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Meeting Report

The Art and Science of Immunosuppression: The Fifth Annual American Society of Transplant Surgeon's State-of-the-Art Winter Symposium

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The 2005 American Society of Transplant Surgeons (ASTS) Winter Symposium entitled 'The Art and Science of Immunosuppression' explored ways to maximize existing immunosuppressive protocols and to develop new strategies incorporating novel agents and emerging diagnostic technologies to customize immunosuppression and reduce side effects. Several presentations evaluated steroid withdrawal or avoidance protocols reflecting the significant difficulties of bone loss, glucose control and growth retardation in children associated with long-term steroid use. Calcineurin-inhibitor related renal dysfunction of both native and transplanted kidneys was identified as significant, but no consensus was reached concerning effective prevention. Similarly, recurrence of Hepatitis C following liver transplantation was identified as problematic without identifying a preferred immunosuppressive regimen in this setting. Control of T-cell mediated rejection was found to be excellent, but recognition and treatment of non-T cell causes of allograft damage (i.e. B- or NK-cell mediated) was identified as an area of current interest. Immunosuppressive agents under development, such as those blocking costimulation or cytokine signals, and JAK-3 inhibitors were discussed. Finally, the available technologies for molecular and genetic diagnostics and the clinical correlation in the post-transplant setting were discussed.

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Introduction

During the last 50 years, solid organ transplantation has changed from a modestly successful therapy offered only to patients with renal failure to a highly successful therapy offered to patients with end-stage failure of the kidney, liver, pancreas, intestine, lung or heart. Much of this change can be attributed to improvements in immunosuppression that have dramatically lowered acute cellular rejection rates, thereby facilitating extrarenal organ transplantation with acceptable patient and graft survival. In the last 10 years, new classes of immunosuppressive drugs with varying potency and side effect profiles have reached the clinic. Moreover, molecular diagnostics have emerged as practical strategies to monitor individual immune responses in real time. Armed with these new tools, the transplantation community can now envision designing and manipulating immunosuppression to fit individual recipients, maximizing outcomes and minimizing morbidity. The Fifth Annual American Society of Transplant Surgeons' State-of-the-Art Winter Symposium aimed to explore the current art and science of immunosuppression.

Overview

As the keynote speaker, Halloran (University of Alberta) highlighted broad opportunities for the science of immunosuppression to improve patient outcomes. He suggested that improved immunosuppression in contrast to tolerance induction, was the more realistic means of achieving what he identified as the Holy Grail of transplantation: 'healthy patients with healthy grafts'. Halloran proposed that the best immunosuppression stabilizes a patient's adaptive response to their graft and suggested that better immunosuppression is predicated on a sophisticated and complete understanding of rejection processes. He also questioned the adequacy of traditional notions of acute rejection as an effector T-cell mediated process best diagnosed by allograft biopsy.

Recent reports show various cell types present during acute rejection in allograft biopsies indicating heterogeneous mechanisms despite homogeneous histopathology (1). He presented his own work in a murine renal model showing that reproducible patterns of gene expression characteristic of rejection appear well before histological changes or renal dysfunction. Defining the molecular signature(s) of rejection-associated events may afford opportunities to assess the presence and strength of effector mechanisms that may cause damage rather than the actual damage itself (2). Moreover, it may be possible to establish molecular profiles associated with stable graft function or toxicities, and to use these profiles to guide therapeutic interventions and clinical management (1–3). Finally, Halloran suggested that these techniques be applied to the investigation of both humoral and chronic rejection, both of which must be controlled if transplantation outcomes are to be further improved.

The Art Of Immunosuppression

Minimization strategies

The extended survival of transplant patients has resulted in an increased cumulative burden of side effects from immunosuppression including renal dysfunction, viral infections, metabolic abnormalities and malignancies (4–6). Magee (University of Michigan) highlighted the incidence of chronic renal insufficiency among transplant recipients. Among non-renal transplant recipients, 16.5% developed chronic renal insufficiency and 4.8% progressed to end-stage renal disease, which is associated with a substantial risk of death (hazard ratio 4.55; 95% confidence interval 4.38–4.74) (6). Unfortunately, there is limited information as to optimal strategies to minimize renal compromise as reports of delayed initiation, withdrawal or minimization of calcineurin inhibitors to improve renal function are frequently from small, retrospective, single-center studies with limited follow-up. Currently, the most prudent approach appears to be heightened awareness to identify those at risk, targeting them for early and aggressive medical interventions such as those generally recommended for other etiologies of chronic renal insufficiency.

The serious morbidity associated with immunosuppression has motivated efforts to develop minimization strategies. A major emphasis has been to reduce or eliminate corticosteroids. In renal transplantation where such strategies have been extensively studied, a common theme has been the use of either polyclonal or monoclonal anti-lymphocyte antibody induction therapy to compensate for the lack of, or rapid withdrawal of steroids in the early post-transplant period. Complete steroid avoidance has even been applied to pediatric transplantation. Sarwal reported the Stanford experience with 57 pediatric kidney recipients treated with extended (pre-operative – 6 months postoperatively) daclizumab induction followed by tacrolimus and mycophenolate mofetil (MMF) maintenance immunosuppression (7). At three years, the 6% incidence of acute rejection in the steroid-free group compared favorably to the 30% incidence observed for historical controls. Steroid-free immunosuppression was also associated with a significant growth advantage.

The deleterious impact of corticosteroids on glucose control has logically suggested that minimizing steroid exposure may be particularly desirable for pancreas or islet transplantation. Kaufmann (Northwestern University Medical School) summarized multiple single-center experiences including that of the group in Nantes, France who found no clinically significant differences between steroid avoidance versus steroid withdrawal in pancreas transplant recipients induced with RATG induction and maintained on cyclosporine and MMF (8). Similarly, the University of Minnesota has used RATG and basiliximab induction, followed by tacrolimus and sirolimus maintenance with similar outcomes. Northwestern has reported excellent 3-year graft survival, low acute rejection rates (<15%), and a significant decrease in the incidence of CMV disease in high risk patients compared to those receiving steroids in 200 pancreas recipients who received either RATG or alemtuzumab induction followed by steroid free maintenance immunosuppression (tacrolimus + sirolimus). Kaufmann concluded that the use of a T-cell depleting agent enabled steroid avoidance with excellent patient and graft survival, low acute rejection rates, and decreased steroid-related side effects.

Successful steroid sparing regimens have also been reported in liver transplantation. Eason (The Ochsner Clinic) spoke of testing polyclonal rabbit anti-thymocyte globulin (RATG) induction followed by tacrolimus monotherapy in a prospective, randomized trial. Compared to the group receiving tacrolimus and steroids, the RATG-tacrolimus monotherapy group had less post-transplant diabetes, cytomegalovirus (CMV) infection, and steroid-requiring rejection (9). Investigators in Germany and Italy have also demonstrated encouraging results with steroid-free protocols using basiliximab induction (10,11). To date, none of these protocols appear to adversely affect patients infected with hepatitis C.

In addition to corticosteroid minimization, several centers have eliminated anti-metabolites, using a regimen of induction followed by tacrolimus monotherapy. Shapiro (Pittsburgh) reported that kidney transplant patients induced with antibody and maintained on tacrolimus monotherapy could be weaned over the first year to once or twice weekly dosing with superior patient and graft survival compared to patients receiving standard immunosuppression. Groups from Miami (12), New Orleans (9) and Pittsburgh (13) report being able to successfully maintain liver transplant patients at very low or undetectable levels of tacrolimus following induction, but were less successful at weaning these patients to spaced monotherapy.

Perhaps the ultimate in minimization strategies is to induce tolerance. Cosimi (Massachusetts General Hospital) presented an overview of his trial for one-haplotype matched kidney transplant recipients using the tolerance induction protocol, which had previously been used in the setting of two-haplotype matched kidney transplant recipients (14). Patients underwent a rigorous conditioning regimen of thymic irradiation, cyclophosphamide and treatment with MEDI-507, a monoclonal antibody directed against CD2 in preparation for simultaneous donor bone marrow infusion and kidney transplantation. Cyclosporine monotherapy was used for maintenance immunosuppression. Three patients were treated; one was weaned off cyclosporine without incident, the second was eventually weaned but experienced a humoral rejection, and the third lost the graft to aggressive humoral rejection. The rejections were thought to be related to MEDI-507's inability to deplete B cells; the protocol will resume with the addition of rituximab (anti-CD20).

Non-T-cell mediated immune processes

The traditional focus of immunosuppression has been to control activation and proliferation of T cells. Ever since crossmatching protocols eliminated hyperacute rejection, antibody-mediated processes driven by B cells were considered to be infrequent and unimportant. Recently, however, it has become known that antibody-mediated rejection (AMR) is a frequent component of acute cellular rejection and, less frequently, can occur independently.

The target of AMR for all transplanted organs is thought to be endothelial cells, but the histopathological picture varies with the transplanted organ (15). Recipients of kidney and heart allografts have the highest incidence of documented AMR. The most reliable histological finding of AMR is demonstration of C4d deposition in capillary endothelium (16). Currently, C4d immunofluorescence or immunohistochemistry may not be routinely performed and may need to be specifically requested if AMR is suspected.

Concomitant with the ability to diagnose antibody-mediated processes has been the emergence of treatment strategies for AMR or pre-transplant sensitization (17). Typically regimens neutralize and/or deplete circulating donor-specific anti-HLA antibodies. Collaborative trials are now underway to optimize patient evaluation and selection, as well as protocol specifics. Most trials combine plasmapheresis to deplete pre-existing antibody, IVIg to inactivate any remaining antibody, anti-B-cell agents such as rituximab or, occasionally splenectomy, to prevent future antibody production.

While the strategies discussed above address pre- and peri-transplant antibody-mediated processes, there is now increasing concern that antibody-mediated processes may also be operative long after transplantation. HLA antibodies produced following transplantation cause a cycle of endothelial damage and repair leading to vessel constriction and subsequent ischemic parenchymal injury. Terasaki (UCLA) presented data regarding the clear association of high levels of anti-donor antibodies and the development of chronic rejection resulting in inferior patient and graft survival after kidney transplantation (18). Since antibody deposition in vessels appear to precede constrictive arteriopathy by several years, periodic screening of transplant recipients for HLA antibodies and consideration of immunosuppression manipulation for those patients in whom antibodies are found may be warranted, particularly if efficacious treatment strategies are developed.

Madsen (Massachusetts General Hospital) discussed another type of non-T-cell mediated allograft damage involving natural killer (NK) cells and the various cytokines they produce. NK cells are a primary component of the innate immune response and, therefore, do not require prior antigen exposure or sensitization to antigen in order to activate. It is thought that self-MHC antigens prevent NK-cell activation, while the absence of 'self' MHC promotes activation. Teleologically, this mechanism was intended to protect against infectious agents. Consequently, the transplant setting might represent a constant and powerful stimulus for NK-cell activation. NK-cell activation and elaboration of cytokines have been implicated in the pathogenesis of chronic allograft damage in the form of chronic rejection in kidney and liver allografts, vasculopathy in cardiac allografts and bronchiolitis obliterans in lung allografts (19). Inhibition of the mammalian target of rapamycin (mTOR) may mitigate the development of these conditions (20,21).

When art (and science) fails

In spite of the remarkable success of immunosuppression, clinical scenarios arise daily which question our immunosuppression practices. Matas (University of Minnesota) discussed clinical management strategies to be employed when immunosuppression fails, as connoted by the occurrence of acute rejection. Determining why rejection occurred in the first place is critical to decision making. If there was failure to achieve the intended regimen, efforts should optimize dosing and/or compliance. If the regimen itself failed, then immunosuppression should be intensified. For example, conversion from cyclosporine to tacrolimus at the time of acute rejection facilitated resolution of the index episode for kidney and lung recipients and reduced the risk of recurrent rejection for kidney recipients (22,23). Unfortunately, the literature remains fairly silent with regard to the appropriate maintenance immunosuppression in the settings of acute humoral rejection, subclinical rejection, late acute rejection and chronic rejection.

In the arena of liver transplantation, Feng (University of California, San Francisco) presented evidence that immunosuppression practices may impact the tempo and severity of recurrent hepatitis C (HCV). The natural history of recurrent HCV is clearly accelerated compared to primary

infection (24). While multiple studies have shown that bolus corticosteroids or OKT3 to treat rejection enhanced HCV progression and worsened outcomes (25–29), two more recent reports claim that rapid corticosteroid taper accelerated fibrosis (30,31). Uncertainty regarding the specific effects of various immunosuppressants on recurrent disease is further exacerbated by the diagnostic ambiguity between acute rejection and recurrent HCV (32). Therefore, there is substantial need to clarify the impact of induction, maintenance, and anti-rejection immunosuppression strategies on recurrent HCV.

The Science of Immunosuppression

There is increasing awareness that immunosuppressants may have biologic and/or immunologic effects well beyond their recognized anti-rejection mechanisms.

Homeostatic proliferation

The depletional strategies increasingly used for induction immunosuppression are known to dramatically alter the circulating lymphocyte population for prolonged periods of time. There is evidence that, upon reconstitution of the lymphocyte compartment, an inverse CD4:CD8 ratio develops and persists for many years (33). The phenotype of these cells appears to be that of memory rather than naïve cells. Since memory cells have a lower threshold for activation compared to naïve cells, these agents may have significant implications for the long-term control of anti-donor immune responses.

Regulatory T cells

Normally, regulatory T cells respond to antigenic stimulation by inhibiting the proliferation of naïve antigen-specific cells by direct cell-to-cell contact or the elaboration of soluble factors. Generation of donor-specific regulatory cells requires that lymphocyte activation occurs in an appropriate, conducive milieu. Most immunosuppressive agents inhibit T-cell activation and therefore may simultaneously inhibit the generation of regulatory T cells. Experimental work from Emory (34) and Oxford (35) show that calcineurin inhibitors diminish or abrogate regulatory activity, whereas mTOR inhibitors do not.

Immunosuppressants in the pipeline

Bromberg (Mount Sinai School of Medicine) reviewed the immunobiology of mammalian responses to alloantigen, pointing out that its very complexity offers multiple targets for directed or engineered immunosuppressive agents (36). While T cells and the receptors involved in actual antigen recognition (Signal 1) have historically been the prime targets, the various components of the co-stimulatory pathway (Signal 2) and the inflammatory cytokines that provide Signal 3, as well as antigen presenting cells have become the new targets of immunosuppressant drug development.

Co-stimulatory blockade agents

Rodent models of transplantation and, to a lesser extent, non-human primate models, have shown that interruption of co-stimulatory pathways can produce remarkable prolongation of allograft survival (37). Initial clinical trials conducted in patients with idiopathic thrombocytopenia purpura (ITP) using a monoclonal antibody directed against CD40 (5C8) suggested the product was safe and efficacious. However, when trials in renal transplant patients began, significant complications of serious thromboembolic events occurred. This, coupled with the lack of efficacy, led to the termination of the study. A second monoclonal antibody (IDEC-131) directed against a different component of the co-stimulatory pathway (CD154) has been tested clinically. There were no safety issues demonstrated; however, there was also no efficacy. A third monoclonal, Chi20, is a chimeric anti-human CD40 antibody that has shown promise by itself and in combination with LEA29Y (high affinity CTLA4Ig) in primate models, but has yet to be tested clinically.

Beyond T cells and co-stimulatory blockade

Vincenti (University of California, San Francisco) outlined a highly novel immunosuppression strategy proposed by Strom combining both established and novel agents selected for their complementary and tolerance-friendly mechanisms (38). The triple regimen uses IL2Fc to enhance apoptosis-induced cell death, mIL15Fc to blocks proliferative and anti-apoptotic activity, and mTOR inhibition (sirolimus) to block the expansion of alloreactive cells while and spare regulatory T cells.

Bromberg discussed FTY720, a unique drug currently in clinical trials that protects transplanted organs by preventing the egress of lymphocytes after chemokine-driven migration into lymph nodes (39,40). First (Astellas, Inc.) described experimental and early clinical trial results for FK778, a malononitrilamide with both anti-T- and B-cell activity, which reduces production of cytokines (including TGF-β) are implicated in the development of allograft fibrosis. Perhaps the most exciting aspect of FK778 is its apparent activity against BK polyoma virus.

Finally, Chan (Pfizer Global Research & Development) described an inhibitor of JAK3, a tyrosine kinase of the Janus family, present primarily in lymphocytes and involved in signal transduction initiated by the γ-chain shared by the receptors for IL-2, 4, 7, 9, 15, and 21. The inhibitor (CP-690,550), by specifically targeting the common γ-chain, may be able to overcome the widely acknowledged redundancy of the immune system. JAK-3 inhibition has been shown to prolong allograft survival with minimal toxicity in a non-human primate kidney transplant model with minimal toxicity (41). Clinical trials of all of these agents are either underway or are being planned.

Immunologic profiling

Recent advances in molecular and genetic diagnostics have suggested that various post-transplant disease states such as rejection and infection are associated with specific gene expression patterns. Nickerson (University of Manitoba) summarized the recent progress in proteomic profiling using NMR spectroscopy, as well as SELDI-TOF-MS, showing the presence of β2-microglobulin cleavage products in the urine of patients with tubular dysfunction including rejection. Hricik (Case Western Reserve) summarized the use of the ELISPOT assay to measure IFN-γ released by recipient cells in response to donor cells or donor peptide since the results appear to correlate with subsequent rejection. Suthanthiran (New York Presbyterian Hospital-Cornell) summarized results from his laboratory showing a correlation between the incidence of acute cellular rejection and CD3, perforin, and Granzyme B levels in urinary white blood cells measured by PCR. In addition, IP-10 and CXCR3 levels correlate with renal allograft inflammation measured by mRNA analysis of urinary white blood cells. Finally, CD103 or integrin alpha-E correlated with the presence of acute rejection.

Brennan (Washington University) discussed the concept of using BK virus infection as a barometer of excessive immunosuppression. He reported that BK virus infection typically occurs within months of renal transplantation and is not dependent on the choice of tacrolimus versus cyclosporine or the use of MMF versus azathioprine. Since patients without viruria do not develop viremia, urine PCR is an excellent screening tool to identify recipients at increased risk. Once viremia is detected, pre-emptive discontinuation of either azathioprine or MMF prevents the progression from viremia to nephropathy. The Cylex immunoassay correlated with BK viremia as a marker of over-immunosuppression.

Conclusion

Approaches for the management of transplant recipients have evolved substantially over the past decade and advances in the art and science of immunosuppression are largely responsible. While the prospect of producing tolerance remains elusive, improved understanding of the biologic consequences of transplantation and administration of immunosuppression has permitted steady improvements in short-term patient and graft survival through the implementation of refined immunosuppressive regimens optimized for reducing adverse side effects and preventing rejection. It is hoped that the continued application of this process will result in durable long-term improvements in quality of life and longevity of transplant recipients in the years to come.

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