THE IMMUNOSUPPRESSION PARADOX
CONTROLLING REJECTION AND
OPTIMIZING PATIENT HEALTH

EDITORS

GABRIEL DANOVITCH, MD
Director, Kidney and Pancreas Transplant Program
David Geffen School of Medicine
Ronald Reagan UCLA Medical Center
Los Angeles, CA

ROBERT S. GASTON, MD
Medical Director, Kidney and Pancreas Transplantation
Kidney Transplant Service
University of Alabama at Birmingham
Birmingham, AL

CHRISTIAN P. LARSEN, MD, DPHIL
Joseph Brown Whitehead Professor and Chairman
Department of Surgery
Emory University School of Medicine
Atlanta, GA

Jointly sponsored by CTI Clinical Trial and Consulting
Services and the University of Kentucky Colleges of
Pharmacy and Medicine

Release Date June 10, 2010 • Expiration Date June 9, 2011
LEARNING OBJECTIVES

By the completion of this enduring material, the participants will be able to:

I. Identify the outstanding medical opportunities for improving long-term renal function and cardiovascular risk in kidney transplant recipients, while maintaining control of rejection.

II. Discuss the potential of pipeline immunosuppressive agents to optimize renal function and to limit cardiovascular and metabolic risk following kidney transplantation.

TARGET AUDIENCE

This enduring material is intended for transplant surgeons, physicians, nephrologists, pharmacists and nurses involved in the referral of transplant candidates and post-transplant care of kidney transplant recipients.

MEDICINE ACCREDITATION STATEMENT

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of the University of Kentucky College of Medicine and CTI Clinical Trial and Consulting Services. The University of Kentucky College of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

The University of Kentucky College of Medicine designates this educational activity for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

PHARMACY ACCREDITATION STATEMENT

The University of Kentucky College of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

This knowledge-based activity has been assigned ACPE # 022-999-10-036-H04-P and will award up to one (1.0) contact hour (0.1 CEU) of continuing pharmacy education credit in states that recognize ACPE providers.

Statements of credit will indicate hours and CEUs based on participation and will be issued online at the conclusion of the activity. Successful completion includes signing in at registration, attending the entire session for which credit is claimed, completing the activity evaluation and requesting credit online at conclusion of the activity. The College complies with the Accreditation Standards for Continuing Pharmacy Education.
EQUAL OPPORTUNITY STATEMENT
The University of Kentucky is an equal opportunity University.

RECOGNITION
“The Immunosuppression Paradox: Controlling Rejection and Optimizing Patient Health” is supported by an unrestricted educational grant from Bristol-Myers Squibb.

FACULTY DISCLOSURE
All faculty members of continuing education activities sponsored by the University of Kentucky Colleges of Pharmacy and Medicine are expected to disclose any real or perceived conflict of interest related to the content of their presentation. Detailed faculty disclosures are provided below:

Dr. Gabriel Danovitch has no disclosures to report.

Dr. Robert Gaston is a paid consultant to Novartis Pharmaceuticals and Astellas Pharma and is a paid consultant and receives grant support from LifeCycle Biopharma and Bristol-Myers Squibb.

Dr. Christian Larsen is a consultant to Bristol-Myers Squibb.

NEEDS ASSESSMENT
The turn of the millennium ushered in a new era of transplantation science, equipped with novel immunosuppressive agents and innovative strategies to improve organ allocation. In the first decade, the adoption of new immunosuppressive regimens has resulted in improved control of acute rejection. Over the same period, the transplant community has realized that acute rejection is only one aspect of ensuring excellent graft survival. Indeed, early renal function has been shown to correlate with the maintenance of graft function long term.

Interestingly, while rejection can be deleterious to allograft function, at least two lines of evidence derived from the United States Renal Data System and the Scientific Registry of Transplant Recipients suggests that rejection and renal function may be disassociated. The findings revealed a relative lack of improvement in chronic allograft failure despite a marked reduction in acute rejection incidence. Later analysis also revealed a minimal impact of acute rejection on graft survival, provided that glomerular filtration rate returned to baseline. These data reflect the seemingly paradoxical effects of the calcineurin inhibitors on rejection and renal vasoconstriction.

Parallel lines of research have established the role of calcineurin inhibitors and other maintenance immunosuppressive agents in exacerbating cardiovascular risk. Control of cardiovascular risk is a clinical priority since it is the primary cause of death with function, responsible for approximately half of all graft loss after the first post-transplant year. The close relationship between renal function and cardiovascular health is underscored by the demonstration that kidney disease and poor renal function are major risk factors for cardiovascular events.

This newsletter will review the requirement for new immunosuppressive management strategies in light of evolving definitions of rejection. The newsletter will then address our current understanding of the relationship between rejection and short- and long-term renal function. Finally, the demonstrated and potential impact of newer immunosuppressive agents on rejection, renal function and cardiovascular and metabolic risk will be discussed.
INTRODUCTION

The American Transplant Congress convened in San Diego, California on May 1, 2010. Among the many scientific offerings, the satellite Continuing Medical Education (CME) symposium entitled “The Immunosuppression Paradox: Controlling Rejection and Optimizing Patient Health” was held on May 3, drawing the attendance of approximately 1,100 congress delegates. The present newsletter summarizes the proceedings of the activity.

THE IMMUNOSUPPRESSION PARADOX

GABRIEL DANOVITCH, MD

To introduce the immunosuppression paradox, Dr. Danovitch summarized the immunologic and non-immunologic stressors affecting long-term kidney allograft function. He focused on cellular and humoral allograft rejection and the activation of latent CMV and BK viral infections as examples of immunologic stressors. He then introduced a list of non-immunologic stressors, including recurrent kidney disease and cardiovascular disease. He pointed out that cardiovascular disease, often an underlying comorbidity among kidney recipients, and nephrotoxicity are exacerbated by maintenance immunosuppressive agents including corticosteroids, calcineurin inhibitors (CNIs) tacrolimus and cyclosporine (CsA), and mammalian target of rapamycin inhibitors (mTOR inhibitors) sirolimus and everolimus.¹

The requirement for lifelong immunosuppression to control the alloimmune response and the impact of immunosuppressive agents on cardiovascular and nephrotoxic adverse events is the central paradox of long-term patient management. Dr. Danovitch primed the attendees with the first in a series of questions related to long-term renal outcomes to be addressed by Faculty over the course of the symposium:

CURRENT QUESTIONS RELATED TO LONG-TERM RENAL ALLOGRAFT OUTCOME

Is there a gap in correlation between the incidence of rejection and long-term renal function?

• Are all rejection episodes created equal?

• What is the impact of rejection on graft survival?

With current immunosuppressive agents can we

• Control rejection and

• Optimize renal function and

• Limit cardiovascular and metabolic risk?
Dr. Gaston addressed these questions in turn, beginning with the evidence that the ultimate effects of rejection are tied to the impact on renal allograft function. Citing the classic pivotal study of the USRDS database published by Terasaki and colleagues in 1995, Dr. Gaston noted that recognition of the association between good kidney function and graft survival is not new. He then went on to present the more recent evidence that high first year serum creatinine (SCr) is associated with, but not predictive of, long-term graft failure. Continuing the argument, he explained that acute rejection has been shown to have the most pronounced impact on graft survival when accompanied by poor renal function (Figure 1).

A poll of the audience revealed an even split concerning their clinical impressions of the effects of acute rejection kidney allograft outcome. Of all respondents, one-third said acute rejection negatively impacts graft survival when it is most severe (corticosteroid resistant), one-third said when it is antibody mediated, one one-third when it impacts GFR or SCr. All rejection episodes are not equal, and the phenotypes seem to be evolving with new therapies.

Next, Dr. Gaston turned to the evidence that renal and cardiovascular/metabolic function are interdependent. First described in the general population,
the link between cardiovascular death and poor renal function is now also documented in transplant recipients, with the risk proportional to an incremental increase in serum creatinine levels (Figure 2).

In the study cited, each 100 μmoL/L (1.1 mg/dL) increase in SCR was associated with a relative risk of 1.89 for a major adverse cardiac event and 2.94 for cardiac death. Despite the risks, Dr. Gaston pointed out that there is wide variability in the use of cardioprotective medications including statins, beta-blockers and aspirin among different transplant programs.

Recent attention has focused on the metabolic syndrome, a constellation of cardiovascular risk factors highly prevalent not only in the general population, but also estimated to affect between one-quarter and almost two-thirds of selected kidney transplant recipients. Integral components of the metabolic syndrome, including elevated blood glucose, atherogenic lipid levels and high blood pressure are all exacerbated by CNIs, corticosteroids and/or mTOR inhibitors, implicating the mainstays of current immunosuppression as prime ingredients of the central paradox of long-term immunosuppressive management. Indeed, these agents are required to suppress the alloimmune response but may also contribute to poor outcomes due to renal and metabolic dysfunction.

Dr. Danovitch commented on Dr. Gaston’s presentation by reviewing the cardiovascular and survival benefits of controlling blood pressure, atherogenic lipid levels and blood glucose in the general population. However, he cautioned that confounding factors including underlying and pre-existing disease, the pressure of immunosuppression, and dialysis history do not allow transplant professionals to directly extrapolate the results to transplant recipients.
To propose a potential resolution of the paradox explored by Dr. Gaston, in his commentary Dr. Danovitch speculated on the feasibility of developing new immunosuppressive agents that fulfill the criteria outlined below.

**AVOIDING THE CALCINEURIN PATHWAY**

**CHRISTIAN P. LARSEN, MD, DPHIL**

Dr. Christian Larsen responded to the challenge by focusing attention on novel agents at varied stages of clinical development. These include immunosuppressants that target non-calcineurin pathways including the Signal 3 JAK-STAT and Signal 2 co-stimulation and adhesion pathways.

Discussing first the JAK-STAT pathway, Dr. Larsen described the action of tasocitinib (CP-690,550), an inhibitor of JAK3-signaling cytokines sharing the common gamma chain (Γc cytokines: IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21). Cytokines that signal through Γc affect T, B and NK cell maturation, proliferation and function. Inhibition of the JAK3 pathway was first shown to prevent organ allograft rejection in a murine model of heart transplantation and in cynomolgus monkey recipients of kidney allografts.

A recent exploratory Phase 2 study in kidney allograft recipients was designed to replace CsA as a maintenance immunosuppressive agent. Compared to CsA, tasocitinib provided good rejection prophylaxis and preservation of renal function. Over-immunosuppression and safety signals included an increased risk of CMV and BK infection as well as mild neutropenia and anemia, possibly due to a crossover JAK2 effect.

An update of clinical progress with tasocitinib, introduced by Dr. Larsen and presented by Dr. Flavio Vincenti at an alternate ATC scientific session, revealed non-inferiority in the incidence of biopsy-proven acute rejection at 6 months (15.06% and 9.55% vs. 18.62%) and statistically significantly higher measured GFR in each of the tasocitinib treatment arms compared with the CsA control group. Interim results revealed a trend to improved glycemic control and lower blood pressure values among tasocitinib-treated patients. Safety signals included a higher incidence of serious infections and opportunistic viral infections, as well as a higher incidence of anemia, neutropenia, and leukopenia.

Focusing next on Signal 2 inhibition, Dr. Larsen described the development path of belatacept, a CD28 co-stimulation...
blocker that has currently completed two Phase 3 clinical trials. A second generation CTLA4 Ig derivative, belatacept has improved avidity for CD80/CD86, increasing its immunosuppressive potency as demonstrated in early non-human primate models of transplantation.

The results of two Phase 3 clinical trials, the first in recipients of standard criteria living or deceased donor organs (BENEFIT), and the second in recipients of extended criteria deceased donor organs (BENEFIT-EXT) have recently been published. Results at one year of follow up revealed equivalent survival in the belatacept treatment arms (one more intense, the second less intense) compared to the CsA group. Across both clinical trials, patients receiving belatacept experienced significantly improved renal function, as determined by measured GFR, over the follow up period. Importantly, in both studies, the time to progression to Stage 4/5 chronic kidney disease was prolonged in patients receiving belatacept (Figure 3).

Co-stimulation blockade was accompanied by an improved atherogenic lipid profile and better blood pressure. Blood glucose was not affected by belatacept treatment. Updated results of the trials, presented at an alternate scientific session at ATC, demonstrated consistency at 2 years of follow up. Safety signals associated with belatacept treatment included an increased incidence and more severe grade of acute rejection in the more intense (MI) regimen arm of the BENEFIT study, perhaps reflecting a disruption in the T effector-T regulatory balance resulting from co-stimulation blockade. Renal function remained better in the belatacept treatment arms among patients who developed acute rejection. The increased incidence of rejection was not reproduced in the

### TIME TO PROGRESSION TO STAGE 4/5 CHRONIC KIDNEY DISEASE

**BENEFIT**

Standard Criteria Living and Deceased Donor Organs

**BENEFIT-EXT**

Extended Criteria Deceased Donor Organs
BENEFIT-EXT study. The incidence of PTLD was also higher among belatacept-treated patients, and found to be most prevalent among EBV seronegative recipients.

Taken together, the results of recent clinical trials of agents closest to the clinic suggest that bypassing the calcineurin activation pathway may provide effective immunosuppression and improve the cardiovascular risk profile of kidney transplant recipients. However, new safety signals are emerging, requiring a shift in clinical surveillance when these agents are administered long-term.

Dr. Larsen then turned attention to the potential of adhesion molecule blockade as a transplant immunosuppressive strategy. Using efalizumab as an example, he described the development pathway from approval in psoriasis to voluntary withdrawal as a result of the development of progressive multifocal leukencephalopathy (PML) in 2 patients maintained on therapy for greater than 3 years. Results of a Phase 1/2 clinical trial in kidney transplant recipients treated for 6 months with two different dosing schedules of efalizumab in combination with full- or half-dose CsA revealed good control of acute rejection and no increased risk of post-transplant lymphoproliferative disorder except in the higher dose efalizumab-full dose CsA treatment arm. Dr. Larsen suggested that adhesion molecule blockade warrants further study in transplantation. At issue are appropriate concomitant medications, including the potential to combine adhesion inhibition with co-stimulation blockade, and attention to the relative risk of PML and PTLD in transplant recipients.

In his commentary on Dr. Larsen’s presentation, Dr. Danovitch itemized some of the challenges to the use of new agents in transplant immunosuppression. These include adequate long-term control of rejection, identifying patient subpopulations with the most favorable benefit-risk profiles, combining newer drugs with currently available immunosuppressants and the potential to spare corticosteroids. These concerns were corroborated by the audience, 42% of whom selected the potential for reactivation of latent viruses and 29% of whom cited an increased risk of severe acute rejection as cause for surveillance following the administration of new immunosuppressive agents. Dr. Danovitch concluded by pointing out that, with a limited patient pool available for the study of agents working through non-calcineurin pathways, heightened surveillance for these and other new adverse events is warranted and close follow up will be required.

**SUMMARY: AVOIDING THE CALCINEURIN PATHWAY**

Understanding of lymphocyte activation has opened rational immunosuppressive drug development

Agents blocking co-stimulation and JAK cytokine response pathways are promising new drug candidates

- Potential to maintain efficacy
- Evidence of reduced cardiovascular and metabolic burden

Surveillance for new adverse events is key to successful development of novel immunosuppressive agents

- Infection
- Malignancy
- Novel metabolic complications

itemized some of the challenges to the use of new agents in transplant immunosuppression. These include adequate long-term control of rejection, identifying patient subpopulations with the most favorable benefit-risk profiles, combining newer drugs with currently available immunosuppressants and the potential to spare corticosteroids. These concerns were corroborated by the audience, 42% of whom selected the potential for reactivation of latent viruses and 29% of whom cited an increased risk of severe acute rejection as cause for surveillance following the administration of new immunosuppressive agents. Dr. Danovitch concluded by pointing out that, with a limited patient pool available for the study of agents working through non-calcineurin pathways, heightened surveillance for these and other new adverse events is warranted and close follow up will be required.
REFERENCES


