anergy induction or clonal deletion, this study suggests a promising approach to suppression of allorecognition and prevention of chronic rejection.

The applicability of gene therapy, with the aim to prolong allograft survival, was assessed by the work of Dr. Suzuki (Tokyo, Japan). In addition to the problem of chronic rejection, graft arterial disease

(GAD) limits long-term survival of recipients in heart transplantation. A gene therapy approach was used in this study to control the inflammation and cell proliferation in the murine and primate cardiac allografts. Double-stranded DNA with specific affinity for NF- κ B (NF- κ B decoy) or E2 transcription factors were delivered intraluminally into allografts using hemagglutinating virus of Japan (HVJ), the liposome method. Both decoys dramatically reduced expression of inflammatory molecules, cell infiltration, and overall GAD in the murine model. Only E2 decoy was used in the primate model and produced a similar drastic suppression of GAD. No complications or dissemination of HVJ into other organs was observed, suggesting that HVJ may be the gene delivery method of choice in organ transplantation. Transplant cardiac sclerosis is another factor limiting the survival time of cardiac transplants. The study presented by Dr. Deuse (Würzburg, Germany) characterized metabolic function of native hearts and grafts by Langendorff perfusion in the heterotopic rat cardiac transplant model. The study demonstrated that VASP Ser¹⁵⁷-phosphorylation is a reliable parameter that can assess the functional state of the transplant.

In kidney transplantation, prolonged cardiac arrest in human donors (> 45 min) leads to progressive end-stage changes in the graft, which are usu-

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ally fatal to the recipient within 6 months. The problems of using organs from non-heart-beating donors (NHBD) were addressed in the animal model study presented by Dr. Gasser on behalf of Dr. Laskowski (Boston, Massachusetts, USA). Allo- or isografts were performed using grafts from either NHBD or live donors (LD) as control. The animals were followed up for 12 weeks, with urinary protein measured monthly, and representative tissue samples for morphology taken at 2 and 12 weeks. All groups received low dose CsA for 10 days and survived throughout the follow-up period. Unlike LD recipients, NHBD allo- and isograft recipients showed progressive proteinuria. Morphologically, kidney isografts from NHBD showed relatively severe early acute tubular necrosis and subsequent moderate interstitial fibrosis and glomerular injury, whereas NHBD allografts developed major injury with massive cortical atrophy, glomerular proliferation, and sclerosis. Iso- and allograft LD kidneys remained relatively unaffected. The results suggest that immunologically independent structural changes in NHBD isografts dramatically increase in NHBD allografts, emphasizing the continuum between initial non-specific donor-associated injury and the effects of alloresponsiveness.

Ongoing studies aimed at the modification of existing protocols and the development of new ones for tolerance induction were reflected in a series of presentations. One method for induction of lasting donor-specific tolerance is a combination of irradiation, T-cell depletion, and donor bone marrow infusion. The study, presented by Dr. Strüber (Hanover, Germany), evaluated a simplified protocol for inducing immune unresponsiveness to pulmonary allografts in the miniature swine model. Before lung transplantation, experimental animals received a single dose whole body and thymic irradiation. All animals, including controls, received immunosuppressive drugs for 28 days after transplantation. Although all control animals were lost to severe acute rejection within 28 h after withdrawal of immunosuppression, severe acute rejection was observed in only 1 out of 7 irradiated animals. Two irradiated animals died of infection, with no signs of rejection. Three irradiated pigs demonstrated unaffected graft function for up to

330 days after withdrawal of immunosuppression. This study suggests that single-dose irradiation may prove to be a powerful tool for prevention of pulmonary allograft rejection. The potentially irreversible impairment of the immune system by irradiation, however, calls for caution in applying this protocol to clinical transplantation. Another aspect of a complex specter of complications following lung transplantation was by Dr. Schade (Dresden, Germany). The long-term survival of lung transplant recipients is limited greatly by the bronchiolitis obliterans syndrome. The effect of Rolipram, a phosphodiesterase 4 inhibitor and anti-inflammatory agent, was compared with that of either CsA alone or the combination of these 2 drugs in rat heterotopic tracheal transplantation model. Rolipram alone was less effective than CsA alone, whereas the combination of these drugs effectively reduced the numbers of proliferating fibroblasts and, subsequently, the luminal obliteration in chronic rejection phase.

Cancer development and recurrence are the ominous risk factors in immunocompromised transplant patients. This problem calls for the development of new protocols and drugs that reduce the risk of cancer while providing long-term immunosuppression. In this regard, the ability of rapamycin to inhibit neovascularization and growth of the murine liver adenocarcinoma and its metastases was reported in the study presented by Dr. Guba (Regensburg, Germany). The effects of daily i.p. injections of rapamycin (1.5 mg/kg) and CsA (10 mg/kg) were compared at day 11 after intraportal implantation of adenocarcinoma cells. Rapamycin treatment dramatically reduced the size of tumor implants when compared with both CsA treatment and control saline injections. Only small avascular metastases were observed in rapamycin-treated mice, whereas CsA induced large vascularized metastases. This effect was apparently due to a marked suppression of angiogenesis, which was probably due to the suppression of vascular endothelial growth factor levels. The authors also suggested that this antiangiogenic effect of rapamycin could decrease the risk of chronic transplant rejection.

An interesting study of apoptotic signaling pathways in tolerized and rejected orthotopic liver allografts was presented by Dr. Zehle (Kiel, Germany).

The authors recently demonstrated that spontaneously tolerized allogeneic liver grafts circumvent acute rejection by deleting allospecific effector cells via expression of Fas-L on graft hepatocytes. The present study focused on the apoptosis-mediating signaling pathways in rejected liver as compared with tolerized liver grafts. Arterialized orthotopic liver allografts were performed in 4 groups of rats: DA→LEW, LEW→DA, LEW→LEW, and DA→DA. Intrinsic tolerance induction in the 2nd group correlated with Fas-L expression on graft hepatocytes, which was not observed in the 1st rejected group or in syngeneic hosts. Assessed by TUNEL staining, hepatocytes expressing Fas-L induced apoptosis of graft-infiltrating effector lymphocytes. In contrast, liver graft rejection correlated with expression of Fas, Granzyme B, and caspase 3 on graft hepatocytes. The authors concluded that liver allograft rejection was mediated by Fas and Granzyme B signaling pathways.

The role of gender in transplant outcomes was examined by 2 groups. Currently, the gender of the recipient is not considered when choosing an immunosuppressive regimen. The study by Dr. Inoue (Japan) titled "Are Women Privileged Organ Recipients?" addressed this issue. The authors retrospectively reviewed 205 recipients who received their 1st renal allograft at Sangenjaya Hospital under the regimen based on either cyclosporine or FK506. The study showed that although there was no difference in demographics and immunosuppressive protocols between genders, the outcomes were more favorable for female recipients. Fewer female recipients lost the graft function (14% versus 35%), and acute rejection and/or chronic allograft nephropathy led to graft loss in 8% of female versus 25% of male recipients. The study poses the question of whether gender physiology alone is responsible for the different outcomes of renal transplants or if behavioral factors also contribute to this difference. In this regard, the role of estrogen in the development of transplant vascular sclerosis in heterotopic rat heart transplantation was assessed in the study presented by Dr. Lange (Würzburg, Germany). Female, ovariectomized F344 rats were used as recipients of heart grafts derived from LEW rats. Three groups of rats received a short-term immunosuppression treatment and either 17-β estro-

diol, estrogen antagonist ICI182.789, or a placebo. The study demonstrated that estrogen therapy led to reduced levels of transplant vascular sclerosis, with a lower level of CD4, CD8, and monocytic cell infiltration, and a lower expression of MHC II antigen expression in the grafts.

Clinical studies of different aspects of chronic rejection were presented in the 2nd session. Three studies focused on the risk factors that may influence the outcome of transplantation. The study presented by Dr. Jungraithmayr (Freiburg, Germany) addressed the role of CMV infection in the long-term outcome of kidney transplants in children and adolescents. In a prospective open-label trial, 66 pediatric renal transplant recipients were subjected to triple therapy of MMF, cyclosporine, and steroids over a 3-year period after transplantation. The correlation of graft survival, function, and rejection rate with the CMV status of donor was evaluated. Under this treatment, patients with high risk of CMV had long-term outcomes similar to other groups. The study suggests that the treatment protocol that includes MMF, CsA, and steroids is efficacious in patients at high risk of CMV infection.

The study presented by Dr. Hergesell (Heidelberg, Germany) evaluated the prevalence of post-transplant diabetes in patients receiving standard, triple immunosuppressive therapy. According to the Collaborative Transplant Study, graft recipients with diabetes have reduced long-term graft outcome after renal transplantation when compared with nondiabetic recipients. Recent studies suggest that hyperglycemia is a harmful cofactor influencing renal graft outcome. The study demonstrated that 35% of patients not classified as diabetics before transplantation developed elevated levels of fasting plasma glucose on day 21 after transplantation. Fifty percent of these patients experienced an acute interstitial and/or vascular rejection episode within this period. The authors concluded that careful monitoring of blood glucose and prompt therapy should be mandatory after renal transplantation.

Hyperhomocysteinemia is an independent risk factor for cardiovascular disease in renal transplant patients, whereas folate treatment is efficacious in correcting elevated levels of homocystein. Elevated, total homocystein levels have been shown to corre-

late with methyltetrahydrofolate reductase (MTHFR) gene polymorphism. The study presented by Dr. Szabo (Budapest, Hungary) focused on the effect of MTHFR C677T polymorphism for the efficacy of folate treatment in reducing homocystein levels in children and adolescents with renal transplants. Thirty renal transplant patients were screened for total serum homocystein and folate levels before and after folate treatment. The study demonstrated the efficacy of folate treatment in normalizing total homocystein level in pediatric and adolescent renal transplants. Dr. Buss (Munich, Germany) reported the clinical experience with 12 cases of pediatric heart-lung transplantation. Indications for the transplant were primary pulmonary hypertension, polycystic lung disease, and lung vein-occlusive disease. Basic immunosuppressive regimen included tacrolimus, mycophenolatomofetil, and prednisolone. In one case, mycophenolatomofetil was substituted with azathioprin because of gastrointestinal side effects, and in 3 patients, tacrolimus was substituted with CsA because of the development of lymphoproliferative disease or acute pulmonary graft rejection. To date, chronic pulmonary graft rejection was observed in 2 patients, at 23 and 60 months after transplantation. The authors noted that, due to the relatively short period of observation, no definite conclusions on the efficacy of the immunosuppressive regimen could be drawn. However, this regimen appeared to maintain a low rate of acute and chronic rejection.

Three groups attempted to develop practical and reliable methods of prognosis for graft outcome, which still poses a problem in transplantation. The study presented by Dr. Wicht (Halle/Saale, Germany) suggested a complex urinary protein analysis that can be used for primary diagnostics of renal transplant dysfunction, as well as for the differentiation of glomerular and tubular dysfunction. The analysis included the evaluation of total protein, creatinine, IgG, albumin, transferrin, β -1-macroglobulin, β -2-microglobulin, retinol binding protein, and urinary NAG activity. The study from the University of Tübingen presented by Dr. Braun demonstrated that with well-controlled blood pressure, newly developed proteinuria, but not arterial blood pressure, affects the outcome of renal transplantation in patients.

The presentation by Dr. Theuerkauf (Bonn, Germany) focused on the changes in liver acinar zone 3 and sinusoidal endothelial cells (SEC) during chronic rejection as prognostic factors in orthotopic liver transplant. Follow-up needle biopsies and explanted grafts were used for morphometric and immunohistochemical analysis of endothelial cell markers (CD31, CD34, and CD105). The correlation of these results with clinical outcomes and radiological findings was assessed. In addition to the characteristic features of chronic liver rejection, the authors reported de novo expression of CD105 by centrilobular SEC, increase in venular fibrosis, and persistent loss of centrilobular hepatocytes. These changes were associated with graft failure within a relatively short period. The authors suggested that these changes might be due to reduced arterial flow caused by arteriopathy and may be useful in graft outcome prognosis in patients with chronic liver rejection.