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Continuing Education for Physicians, Transplant Nurses and Coordinators, Pharmacists, and Case Managers

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THE IMMUNOLOGY REPORT™
AN ACADEMIC PERSPECTIVE

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Rationale and Purpose
The ability to transplant organs successfully from one human being to another has transformed the practice of medicine and prolonged the lives of thousands yearly. This issue of The Immunology Report™ reviews recent information on novel therapies aimed at improving outcomes in transplant recipients and minimizing the side effects associated with broad-based immunosuppression, current methods of matching organ donors to recipients, analyses of donor and transplant registries to offer insight into the experiences of both donors and recipients after surgery, differences in transplant outcomes between living and deceased donors, problems experienced by African-American transplant recipients and those with infectious diseases, and strategies to provide organs to recipients who do not match their intended donors. The articles within are based upon presentations delivered during the American Transplant Congress 2007, held May 5–9, 2007, in San Francisco, California.

The articles in this issue, written from the academic perspective of physicians in training at leading medical institutions, summarize the import of these new findings and place them into clinical context. This activity has been developed and approved by a planning committee of nationally recognized thought leaders, under the direction of Beam Institute, to meet a perceived educational need to provide immunologists, transplant specialists, and other health professionals with strategies to help them perform their medical roles.

Learning Objectives
After reading this issue of The Immunology Report, participants in this educational activity should be able to:

- Understand some of the risk factors for organ transplant failure, including ethnicity, age, weight, infections, and comorbidities.
- Describe the results of studies examining the long-term outcomes of organ donors and of various populations of transplant recipients.
- Discuss how the costimulation blockade may provide an effective pathway toward induction of graft tolerance.
- Recount findings on immunosuppressive regimens to minimize toxicity and optimize efficacy.
- Explain how the coagulation cascade is closely related to the inflammation process and is a potential target for manipulating the immune response.

Target Audience
Immunologists and other physicians significantly involved in organ transplantation, transplant nurses, transplant coordinators, pharmacists, and transplant case managers should find participation in this educational activity valuable.

Accreditation
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCMED) through the joint sponsorship of Beam Institute and Direct One Communications, Inc. Beam Institute is accredited by the ACCME to provide continuing medical education for physicians.

The American Association of Colleges of Nursing (AACN) and the American Board for Transplant Certification (ABTC) have approved the International Transplant Nurses Society (ITNS) as a provider of CEU/ABTC credits from their organizations.

TG Medical Education is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Faculty Disclosures
In compliance with the ACCME’s Standards for Commercial Support, any person who was in a position to control the content of this CME activity was required to disclose all relevant financial relationships that created conflicts of interest. Beam Institute has identified and resolved all conflicts of interest prior to the publication of this educational activity. All faculty have been offered a modest honorarium for their participation in this activity.

Stuart J. Knechtle, MD, Professor of Surgery, Division of Transplantation, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, has nothing to disclose.

Jeremy Goodman, MD, Clinical Instructor of Surgery and Transplant Surgery Fellow, University of Wisconsin School of Medicine, Madison, Wisconsin, has nothing to disclose.

Jonathan C. Hundley, MD, an Abbdominal Transplant Surgery Fellow at the University of Alabama at Birmingham, has nothing to disclose.

Erik B. Finger, MD, PhD, a Transplant Fellow and Clinical Instructor of Surgery at the University of California, San Francisco, has nothing to disclose.

Alexander H. Toledo, MD, an Immunology Fellow at Northwestern University Feinberg School of Medicine, Chicago, Illinois, has nothing to disclose.

Erin Lynn McCann, PharmD, BCPS, a Transplant Pharmacy Resident at Duke University Medical Center, Durham, North Carolina, has nothing to disclose.

Continuing Education Credit
Physicians: The beam institute designates this educational activity for a maximum of 2 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Transplant nurses and coordinators: ITNS has applied to the ABTC for providership approval of Continuing Education Points for Transplant Certification (CEPTC) credits for transplant coordinators who complete this educational activity. Application has also been made to the AAN for (CEUs) continuing nursing education credits.

Pharmacists: This activity is approved for 2 credit hours (0.2 CEU). The program number is 454-999-07-020-H01-P, the initial release date is August 11, 2007, and the expiration date is August 11, 2010.

Case managers: This activity is approved by the Commission for Case Manager Certification for 2 clock hours through December 31, 2007.

Disclaimer
This activity is an independent educational activity under the direction of Beam Institute. The activity was planned and implemented in accordance with the Essential Areas and policies of the ACCME, the Ethical Opinions/Guidelines of the American Medical Association, the US Office of Inspector General of the US Department of Health and Human Services, and the Pharmaceutical Research and Manufacturers of America Code on Interactions With Healthcare Professionals, thus assuring the highest degree of independence, fair balance, scientific rigor, and objectivity.

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Introduction

Selected Reports from the American Transplant Congress 2007

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This issue of The Immunology Report summarizes some of the highlights of the American Transplant Congress (ATC), held May 5–9, 2007, in San Francisco, California. This meeting represents the largest annual conference to discuss advances in the field of organ transplantation and related subtopics, including transplant immunology, organ allocation and preservation outcomes, ethics, and organ-specific issues. Under the auspices of sponsorship by Astellas, five outstanding transplant fellows from the University of Wisconsin–Madison, University of Alabama–Birmingham, University of California–San Francisco (UCSF), Northwestern University, and Duke University attended the conference and wrote the summary articles in this issue. These papers represent a concise report of the meeting, touching on many, but not all, topics.

Dr. Jeremy Goodman from the University of Wisconsin–Madison discusses a costimulation blockade and its application to transplant tolerance and gives up-to-date descriptions of the CD28/B7 superfamily and TNF (tumor necrosis factor)/TNF receptor superfamily of costimulatory markers. Although most research in costimulation has been carried out in rodents, there have been significant advances recently in nonhuman primate and human applications, with belatacept now in clinical trials.

Dr. Jonathan Hundley from the University of Alabama–Birmingham has written a summary of the use of living donors in kidney and liver transplantation. He addresses some of the ethical issues involved, as well as paired kidney donation, donor risks, living/deceased donor list exchange, and domino paired kidney donation. Given the fact that living kidney donation has accounted for the principal increase in kidney transplant volume in the United States, this timely and important topic was well covered at the meeting and in this review.

Dr. Erik Finger from UCSF summarizes a number of drug minimization trials, immunosuppression in the highly sensitized patient, and recurrent disease in liver transplantation. He also includes a nicely done summary of basic science studies focusing on various mechanisms, including costimulation blockade, indoleamine 2,3-dioxygenase (IDO), TH17 cells, and T regulatory cells. Progress in understanding of the adaptive immune response, the innate immune response, and the graft response to injury is well referenced.

Dr. Alexander Toledo summarizes talks by Dr. Simon Robson on the role of platelet activation, vascular injury, and immunity in graft function and injury. Summaries of additional talks on platelet and monocyte activation in alloimmunity by Dr. Allan Kirk and on coagulation and vascular injury by Dr. Anthony Dorling follow. This thematic discussion of coagulation and its relationship to innate and adaptive immunity again represents some basic science progress in our understanding of alloimmunity.

Finally, Dr. Erin Lynn McCann from Duke University provides a cogent summary of racial disparities in terms of access and outcomes in transplantation and reasons for these disparities. She also summarizes presentations by Drs. Herwig-Ulf Meier-Kriesche and Tim Pruett on the impact of age and weight as comorbidities in transplantation and immunosuppression for hepatitis C, respectively. Thus, in the report that follows, a thorough and well-written summary of the scientific and clinical progress in organ transplantation is presented. I would like to express my thanks to Astellas for taking an educational role in sponsoring attendance at ATC 2007 by these accomplished transplant fellows and for providing this venue for them to summarize their observations of the meeting for the current readership.
Costimulation: Tolerance vs Immunosuppression

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University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin

Costimulation blockade represents an exciting new avenue of discovery and application in the field of transplant pharmacotherapy. The development of focused therapies aimed at specific points along the T-cell activation cascade some day may improve short- and long-term outcomes of transplant patients and minimize the side effects associated with broad-based immunosuppression. Positive costimulation may be responsible for such signaling instructions as proliferation, cytokine production, prevention of anergy, and differentiation into effector and memory populations, whereas negative costimulation may lead to anergy, apoptosis, and the induction of regulatory cells. This article summarizes recent developments in the field of costimulation blockade and looks to the future to reflect information presented at a symposium held during the American Transplant Congress 2007. Results from preclinical human trials of costimulation blockade have been very encouraging; although translation of these results to clinical trials has been disappointing, the study of newer agents is showing promise.

Over the past half-century, outcomes in transplantation have been influenced dramatically by the introduction of potent immunosuppressants. Years ago, knowledge of immune cell biology was limited, and treatment strategies were unfocused. As researchers gained further insight into the mechanisms of T-cell activation and proliferation, they began to target specific molecular pathways that could affect the acceptance of foreign grafts by the human body.

It is now apparent that T-cell activation is the product of three distinct, but complementary, signaling pathways (Figure 1). In “signal 1,” antigen-presenting cells (APCs) trigger T cells when antigenic peptide epitopes displayed in the context of the class I or II major histocompatibility complex bind to the T-cell receptor (TCR)/CD3 complex. In “signal 2,” also known as costimulation, various ligand-receptor complexes may be involved in the requisite reactions required for T-cell activation; this pathway will be the focus of this discussion. Finally, in “signal 3,” various cytokines, including interleukin-2, bind transmembrane receptors such as CD25 to trigger cell proliferation via the mammalian target of rapamycin (mTOR) pathway.

Existing immunosuppressants have not had the long-desired impact on long-term graft survival; further, many regimens are toxic to both the patient and the graft. Therefore, investigators have focused their attention on such novel therapies as those involving costimulation blockade to keep grafts and patients healthy. Initial results in rodent models suggested that costimulation blockade may provide an effective pathway toward induction of tolerance to a transplanted organ. However, because nonhuman primate and human studies have failed to support this conclusion thus far, attention has shifted to maintaining an immunosuppressed state rather than to inducing tolerance.

At a symposium on costimulation held during the American Transplant Congress 2007 in San Francisco, California, leaders in the field provided an overview of emerging concepts, nonhuman primate studies, and clinical trials in this promising new area of immunologic research.

Evolution of the Concept of T-Cell Costimulation in Transplantation

Adapted from a presentation by Mohamed H. Sayegh, MD, Professor of Transplantation Medicine, Harvard Medical School, Boston, Massachusetts.

An emerging concept in T-cell costimulation is that “signal 2” results from complex interactions between positive and negative pathways. Positive costimulation may be responsible for various signaling instructions, including proliferation, cytokine production, prevention of anergy, and differentiation into effector and memory.
populations. Conversely, negative costimulation may lead to anergy, apoptosis, and the induction of regulatory cells. As shown in Figure 2, costimulation pathways may be broadly grouped into two major families—the CD28/B7 family and the tumor necrosis factor (TNF)/TNF receptor (TNF-R) family. In addition, laboratory investigators have expressed great interest in a third group, known as the T-cell Ig mucin protein domain (TIM) family.

The CD28/B7 Family

The CD28 costimulatory pathway probably is the best understood and most studied channel in transplantation. CD28 is expressed constitutively by a majority of CD4+ T cells and by approximately 50% of CD8+ cells. Along with TCR/CD3 ligation, positive signaling via this receptor by B7-1 (CD80) and B7-2 (CD86) results in proliferation, cytokine secretion, and increased survival. CD28 ligation also promotes T-cell differentiation toward both the T-helper 1 (Th1) and T-helper 2 phenotypes.

Conversely, binding of B7-1 and B7-2 by cytotoxic T-lymphocyte-associated protein 4 (CTLA-4; CD152) appears to provide negative costimulation. CTLA-4 binds to B7 with much greater affinity than does CD28. Unlike CD28, CTLA-4 is not expressed constitutively on the surface of T cells. Instead, CTLA-4 expression is induced by T-cell activation; it reaches maximum expression after 48–72 hours. CTLA-4 likely provides an “off switch” to counterbalance positive costimulation by CD28. In studies of CTLA-4−/− mice, lethal uncontrolled T-cell activation and proliferation develop. In rodent models, interruption of the CD28 pathway via either antibodies to B7 or CTLA4-immunoglobulin (Ig), also known as abatacept, may prevent acute rejection and even may induce tolerance in some limited settings. However, these strategies are not sufficient to ensure long-term graft survival, especially in immunologically stringent models, thus illustrating the great need for alternative pathways.

Inducible T-cell costimulator molecule (ICOS) is rapidly produced on T cells following TCR ligation, suggesting its importance in augmenting activated T cells. Further, CD28 costimulation leads to increased ICOS expression. ICOS ligand (ICOS-L) is expressed on parenchymal and
hematopoietic cells; it may be responsible for maintaining costimulation in circulating, activated cells. Experimentally, ICOS blockade may provide some protection from rejection, especially when it works in concert with obstruction of other pathways. Delayed blockade of ICOS (eg, during the effector/differentiation phase) may be more effective than early blockade, which supports the importance of the different stages of the alloimmune response cascade.

Programmed death-1 (PD-1) and its ligand PD-L represent a third costimulation pathway in the CD28/B7 family. PD-1 is expressed by stimulated, activated CD4+ and CD8+ T cells, B cells, and myeloid cells. The role of the PD-1/PD-L pathway is unclear. In the setting of activated T cells, ligation of PD-1 by PD-L inhibits proliferation and cytokine production. Conversely, ligation of PD-1 costimulates T-cell proliferation of resting T cells, leading to enhanced proliferation and increased cytokine production.

Highlighting the importance of interactions between different costimulation pathways, Albin et al recently reported that blockade of PD-1/PD-L overcame the graft-prolonging effects of abatacept, resulting in acute cellular rejection. Further, transplantation among PD-L-deficient donor or recipient mice led to accelerated acute rejection of heart allografts, with increased cytokine production and T-cell proliferation.

The TNF/TNF-R Family

Following initial costimulation through the CD28/B7 pathway, maintenance of T-cell activation may be provided by members of the TNF/TNF-R family, of which CD40 and CD154 (CD40L) are the best characterized.

CD40 is expressed constitutively on APCs and may be induced in endothelial cells and fibroblasts. It promotes B-cell activation and maturation of dendritic cells (DCs). CD154, the ligand for CD40, is induced on CD4+ and CD8+ T cells following activation. Rodent studies of CD40 blockade and obstruction of other costimulatory pathways produced impressive results in prolonging allograft survival, with simultaneous blockade of the CD28 and CD40 pathways able to sustain both vascularized cardiac allografts and skin grafts. Further, blockade of ICOS and CD40L in nonobese diabetic (NOD) mice led to islet-allograft tolerance and prevented development of autoimmune diabetes. However, although nonhuman primate studies of CD154 blockade have been promising, human trials have not been successful.

CD27 has been implicated in T-cell activation; its ligand, CD70, is expressed constitutively on medullary thymic epithelium and is induced on activated T and B cells. By blocking this pathway, investigators have prolonged vascularized cardiac allograft survival. In conjunction with CD28 blockade, long-term survival of allografts has been achieved with CD27/CD70 obstruction.

CD134 (OX40) expression is induced on activated T cells; CD134L, its ligand, is expressed on activated APCs, B cells, and vascular endothelial cells.

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**Figure 2**

Costimulatory molecules and their ligands. TNF = tumor necrosis factor; TNF-R = tumor necrosis factor receptor; HVEM = herpes virus entry mediator; ICOS-L = inducible T-cell costimulator ligand; MHC = major histocompatibility complex; CTLA = cytotoxic T lymphocyte-associated protein; BTLA = B and T lymphocyte attenuator; PD = programmed death; ICOS = inducible costimulation molecule. Reproduced, with permission, from Clarkson and Sayegh.
via this pathway may enhance cytokine production and proliferation of CD4+ T cells.\textsuperscript{15} As with other members of this costimulation family, blockade of CD134 and CD28 synergistically prolongs cardiac and skin allograft survival in a rodent model.\textsuperscript{16}

Many other pathways are involved in this family as well. For example, 4-1BB/4-1BBL signaling appears to be important in sustaining CD8\textsuperscript{+} T-cell responses.\textsuperscript{16} LIGHT, a recently defined member of the TNF superfamily, is induced upon activation of CD4\textsuperscript{+} and CD8\textsuperscript{+} T cells, monocytes, and natural killer cells. Costimulation occurs upon binding of LIGHT to its receptor, herpesvirus entry mediator. LIGHT appears to be involved in allograft rejection; it may exert its effects in a CD28-independent manner.\textsuperscript{15}

**The TIM Family**

The TIM family of costimulatory receptors and ligands may provide restraint of Th1 effector cells and may have important implications for autoimmune diseases as well as allograft rejection and tolerance. TIM-3 may serve as a negative regulator of Th1 responses by inhibiting aggressive auto- and alloimmune responses. Experimental TIM-3 blockade accelerates the development of diabetes in NOD mice and prevents tolerance induction resulting from costimulation blockade.\textsuperscript{17}

**Summary**

T-cell activation and proliferation involve a complex set of interactions between multiple signaling pathways. Effective antirejection therapy and tolerance induction require the targeting of several of these pathways at different time points to balance positive and negative costimulatory effects. Future challenges include understanding the expression of various costimulatory molecules in vivo; determining their ability to function at various time points within the immune cascade; and defining the feasibility, safety, and efficacy of combining various immunosuppressive regimens and biologic agents to obtain a positive effect.

**Costimulation Blockade in Primates: The Evidence for Tolerance**

*Adapted from a presentation by Richard N. Pierson, III, MD, Professor of Surgery, University of Maryland, Baltimore.*

The definition of tolerance in the transplantation setting includes graft acceptance both without ongoing therapy and with intact protective immunity to other antigens. Induction of durable peripheral tolerance requires active modulation of the immune response to donor antigens and involves a balance among effector, memory, and regulatory/suppressor T cells. Regulatory DCs, endothelial cells, and antigen-specific B cells also play a role.

Despite the large body of experimental evidence described above, very few regimens have translated from the rodent model to humans successfully. Nonhuman primate models, therefore, serve as a vehicle to further investigate mechanisms, demonstrate proofs of principle, develop and test diagnostic tools, and establish the safety and efficacy of drug withdrawal in the setting of tolerance induction trials.

**CD28 blockade**

Interruption of the CD28/B7 pathway has been attempted by blocking antibodies directed against B7 and by using abatacept, which inhibits B7 interaction with CD28. Combined blockade of B7-1 and -2, using either blocking antibodies or abatacept, has prolonged allograft survival, although it has not induced tolerance.\textsuperscript{18}

LEA29Y (belatacept) is a modified version of CTLA\textsuperscript{18} that has a higher affinity for B7-2. Monotherapy with this drug has prolonged islet-cell and renal allografts in Rhesus macaques.\textsuperscript{19,20} It has not achieved reliable tolerance, however.

**CD40/CD154 blockade**

Multiple antibodies against CD154 have been tested in nonhuman primates. Monotherapy with anti-CD154 agents has led to long-term acceptance of various allografts, although it ultimately results in rejection.\textsuperscript{18}

Tolerance to influenza antigen has been demonstrated in cynomolgus macaques immunized with anti-CD154 monotherapy. This treatment, however, has not induced sufficient tolerance to heterotopic cardiac transplants.\textsuperscript{21} Anti-CD154 therapy used with sirolimus and donor-specific transfusion has induced operational tolerance in a nonhuman primate renal and skin transplant model.\textsuperscript{22}

Other experiments of anti-CD154 treatment have added CD28 or ICOS blockade to help promote tolerance.\textsuperscript{23} Alloantibody production is a common feature following anti-CD154 treatment, and the targeting of CD20 to eliminate B cells may prove helpful. Favorable results also have been achieved with anti-CD40 antibodies, but tolerance has not been demonstrated.

**Summary**

Nonhuman primate trials will continue to bridge the transition of costimulation blockade from the laboratory to the clinic. Mechanisms of costimulation and tolerance induction in rodent models continue to be better defined—and testing in nonhuman primates provides crucial safety and efficacy information that may allow these novel therapies to be used in humans in the future.
Clinical Trials with Costimulation Blockade

Adapted from a presentation by Flavio Vincenti, MD, Clinical Professor of Medicine, University of California at San Francisco.

As physicians’ understanding of the importance of costimulation in the alloimmune response evolves, they will exploit blockade of these pathways to attenuate or even eliminate alloreactivity. Unfortunately, relatively few strategies that have been encouraging in animals have translated well to humans. Some early clinical trials have been disappointing, although testing of newer agents has shown promise.

Anti-CD154

Following the promising results gained by targeting the CD40/CD154 pathway in nonhuman primates,24 Hu5C8, a humanized monoclonal antibody against CD154, was tested in a limited pilot study of renal transplant recipients; however, the trial was halted after rejection occurred in 5 of 7 patients and significant thromboembolic events developed.25

CD154 is present on activated platelets; thus, this interaction may have contributed to the thrombotic side effects. Anti-CD154 therapy is being pursued in hematologic and autoimmune conditions; however, studies of this therapy in transplantation are not ongoing.

CD28 pathway

Progress in the blockade of the CD28 pathway has been more encouraging. In a phase I trial, h1F1 (anti-B7-1) and h3D1 (anti-B7-2) were used with cyclosporine, mycophenolate mofetil, and corticosteroids.25 Early results suggested that the agents were safe and effective; however, further research has not been pursued.

Abatacept

Abatacept was developed to inhibit the CD28 pathway by preventing binding of B7. This agent binds B7 more avidly than does native CTLA-4, although differential binding characteristics lead to less effective inhibition of B7-2.26 The drug has been used successfully in treating rheumatoid arthritis, although it did not demonstrate significant effectiveness in nonhuman primate transplant trials.

Belatacept

Later, a second-generation drug, belatacept, has improved binding characteristics to B7-2.26 Results from a phase I study of this drug in renal transplantation were encouraging. The first significant clinical success with costimulation blockade was reported by Vincenti and others,27 who conducted a phase II, multicenter study in which 218 patients were randomized to receive intensive belatacept therapy, less-intensive belatacept therapy, or cyclosporine; all patients received basiliximab, mycophenolate mofetil, and corticosteroids.

The incidence of acute rejection at 6 months was similar among all groups. However, patients taking belatacept had a significantly higher measured glomerular filtration rate at 12 months than did those given cyclosporine; the belatacept group also had a lower incidence of chronic allograft nephropathy on biopsy and a tendency toward improved cardiovascular and metabolic profiles. The frequency of infection was similar between groups. There were three cases of post-transplant lymphoproliferative disorder (PTLD) among belatacept-treated patients; however, a long-term extension of the protocol that includes half of the study patients has identified no further PTLD cases and has shown no significant difference in infectious or cardiovascular complications. Currently, two phase III trials of belatacept are ongoing.

Other belatacept studies that are under way include protocols on eventual drug withdrawal in living-donor recipients, corticosteroid elimination, conversion of calcineurin-inhibitors to belatacept, and thymoglobulin and belatacept used with avoidance of corticosteroids and calcineurin inhibitors. Future directions of study may include belatacept used with donor-specific transfusion to induce tolerance and belatacept used with other biologic agents, such as CD40 or adhesion molecule blockade.

Summary

Progress in bringing costimulation blockade to the clinic has been slow, but recent successes are encouraging. In the future, clinicians may expect reports on greater use of costimulation blockade to minimize or eliminate exposure to such nephrotoxic agents as calcineurin inhibitors and to induce donor-specific tolerance.

Conclusion

Costimulation blockade represents an exciting new method of preventing allograft rejection and of inducing tolerance. Unfortunately and predictably, clinical results lag far behind laboratory advances. The challenges of translating preclinical developments into effective agents for human use are formidable, but successes with agents such as belatacept suggest that outcomes and reductions of adverse reactions will improve. Ultimately, clinical investigators hope to perfect drug-withdrawal or drug-sparing regimens that will protect transplant patients from graft rejection.
**References**


Living Donor Transplantation:
Vital Solution or Mere Mirage?

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The number of patients awaiting organ transplant continues to rise as the transplantation community struggles to figure out new ways to supply more grafts to more individuals. One problem is the scarcity of organs; despite great media coverage about the need for viable tissues for transplant, too few organs are donated by grieving families or by living individuals trying to save relatives and friends. The incidence of kidney transplantation has increased dramatically in the United States over the past 17 years. Much of this increase has resulted from greater numbers of donations from living persons. This article discusses different aspects of the transplant process, from the long-term outcomes of the altruistic individuals who choose to undergo complete or partial loss of an organ so that someone else may live to the fortunes of patients who receive these grafts. In addition, different schemes to help patients who have willing donors with unsuitable organs are discussed, as are important basics concerning liver transplantation.

According to Wolfe et al, the annual death rate for recipients of deceased donor kidney transplants (DDKTs; 3.8%) was substantially lower than for patients on the waiting list for a graft (6.3%) and for patients on dialysis (16.1%); further, the projected increase in life span conferred by DDKT was approximately 10 years. In general, a larger survival benefit was seen among younger patients, especially those with diabetes.

Living donor kidney transplant (LDKT) results in superior graft and patient survival when compared with DDKT. In a recent Scientific Registry of Transplant Recipients (SRTR) database analysis, Schold et al studied the survival figures associated with LDKT and from kidney transplants derived from standard- and expanded-criteria DDKT. Figure 1 shows the projected life expectancy after development of ESRD segregated by treatment modality. Among all age groups, kidney transplantation conferred a demonstrable survival advantage over maintenance dialysis, although this advantage decreased significantly with older patient age. Overall, LDKT conferred the best survival advantage,
followed closely by standard-criteria DDKT. Finally, expanded-criteria DDKT conferred only a small survival advantage over maintenance dialysis.

**Early Transplantation Results in Improved Patient and Graft Survival**

Perhaps the most significant modifiable risk factor for kidney transplant outcomes is the duration of ESRD and dialysis prior to transplant. Cardiovascular mortality is approximately 15 times higher among dialysis patients than among the general population. Kidney transplantation appears to stop the progress of cardiovascular disease, which accounts for a large part of the overall survival advantage conferred by transplantation.

Meier-Kriesche et al. showed that transplantation within 6 months of starting dialysis conferred a greater survival advantage than did transplantation occurring beyond 2 years of dialysis initiation. In a separate study, Meier-Kriesche et al. compared the outcomes of patients given a kidney from any of 2,405 deceased donors; one kidney from each donor was transplanted into a recipient who had received dialysis for more than 2 years (mean, 51 months), and the other was transplanted into a recipient who had received dialysis for less than 6 months (mean, 1 month). The 10-year unadjusted graft survival was significantly worse (29% vs 63%) among recipients given more than 2 years of dialysis. The investigators then compared outcomes of all DDKTs with all LDKTs that occurred between 1988 and 1998; with both types of donation, duration of dialysis treatment before transplantation strongly predicted graft failure (Figure 2).

These dramatic differences in graft and patient survival underscore the importance of early transplantation.

**Summary**

The survival benefit of kidney transplantation applies to most recipients, irrespective of their age, ESRD etiology, and race—and this fact has led to an ever-increasing demand for kidney transplants. Early transplantation confers a significant graft survival advantage, particularly...
when it is performed before patients begin dialysis. The median waiting time for a kidney transplant in the United States is 2.5–5.5 years, depending upon blood type. Thus, for most patients on the waiting list, a living kidney donation stands as the only hope for early transplantation.

**Long-Term Follow-Up of Kidney Donors**

*Adapted from a presentation by Robert Gaston, MD, Professor of Medicine and Professor of Surgery, University of Alabama, Birmingham.*

Living kidney donors must understand all potential risks before proceeding with their donation. Attempts to define these risks are based primarily on retrospective case series with short-term follow-up. A national database that provides data on long-term follow-up of kidney donors is needed to define such donor risks precisely; they may include perioperative complications, the long-term risks of hypertension and renal dysfunction, and adverse psychosocial outcomes.

**Perioperative Complications**

The risk of morbidity directly related to donor nephrectomy apparently is quite low; however, prolonged ileus, bleeding, intestinal obstruction, chylous ascites, splenic injury, diaphragmatic injury, bowel injury, vascular injury, pneumothorax, deep venous thrombosis, pulmonary embolism, rhabdomyolysis, incisional hernia, and death have been reported. The overall incidence of perioperative donor death in the United States is 2–6 per 10,000 living kidney donor operations.

Matas et al reviewed morbidity and mortality data from 10,828 kidney donors taken from a survey of 171 kidney transplant programs listed with the United Network for Organ Sharing (UNOS). A slight majority (52.7%) of operations were performed via an open approach, whereas the remaining were laparoscopic. Two donors (0.02%) died from surgical complications. Approximately 1.2% of donors had major complications. Reoperation was necessary in 66 donors (0.6%), and major complications that did not require operative intervention occurred in 65 others (0.6%). Importantly, the design of this large study likely underestimated the actual complication rate.

A review of 600 laparoscopic living kidney donations at one institution found a donor complication rate of 7.2%; 4.3% of these complications were classified as “potentially life-threatening,” and only 2 patients (0.3%) had a lasting disability (chyloous ascites).

**Long-Term Mortality**

A retrospective study of 459 living kidney donors in Sweden found that 85% were alive 20 years after donation; interestingly, just 66% of an age-matched control survived this time period. The authors noted that the improved survival was probably due to the selection of healthy people for organ donation, and they concluded that kidney
Living Donor Transplantation

donation did not appear to constitute any long-term risk of early mortality. Similarly, a report of 56 World War II soldiers who underwent nephrectomy due to trauma shed light on the long-term risk of nephrectomy in young, healthy males.10 When the outcomes of this group were compared with those of a similar cohort of uninjured soldiers after a mean of 36.8 years of follow-up, investigators found no difference in long-term mortality. The authors concluded that nephrectomy was well tolerated and caused no adverse consequences in this cohort.

These retrospective reports suggested that kidney donors are not at risk for premature mortality; however, a prospective randomized trial on survival after voluntary nephrectomy is needed.

Hypertension and Renal Dysfunction

The risk of clinically significant hypertension after kidney donation remains uncertain. A recent meta-analysis evaluating blood pressure in 5,145 living kidney donors from 48 studies showed that the donors apparently experienced a 5 mm Hg increase in blood pressure within 10 years of donation.11 However, this finding is clinically insignificant in most patients.

A recent review and meta-analysis by the Donor Nephrectomy Outcomes Research (DONOR) Network12 attempted to answer two critical questions. First, how frequently do kidney donors develop proteinuria? Second, do kidney donors have an accelerated loss of glomerular filtration rate (GFR) after the initial decrement following nephrectomy? Investigators found that urinary protein levels, which may result from single nephron hyperfiltration from reduced renal mass, were higher among donors (147 mg/d) than among controls (83 mg/d); these increases were not clinically significant in the vast majority of patients. The average GFR for donors was 86 mL/min 7 years post surgery. An initial drop in GFR was not accompanied by accelerated losses over a subsequent 15 years of follow-up.

The risk of ESRD in kidney donors is not known. In 2002, an UNOS database analysis of almost 48,000 living donors showed that 20 donors (0.04%) had been listed for DDKT. The actual number of patients who develop ESRD after living donation is unknown, but the estimated prevalence of 0.04% is similar to the 0.03% incidence of the general population.13

Ramcharan and Matas14 attempted to contact 773 living kidney donors who underwent nephrectomy from 1963–1979 at a single institution (follow-up range, 20–37 years). Of 464 donors who were successfully contacted, 5 donors (1.1%) had progressed to ESRD. The authors raised an important question—if donors develop kidney disease in the years after donation, will they have an accelerated course to kidney failure? The answer, unfortunately, is unknown.

Adverse Psychosocial Outcomes

For most donors, the psychosocial, altruistic benefits of giving someone an organ outweigh any physical harm. The majority of donors report an unchanged or improved relationship with organ recipients (86%–100%) and other family members (82%–100%), no depression (77%–95%), no anxiety (86%–94%), and no change in their perceived attractiveness (83%–93%). Still, a small fraction of kidney donors have adverse psychosocial outcomes.15

Summary

LDKT is performed with the expectation that the risk of any physical harm to the donor is outweighed by the donor’s psychological benefits from altruism and the obvious clinical benefit to the recipient. However, a small proportion of kidney donors have adverse clinical and psychosocial outcomes. It is vital that informed consent includes a careful description of all potential risks, including perioperative morbidity and mortality, hypertension, renal failure, and adverse psychosocial outcomes.

Paired Kidney Donation

Adapted from a presentation by Francis Delmonico, MD, Professor of Surgery, Harvard Medical School, and Medical Director, New England Organ Bank, Boston, Massachusetts.

As previously noted, the waiting time for a renal transplant continues to rise. Of 71,000 patients currently on the UNOS DDKT waiting list, approximately 6,000 have donors willing and able to donate but who are incompatible because of either ABO-incompatibility or positive crossmatch.16

Many centers have initiated paired kidney donor exchange programs to provide additional organs to the donor pool and to avoid the long waits for a DDKT. To date, 254 living donor kidney exchange transplants have occurred—180 have been performed using paired living donor exchange, 73 using living/deceased donor list exchange, and 1 using domino-paired kidney donation.1

Paired Living Donor Exchange

Paired living donor exchange was first proposed by Rapaport17 in 1986. In this scheme, an individual wants to donate a kidney to a patient, but these two people are not ABO-compatible. However, that donor may be compatible with another patient in need of a kidney who also has an ABO-incompatible donor. Through an exchange arrangement between the two incompatible donor–recipient pairs, donor X provides a kidney to ABO-compatible
recipient Y, and donor Y provides a kidney to ABO-compatible recipient X (Figure 3). Because this type of paired kidney donation does not affect the deceased donor list, it poses few inherent ethical considerations.

**Living/Deceased Donor List Exchange**

In this situation, the “intended” donor-recipient pair cannot be matched for a paired living donor exchange. If the intended recipient meets certain eligibility criteria for a list exchange (Table 1), then the intended donor gives a kidney to an unrelated third-party recipient of the donor’s blood type who is at the top of the DDKT waiting list. In turn, the intended recipient is given priority on the DDKT waiting list, which stipulates that patients be affiliated with previous living donors, be completely compatible with the donors, and be highly sensitized, with children given higher priority. The intended recipient is given “right of first refusal” until transplantation.

The biologic reality is that a donor with blood type O rarely participates in paired kidney donation. Therefore, deceased donor kidneys of the O blood type become the main source for the exchange recipient. This situation involves a blood type A donor and a type O recipient (Figure 4). The type A donor gives an organ to an unrelated, third-party, type A recipient at the top of the DDKT waiting list. The living donor’s intended type O recipient then is given priority on the DDKT waiting list.

Although this method increases the number of available kidneys for type A recipients, it also adds another type O recipient to the list and further increases the long waiting time for patients on the type O list. Because the exchange recipient is not placed at the bottom of the type O list, proponents of list exchange argue that the small initial disadvantage to the type O list disappears once an exchange program has been in place for a period of time and eventually equals the median waiting-list time threshold for unsensitized type O patients in that region.

**Domino-Paired Kidney Donation**

Living nondirected (LND) donors, also known as altruistic donors, have accounted for 422 kidney transplants to date. To maximize the LND donor’s gift, Montgomery and colleagues performed domino-paired kidney donation, in which the LND donor is matched to a recipient who has an incompatible donor (Figure 5). The recipient’s incompatible donor can agree to give a kidney to the next compatible patient on the waiting list, producing a domino effect. Using this method, the LND donor’s gift is multiplied.

**Regional/National Paired Kidney Exchange**

During the early stages of paired kidney donation, single centers did not have sufficient incompatible pairs to generate a significant number of matches, and the need for regional or national systems of listing and matching became apparent. Several regions have demonstrated that paired kidney donation can work at a regional level; however, the full potential of paired kidney donation will be realized only when a national paired donation network is achieved.
Presently, multiple regional consortiums promote regional paired kidney donations. Hopefully, when an adequate computer algorithm becomes available, a national network ultimately will be put into place.

**Conclusion**

Currently, over 6,000 patients on the UNOS DDKT waiting list have donors who are willing and able to donate but cannot because of either ABO-incompatibility or positive crossmatch. However, several paired kidney donation programs have matched these donor-recipient pairs effectively. Despite increasing popularity and notoriety of these programs, however, relatively few transplants have resulted from paired kidney donation. Unfortunately, this program will not realize its full potential until a national paired donation network is in place.

**Living Donor Liver Transplantation**

Adapted from a presentation by John Fung, MD, PhD, Department Chair, General Surgery, and Director of the Transplant Center, The Cleveland Clinic, Ohio.

Before living donor liver transplantation (LDLT) was introduced, the mortality for children awaiting deceased donor liver transplantation (DDLT) exceeded 25%.24 In 1987, Strong et al25 performed the first successful LDLT from a mother to her son in Australia. Since that time, over 12,000 LDLTs have been performed worldwide.26 Further, after the initial success of adult-to-child LDLTs using the left lateral segment, Japanese surgeons began to offer the procedure to adult recipients as well, first with the left lobe and then with the right lobe.27

The initial US experience with left-lobe LDLTs resulted in a high incidence of small-for-size syndrome, which is characterized by synthetic dysfunction, transaminitis, prolonged cholestasis, and, rarely, irreversible liver failure and death.28 Consequently, US centers began to favor right-lobe LDLTs for adult-to-adult donation. In 2006, LDLTs accounted for approximately 3.7% of adult liver transplants and 11.3% of pediatric liver transplants in the United States.1

LDLT has several advantages over DDLT, particularly when adult-to-child transplantation is involved. The graft generally is in excellent condition, the ischemic time is short, and the timing of transplantation can be optimized.26 Despite these obvious benefits, LDLT must be approached cautiously because of the risk of donor morbidity and mortality.

**LDLT Recipient Outcomes**

Overall, most series and reviews in the literature report favorable survival data for LDLT recipients. For all ages, patient and graft survival rates of LDLT recipients compare favorably with those of DDLT recipients (Table 2).29 Data from the SRTR found that for recipients under 2 years of age, LDLT provides statistically superior graft survival than does DDLT.30

**LDLT Donor Outcomes**

The exact risks of partial liver donation are difficult to quantify, because no formal international registry exists to follow these patients prospectively. The estimated mortality risk varies according to the extent of resection: 0.4% for right hepatectomy and 0.1% each for left hepatectomy and left lateral segmentectomy.26

Right hepatectomy LDLT is associated with an increased morbidity (range, 2%–60%; overall, approximately 35%) and more severe complications than is left hepatectomy or left lateral segmentectomy.31 Complications include bleeding, bile stricture or leak, liver insufficiency, deep venous thrombosis, pulmonary embolism, infection, need for reoperation, portal vein thrombosis, pancreatitis, incisional hernia, gastric perforation, wound

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**Figure 5**

Domino-paired kidney donation. Adapted from Montgomery et al.21

**Table 2**

Graft and Patient Survival by Age at First Transplant

<table>
<thead>
<tr>
<th></th>
<th>Graft survival, %</th>
<th>Patient survival, %</th>
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<tbody>
<tr>
<td></td>
<td>1 year 3 year</td>
<td>1 year 3 year</td>
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<tr>
<td>Deceased donor:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adult (age ≥ 18 years)</td>
<td>81.9 72.7</td>
<td>86.3 78.0</td>
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<tr>
<td>Child (age &lt; 18 years)</td>
<td>84.9 76.8</td>
<td>91.9 86.9</td>
</tr>
<tr>
<td>Living donor:</td>
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<td></td>
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<tr>
<td>Adult</td>
<td>83.0 74.6</td>
<td>89.5 81.3</td>
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<tr>
<td>Child</td>
<td>89.2 74.8</td>
<td>95.2 83.1</td>
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</table>

Adapted from Scientific Registry of Transplant Recipients data32
infection, pleural effusion, pneumonia, and death.31

The Vancouver Forum

During an international conference of transplant physicians held in Vancouver, British Columbia, Canada, in 2005, to address the care of the live lung, liver, pancreas, and intestine organ donor, the basic principles of LDLT were defined31:

- LDLT should be performed only if the risk to the donor is justified by the expectation of an acceptable outcome in the recipient.
- For adult recipients, the patient and graft survival of LDLT should approximate the expected outcomes for DDLT. For pediatric recipients, the patient and graft survival of LDLT should be superior to the expected outcomes for DDLT.
- The indications for LDLT should be the same as those established for DDLT.
- LDLT should offer an overall advantage to the recipient when compared with waiting for an acceptable deceased donor organ to become available for transplantation.
- Living donor right hepatectomy for LDLT has an estimated mortality of 0.4% and morbidity of 35%.

Summary

LDLT has emerged as an important source of organs, particularly among small pediatric patients and adults who are disadvantaged by the current Model for End-stage Liver Disease (MELD) scoring system.34 It is imperative that the potential donor be educated thoroughly about the high risk of morbidity and mortality associated with partial liver donation. The principles set forth by the Vancouver Forum should be used to determine eligibility for LDLT.

References

**What’s New, What’s Hot in Organ Transplantation**

Erik B. Finger, MD, PhD
University of California, San Francisco

Recent progress in tissue transplantation is building on past research results. During the American Transplant Congress 2007, held in San Francisco, California, clinical researchers reported on immunosuppressive regimens to minimize toxicity and optimize efficacy, drug combinations to avoid complications from over-immunosuppression, methods to build tolerance of transplanted grafts, ways to avoid recurrent hepatitis infection following liver transplantation, and changes in trends for hepatic transplantation. In addition, investigators at the meeting discussed such basic research topics as costimulation and crosstalk between cells, factors that affect transplant tolerance, and substances that may modify tissue response to inflammatory injury resulting from transplantation.

The most dramatic results of transplant surgeries often are those reported by the popular media, but many of the most significant, far-reaching studies are published in medical journals and discussed in auditoriums among healthcare professionals. The annually popular session “What’s New, What’s Hot?” given during the American Transplant Congress 2007 in San Francisco, California, brought the transplant community up-to-date on some of the important new research described at the meeting. The session was chaired by Goran Klintmalm, MD, PhD, Director of Transplantation Services at the Baylor University Medical Center, Dallas, Texas, and Flavio Vincenti, MD, Professor of Clinical Medicine at the University of California, San Francisco.

**Clinical Transplantation**

Adapted from a presentation by Paul Martin, MBBCH, Professor of Internal Medicine and Surgery, and Associate Chief, Division of Liver Diseases, Mount Sinai School of Medicine, New York.

Each year, new results about drug therapies to suppress the immune response and keep organ grafts healthy are shared among the medical community. Recently, presentations from leaders in organ transplantation reported on studies having four recurring themes—immunosuppression and complications, tolerance, recurrent disease, and changes in indications for liver transplantation.

**Immunosuppression Efficacy vs Toxicity**

Recent developments and advances have furthered the balance between efficacy and complications in transplant immunosuppression. Ojo et al investigated death with graft function (DWGF) in transplant recipients to identify complications in the immunosuppressed patient and specific predictors of DWGF. Currently, investigators are comparing immunosuppressive regimens to optimize efficacy and minimize toxicity.

Pascual et al evaluated the effects of corticosteroid avoidance or early corticosteroid withdrawal in kidney transplant recipients. Results of this meta-analysis of 34 studies showed that steroid avoidance was associated with an increased risk of acute rejection episodes and with less diabetes, lower mortality, and increased risk of graft loss. Thus, corticosteroid avoidance was acceptable in patients having a low-to-moderate risk of rejection.

Wali et al are testing a switch from a calcineurin-based immunosuppressive regimen (mycophenolate mofetil plus tacrolimus) to a sirolimus-based regimen (mycophenolate mofetil plus sirolimus) in kidney transplant recipients. This substitution is improving graft function and yielding an annual incidence of acute rejection that is less than 10%.

Etienne et al reported results from the DICAM study, in which kidney transplant patients were given either a standard regimen that included cyclosporine and mycophenolate mofetil after corticosteroid withdrawal or a similar regimen that featured a 50% reduction in
cyclosporine regimen had lower blood pressure, a higher glomerular filtration rate, and less anemia with no loss in graft function when compared with those who used higher cyclosporine doses. Thus, stable kidney transplant patients may enjoy likely improvement in renal allograft function and decreased cardiovascular risk if they are given lower calcineurin inhibitor doses and avoid corticosteroid use.

Findings in liver transplant patients also pointed to certain risk factors for renal dysfunction and methods to avoid this complication. For example, Pascual et al reported that of a large series of liver transplant recipients, 29% eventually developed severe chronic renal dysfunction with glomerular filtration rates < 30 mL/min. Risk factors for renal dysfunction were older age, female gender, and low body mass index (BMI). In addition, Ojo et al found that in liver transplant patients, addition of mycophenolate mofetil to a corticosteroid-based immunosuppressive regimen that included a calcineurin inhibitor resulted in less of a decline in renal function than did a regimen that did not include mycophenolate mofetil.

**Over-Immunosuppression**

Polyomavirus BK-associated nephropathy (PVAN) may result from over-immunosuppression. This complication is more commonly detected over time and is predicted by corticosteroid dose, episodes of acute rejection, and use of tacrolimus instead of cyclosporine.

In studying kidney-pancreas transplant recipients, Medipalli et al reviewed the usefulness of protocols to detect infection with the BK virus during three eras within 9.5 years—the first 5 years, the next 3 years, and the last 1.5 years. Patients with BK viremia were treated with reduced immunosuppression. The most recent era, which featured improved viral screening, had the lowest rate of progression to BK nephropathy and the best overall graft survival when compared with prior eras. The authors concluded that aggressive screening for BK viremia resulted in earlier diagnosis, lower prevalence of BK nephropathy, and improved graft survival.

**Immunosuppression in the Highly Sensitized Patient**

Immunosuppressive conditioning regimens in the highly sensitized patient using intravenous immunoglobulin (IVIg) and rituximab therapy have been effective, but cumbersome, methods for overcoming the sensitization barrier. Previously, these protocols required up to 4 months of induction therapy. However, Vo et al reported on a safe and effective induction protocol using IVIg and rituximab that required only 4 weeks of pretransplant induction therapy. This protocol called for administration of 2 g/kg of IVIg on days 1 and 30 and 1 g of rituximab on days 7 and 22. This combination reduced both the number of IVIg doses needed and the time to desensitization. Importantly, the IVIg did not hamper rituximab’s ability to suppress the B-cell population, and no patient developed human antichimeric antibodies. Patient and graft survival at 6 months was 100%.

**Tolerance**

Tolerance remains an elusive goal in transplantation. Advances in clinical transplant tolerance were highlighted by Kawai et al, who reported their results of combined bone marrow and kidney transplants in five human leukocyte antigen-mismatched recipients. A conditioning regimen including cyclophosphamide, thymic irradiation, anti-CD2 monoclonal antibody, a calcineurin inhibitor, and anti-CD20 monoclonal antibody (in a subset of patients) was used. Following withdrawal of immunosuppression, four of the five patients continued to have functioning kidney allografts for up to 3 years after transplant surgery, and one rejected the graft at day 10.

**Recurrent Disease**

Recurrent hepatitis C virus (HCV) infection after liver transplantation is a well-established cause of reduced graft and patient survival. Sinan et al analyzed the use of the Donor Risk Index and Model End-Stage Liver Disease (MELD) score to predict early, severe, recurrent HCV infection. The authors found that older donors and those having a high Donor Risk Index score were at increased risk of early and severe HCV infection. However, the MELD score did not predict early or late recurrence of HCV infection.

Lilly et al examined the impact of calcineurin inhibitors on the response of liver transplant patients with recurrent HCV infection to antiviral therapy. They found that the transplant patients who were treated with antiviral therapy had response rates similar to those seen in the nontransplant setting; further, the impact of viral genotype was similar between the groups. Overall, patients with recurrent HCV infection who were treated with cyclosporine had a greater sustained virologic response to antiviral treatment than did those given tacrolimus.

Fasola and Klintmalm reported the results of the Hepatitis C Three trial that compared liver transplant immunosuppression using tacrolimus plus corticosteroids, mycophenolate mofetil and tacrolimus plus corticosteroids, or mycophenolate mofetil, tacrolimus, and daclizumab. They found similar graft survival among the three arms, although the tacrolimus/corticosteroid arm had increased recurrent fibrosis. They concluded that a corticosteroid-free regimen that included tacrolimus,
mycophenolate mofetil, and daclizumab was an acceptable immunosuppressive regimen for patients undergoing liver transplantation for HCV infection.

Changing Indications for Liver Transplantation

Increasing obesity among residents of the United States is well established, and a corresponding increase in end-stage liver disease attributed to nonalcoholic fatty liver disease (NAFLD) has developed in parallel. Leonard et al17 investigated the impact of BMI on patient and graft survival in liver transplant recipients. Interestingly, BMI corrected for weight from ascites did not predict a decrease in patient or graft survival, although each liter of ascites was associated with a decrease in both. Additionally, Malik et al18 showed that although nonalcoholic steatohepatitis recurrence was found in 21% of patients, it did not negatively affect patient or graft survival.

Conclusion

In all, a broad spectrum of developments in clinical transplantation have been added to the considerable available literature on organ transplantation and immunosuppression. Put succinctly, less immunosuppression is perfectly acceptable for some patients, recurrent disease still is an important problem among the transplant population, and increasing numbers of patients are developing sequential organ failure after transplant, as seen among liver transplant patients who develop renal failure.

Basic Science

Adapted from a presentation by Anthony Jevnikar, MD, Professor of Medicine, Immunology, and Microbiology, Schulich School of Medicine and Dentistry, and Director of Transplantation Nephrology, London Health Sciences Centre, The University of Western Ontario, London, Ontario, Canada.

Basic science research as it relates to immunology and transplant biology is an immensely broad-reaching area. Among important subjects are costimulation and crosstalk between cells, factors that affect transplant tolerance, and substances that may modify tissue response to inflammatory injury resulting from transplantation.

Costimulation Continues to Grow

Costimulation remains an important field of research in transplant biology. In particular, crosstalk that takes place between T cells and antigen-presenting cells (APCs) or parenchymal cells has been a hot topic of research. Habicht et al19 showed that blockade of the T-cell Ig mucin protein domain (TIM)-1:TIM-4 costimulation pathway prolonged cardiac allograft survival, especially when used with subtherapeutic doses of rapamycin. This prolongation of graft survival depended upon T regulatory (Treg) cell function as depletion of Treg cells abrogated efficacy. Blockade of TIM-1 pathways impaired Treg function and prevented the transition of CD4+FoxP3+ T cells into FoxP3+ Treg cells.20

Wang et al21 described a new B7 family member, B7-H4, that apparently had a negative costimulatory function. Knockout mice rejected cardiac allografts at the same time as did wild-type recipients but were resistant to tolerating treatment with anti-CD40 ligand (anti-CD40L) and donor-specific transfusion (DST).

The negative costimulatory molecule known as PD-1 (programmed death-1) was the focus of several studies. Albin et al22 showed that blockade of PD-1 and its ligand (PDL) prevented both induction and maintenance of tolerance. PDL-1 knockout mice treated with cytotoxic T-lymphocyte-associated protein 4-immunoglobulin (CTLA4-Ig) had prolonged graft survival but still were susceptible to chronic graft vasculopathy. Yang et al23 showed that in a class II mismatched heart transplant model, PDL-1 expression both on the cardiac allograft and on passenger leukocytes was required for long-term graft survival. Expression on the graft or passenger leukocytes alone improved survival over fully deficient knockout grafts but was insufficient for long-term graft survival.

Vu and others24 discussed costimulation of OX40, a member of the tumor necrosis-factor family of receptors. Blockade of OX40 impaired the suppression of effector T cells by Treg cells in co-culture proliferation assays and prevented transplant acceptance in islet transplant models using DST and anti-CD40L monoclonal antibody.24

Blockade of the CD40:CD40L pathway has been a promising avenue for inducing tolerance in mice. The utility of monoclonal antibody against CD40L has been disappointing, however, because of implications of increased incidence of thrombotic events associated with its usage. New investigations using blockade of its counter–receptor, CD40, may be effective and, hopefully, may avoid the complications of thrombosis. The anti-CD40 monoclonal antibody 4D11 showed promise in prolonging renal allograft survival in nonhuman primates,25 although further tissue analysis revealed poor graft histology. Further, adding tacrolimus to anti-CD40 therapy improved overall graft survival and appearance of grafts on histologic evaluation.26

Indoleamine 2,3-dioxygenase (IDO)

Since Munn et al27 described the role of indoleamine 2,3-dioxygenase (IDO) in maternal–fetal tolerance, IDO has been examined for its potential role in transplant tolerance. CTLA4-Ig-induced tolerance partially results from engagement of B7 receptors on dendritic cells, which leads to interferon (IFN)-γ secretion; with paracrine stimula-
tion, they induce an increase in IDO expression.28

Coley et al29 confirmed these findings by showing that IFN-γ was required for CTLA4-Ig-induced tolerance, even in mice lacking the receptor for IFN-γ, presumably because of IFN-γ-induced IDO upregulation in allografts and subsequent inhibition of alloreactive T-cell responses. Overexpression of IDO in islet allografts resulted in a smaller memory T-cell population and prolonged graft survival.30,31 Contrary to the benefits seen in islet transplants, expression of IDO in renal allografts resulted in increased apoptosis of tubular epithelial cells and inflammatory graft injury.32

TH17 Cells

The role of interleukin (IL)-17 and so-called T helper (Th) 17 cells in immune responses and tolerance has gained significant attention recently.33 In contrast to other groups, Tao and others34 showed that IL-17 was required for Treg cell function and to induce and maintain tolerance in their transplant model. Blockade of IL-17 function in nonobese diabetic mice prevented progression to diabetes if given at week 10 of life, when islet inflammation began to progress to a pathogenic phenotype; however, it was not effective if given to younger mice.35

Burrell et al16 characterized a CD8+ Th17 cell that developed independently from traditional CD4+ Th17 cells and that was resistant to anti-CD40L monoclonal antibody-induced tolerance. The development of these CD8+ Th17 cells was dependent on transforming growth factor-β.36 Interestingly, CD4+ Th17 cells from older graft recipients expressed more IL-17 than did the same cells from younger recipients.38

Treg Cells

Treg cells are a subset of T cells that can suppress the function of potentially pathogenic alloreactive cells in the periphery. As in recent years, studies of Treg biology and function continue to be a popular topic.

The theoretical impact of immunosuppressive drug regimens on Treg homeostasis and function may be very significant when investigators attempt to induce long-standing immunologic tolerance. Bluestone et al39 followed Treg cells in human recipients of kidney allografts after treatment with belatacept, a re-engineered CTLA4-Ig with two amino acid substitutions in the CTLA4 binding domains, and IL-2R monoclonal antibody. They found that costimulatory blockade with CTLA4-Ig did not interfere with Treg homeostasis. Anti-IL-2R (CD25) monoclonal antibody treatment resulted in a decrease in the peripheral Treg cell population, but the number of cells rebounded after treatment.

Creation of an allospecific Treg population capable of specifically suppressing alloreactive T-cell responses was the subject of considerable investigation. In vitro expansion of allospecific Treg cells was achieved by culturing CD4+CD25+ T cells with APCs and allo-major histocompatibility complex peptide in the presence of IL-2.40 These cells could suppress allograft rejection when infused with an induction course of rapamycin.

Expansion of the Treg cell population also may be pursued in vivo. Treatment of mice with anti-CD45RB monoclonal antibody experienced nonspecific expansion of the Treg cell population in the absence of specific antigen stimulation.41 This may have resulted from proliferation of existing Treg cells or conversion from other cell types.

Bloom et al42 showed that treatment with alemtuzumab increases the Treg cell population for up to 1 year after treatment. Withdrawal of tacrolimus further increases the number of Treg cells in peripheral blood of renal transplant patients.

In all, the research described demonstrated two avenues of research into developing a Treg cell population that can suppress alloimmune rejection.

Modifying Graft Response to Tissue Injury

Many studies investigated ways to modify the response of tissue to inflammatory injury related to transplantation. The use of the new techniques of small interfering RNA (siRNA) inhibition of gene expression had interesting results.

Zheng et al43 used a new method of delivering siRNA that specifically targeted tumor necrosis factor (TNF), Fas, and C3 genes to abrogate the ischemia/reperfusion injury caused by prolonged cold ischemic storage of cardiac heart grafts. Additional work by Parker et al44 demonstrated delivery of C3-suppressing siRNA in kidney grafts using nanoparticles. Further, Zhang et al45 showed that use of β4 integrin–suppressing siRNA could disrupt intracellular signaling downstream from human leukocyte antigen (HLA) class I molecules on endothelial cells, thereby implicating the need for these integrins in HLA function.

Other modifiers of tissue response to injury were reported. Emamaullee et al46 demonstrated a caspase inhibitor EP1013 that could restore normoglycemia in animal recipients of marginal mass islet transplants, presumably via increased cellular survival during the transplant procedure. Raiss et al47 showed that the senescence mediator p16INK4a contributed to ischemia/reperfusion injury in kidneys. Hertig et al48 showed that the transformation of tubular epithelial cells to mesenchymal cells occurred with acute rejection and ischemia/reperfusion; this could be a good target to diagnose or intervene at either of these causes of graft dysfunction.
Steroid avoidance or very early withdrawal in kidney transplant recipients with graft injury. The future of basic research in transplant biology will lie in the study of the intersection of these three broad categories: the adaptive immune response, the innate immune response, and allograft vascular injury. The next meeting of the American Transplant Congress showed recurrent themes.

### Conclusion

As in prior years, much of the laboratory data presented at this important meeting showed recurrent themes. Overall, the data for research could be grouped into three main categories: the adaptive immune response, the innate immune response, and graft response/resistance to injury. The future of basic research in transplant biology will lie in the study of the intersection of these three broad fields of study.

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Coagulation: A Pivotal Link Between Innate and Adaptive Immunity

Alexander H. Toledo, MD
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The coagulation cascade is closely related to the inflammation process and is a potential target for manipulating the immune response. Within the context of transplantation, numerous mediators of coagulation that initiate and activate the immune response and possibly cause vascular injury are now being identified and studied. During a symposium presented at the American Transplant Congress 2007 in San Francisco, California, experts discussed the effect of platelets, monocytes, and coagulation as they affect alloimmunity and vascular injury.

Coagulation-Mediated Platelet Activation and Vascular Injury

Adapted from a presentation by Simon C. Robson, MD, PhD, Professor of Medicine/Gastroenterology, Harvard Medical School, Boston, Massachusetts.

Inflammation and coagulation are critical pathways in both allograft and xenograft rejection. The targeting of these areas will become increasingly relevant as immunosuppressive protocols continue to be formulated. One crucial step in the intricate coagulation-mediated immune response is accomplished via CD39, a critical thromboregulatory molecule on the luminal surface of endothelial cells.

The Functions of CD39

CD39 is an extracellular nucleotide found in the vascular endothelium that is active in thrombosis and inflammation. CD39 converts adenosine triphosphate (ATP) and adenosine diphosphate (ADP) into adenosine monophosphate, a precursor to the potent antithrombotic and anti-inflammatory mediator adenosine. This mediator, in turn, helps to regulate the activity of purinergic type-2 receptors on platelets and vascular cells; this action is key to inducing vascular thrombosis and inflammation. The hydrolysis of ATP and ADP subsequently blocks platelet aggregation.

The spatial and temporal expression of CD39 and other ectonucleotidases also controls thrombus size and stability. CD39 can function without the presence of nitric oxide and prostacyclin; however, its bioactivity is significantly enhanced by these substances.

Relevance to Laboratory Studies

Many animal models have been used to evaluate the various effects of CD39 in vivo; manipulation of the CD39 pathway has been very interesting to investigators studying vascular injury and thrombosis in xenograft transplantation. For example, oxidative inactivation of CD39 during ischemia/reperfusion (I/R) of unaltered animals led to a progressive decline in CD39 activity.
CD39 plays a key role in thrombosis and inflammation along the vascular endothelium. Its overexpression has been linked to improved survival and graft function in numerous animal models, including those involving I/R injury; these results offer strong evidence of an altered immune response via CD4+ T cells. The use of CD39 transgenic cells may have future therapeutic applications in improving protocols for xenotransplantation and for procedures associated with vascular injury and coagulation.

**Platelet and Monocyte Activation**

Adapted from a presentation by Allan Kirk, MD, PhD, Professor of Surgery, Emory University School of Medicine, Atlanta, Georgia.

The immune system is a well-regulated mechanism that provides the body with protection via closely controlled responses to specific threats. As such, it must turn responses to invaders both “off” and “on,” and it carries the potential of causing and preventing rejection of transplanted organs. Thus, investigative teams currently are studying transplant tolerance, in which the immune response may favor organ acceptance rather than its rejection.

A theory of particular interest involves the expression of CD154 on activated platelets and its implications for activating immunity caused by surgical trauma. Interactions between platelets and monocytes are particularly interesting, along with the hypotheses that platelet activation induced by trauma contributes to initial activation and maturation of antigen-presenting cells (APCs).

**Monocytes**

In human renal transplant patients undergoing extreme T-cell depletion resulting from use of preparations containing monoclonal antibody, rejection characterized by monocyte infiltration in the graft persists in the face of severe lymphopenia. Kirk et al. reported that kidney transplant patients given alemtuzumab experienced lymphocyte eradication; however, rejection was completely absent until approximately the 3-week mark, when monocytes first became available in the peripheral circulation. Graft dysfunction corresponded with the arrival of activated monocytes, even without a prominent T-cell infiltrate.

Traditionally, this initial acute allograft rejection has been considered to be a largely T-cell-mediated process. However, this clinical scenario illustrates that the manner in which T cells and other lymphocytes recognize donor antigen and become activated still is being elucidated. Some animal models have demonstrated that allograft parenchymal and endothelial cells cannot directly present alloantigen or initiate rejection, even in the presence of T cells. In fact, other links between the graft and naïve T cells must be present, and evidence is growing that monocytes are active in this capacity.

A model of human renal transplant I/R injury showed increased levels of gene transcripts involved in cellular adhesion, chemotaxis, apoptosis, and monocyte recruitment/activation, although T-cell transcripts generally were absent during this period. Histologically, the im-
mediate post-reperfusion state showed tubular injury and monocyte infiltration; allografts in the recovery phase with normal graft function, however, showed a significant presence of T cells and its costimulators.

More recent data further support monocytes acting as a bridge between allograft and T-cell immunity. T cells proliferate poorly until autologous monocytes first contact allogeneic endothelial cells via scavenger receptors and then prepare to initiate T-cell activation. This prominent role for monocytes in alloimmunity should prove to be the basis for more novel therapeutic avenues related to allograft transplantation.

**Platelets and CD154**

The CD40 receptor has been found on dendritic cells (DCs), other APCs, and T and B cells. The binding of CD40 on APCs to the CD154 ligand on activated T cells mediates endothelial and APC activation and facilitates interactions with T cells and platelets. Further, CD40/CD154 binding results in interleukin (IL)-12 production by APCs and subsequent interferon-γ production by T cells; it also induces APC maturation, thereby enabling the differentiation of naïve T cells into effector cells.

Manipulation of this interaction has been successful in modulating the immune response in various animal models. For example, the administration of a CD154-specific monoclonal antibody prevented renal allograft rejection in nonhuman primates. Similarly, anti-CD154 treatment allowed for long-term survival and function of intrahepatic islet allografts in monkeys.

Recent data further support monocytes acting as a bridge between allograft and T-cell immunity. T cells proliferate poorly until autologous monocytes first contact allogeneic endothelial cells via scavenger receptors and then prepare to initiate T-cell activation. This prominent role for monocytes in alloimmunity should prove to be the basis for more novel therapeutic avenues related to allograft transplantation.

**The Initiation of Vascular Injury**

Adapted from a presentation by Anthony Dorling, PhD, FRCP, Imperial College, London, United Kingdom.

Coagulation proteases mediate numerous fibrin-independent processes, including adaptive immunity and chronic inflammation. The effects largely transpire via protease-activated receptors (PARs), which are expressed on endothelial cells, monocytes, and other cells involved in alloimmunity. Stimulation of PARs promotes induction of numerous pro-inflammatory mediators, including IL-6, IL-8, transforming growth factor-β, and monocyte chemotactic protein (MCP)-1.

This pathway is involved in the modulation of DCs. The addition of thrombin to DC cultures promotes an enhanced T-cell response in an allogeneic mixed-lymphocyte reaction. Given the known expression of PARs on DCs and the constant levels of major histocompatibility complex II, CD80, CD86, CD40, and other costimulatory molecules after exposure to thrombin, DCs likely are modulated via this coagulation protease/PAR pathway.

**Coagulation and Alloimmunity**

The link between coagulation (specifically as it relates to thrombin) and alloimmunity is a young field of investigation, yet studies into its properties are yielding promising data. The development of transgenic animals that express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance. Further, the ability of animals to express anticoagulants within their grafts has been a major advance.

Fibrinogen depletion did not have the same impact on graft survival as did models of thrombin inhibition. When NK-cell depletion was added to the fibrinogen depletion, graft survival improved; this led to speculation that acute humoral rejection may be mediated by NK cells and coagulation proteases.

Investigators seek to define this complex, but instrumental, mechanism that links coagulation proteases and
the immune response more precisely. Dorling et al. blocked only PAR-1 in a fibrinogen-depleted rodent heart xenograft model and found that these organs had prolonged graft survival with no evidence of macrophage or NK cell infiltrates. However, when a PAR-1 agonist was added, a significant decrease in graft survival and the presence of prominent NK and macrophage infiltrates were noted. However, addition of PAR-2 and PAR-4 agonists had no significant effects in these domains. Interestingly, enzyme-linked immunosorbent assay studies revealed that markers for NK cell (interferon-γ) and macrophage activation (IL-6 and tumor necrosis factor) depended upon signaling via PAR-1. MCP-1 also was dependent on PAR-1 signaling. Furthermore, blocking MCP-1 inhibited the actions of a PAR-1 agonist, thereby prolonging survival and inhibiting NK-cell and macrophage infiltration.

These elegant experiments demonstrated that thrombin, via PAR-1, is essential for significant production of MCP-1, which is required for infiltration and activation of NK cells and macrophages. This pathway, which links thrombin to acute humoral rejection, apparently will be a valuable key to aiding the survival of xenotransplants and allograft transplants in the future.

Conclusion

The exciting developments discussed in this article illustrate the vast realm of experimentation into the coagulation system and its costimulants beyond the study of fibrin production. In various animal transplant models, coagulation and protease-dependent pathways increasingly are being identified as prerequisites to APC activation and subsequent T-cell activation and maturation.

Numerous platelet ligands also are considered to be critical factors in initiating alloimmunity. Likewise, acute allograft rejection obviously involves more than the largely T-cell-mediated process traditionally described—and therefore the role of monocytes and NK cells is being reassessed.

Of course, new targets for modulating the immune response will arise as novel links between coagulation, vascular injury, and alloimmunity are found. Ultimately, this interface between coagulation and innate and adaptive immunity promises to be a dynamic topic within the transplantation community.

References

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Tailoring Immunosuppression to the Individual Patient

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Pharmaceutical immunosuppression currently is the only mechanism to prevent allograft rejection. It typically is achieved by offering patients a three-drug cocktail; the mechanisms of action of these drugs are different, yet complimentary. Healthcare practitioners now are designing individualized antirejection regimens to suit the needs of varying patient populations. In particular, clinical investigators have been focusing on differences in ethnicity, age, size, and such comorbidities as viral hepatitis among patients. Ethnicity impacts patient outcomes; African-American patients tend to experience suboptimal rates of pretransplant evaluation and transplant listing and higher risks of suboptimal posttransplant patient and graft survival than do Caucasians. Elderly patients tend to be more immunotolerant and to experience less acute cellular rejection than do younger individuals, yet they are at highest risk of death related to infection. In addition, body size impacts the tailoring of immunosuppressant dosages. Comorbidities must be considered carefully; many adverse effects of immunosuppressants may exacerbate other disease states and possibly decrease graft and patient survival. Finally, baseline exposure and activity of hepatitis B or C must be considered when an immunosuppressive plan is made to ensure adequate host defenses and prevent reactivation.

Advances in the development of immunosuppressants during the 1990s have led to minimal acute cellular rejection and, ultimately, direct graft loss. However, there currently is a drought of novel immunosuppressants entering the solid organ transplant market.

Most importantly, physicians must consider patient characteristics when prescribing immunosuppressants. Fortunately, clinicians have become increasingly savvy about individually tailoring drug regimens. This article reviews information presented at a symposium held during the American Transplant Congress 2007 in San Francisco, California. It discusses how ethnicity, age, weight, comorbidities, and viral hepatitis infection affect the transplant process and the management of immunosuppression in transplant patients.

The Impact of Ethnicity

Adapted from a presentation by Velma Scantlebury, MD, Professor of Surgery, Director of Kidney Transplantation, University of Southern Alabama, Mobile, Alabama.

The transplant community has made great advances in managing organ donors and in urging donation regions to meet the Health Resources and Services Administration’s target of 3.75 organs donated per donor. Unfortunately, a disproportionate number of persons in the United States still are awaiting a solid organ transplant—and racial disparities in the dissemination of these organs are obvious.

Disparities in Listing Rates, Transplantations, and Outcomes

Over the past 10 years, there has been a difference in the number patients listed for transplant compared with the number of those receiving a transplant. Despite escalating numbers of living-donor transplantations recorded since 2004, some 50,000 patients still await a kidney transplant. Interestingly, over 20,000 of the patients on the lists are African-American.

The incidence of end-stage renal disease (ESRD) among African-Americans is four times higher than it is among Caucasians. Ethnic minorities suffer disproportionately from diseases necessitating transplantation (eg, hypertension, diabetes), and they may have additional risk factors for less access to appropriate medications and transplant-knowledgeable healthcare providers. Additionally, lack of private insurance among African-Americans and Hispanic-Americans may be a barrier to transplantation.

Dr. McCann is a Transplant Pharmacy Resident at Duke University Medical Center, Durham, North Carolina.
Minority populations not only have required more transplants over the past 10 years, they also have shown drastically lower referral rates (African-Americans, 91%; Caucasians, 98%; \(P = 0.0008\)) and listing rates (African-Americans, 71%; Caucasians, 86.7%) than have Caucasians.\(^2\) Overall, African-Americans have a transplantation rate 18% lower than that of Caucasians (relative risk = 0.82).\(^2\) Unfortunately, graft survival and overall outcomes are inferior among minorities; as shown in Table 1,\(^2\) African-Americans have a significantly lower 3-year kidney, liver, and heart graft survival than do Caucasians. Review of the United Nations Organ Sharing (UNOS) orthotopic liver transplant data from 1988–1996 showed that being African-American (hazard ratio [HR] 1.36, 95% confidence interval [CI] 1.16–1.60, \(P < 0.0007\)) or Asian (HR 1.25, 95% CI 1.01–1.56, \(P = 0.03\)) was a predictor of poor 2-year patient survival when compared with being Caucasian.\(^3\)

Proposed factors affecting decreased graft survival include severity of the underlying indication for transplant, diagnosis of comorbidities, development of posttransplant diseases, presence of obesity or poor nutritional status, access to necessary medications, receipt of human leukocyte antigen (HLA) -mismatched transplants, and presence of stronger allogeneic response, genetic differences that may affect drug absorption and metabolism, and socioeconomic differences.

Similar trends in listing and organ allocation have been documented in pediatric transplantation. Children of college-educated parents were more likely to be recommended for transplantation than were children of parents who did not finish high school. Interestingly, although compliant pediatric candidates were more likely to be recommended for transplant, compliant Caucasian patients were twice more likely to be referred than were compliant African-American patients.\(^4\)

**Socioeconomic Factors**

Socioeconomic profile differences between Caucasians, Hispanic-Americans, and African-Americans have been suggested as a risk factor for decreased allograft and patient survival. An analysis of US census data showed Hispanic-Americans and African-Americans to have similar socioeconomic status (ie, income, employment, education level).\(^5\) When 6-month graft survivals of Hispanic-American and Caucasian kidney transplant recipients were compared, no significant differences were found.

Thus, although the Hispanic-American population had a similar socioeconomic status as did the African-American population, Hispanic-American transplant outcomes more closely reflected Caucasian outcomes.

Socioeconomics, however, do not completely supply an answer for the disparities in graft survival among the races. In a study of the relationship of African-American heritage to graft survival after pediatric heart transplant, Mahle et al\(^6\) reported that African-Americans had a median graft survival that was less than half that of other racial groups—yet this disparity was not related primarily to economic differences.

**Access and Education**

Foster et al\(^7\) assessed minority access to kidney evaluation and transplantation to determine ways to lower cadaveric transplant waiting times (national average, 647 days for Caucasians vs 1,335 days for African-Americans) and increase rate of transplantation in African-Americans. By establishing educational sessions directed at healthcare providers, potential transplant recipients, and family members at dialysis centers and local/regional community hospitals, they increased live donation rates and graft and patient survival rates. Although no single intervention was responsible for these results, access to primary-care evaluation via a physician outreach program and substantial recipient and family education that included written, verbal, and video materials were believed to improve outcomes.

**HLA Matching and Genetic Variability**

African-Americans express extensive polymorphisms of HLA phenotypes and, theoretically, are more difficult to “perfectly” match for transplant than are Caucasians.

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**Table 1**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Caucasian, non-Hispanic</th>
<th>African-American</th>
<th>Hispanic/ Latino</th>
<th>Asian-American</th>
<th>Other/multiracial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney, non-ECD</td>
<td>81.6%</td>
<td>73.9%*</td>
<td>83.6%*</td>
<td>85.5%*</td>
<td>83.0%</td>
</tr>
<tr>
<td>Pancreas, only</td>
<td>63.5%</td>
<td>58.6%</td>
<td>78.1%</td>
<td>–</td>
<td>28.2%</td>
</tr>
<tr>
<td>Liver</td>
<td>73.6%</td>
<td>66.9%*</td>
<td>74.0%</td>
<td>74.1%</td>
<td>71.7%</td>
</tr>
<tr>
<td>Intestine</td>
<td>55.0%</td>
<td>37.9%</td>
<td>50.0%</td>
<td>50.5%</td>
<td>–</td>
</tr>
<tr>
<td>Heart</td>
<td>80.4%</td>
<td>72.8%*</td>
<td>78.9%</td>
<td>81.5%</td>
<td>81.7%</td>
</tr>
<tr>
<td>Lung</td>
<td>62.6%</td>
<td>61.0%</td>
<td>62.3%</td>
<td>77.5%</td>
<td>39.8%</td>
</tr>
</tbody>
</table>

* Significantly different from non-Hispanic Caucasians (\(P < 0.05\))

Omitted data denote insufficient percentage of patients in that specific group

ECD = expanded criteria donor

Adapted from Higgins and Fishman\(^2\)
Only 3% of all African-American renal transplant recipients in the United States receive HLA-matched transplants. However, there is no difference in organ half-life when HLA-matched (8.0 years) and -mismatched renal transplants (6.9 years) are compared; however, there is a profound difference in graft longevity when these numbers are compared with the half-life of Caucasian HLA-matched grafts (17.1 years).

Interestingly, a comparison of French-Caucasian and African-European (eg, sub-Saharan or Caribbean origin) kidney recipients showed similar 1-, 5-, and 10-year allograft and patient survival. The sub-Saharan-Africans were native to Africa and resided in France; their gene pool was considered to be of African origin only. On the other hand, the Caribbean-Africans were similar to African-Americans with a “mixed-African” gene pool, due to common ancestral movement from Africa into slavery during the 17th and 18th centuries. The Caucasian and African-European groups had similar outcomes. The gene-dose effect was absent, since there were no differences between the “African,” “mixed-African,” and “Caucasian” gene pools. Thus, since African-Europeans and African-American share the same background genetically, the question of why racial disparities in the United States exist when they do not in Europe is valid. Other differences, both genetic and environmental, must be evaluated to explain the increased risk of allograft loss among African-Americans.

Genetics and Drug Metabolism

Genetic polymorphisms in specific biological pathways may impact the metabolism of the calcineurin inhibitors tacrolimus and cyclosporine, which are degraded extensively into inactive metabolites by the CYP3A system. CYP3A4*1B is a polymorphism of the gene encoding CYP3A4, 10%–40% of which is responsible for approximately 50% of the hepatic CYP3A metabolism of tacrolimus, 55% among African-Americans (55%), followed by Asians (33%) and then Caucasians (10%–40%), express the wild-type polymorphism, which may account for the increased hepatic clearance of the drug among the African-American population.

Polymorphisms have been identified in the MDR1 gene, which encodes for P-glycoprotein (PGP); this drug-efflux pump located in the intestinal cell walls allows for movement of calcineurin inhibitors back into the intestinal lumen for further metabolism, which limits total oral bioavailability. Although the significance of one polymorphism is debatable, the simultaneous linking of three polymorphisms (most commonly seen among Caucasians) may cause a 40% decrease in PGP production, thereby increasing bioavailability and decreasing metabolism of calcineurin inhibitors. Thus, such genetic variations may explain why African-Americans require more immunosuppressive therapy to prevent graft rejection.

Translation Into Clinical Trial Outcomes

The full effects of genetic variability in drug metabolism among African-Americans is not completely understood, but many clinical trials have documented specific drug-related racial advantages and outcomes. Gonwa et al11 assessed combined use of tacrolimus plus either mycophenolate mofetil or azathioprine with cyclosporine/mycophenolate mofetil in a subset of African-cadaveric kidney transplants. Groups receiving tacrolimus fared better and had less frequent biopsy-proven acute rejections. However, African-Americans needed higher tacrolimus doses to achieve target concentrations.

In a study assessing the efficacy of adding sirolimus to cyclosporine plus corticosteroids in an African-American population, Podder and others12 found a reduction of acute cellular rejection episodes in the group given the three drugs (19.2% vs 43.3%, \( P = 0.004 \)) that was comparable with that of Caucasians given triple therapy. Graft survival at 2 years in the group given all three drugs was significantly higher than in the cyclosporine-plus-corticosteroid group (97.9% vs 85.6%, \( P = 0.048 \)) and was comparable with the graft survival of Caucasians.

Transplantation rates of minorities are suboptimal, and listing times for transplants remain lengthy. However, practitioners must foster access to transplant resources (eg, healthcare professionals, educational materials) and use lessons learned from clinical trials to optimize pharmacotherapy for enhancement of allograft and patient survival.

Considerations of Age, Weight, and Comorbidities

Adapted from a presentation by Herwig-Ulf Meier-Kriesche, MD, Associate Professor of Medicine, Clinical Director of Renal Transplant in the Department of Medicine, University of Florida, Gainesville, Florida.

With advances in the monitoring of immunosuppression and the development of new information that can be applied to old immunosuppressants, many transplant centers are moving away from the “one-size-fits-all” immunosuppression approach. Centers are tailoring
regimens according to patient-specific factors, as well as to pharmacokinetic and pharmacodynamic properties of drugs used.

**Age**

Age as a factor for modulating immunosuppression must be considered on two levels. First, increased donor age is a significant risk factor for kidney graft failure in cadaveric kidney and simultaneous kidney-pancreas transplants (RR 1.014, 95% CI 1.01–1.02, \( P < 0.001 \)).\(^{13} \) National trends for 1995–2000 describe an increase in renal transplants from donors over 55 years of age.\(^{14} \)

Although this may correlate with an increased risk of acute cellular rejection, donor age is a difficult consideration for the preemptive modification of baseline immunosuppression. Recipient age requires more consideration when weighing the risk-benefit ratio.

Elderly populations may be less immunogenic, as documented by lower rates of acute and chronic rejection.\(^{15} \) Immune tolerance in elderly populations may stem from altered actions of natural killer cells. Transplant recipients over age 60 do not die from graft failure; instead, they succumb to malignancy, infections, and cardiovascular complications.\(^{15} \) Older patients also may have diminished baseline hepatic function or CPY3A activity that requires less immunosuppression than seen in younger recipients.

Age-related risk factors for infectious death after transplantation were described retrospectively in a large renal transplant population.\(^{16} \) Oldest patients (> 65 years of age) had a 6.2-fold increased relative risk of death due to infection within the first 24 months (\( P < 0.001 \)) post-transplant and a decreased risk ratio (RR) of acute rejection (0.6) when compared with the reference age group (18–29 years of age). Criteria associated with a decreased RR of death included receiving a living donor transplant, being of African-American heritage, and using mycophenolate mofetil instead of azathioprine.\(^{15} \)

Despite the increased RR for infection-related death, the mortality benefit is maintained even when wait-listing is considered; thus, transplantation of older patients is a feasible option.\(^{16} \)

**Weight**

For the most part, immunosuppressive dosing can be achieved primarily via two mechanisms.\(^{17} \) First, the literature-defined or institution-specific fixed dosages of basiliximab, mycophenolate mofetil or sodium, sirolimus, and the calcineurin inhibitors are the easiest for clinicians to remember. However, when prescribing daclizumab and rabbit anti-thymocyte globulin (RATG), physicians must consider the patient’s weight. These mechanisms appear to be definitive, yet many immunosuppressants may fall within categories (eg, weight-based dosing of tacrolimus and cyclosporine) or into a third category based on targeted drug levels.

Weight-based dosages are calculated from actual body weight. Little published data has assessed the possibility of immunosuppression overdose based on actual body weight compared with dosages based on ideal or adjusted body weight. Srinivas and colleagues\(^{18} \) showed a higher incidence of BK viremia (BKV) at 6 months with increased total induction RATG doses (26% at a total dose > 500 mg vs 16% at a total dose < 500 mg).\(^{18} \) Obesity was associated with a higher incidence of BKV (32%) than seen among nonobese patients (15%). Conversely, dosing according to body weight showed no increased risk for BKV.

Despite the varying results, this study was an excellent example that the patient’s most appropriate weight, actual or ideal, must be assessed before immunosuppressants are prescribed. Drugs with low volumes of distribution, such as RATG, will remain intravascular. Although obese patients may weigh more than 50% in excess of their ideal body weights, their intravascular volumes would not rise proportionally. Therefore, in dosing larger patients, we provide excessive drug if we prescribe dosages based on the patients’ actual body weights.

Alternative methods for dosing do exist. Whereas body surface area is very important when prescribing chemotherapy, it is of little value when prescribing immunosuppressants (with the exception of pediatric dosing of mycophenolate mofetil/sodium). Additionally, body mass index (BMI) has been assessed more from an outcomes perspective than from an alternative-dosing perspective. In the setting of renal transplant, BMI is strongly correlated with superior patient and graft survival outcomes, except when patients have extremely high or low BMIs.\(^{19} \)

**Comorbidities**

Due to the limited pharmacologic options available to prevent and treat rejection in recipients of solid-organ transplants, comorbid disease states minimally impact the initial choice of immunosuppressants.

**Conditions of the Kidney**

As patients approach a lower risk for rejection outside of the initial 6-month time frame, their immunosuppressive cocktails may be tailored to decrease the synergistic adverse events of its components.

For example, high concentrations of calcineurin inhibitors may cause acute renal insufficiency via vasoconstriction at the renal afferent arteriole, and prolonged administration of these drugs may cause fibrosis of the renal
Therefore, patients with renal insufficiency may derive nephroprotection by having minimal to no exposure to calcineurin inhibitors after transplantation. In addition, although sirolimus was once believed to be “nephro-friendly,” it recently was associated with increasing proteinuria post-transplantation, which may be of concern during treatment of diabetic patients.

Conditions of the Heart

Cardiovascular-related mortality is the second leading overall cause of death at 5 years post-transplantation (Figure 1), with many patients having baseline risk factors before transplant. Additional risk factors for cardiac problems are related to use of immunosuppressants and include diabetes, hypertension, and dyslipidemia.

Corticosteroids have been linked directly to the development of post-transplant diabetes mellitus (PTDM) via insulin resistance, increased gluconeogenesis, and pancreatic glucagon release. Also, the use of corticosteroids with tacrolimus has been associated with PTDM more frequently than has their combined use with cyclosporine. Use of cyclosporine monotherapy provokes the development of hypertension due to imbalances of vasoconstriction and vasodilation, sympathetic activation, and renal tubular sodium re-absorption more often than does tacrolimus used alone; a similar phenomenon has been noted with combined use of cyclosporine and corticosteroids. Dyslipidemia may be aggravated further by corticosteroids, sirolimus, and cyclosporine, resulting in elevated low-density lipoprotein and triglyceride levels.

Although only the major adverse events have been highlighted here, many additional dermatologic, hematologic, and neurologic outcomes may develop from immunosuppressant therapy. These events may entice physicians to prescribe one agent instead of another. However, the “entire patient” must be considered when immunosuppressant therapy is prescribed so that development of comorbidities is not exacerbated or induced.

Individualizing Immunosuppression in Transplant Recipients with Hepatitis

Adapted from a presentation by Timothy L. Pruett, MD, Professor of Surgery and Associate Professor of Internal Medicine, Division Head, Division of Transplantation, University of Virginia, Charlottesville, Virginia.

In the United States, infections with hepatitis B virus (HBV) and/or hepatitis C virus (HCV) are common causes for hepatocellular damage and chronic cirrhosis that require liver transplantation. HCV rarely is a cause of fulminant hepatic failure. However, a recent US case review found that HBV fulminant liver failure occurred in 10% of patients; these cases were associated with a 10% spontaneous recovery rate and an overall 15% survival rate without transplantation.

Transplanting patients with either active HBV infections or active poor prognostic risk factors for HCV such as sustained alcohol use is associated with some risks. In addition, virally naïve patients may develop acute HBV or HCV without having a previous immune response. Regardless of how patients acquire HBV or HCV, their immunosuppressive regimen must be assessed to maintain a balance between preventing organ rejection and enhancing viral expression due to impaired immune response.

Minimization of Corticosteroids

Effects of bolus corticosteroid administration on HCV replication in vitro and in vivo have been assessed in liver transplant patients undergoing treatment for acute cellular rejection. HCV RNA was detected in peripheral blood mononuclear cells in vitro, with levels peaking twice on days 7 and 15 in the presence of corticosteroids; however, this phenomenon did not occur in vivo with high-dose corticosteroid treatment for acute cellular rejection. Additionally, elevated viral RNA levels decreased within 48–72 hours of corticosteroid discontinuation.

Corticosteroid-free protocols and “quick-weep” protocols have been assessed in HCV-RNA-positive patients undergoing transplants. HCV-positive orthotopic liver transplant recipients receiving tacrolimus, mycophenolate mofetil, and daclizumab had similar 1-year biopsy results when compared with cyclosporine-based protocols.
for advanced signs of fibrosis, less PTDM, and similar rejection episodes at 3, 6, and 12 months as did patients given tacrolimus, mycophenolate mofetil, and corticosteroids. Tacrolimus monotherapy has been attempted in HCV-positive patients; in a 5-year follow-up of post-necrotic cirrhosis liver transplant recipients randomized to tacrolimus alone or with corticosteroids, tacrolimus monotherapy produced better 1-, 3-, and 5-year patient survival despite minimal decreases in incidence or severity of acute HCV infection.

Bolus corticosteroid administration has been associated with increases in serum HCV RNA in excess of 4- to 100-fold. Thus, bolus corticosteroids should be avoided, if possible. In addition, total prolonged administration of corticosteroids in HCV-positive transplant recipients should be minimized after transplantation. Likewise, corticosteroid use in HBV-positive patients may promote viral replication and induce escape mutations. Conversely, minimal data exists assessing the outcomes of corticosteroid minimization with HBV reinfection post-transplantation.

**Cyclosporine—The Calcineurin Inhibitor of Choice?**

Cyclosporine has been proposed to be the calcineurin inhibitor of choice when treating HCV-positive transplant recipients. This proposition partially is due to the results of studies with Huh7/Rep-Feo cells that resulted in dose-dependent suppression of HCV replication after exposure to cyclosporine as compared with the minimal inhibitory effects seen with tacrolimus exposure.

A novel, synthetic, non-immunosuppressive cyclosporine, DEBIO-025, has shown promise in vitro for stronger suppression of HCV replication in Huh 5-2 cells; the 50% effective concentration of DEBIO-025 was 10-fold lower than that of cyclosporine.

Viral replication potency of DEBIO-025 was confirmed via two additional HCV replicon models.

Moving from bench top to bedside, a small, randomized trial compared tacrolimus to cyclosporine in HCV-positive liver recipients. Despite similar rates of survival, and HCV recurrence, patients using cyclosporine showed a trend toward increased rejection (50%) when compared with those using tacrolimus (24%). Altschuler et al recently presented the results of a meta-analysis that provided similar trends in rejection and survival rates, although the results were not statistically significant. Importantly, HCV-positive patients have a three-fold increased risk of death associated with an episode of acute cellular rejection. Owing to the lack of minimizing recurrence rates and the upward rejection trend, however, cyclosporine may not be the definitive first-line agent.

Despite the increase in published literature that adds to the debate over minimizing or discontinuing corticosteroids or the possible calcineurin inhibitor of choice, no clear consensus on how HCV-positive liver transplants should be treated is available. Even less data is available to assess these issues in HBV-positive transplant recipients.

The effects of viral hepatitis outside of the realm of liver transplantation recently were revisited. Although HCV-antibody-positive patients at the time of kidney transplant do not have a greater risk of death than do antibody-negative recipients, their use of immunosuppressants has been better studied. Aull and colleagues assessed the effects of corticosteroid-sparing regimens on HCV-positive kidney transplant recipients. Rejection-free survival was significantly better at 12 months among patients using tacrolimus plus mycophenolate mofetil than among patients using those two drugs plus corticosteroids. A trend also existed for decreased PTDM with the corticosteroid-sparing group.

**Conclusion**

Many factors must be assessed before an immunosuppressive regimen is begun or changed. When working with patients of different ethnic backgrounds, physicians first must understand the issues involving access to medical care among these populations. Thereafter, medical personnel must work to educate both potential recipients and their families about various aspects of the transplant process to ensure senses of empowerment and involvement in managing the disease. Once patients receive new organs, physicians must appreciate genetic differences in immunosuppressant absorption and metabolism and, yet again, problems with access to healthcare to ensure optimal graft outcomes.

Each transplant recipient has a different age, size, and physical condition. Age is important in balancing the risks of rejection with infection and malignancy. Size is important in discerning appropriate dosages of medications. And, of course, patients’ comorbidities influence decisions about immunosuppression that must be made.

In addition, the body of literature that assesses how immunosuppression should be managed in HBV- and HCV-positive transplant recipients continues to grow. Thus far, minimization of immunosuppression appears to be the key to successful HCV-positive hepatic and renal transplants.

Finally, clinicians must focus on the patient as a whole—each individual possesses many more than one critical factor that the physician must consider when tailoring an immunosuppressive regimen.
References


1. In rodent models, interruption of the CD28 pathway via either antibodies to B7 or __________ may prevent acute rejection and even induce tolerance in some limited settings.
   a. Abatacept  
   b. Etanercept  
   c. Alefacept  
   d. Efalizumab

2. Vincenti et al reported that renal transplant patients taking belatacept as part of an immunosuppressive regimen showed which of the following when compared with patients taking cyclosporine?
   a. A higher risk of chronic allograft nephropathy  
   b. A higher frequency of infection  
   c. A tendency toward improved cardiovascular and metabolic profiles  
   d. A significantly lower risk of acute graft rejection at 6 months

3. A recent analysis of the Scientific Registry of Transplant Recipients database found that the highest survival advantage from kidney transplant was derived with use of grafts taken from standard-criteria deceased donors.
   a. True  
   b. False

4. Which of the following types of living donor liver transplants is associated with increased morbidity and more severe complications than the others?
   a. Left hepatectomy  
   b. Left lateral segmentectomy  
   c. Right hepatectomy  
   d. All of the above have similar rates of morbidity and severe complications

5. Faleo et al showed that exposure to carbon dioxide may reverse chronic allograft nephropathy by activating the hypoxia inducible factor/vascular endothelial growth factor pathway and re-establishing vascular integrity.
   a. True  
   b. False

6. In reporting results from the DICAM study, Etienne et al noted that kidney transplant patients given a regimen featuring mycophenolate plus a 50% reduction in cyclosporine dose after corticosteroid withdrawal experienced which of the following when compared with patients given standard cyclosporine doses?
   a. Higher blood pressure  
   b. More anemia  
   c. No loss in graft function  
   d. All of the above

7. Kirk et al reported that kidney transplant patients given alemtuzumab experienced no rejection until approximately the 3-week mark, when phagocytes first became available in the peripheral circulation.
   a. True  
   b. False

8. The CD40 receptor has been found on:
   a. Dendritic cells  
   b. Antigen-presenting cells  
   c. T and B cells  
   d. All of the above

9. When compared with Caucasians, African-Americans have a significantly lower 3-year graft survival of which of the following organs?
   a. Kidney  
   b. Liver  
   c. Heart  
   d. All of the above

10. The second leading overall cause of death 5 years after solid-organ transplant is:
    a. BK viremia  
    b. Cancer  
    c. Cardiovascular-related conditions  
    d. Invasive aspergillosis
Evaluation

Your candid and thorough completion of this evaluation will help Beam Institute improve the quality of its CME/CE activities. Thank you for your participation.

1. As a result of this activity…
   a. I am more knowledgeable about the risk factors for organ transplant failure. □ □ □
   b. I am more familiar with the long-term outcomes of organ donors and various populations of transplant recipients. □ □ □
   c. I have a better understanding of how costimulation blockade may provide an effective pathway for induction of graft tolerance. □ □ □
   d. I can discuss the relation of coagulation to the immune response. □ □ □
   e. I know more about selecting immunosuppressive regimens to minimize toxicity and optimize efficacy in transplant recipients.

2. I found the content of this educational activity…
   a. Clearly written and well organized. □ □ □
   b. Accurate and timely. □ □ □
   c. Related to its overall objectives. □ □ □
   d. Free from commercial bias. □ □ □
   e. Relevant to my own clinical practice. □ □ □

3. Did the information you received from this CE/CME activity:
   a. Confirm the way you currently manage your patients? □ □ □
   b. Suggest new options for managing your patients that you might apply in the future?

4. I used the information in this issue for … (check all that apply)
   □ □ □

5. Approximately how long (in minutes) did it take you to complete this activity, including this evaluation? _____ minutes

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