VOLUME 9 NUMBER 1 | SUMMER 2012

The Immunology REPORT

Selected Reports from the

2012 American Transplant Congress

Dixon B. Kaufman, MD, PhD, FACS, Guest Editor
University of Wisconsin School of Medicine and Public Health

Antibodies in Kidney Transplantation

Stephen H. Gray, MD, MSPH
University of Alabama at Birmingham

New Immunosuppressants in Kidney Transplantation

Phillip S. Weems, MD
University of Wisconsin School of Medicine and Public Health

Current Status of Risk Evaluation and Mitigation Strategies (REMS) in Organ Transplantation

Satish N. Nadig, MD, DPhil
University of Michigan Medical School

Long-Term Primary Care Issues in the Transplant Population

Jared Brandenberger, MD
University of Washington Medical Center

CONTINUING EDUCATION 2.0 CREDITS AVAILABLE

astellas

This activity is supported by an educational grant from Astellas Pharma US, Inc.

Guest Editor: Dixon B. Kaufman, MD, PhD, FACS

This publication was made possible through an educational grant from Astellas Pharma US, Inc.

VOLUME 9 NUMBER 1 | SUMMER 2012

The Immunology REPORT

Selected Reports from the 2012 American Transplant Congress

Dixon B. Kaufman, MD, PhD, FACS, *Guest Editor*

About This CME/CE Activity

RATIONALE AND PURPOSE

The complexities of organ transplantation involve many different metabolic pathways and clinical considerations. This issue of *The Immunology Report* covers a variety of topics related to the ongoing therapeutic revolution in organ transplantation, beginning with our current understanding of antibody-mediated rejection and the hazard it represents to long-term renal transplant survival. These reports stress the great strides scientists have made in understanding organ rejection and in developing novel diagnostics and therapeutics to prevent this process and maintaining the health and well-being of transplant patients and their grafts for prolonged periods. Conventional immunosuppressants remain the backbone of therapy following organ transplant, but novel immunosuppressants recently approved by the US Food and Drug Administration (FDA) or currently in development are producing great optimism for continued success in the field. Follow-up is especially important during long-term drug therapy after transplant; an examination of Risk Evaluation and Mitigation Strategies (REMS) imposed by the FDA to detect serious postmarketing safety problems covers the grueling processes that influence regulatory approval and continued scrutiny of new therapeutics. Finally, both short- and long-term follow-up after surgery is a critical facet of organ transplantation; primary care approaches to preventing infection, treating hypertension and diabetes, and screening transplant recipients for malignancy ultimately lead to better outcomes and save patients' lives. The articles within are based upon presentations delivered during the 2012 American Transplant Congress, held June 2–6, 2012, in Boston, Massachusetts.

The articles in this issue, written from the academic perspective of physicians in training at leading medical centers, 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 to meet a perceived educational need to provide immunologists, transplant specialists, and other healthcare professionals with the latest knowledge and tools to help them perform their medical roles.

LEARNING OBJECTIVES

After studying this issue of *The Immunology Report,* participants in this educational activity should be able to:

- Describe antibody-mediated rejection, its early detection and diagnosis, and current trends in its management in patients at risk.
- Compare and contrast the advantages and disadvantages of conventional and novel immunosuppressants for preventing graft rejection.
- Outline the background and clinical implications of the FDA's development of REMS to minimize the risks of drug therapy.
- Summarize the key issues involved in long-term care of transplant patients in regard to avoiding infection, maintaining cardiovascular health, managing diabetes, and cancer prevention and screening.

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 AND CREDIT DESIGNATION

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

The University of Cincinnati designates this Enduring Material Activity for a maximum of 2.0 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Transplant nurses and coordinators: The American Board for Transplant Certification (ABTC) has approved the International Transplant Nurses Society (ITNS) as a provider of CEU/ABTC credits from its organization. This CNE activity, sponsored by the International Transplant Nurses Society, has been approved by the ABTC for 2.0 Category 1 CEPTCs (Program Reference No. 3000-347).

Pharmacists: Northeastern University Bouvé College of Health Sciences School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider of continuing pharmacy education. This activity is approved for 2.0 credit hours (0.20 CEU). The ACPE activity number is 0027-9999-12-053-H01-P, the initial release date is September 14, 2012, and the expiration date is September 14, 2015.

Case managers: This activity is approved by the Commission for Case Manager Certification for 2.0 clock hours through December 31, 2012.

CREDIT AVAILABILITY

Activity release date: September 14, 2012
Expiration date: September 15, 2013

METHOD OF PARTICIPATION

This Enduring Material Activity is available in print and online at **www.ImmunologyReport.com** and consists of an introduction, four articles, a postactivity assessment, and an evaluation. Estimated time to complete the activity is 2.0 hours.

To receive credit, participants must read the CME/CE information on these two pages, including the learning objectives and disclosure statements, as well as the full content of this monograph, and then complete the post test and evaluation form

online at www.ImmunologyReport.com. Upon successful completion of the post test (80% correct) and evaluation form, a CME/CE certificate of participation will be awarded automatically. The certificate may be printed directly from the Web site or e-mailed and printed later.

There are no fees for participating in or receiving credit for this activity.

CME REVIEWER

Rick Ricer, MD
Adjunct Professor of Family Medicine
University of Cincinnati
Cincinnati, Ohio

CME ACCREDITATION

Susan P. Tyler, MEd, CMP, CCMEP
Director, Continuing Medical Education
University of Cincinnati
Cincinnati, Ohio

CPE ACCREDITATION

Anita Young, EdD, RPh
Director, Continuing Pharmacy Education
Northeastern University Bouvé College of Health Sciences School of Pharmacy
Boston, Massachusetts

FACULTY DISCLOSURES

All faculty members (or anyone else in a position to control content, such as activity planners) are required to complete a Disclosure of Commercial Interest and Resolution form and to cooperate with identified methods for resolving conflict of interest prior to participating in the activity. The University of Cincinnati requires disclosure to the learners of all relevant financial relationships and adheres strictly to the ACCME Standards for Commercial Support.

Dixon B. Kaufman, MD, PhD, FACS, is Ray D. Owen Professor of Surgery and Chairman, Division of Transplantation, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin. He has received research/grant support from Bristol-Myers Squibb.

Stephen H. Gray, MD, MSPH, Assistant Professor of Surgery, Division of Transplant Surgery, University of Alabama at Birmingham, Birmingham, Alabama, has nothing to disclose.

Phillip S. Weems, MD, Clinical Instructor of Surgery, Division of Abdominal Transplantation, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, has nothing to disclose.

Satish N. Nadig, MD, DPhil, Clinical Lecturer/Fellow in the Section of Transplantation Surgery, Department of Surgery, University of Michigan Medical School, Ann Arbor, Michigan, has nothing to disclose.

Jared Brandenberger, MD, Acting Instructor and Senior Fellow in Transplant Surgery, University of Washington Medical Center, Seattle, Washington, has nothing to disclose.

Rick Ricer, MD, has nothing to disclose.

Susan P. Tyler, MEd, CMP, CCMEP, has nothing to disclose.

Anita Young, EdD, RPh, has nothing to disclose.

Jacqueline Keenan and **Edwin S. Geffner**, of Direct One Communications, Inc., have nothing to disclose.

DISCLAIMER

This activity is an independent educational activity under the direction of the University of Cincinnati. 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 Food and Drug Administration, the 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.

However, the planning committee, faculty, University of Cincinnati, ITNS, Northeastern University Bouvé College of Health Sciences School of Pharmacy, Astellas Pharma US, Inc., and Direct One Communications, Inc. shall in no way be liable for the currency of information or for any errors, omissions, or inaccuracies in this activity. Participants in this activity are encouraged to refer to primary references or full prescribing information resources.

The opinions and recommendations presented herein are those of the faculty and do not necessarily reflect the views of the provider, producer, or grantors.

DISCLOSURE OF UNAPPROVED/OFF-LABEL USE

Discussions concerning drugs, dosages, and procedures may reflect the clinical experience of the planning committee, may be derived from the professional literature or other sources, or may suggest uses that are investigational and not approved labeling or indications.

In this issue of *The Immunology Report,* Dr. Gray describes the off-label use of bortezomib to treat antibody-mediated rejection and acute cellular rejection with minimal toxicity. Dr. Weems mentions the use of tofacitinib, diannexin, QPI-1002, ASKP1240, TOL101, and sotrastaurin to prevent graft rejection; none of these drugs has been approved by the FDA for any indication.

CONTACT INFORMATION

We would like to hear your comments regarding this or other educational activities produced by Direct One Communications, Inc. In addition, suggestions for future activities are welcome. Contact us at:

Direct One Communications, Inc.
1424 Ridge Road
Syosset, NY 11791
Phone: 516-364-1020
Fax: 516-364-4217
Web: www.CMEdirect.net

Introduction

Selected Reports from the 2012 American Transplant Congress

Dixon B. Kaufman, MD, PhD, FACS

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

Organ transplantation represents one of the great achievements of modern medicine in the last half of the 20th century. Advances continue to be accomplished through the multidisciplinary approach to transplant patient care. Members of a multidisciplinary team must evaluate a transplant candidate's physical condition, prepare that patient to receive and accept a foreign organ, surgically graft the donated organ into the recipient's body, and then follow the transplant patient for life to ensure the health of both the graft and the recipient. An enormous wealth of information emerging from the laboratory and the clinic provides transplant teams with a more complete picture of the successes and risks inherent in the organ transplantation process.

The articles in this edition of *The Immunology Report* are based upon clinical and scientific presentations delivered during the 2012 American Transplant Congress, the joint annual meeting of the American Society of Transplant Surgeons and the American Society of Transplantation, held June 2–6, 2012, in Boston, Massachusetts. Transplant surgeons, physicians, scientists, immunologists, and nephrologists were privy to the results of pivotal clinical trials and theories on physiologic pathways, optimal immunosuppressive regimens, postsurgical follow-up, and other aspects of patient care. The authors, all first beginning their careers in transplant medicine and surgery, attended a number of these scientific sessions to share important information on trends in transplantation and immunosuppression.

Dr. Kaufman is Ray D. Owen Professor of Surgery and Chairman, Division of Transplantation, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.

Antibody-mediated rejection (AMR) is a challenging issue impeding progress toward the attainment of long-term survival in kidney transplant recipients. Stephen H. Gray, MD, MsPH, from the University of Alabama at Birmingham, describes the immunologic pathways that may lead to AMR. In addition, he reviews current information on diagnostic criteria and markers of AMR, tests that can detect rejection early, and drug therapy that may be tried to prevent rejection and allow renal allografts to survive for prolonged periods. In addition, Dr. Gray relates information about the monitoring of antibodies in sensitized and unsensitized recipients of kidney transplants.

Tried-and-true immunosuppressive regimens save both donated organs and the lives of their recipients, but they also have serious adverse effects—and they can fail transplant patients. Phillip S. Weems, MD, from the University of Wisconsin School of Medicine and Public Health, reviews the advantages and disadvantages of various immunosuppressants, including calcineurin inhibitors, mammalian target of rapamycin (mTOR) inhibitors, monoclonal antibody fusion proteins, Janus kinases, and novel biologic agents currently being evaluated in phase I/II trials to suppress the immune systems of transplant patients. In particular, he discusses the pros and cons of several immunosuppressant drug combinations and the clinical implications of switching renal transplant patients from calcineurin inhibitors to mTOR inhibitors.

Even after the US Food and Drug Administration (FDA) approves the marketing of a new drug, its safety continues to be closely scrutinized. Satish N. Nadig, MD, DPhil, from the University of Michigan Medical School in Ann Arbor, offers an abbreviated history of the health crises that lead to present drug regulatory practices in the United States and then describes the current demands imposed by Risk Evaluation and Mitigation Strategies (REMS) on the transplantation community. As of 2007, REMS provide materials to inform patients about the serious risks related to using a drug, to minimize the chance that such a drug might interact adversely with another drug or disease entity, and to prevent the risk of fetal exposure to potentially teratogenic agents. In addition, they represent a means to accomplish postmarketing surveillance of these pharmaceuticals. This article reviews various components of REMS, duties that these strategies require from healthcare personnel and patients, and specific REMS associated with currently used immunosuppressants.

Care of the transplant patient hardly ends with implantation of a donated organ. Postoperative management of transplant patients is complicated and risky. Jared Brandenberger, MD, from the University of Washington Medical Center in Seattle, reviews primary care issues that may threaten the health of a graft and, ultimately, the patient. Topics covered in his article include the management of diabetes mellitus and hypertension in the transplant population. In addition, Dr. Brandenberger details methods to prevent infection following organ transplant and to screen transplant recipients for malignancies.

The authors of this report have done a great service by sharing expert insights on a variety of topics of vital interest to the transplantation community. We thank them for their efforts and look forward to groundbreaking results of clinical trials and more data on the safety and efficacy of novel therapeutics now being tested.

Antibodies in Kidney Transplantation

Stephen H. Gray, MD, MSPH

University of Alabama at Birmingham, Birmingham, Alabama

Abstract A significant and constant obstacle to the long-term survival of renal allografts is antibody-mediated rejection. During the 2012 American Transplant Congress held in Boston, Massachusetts, this past June, experts in organ transplantation discussed the mechanism of this phenomenon, the identification of its markers, the development of diagnostics to detect rejection early in the process, and the evaluation of drugs to prevent antibody-mediated rejection and improve the long-term survival of renal allografts.

Antibody-mediated rejection (AMR) is a serious problem that bedevils the transplant community. In recent years, laboratory researchers and clinical investigators have collaborated to develop strategies to detect organ rejection; they also have begun reporting successful prophylactic and therapeutic protocols for managing AMR. These efforts have resulted in excellent outcomes, even in individuals who were highly sensitized to foreign substances before an organ transplant took place.

During the 2012 American Transplant Congress, experts in organ transplantation explored novel methods of diagnosing AMR, strategies for monitoring antibody levels in sensitized and unsensitized recipients of organ grafts, and new directions for managing patients at risk of transplant rejection. The symposium was moderated by Howard Gebel, PhD, Professor of Pathology and Laboratory Medicine, Emory University Hospital, Atlanta, Georgia, and Milagros D. Samaniego-Picota, MD, FACP, FASN, Associate Professor of Internal Medicine, Division of Nephrology, University of Michigan Medical School, Ann Arbor, Michigan.

Dr. Gray is Assistant Professor of Surgery, Division of Transplant Surgery, University of Alabama at Birmingham, Birmingham, Alabama.

NOVEL METHODS TO DIAGNOSE AMR

Based on a presentation by Lorraine Claire Racusen, MD, Professor of Pathology, Johns Hopkins Hospital, Baltimore, Maryland

The current diagnosis of AMR is based on the Banff criteria, which require morphologic findings of tissue injury, immunohistologic evidence of complement in tissue, and the presence of donor-specific antibodies (DSA) in the circulation.

C4d Deposition

Endothelial deposition of the complement split product C4d is an established marker of acute AMR in renal allografts. In biopsy-proven acute rejection episodes, the presence of anti–class I antibodies correlates with severe vascular lesions, glomerulitis, and infarction, whereas rejection episodes in the absence of antibodies are associated with more predominant severe tubulitis.[1] Detection of DSA has been associated with greater graft loss.

Regele and colleagues[2] described a link between immunohistochemically detected endothelial C4d deposition in peritubular capillaries (PTCs) and morphologic features of chronic renal allograft injury. Endothelial C4d deposition was associated with chronic transplant glomerulopathy; it also was linked to basement membrane multilayering and accumulation of mononuclear inflammatory cells in PTCs. Likewise, complement activation in the renal microvasculature, which indicates humoral alloreactivity, contributed to chronic rejection, characterized by chronic transplant glomerulopathy and basement membrane multilayering in PTCs (Figure 1).[2]

The distinction between AMR and acute cellular rejection (ACR) in renal allografts is therapeutically important but pathologically difficult. Histologically, AMR is characterized by glomerular thrombi, mesangiolysis, PTC neutrophil infiltration, interstitial hemorrhage, necrosis, and C4d deposition. Immunohistochemically detected C4d in PTC walls distinguishes AMR from ACR; C4d is more specific and sensitive than traditional criteria and represents a potentially valuable adjunct to diagnosing graft dysfunction.[3] Additionally, glomerular thrombi appear early in AMR; their appearance prior to graft dysfunction may allow therapeutic intervention.[4]

In renal allograft biopsies, C4d deposition within PTC is a specific marker of the antibody-graft interaction that is extremely useful for diagnosing AMR. The presence of PTC C4d itself is not diagnostic of AMR, but this finding usually is accompanied by histologic features of acute and/or chronic AMR.[5] In the setting of chronic rejection, a substantial fraction is mediated by antibodies. Detection of C4d can be used to separate this group of

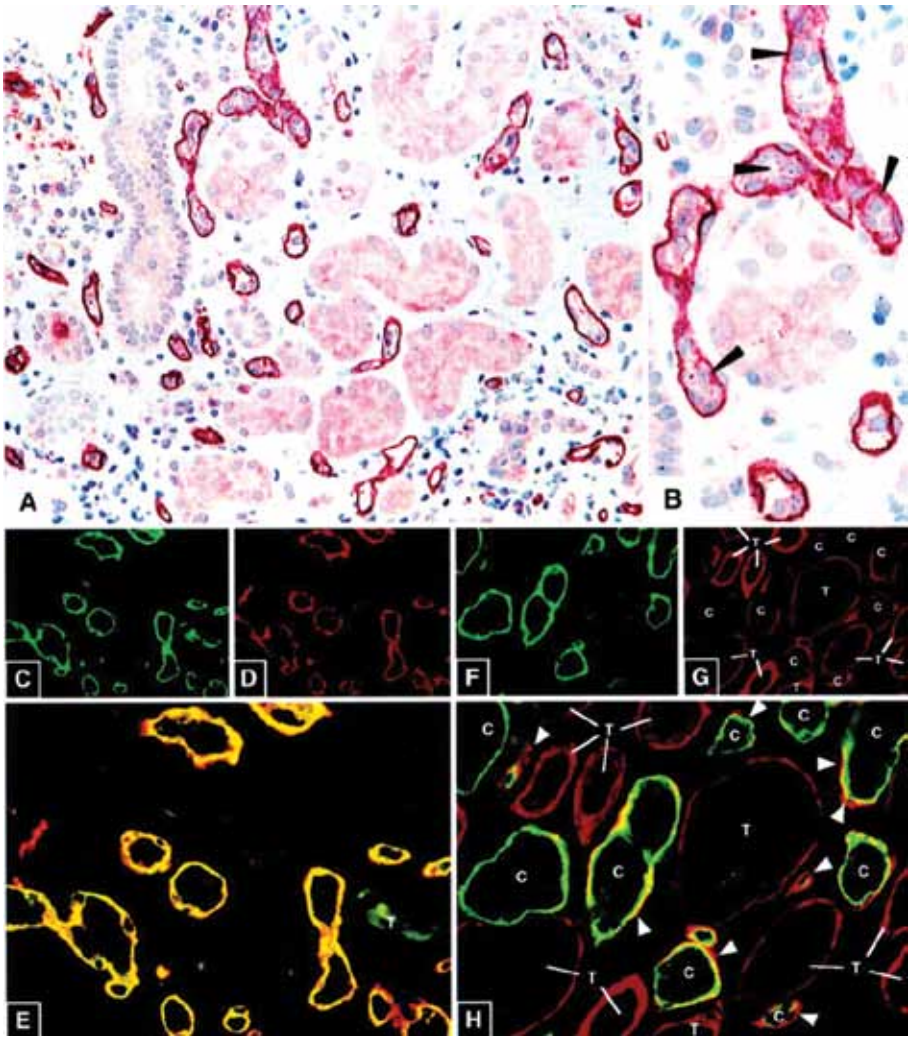

FIGURE 1 Immunohistochemical detection of endothelial C4d deposits in peritubular capillaries (PTC) on paraffin sections of renal allograft biopsies. (A) Linear C4d deposits along the walls of PTC. (B) C4d-positive PTC congested with mononuclear inflammatory cells (triangles; detail from A). (E) Yellow staining along the inner aspect of PTC indicating perfect co-localization of green staining for C4d (C) and red staining for CD31 (labeling endothelial cells) (D). (H) PTC showing only focal overlap (yellow staining) but no widespread co-localization of green staining signals for C4d (F) and red staining for collagen type IV (G). Both tubular and capillary (triangles) basement membranes are labeled by an anti-collagen type IV antibody (F, G). (A, B) Indirect immunoperoxidase staining with C4dpAb on paraffin sections. (C–G) Indirect immunofluorescent double-staining of paraffin sections with C4dpAb, monoclonal anti-CD31, and monoclonal anti-collagen type IV; C = peritubular capillary; T = tubule. Magnification: (A) 275×; (B) 550×; (C, D, F, G) 230×; (E, H) 460×. Reproduced, with permission, from Regele et al.[2]

patients with chronic rejection from the nonspecific category of individuals experiencing chronic allograft nephropathy and may guide successful treatment.[6]

De Novo DSA Production

Acute rejection associated with de novo production of DSA is a clinicopathologic entity that carries a poor prognosis. In most cases, the presence of DSA at the time of rejection is linked to widespread C4d deposits in PTCs, suggesting a pathogenic role of the circulating alloantibody. Combined DSA testing and C4d staining provides a useful approach for the early diagnosis of AMR, a condition that often necessitates use of a more intensive therapeutic rescue regimen.[7]

Test availability and sensitivity. Various assays are available to detect antibodies. The cytotoxicity assays that became available first are inexpensive, and they supply rapid results; because of their low specificity, they currently are used for screening. Flow cytometry, the current standard used, offers better sensitivity. Solid-phase assays (eg, enzyme-linked immunosorbent assay [ELISA], B-phase) are more sensitive and specific.

Contemporary technology clearly is advancing the detection of various antibodies that can contribute to AMR. Still, continued work is needed to elucidate the relevance of very low levels of human leukocyte antigen (HLA)-specific antibody and the importance of antibodies to other alloantigens and autoantigens.[8]

Issues with the Banff Criteria

Histopathologic changes such as glomerulitis, capillaritis, and microangiopathic changes are nonspecific. According to the current classification, AMR also can be identified by severe arteritis involving the muscle layers.[9]

Significance of histologic lesions. The Banff classification empirically established scoring of histologic lesions, but the relationships of lesions to each other and to underlying biologic processes remain unclear. Using cluster analysis, Sis et al[10] found that intimal arteritis clustered with DSA, C4d deposition, and microcirculation inflammation, but it also correlated with tubulitis. This observation suggested that pathologic lesions found on biopsy represented distinct pathogenic forces: microcirculatory changes, reflecting the stress of DSA; scarring, hyalinosis, and arterial fibrosis, evidencing the cumulative burden of injury over time; and tubulointerstitial inflammation. Other recent studies demonstrated that milder lesions may represent AMR.[11]

A number of studies have identified morphologic lesions of AMR in protocol biopsies of normally functioning renal allografts, and particularly in sensitized recipients, which correlate with later chronic changes in the graft, such as transplant glomerulopathy.[12,13] These same studies and molecular research involving biopsies

of conventional renal allografts have noted evidence of microvascular injury, which, in the presence of DSA but the absence of C4d deposition in PTCs, is associated with development of transplant glomerulopathy and graft loss. Finally, intimal arteritis, which was believed to represent a lesion of cell-mediated rejection (CMR), and bland arterial intimal fibrosis resembling arteriosclerosis may be manifestations of DSA-induced graft injury.[14]

The role of C4d. Recently, there has been an immunohistologic emphasis on improving the interpretation, detection, and quantification of C4d. Over the past 10 years, the recognition of alloantibody responses in organ transplantation has grown, although AMR-specific responses, unfortunately, remain incompletely defined. For example, Loupy and others[12] reported that the C4d Banff scores (1, 2, 3) in protocol biopsies of kidney transplant patients with preformed DSA were associated with significant increments of microcirculation inflammation at 3 months and 1 year post transplant, worse transplant glomerulopathy, and higher class II DSA mean fluorescence intensity. However, C4d staining was not a sensitive indicator of parenchymal disease. Upon further analysis, the presence of microcirculation inflammation and class II DSA at 3 months was associated with a fourfold increased risk of progression to chronic AMR, which was independent of C4d status. Additionally, there was significant fluctuation in C4d deposition over time.

Sis and Halloran[15] described C4d-negative AMR using biopsy evidence of active antibody-mediated damage. C4d-negative AMR is characterized by high within-graft endothelial gene expression, the presence of alloantibodies, histology reflecting chronic AMR (and, less frequently, acute AMR), and poor outcomes. Thus, the endothelial molecular phenotype in biopsies with circulating antibody detects the degree of active graft injury, and many of these transcripts reflect endothelial activation. C4d-negative AMR is noted twice as often as C4d-positive AMR. Recognition of this new phenotype reveals C4d-positive or C4d-negative AMR to be the most common cause of late kidney transplant loss. However, although C4d staining is useful, it is not sensitive enough to detect AMR. Measuring endothelial gene expression in biopsies from kidneys with alloantibodies is a sensitive, specific method for diagnosing AMR and predicting graft outcomes.

Challenges to analysis. Obtaining information about antigens can be challenging, since their concentrations and conditions may vary. Further, both internal and external factors can interfere with the analysis of antigens, and different laboratories use various detection hardware. The detection of nontraditional antibodies also is problematic—most assays focus on HLA-A, HLA-B, and HLA-DR. Standardization of positive results is likewise problematic, because each laboratory establishes its own positive and negative cutoffs. Finally, establishing the sensitivity threshold between detectable and pathogenic levels is difficult.

> C4d-positive or C4d-negative antibody-mediated rejection is the most common cause of late kidney transplant loss.

In summary, researchers must decide on whether to focus upon important physiologic and pathologic findings; for example, a single target for an antibody is an artificial laboratory construct that is not physiologic.

Future Directions

Histopathology in this field remains focused on microcellular circulation, inflammation, and injury. State-of-the art screening for glomerulitis and PTCs currently is available. The transplant community as a whole is working on evaluating and improving semiquantitative grading based on outcome studies.

Additional effort has been directed at improving interobserver agreement. Strategies include using additional immunohistochemical stains to define the severity and extent of AMR, which has led to the development of a new algorithm for predicting the presence of DSA. Sis et al[16] studied the significance of microcirculation inflammation in 329 indication biopsies from 251 renal allograft recipients who were mostly non-presensitized (crossmatch-negative). The decision tree revealed that the sum of the glomerulitis score and the PTC score (g + PTC) was the best predictor of DSA, followed by time elapsed post transplant and then C4d deposition, which had a small role. Late biopsies having a g + PTC > 0 showed a higher frequency of DSA than did early biopsies having a g + PTC > 0 (79% vs 27%). The decision tree predicted the presence of DSA with a higher sensitivity and accuracy than did C4d staining (Figure 2).[16] Finally, any degree of microcirculation inflammation in late kidney transplant biopsies strongly indicated the presence of DSA and predicted progression to graft failure.

Efforts have also been directed at improving the grading of immunohistology of C4d staining. Additional studies have begun looking at the membrane attack complex and complement regulatory molecules. Further studies with CD34 may help to define capillaritis and assess capillary injury. A C4d/CD34 double-immunofluorescence staining protocol for renal allograft frozen sections allows rapid and sensitive detection of C4d positivity and more accurate estimation of the C4d-positive fraction of PTCs.[17]

Improvements in antibody detection have been used to identify HLAs corresponding to the major histocompatibility complex (eg, HLA-CW, HLA-DQ, and HLA-DP). Non-HLA and complement assays have been developed to assess antibody function; because all antibodies do not produce rejection, function is important. Antiendothelial antibodies have been associated with hyperacute AMR, poor outcomes, increased CMR, and elevated creatinine levels.[18]

Antibody detection also is improved by automation of the process with decreased run-to-run variation. The standard method of detecting pretransplant antibodies

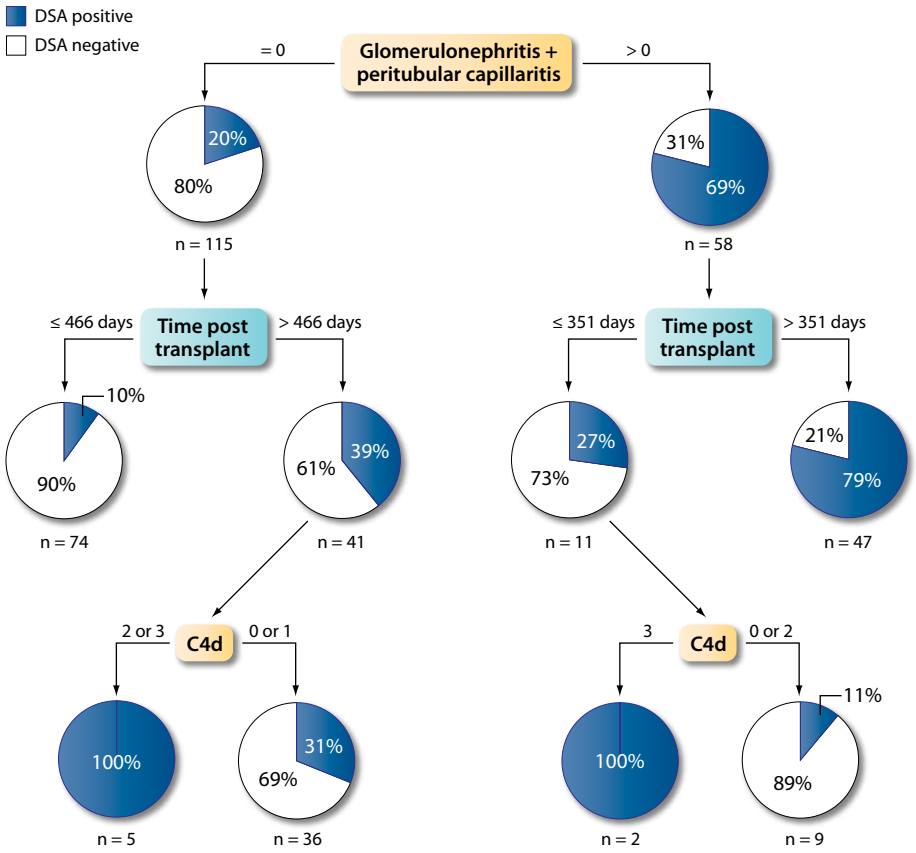

FIGURE 2 New diagnostic algorithm for antibody-mediated microcirculation inflammation in kidney transplants. DSA = donor-specific antibodies. Adapted, with permission, from Sis et al.[16]

has been the complement-dependent cytotoxicity test of donor leukocytes. Solid-phase assays to detect HLA antibodies in pretransplant serum have revealed a greater number of sensitized patients, but the clinical impact of this finding is less certain. Smith et al[19] described a method of detecting C4d-fixing HLA antibodies on Luminex beads in heart transplant recipients; detection of Luminex-positive DSA in pretransplant serum provides a powerful negative predictor of graft survival, especially if it binds C4d.

Identification and staining of natural killer (NK) cells may lead to an additional unique marker for AMR. NK-cell transcripts are increased in biopsies with AMR, whereas T-cell transcripts are increased in T-cell–mediated rejection. However, NK and T cells share many features, creating potential ambiguity. Research supports the distinct role of NK cells in late AMR, but it also indicates a role for NK transcript-expressing cells (NK or T cells with NK features) in both T-cell–mediated rejection and inflammation associated with injury and atrophy scarring.[20]

ANTIBODY MONITORING IN TRANSPLANT RECIPIENTS

Based on a presentation by David N. Rush, MD, Professor and Head, Section of Nephrology, Department of Internal Medicine, University of Manitoba Health Sciences Center, Winnipeg, Manitoba, Canada

Monitoring DSA in Sensitized Renal Transplant Recipients

Renal transplant candidates with evidence of DSA have an increased risk of AMR. The baseline DSA level correlates with risk of early and late antibody-mediated graft injury. Patients having a very high DSA level also have high rates of AMR and poor long-term allograft survival, which highlights the need for improved therapy.[21]

Low-level DSA that is detectable using single-antigen flow beads (SAFBs) but not detectable using complement-dependent cytotoxicity crossmatching represents a risk factor for early graft rejection.[22] AMR is associated with the development of high DSA levels post transplant, and protocols aimed at maintaining DSA at lower levels may decrease the incidence of AMR.[23]

The monitoring of alloantibody levels following transplantation might facilitate the early diagnosis of chronic rejection. In a recent study by Kimball et al[24] in patients who exhibited positive flow cytometric crossmatch (FCXM) at the time of transplant, distinct posttransplant profiles emerged that were associated with different clinical outcomes. Two thirds of patients showing complete elimination of FCXM and solid-phase assay reactions within 1 year had few adverse events and 95% 3-year graft survival. In contrast, the remaining third failed to eliminate FCXM or solid-phase reactions directed against HLA class I or II antibodies. The inferior graft survival (67%) with loss in this latter group was primarily due to chronic rejection. The systematic assessment of longitudinal changes in alloantibody levels, by either FCXM or solid-phase assay, can help in the identification of patients at increased risk of developing chronic rejection.

Biopsies are useful in detecting AMR among patients with DSA. Surveillance biopsies obtained during the first year post transplant in patients with positive crossmatches have been shown to be useful by uncovering clinically occult processes and phenotypes, which, without intervention, could diminish allograft survival and function.[25] Screening biopsies also may be useful in identifying patients who are more likely to develop subclinical AMR.[26]

The baseline DSA level correlates with the risk of early and late alloantibody-mediated allograft injury.[21] The risk of both AMR and graft loss directly correlates with peak HLA-DSA strength. Quantification of HLA antibodies allows stratification of immunologic risk.[27] Defining the clinical relevance of DSA detected by SAFBs is important, because these assays are increasingly used for pretransplant risk assessment and organ allocation. Research supports the use of SAFBs for risk assessment and organ

allocation; findings suggest that improvement of the positive predictive value of HLA-DSA defined by SAFBs will require an enhanced definition of pathogenic factors of HLA-DSA.[28]

The persistence of elevated DSA levels after treatment is more frequent in patients who experience graft loss than in those with preserved renal function. DSA post rejection can be quantified using solid-phase assays; 3 months after AMR, DSA titers are elevated in patients with graft loss.[29]

Monitoring for De Novo DSA

The production of panel-reactive lymphocytotoxic antibodies (PRA) in recipients of renal transplants is associated with antidonor reactivity and poor graft outcome.[30] The presence of HLA antibodies post transplantation is predictive of subsequent graft failure, and the predictive value is increased among patients with elevated serum creatinine levels.[31]

The development of de novo DSA (dnDSA) at the time of late biopsy is primarily directed against class II antibodies and is associated with microcirculatory changes and subsequent graft failure.[32] Pathology consistent with AMR can occur and progress in patients with dnDSA in the absence of graft dysfunction.[33] The presence of HLA antibodies significantly correlates with lower graft survival, poor transplant function, and proteinuria. Screening for HLA antibodies post transplantation could be a good tool to follow patients who receive a renal transplant and would allow for timely modification of a patient's immunosuppressive regimen.[34,35]

Multiple studies have shown that dnDSA develops prior to graft failure and before the onset of proteinuria or elevated serum creatinine levels.[33] Serial DSA measurement during treatment of AMR revealed that patients who had a > 50% reduction in solid-phase mean fluorescence intensity within 14 days of starting treatment experienced improved transplant survival at 21 months.[35]

Early studies of de novo HLA antibody titers used cytotoxicity assays that were less sensitive and accurate than those now available or used ELISA assays, which did not determine donor specificity. Most early studies only analyzed antibodies at one point in time, early post transplant, whereas DSA often first appears late post transplant.[35,36] A recent study found that dnDSA developed in 15% of low-risk renal transplant recipients more than 5 years post transplant; it was associated with a 40% decrease in 10-year graft survival.

Independent risk factors for dnDSA development are HLA-DRβ1 mismatch, nonadherence, and a strong trend toward clinical rejections before dnDSA onset.[33] The dominant strategy for detecting AMR in patients with pretransplant DSA should be surveillance biopsy. Serial DSA monitoring should supplement biopsy data. Screening for dnDSA in unsensitized patients should be based on serial HLA antibody screening, starting 6 months post transplant.

TREATMENT OF DETECTED ANTIBODY AND AMR: WHAT'S NEW?

Based on a presentation by Mark D. Stegall, MD, Professor of Surgery, Mayo Clinic, Rochester, Minnesota

Increases in DSA levels post transplant are associated with AMR, but this increase may be transient. Burns et al[23] made several important points regarding AMR in crossmatch-positive kidney transplant recipients. First, AMR occurs across a wide spectrum of baseline DSA levels, as determined by T-cell and B-cell flow crossmatch (BFXM) levels, including those associated with a negative T-cell antihuman-globulin crossmatch. Second, the risk of AMR generally increases with increasing baseline DSA levels, but the occurrence is still unpredictable. Third, prior kidney transplant does not increase the incidence or severity of AMR when compared with other methods of sensitization. Fourth, anti-class II DSA alone or with anti-class I alloantibodies plays an important role in AMR and may be the sole cause of AMR. Therefore, post-transplant monitoring with BFXM or SAFBs coupled with early intervention to prevent or ameliorate the impact of AMR has been recommended.

Different strategies appear to improve the success of AMR management, but no best method has yet emerged. Recent data from a study of AMR treatment by Lefaucheur and colleagues[29] showed that administration of high doses of intravenous immune globulin (IVIG) alone is inferior to combined use of plasmapheresis, IVIG, and treatment with anti-CD20 monoclonal antibody to treat AMR. In addition, DSA post rejection could be quantified using solid-phase assays; 3 months after AMR, DSA titers are elevated in patients with graft loss.

Sensitized renal transplant recipients with high DSA titers commonly develop AMR, which may cause acute graft loss or shorten allograft survival. Stegall et al[37] reported that inhibition of terminal complement activation with eculizumab decreases the incidence of early AMR in sensitized renal transplant recipients.

Current antihumoral therapies used in transplantation and the treatment of autoimmune disease do not target the mature antibody-producing plasma cell. Bortezomib is a first-in-class proteosomal inhibitor that was approved by the US Food and Drug Administration for the treatment of plasma cell–derived tumors. Bortezomib therapy provides effective treatment of AMR and ACR with minimal toxicity and results in sustained reduction in immunodominant and non-immunodominant DSA levels.[38]

CONCLUSION

Current research has led to better understanding of both acute and chronic AMR. The results of ongoing prospective, randomized, long-term studies should lead to further understanding of the intricate pathways of organ rejection. Pretransplant protocols that desensitize patients by depleting antibody-secreting plasma cells are needed. Post-transplant protocols that prevent or treat transplant glomerulopathy are a focus for future research. Developing and defining the role of prolonged eculizumab therapy are needed.

REFERENCES

1. Trpkov K, Campbell P, Pazderka F, Cockfield S, Solez K, Halloran PF. Pathologic features of acute renal allograft rejection associated with donor-specific antibody: analysis using the Banff grading schema. *Transplantation.* 1996;61:1586–1592.

2. Regele H, Bohmig GA, Habicht A, et al. Capillary deposition of complement split product C4d in renal allografts is associated with basement membrane injury in peritubular and glomerular capillaries: a contribution of humoral immunity to chronic allograft rejection. *J Am Soc Nephrol.* 2002;13:2371–2380.

3. Collins AB, Schneeberger EE, Pascual MA, et al. Complement activation in acute humoral renal allograft rejection: diagnostic significance of C4d deposits in peritubular capillaries. *J Am Soc Nephrol.* 1999;10:2208–2214.

4. Fidler ME, Gloor JM, Lager DJ, et al. Histologic findings of antibody-mediated rejection in ABO blood-group-incompatible living-donor kidney transplantation. *Am J Transplant.* 2004;4:101–107.

5. Haas M. The significance of C4d staining with minimal histologic abnormalities. *Curr Opin Organ Transplant.* 2010;15:21–27.

6. Mauiyyedi S, Pelle PD, Saidman S, et al. Chronic humoral rejection: identification of antibody-mediated chronic renal allograft rejection by C4d deposits in peritubular capillaries. *J Am Soc Nephrol.* 2001;12:574–582.

7. Crespo M, Pascual M, Tolkoff-Rubin N, et al. Acute humoral rejection in renal allograft recipients: I. Incidence, serology and clinical characteristics. *Transplantation.* 2001;71:652–658.

8. Leffell MS, Zachary AA. Antiallograft antibodies: relevance, detection, and monitoring. *Curr Opin Organ Transplant.* 2010;15:2–7.

9. Sis B, Mengel M, Haas M, et al. Banff '09 meeting report: antibody mediated graft deterioration and implementation of Banff working groups. *Am J Transplant.* 2010;10:464–471.

10. Sis B, Einecke G, Chang J, et al. Cluster analysis of lesions in nonselected kidney transplant biopsies: microcirculation changes, tubulointerstitial inflammation and scarring. *Am J Transplant.* 2010;10:421–430.

11. Singh N, Sun Q, Nadasdy T, et al. The pathogenesis of acute allograft dysfunction in desensitized renal transplant recipients. *Clin Transplant.* 2012;26:E402–E411.

12. Loupy A, Hill GS, Suberbielle C, et al. Significance of C4d Banff scores in early protocol biopsies of kidney transplant recipients with preformed donor-specific antibodies. *Am J Transplant.* 2011;11:56–65.

13. Sis B, Jhangri GS, Bunnag S, Allanach K, Kaplan B, Halloran PF. Endothelial gene expression in kidney transplants with alloantibody indicates antibody-mediated damage despite lack of C4d staining. *Am J Transplant.* 2009;9:2312–2323.

14. Haas M. Pathologic features of antibody-mediated rejection in renal allografts: an expanding spectrum. *Curr Opin Nephrol Hypertens.* 2012;21:264–271.

15. Sis B, Halloran PF. Endothelial transcripts uncover a previously unknown phenotype: C4d-negative antibody-mediated rejection. *Curr Opin Organ Transplant.* 2010;15:42–8.

16. Sis B, Jhangri GS, Riopel J, et al. A new diagnostic algorithm for antibody-mediated microcirculation inflammation in kidney transplants. *Am J Transplant.* 2012;12:1168–1179.

17. Jen KY, Nguyen TB, Vincenti FG, Laszik ZG. C4d/CD34 double-immunofluorescence staining of renal allograft biopsies for assessing peritubular capillary C4d positivity. *Mod Pathol.* 2012;25:434–438.

18. Holgersson J, Elsheikh E, Grufman P, Sumitran-Holgersson S, Tydén G. A case of acute vascular rejection caused by endothelial-reactive non-HLA antibodies. *Clin Transpl.* 2006:535–538.

19. Smith JD, Hamour IM, Banner NR, Rose ML. C4d fixing, Luminex binding antibodies—a new tool for prediction of graft failure after heart transplantation. *Am J Transplant.* 2007;7:2809–2815.

20. Hidalgo LG, Sellares J, Sis B, Mengel M, Chang J, Halloran PF. Interpreting NK cell transcripts versus T cell transcripts in renal transplant biopsies. *Am J Transplant.* 2012;12:1180–1191.

21. Gloor JM, Winters JL, Cornell LD, et al. Baseline donor-specific antibody levels and outcomes in positive crossmatch kidney transplantation. *Am J Transplant.* 2010;10:582–589.

22. Bachler K, Amico P, Honger G, et al. Efficacy of induction therapy with ATG and intravenous immunoglobulins in patients with low-level donor-specific HLA-antibodies. *Am J Transplant.* 2010;10:1254–1262.

23. Burns JM, Cornell LD, Perry DK, et al. Alloantibody levels and acute humoral rejection early after positive crossmatch kidney transplantation. *Am J Transplant.* 2008;8:2684–2694.

24. Kimball PM, Baker MA, Wagner MB, King A. Surveillance of alloantibodies after transplantation identifies the risk of chronic rejection. *Kidney Int.* 2011;79:1131–1137.

25. Kraus ES, Parekh RS, Oberai P, et al. Subclinical rejection in stable positive crossmatch kidney transplant patients: incidence and correlations. *Am J Transplant.* 2009;9:1826–1834.

26. Loupy A, Suberbielle-Boissel C, Hill GS, et al. Outcome of subclinical antibody-mediated rejection in kidney transplant recipients with preformed donor-specific antibodies. *Am J Transplant.* 2009;9:2561–2570.

27. Lefaucheur C, Loupy A, Hill GS, et al. Preexisting donor-specific HLA antibodies predict outcome in kidney transplantation. *J Am Soc Nephrol.* 2010;21:1398–1406.

28. Amico P, Honger G, Mayr M, Steiger J, Hopfer H, Schaub S. Clinical relevance of pretransplant donor-specific HLA antibodies detected by single-antigen flow-beads. *Transplantation.* 2009;87:1681–1688.

29. Lefaucheur C, Nochy D, Andrade J, et al. Comparison of combination plasmapheresis/IVIg/anti-CD20 versus high-dose IVIg in the treatment of antibody-mediated rejection. *Am J Transplant.* 2009;9:1099–1107.

30. Martin S, Dyer PA, Mallick NP, Gokal R, Harris R, Johnson RW. Posttransplant antidonor lymphocytotoxic antibody production in relation to graft outcome. *Transplantation.* 1987;44:50–53.

31. Terasaki PI, Ozawa M. Predictive value of HLA antibodies and serum creatinine in chronic rejection: results of a 2-year prospective trial. *Transplantation.* 2005;80:1194–1197.

32. Hidalgo LG, Campbell PM, Sis B, et al. De novo donor-specific antibody at the time of kidney transplant biopsy associates with microvascular pathology and late graft failure. *Am J Transplant.* 2009;9:2532–2541.

33. Wiebe C, Gibson IW, Blydt-Hansen TD, et al. Evolution and clinical pathologic correlations of de novo donor-specific HLA antibody post kidney transplant. *Am J Transplant.* 2012;12:1157–1167.

34. Hourmant M, Cesbron-Gautier A, Terasaki PI, et al. Frequency and clinical implications of development of donor-specific and non–donor-specific HLA antibodies after kidney transplantation. *J Am Soc Nephrol.* 2005;16:2804–2812.

35. Everly MJ, Everly JJ, Arend LJ, et al. Reducing de novo donor-specific antibody levels during acute rejection diminishes renal allograft loss. *Am J Transplant.* 2009;9:1063–1071.

36. Li X, Ishida H, Yamaguchi Y, Tanabe K. Poor graft outcome in recipients with de novo donor-specific anti-HLA antibodies after living related kidney transplantation. *Transpl Int.* 2008;21:1145–1152.

37. Stegall MD, Diwan T, Raghavaiah S, et al. Terminal complement inhibition decreases antibody-mediated rejection in sensitized renal transplant recipients. *Am J Transplant.* 2011;11:2405–2413.

38. Everly MJ, Everly JJ, Susskind B, et al. Bortezomib provides effective therapy for antibody- and cell-mediated acute rejection. *Transplantation.* 2008;86:1754–1761.

New Immunosuppressants in Kidney Transplantation

Phillip S. Weems, MD

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

Abstract Different classes of immunosuppressive drugs offer varied advantages and disadvantages for patients who have undergone kidney transplantation. At a symposium held during the 2012 American Transplant Congress, leaders in the field discussed the use of conventional and novel agents to suppress the immune system following transplant. The speakers provided an overview of past and current best practice and then focused on the results of clinical trials involving everolimus, belatacept, and tofacitinib. In addition, these experts described studies evaluating the safety and efficacy of immunosuppressive drugs in development.

Until recently, immunosuppression for renal transplant patients was limited mainly to corticosteroids, calcineurin inhibitors (cyclosporine, tacrolimus), azathioprine, and mycophenolate mofetil (MMF). Despite the excellent short- and mid-term outcomes achieved with these agents, side effects and toxicity represent an ongoing challenge which may ultimately hamper long-term graft and patient survival. The development of novel biologic agents with different mechanisms of action has pointed the transplant community toward new directions in immunosuppression.

At a symposium held during the 2012 American Transplant Congress, speakers discussed the advantages and disadvantages of using different classes of conventional and novel immunosuppressants. In addition, they reviewed the results of clinical studies comparing different immunosuppressants in patients who have undergone renal transplant. These experts also delved into the practice of switching immunosuppressive drug classes during prolonged therapy and peered into the future of medical suppression of the immune system.

The symposium was moderated by Martha Pavlakis, MD, Associate Professor of Medicine, Beth Israel Deaconess Medical Center, Boston, Massachusetts, and Rita Alloway, PharmD, Research Professor of Medicine, University of Cincinnati College of Medicine, Cincinnati, Ohio.

OVERVIEW OF IMMUNOSUPPRESSANTS

A number of different drug classes are used for immunosuppression following organ transplantation. Comparisons of these agents underscore their advantages and disadvantages in renal transplantation.

Calcineurin Inhibitors (CNIs)

An examination of kidney transplant outcomes from registry data shows a marked improvement in graft survival 1–4 years post transplantation that can be attributed to treatment with CNIs. However, the impact of long-term immunosuppression beyond 4 years has not been as obvious. In fact, current graft survival beyond 10 years after transplantation is somewhat worse than that noted during the 1970s. Some registry data suggest that patients maintained on CNIs for prolonged periods do worse than do those not using such drugs. Therefore, the development of new agents that offer a CNI-free regimen could positively impact graft survival and greatly benefit our patients.

The multihit hypothesis of graft loss/destruction relies on the theory that early in the life of a transplanted allograft, ischemia and acute/subclinical rejection are replaced by CNI toxicity, the harmful effects of underlying chronic disease, and chronic antibody-mediated rejection (AMR). CNIs effectively prevent acute and chronic rejection, but they carry the added detriment of long-term toxicity, which leads to interstitial fibrosis and arteriolar hyalinosis. Thus, as with many topics in this field, a short-term benefit is accompanied by a long-term price to pay.

Molecular Target of Rapamycin (mTOR) Inhibitors

The class of immunosuppressant drugs known as mTOR inhibitors—sirolimus and everolimus—comprises non-nephrotoxic agents that target downstream cytokine receptors. In addition to their immunosuppressive effects, mTOR inhibitors offer added antiproliferative mechanisms that may play a role in vascular remodeling. In cardiac transplantation, intravascular ultrasound data have shown that the coronary arteries of patients given sirolimus and cyclosporine have a thinner vascular intima and media, a wider mean lumen area, and lower plaque burden than the arteries of patients treated with azathioprine and cyclosporine.[1]

Dr. Weems is Clinical Instructor of Surgery, Division of Abdominal Transplantation, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin.

One of the Achilles' heels of mTOR inhibitor therapy has been poor tolerability. In the ELITE-Symphony study,[2] kidney transplant recipients received induction with standard-dose cyclosporine, MMF, and corticosteroids *or* daclizumab induction, MMF, and corticosteroids given with a low dose of cyclosporine, tacrolimus, or sirolimus. A higher withdrawal rate was noted among the low-dose sirolimus arm. Combined use of daclizumab, MMF, and corticosteroids plus low-dose tacrolimus was advantageous for renal function, allograft survival, and acute rejection rates when compared with regimens involving daclizumab induction plus either low-dose cyclosporine or low-dose sirolimus or standard-dose cyclosporine without induction. These results and others from studies involving sirolimus therapy indicated that de novo CNI elimination with mTOR inhibitor therapy may lead to poorer outcomes.

EVEROLIMUS IN KIDNEY TRANSPLANTATION

Based on a presentation by Philip O'Connell, MD, PhD, Clinical Professor of Medicine, Director of the Centre for Transplant and Renal Research, and Director of Transplant Medicine, Westmead Millennium Institute, New South Wales, and the University of Sydney, Australia

The first registration trials of everolimus compared the use of low (1.5 mg/d) or high (3 mg/d) doses of the drug plus standard doses of cyclosporine with the then-current standard of care, 2 mg/d of MMF plus standard-dose cyclosporine.[3] Graft losses and rejection episodes were similar among patients receiving everolimus or MMF with cyclosporine, but those taking everolimus experienced a greater loss in overall graft function, as evidenced by a reduction in creatinine clearance. The investigators concluded that combining an mTOR inhibitor with a CNI may enhance the inherent nephrotoxicity of these drugs.

Later studies with the same two doses of everolimus and smaller doses of cyclosporine (~ 60% trough concentrations) revealed that everolimus was noninferior to cyclosporine in terms of efficacy, graft loss, survival, and rejection episodes, with equivalent graft function across all three study arms.[4] A subsequent meta-analysis confirmed this finding, showing that use of minimal cyclosporine doses with sirolimus or everolimus may lead to better overall graft function.[5]

Because high intracellular concentrations of CNIs can amplify the potential nephrotoxicity of everolimus, physicians planning to use the drug as de novo therapy with a CNI should use low doses of the CNI. Use of a CNI-free regimen without the addition of everolimus de novo is not recommended.

Switching from CNI Therapy to mTOR Inhibitor Therapy

If CNI therapy is beneficial in preventing early rejection, why not place patients on CNIs initially and then switch them to an mTOR inhibitor later? The ASCERTAIN study was one of the first to evaluate this question.[6] This 24-month, open-label, multicenter study involved a fairly large number of patients who were randomized to one of three study arms. In the first arm, patients continued on CNI therapy; in the other two arms, patients also were given everolimus with reduced or discontinued CNI therapy. Patients in the everolimus arms were eligible for a switch any time from 6 months to 10 years post transplantation. The mean time for the switch to occur was at 5.6 years; therefore, the conclusions may not be applicable as an "early-switch" model. Overall, there was no difference in renal function (mean glomerular filtration rate [GFR] at 24 months from the time of switching therapy) or histology among the three study groups.

Switching early. What about early everolimus switching? In the European ZEUS study,[7] patients were recruited prior to transplant, started on basiliximab induction, and placed on maintenance therapy using MMF, cyclosporine, and corticosteroids. At 4.5 months post transplantation, all patients were randomized either to continue the prior course of therapy or to add everolimus while gradually discontinuing use of the CNI. At 12 months, patients switched to the everolimus arm experienced an average increase of ~ 10 mL/min in GFR. However, at 36 months, this GFR increase was reduced to an average of about 4–5 mL/min.[6] Therefore, the long-term benefits of everolimus therapy may not be quite as good as expected.

The benefits of early switching also were shown in different areas of the ZEUS trial.[7] No differences in adverse events or serious infections were reported. However, when compared with patients in the cyclosporine group, those in the everolimus group showed higher rates of herpesvirus infection (6% vs 14%, respectively; $P = 0.02$), anemia (23% vs 27%; $P = 0.51$), thrombocytopenia (3% vs 17%; $P = 0.01$), and aphthous stomatitis (3% vs 17%; $P < 0.0001$).

Thus, an early switch from CNI therapy to the use of everolimus provides superior renal function with equivalent rejection rates; it seems that the earlier patients are switched to mTOR inhibitor therapy, the greater their chances of successful outcomes. Late switching to everolimus can be accomplished safely in selected patients with relatively good renal function (GFR > 40 mL/min; proteinuria < 500 mg/d). Although late switching from CNI therapy to treatment with everolimus has not been associated with improved renal function, it may benefit patients who develop intolerance to CNIs.

Patient selection. A tricky question remains—which patients would benefit most from switching to mTOR inhibitor therapy, and when should they be switched? When evaluating a switch to an mTOR inhibitor from a CNI, all effects of the mTOR inhibitor must be considered. For example, sirolimus therapy is strongly associated with the development of new-onset diabetes after transplant.[8]

Transplant patients have a higher incidence of new onset of both skin and solid organ cancers than do age-matched cohorts. Results of the A2309 study revealed a reduced, although not statistically significant, incidence of neoplasms after 12 months of everolimus therapy.[4] According to the results of other studies, a change in therapy from a CNI to an mTOR inhibitor is associated with a significantly lower malignancy rate at 2 years.[10] For solid organ cancers, good data suggest that mTOR in-

hibitor therapy is associated with fewer de novo malignancies, compared with CNI therapy.[10] In nonmelanoma skin cancers, the use of CNIs was associated with a statistically reduced incidence of squamous cell carcinoma and a numerically, but not statistically, significant reduction in that of basal cell carcinoma.[11]

In summary, patients using a CNI who have a history of solid organ or skin malignancies, particularly nonmelanoma skin cancers, would benefit significantly from a switch to an mTOR inhibitor such as everolimus. In addition, such a switch also may benefit patients at high risk of cytomegalovirus (CMV) disease. CNI therapy is associated with abnormal lipid profiles, so a change to treatment with an mTOR inhibitor may reduce the risk of development of cardiovascular disease. Patients who are intolerant to CNI therapy or who suffer from its nephrotoxic side effects would benefit from such a switch.

On the other hand, patients who would not benefit from a switch from a CNI to an mTOR inhibitor include those at high immunologic risk, because mTOR inhibitors are less immunosuppressive than are CNIs. Finally, renal transplant patients with poor graft function, proteinuria, or lung disease and those at risk for new-onset diabetes would not benefit from a switch to mTOR inhibitor therapy.

BELATACEPT

Based on a presentation by Robert S. Gaston, MD, Outgoing President of the American Society of Transplantation and Endowed Professor of Transplant Medicine and Medical Director of the Kidney and Pancreas Transplant Program, The University of Alabama at Birmingham

Belatacept is a monoclonal antibody fusion protein designed to act as a selective costimulation blocker. It binds to CD80/86 on antigen-presenting cells (APCs), blocking CD28-mediated costimulation of T cells. Costimulation blockade inhibits cell division, cytokine production, anergy, and apoptosis.

When compared with CNI-based therapy, belatacept use is associated with significant advantages that seem to translate into better long-term allograft survival, including preservation of the GFR and a favorable metabolic profile. In addition, patients taking belatacept have fewer "late" rejections and experience an impact on de novo donor-specific antibody (DSA) formation.

BENEFIT and BENEFIT-EXT Studies

In both the BENEFIT study[12] (using standard-criteria donor allografts) and the BENEFIT-EXT study[13] (using extended-criteria donor allografts), patients received basiliximab induction and a corticosteroid taper; MMF and cyclosporine were given as maintenance immunosuppressants. The patients then were randomized into one of two study arms. Both the more-intensive and the less-intensive arms received 10 mg/kg of belatacept for the first month. Between months 1 and 6, the more-intensive therapy arm was maintained on 10 mg/kg of belatacept, whereas the less-intensive therapy arm was given 5 mg/kg of the drug. At month 6, patients in both arms were maintained on 5 mg/kg of belatacept given every 28 days.

The BENEFIT[12] and BENEFIT-EXT[13] studies had a composite endpoint of time to a calculated GFR < 30 mL/min/1.73 m^2, graft loss, or death. Both studies revealed a significant increase in mean GFR when compared with a cyclosporine control group. If the data were pooled, a survival advantage among patients maintained on belatacept, as compared with those using cyclosporine, would be noted. In fact, the GFR data were strikingly similar to those of nontransplanted, nephrectomized patients having one kidney. The less-intensive BENEFIT group also experienced advantageous reductions in both systolic and diastolic blood pressure and favorable decreases in lipid and triglyceride profiles when compared with patients given cyclosporine.

DeKAF Study

Over time, we have learned that antibody-mediated renal injury compromises long-term graft survival. The DeKAF study[14] evaluated patients who underwent late biopsies 7 ± 5 years post transplantation; 69% of patients diagnosed with CNI toxicity evidenced C4d deposition and/or DSA formation on biopsy. Patients with neither C4d deposition nor DSA formation experienced excellent long-term graft survival, but those with evidence of antibody-mediated injury did poorly. DSA formation and the development of a humoral immune response to the donor clearly are important for long-term graft survival, and patients maintained on belatacept seem to be less predisposed to DSA formation.

Advantages and Disadvantages

The relationship between immunosuppression and histology is considerable.[15–17] Histologic findings of peritubular capillaritis 3 months after renal transplantation have been shown to predict the development of chronic AMR at 12 months. Further, biopsy-proven AMR and low tacrolimus exposure at 3 months are associated with high AMR chronicity at 12 months. Both of these phenomena may result in graft fibrosis and significant impairment of long-term graft survival. In these studies, nonadherence to the immunosuppressant regimen has been associated with greater C4d deposition, graft fibrosis, and subsequent atrophy. One benefit of belatacept, therefore, may be that the drug is given once monthly as an infusion, potentially fostering adherence, but it can also be a disadvantage because of the logistical difficulties in scheduling monthly office visits.[18]

Treatment with belatacept may have its disadvantages. Within the first 12 months, patients using belatacept show a higher incidence of acute rejection, compared with other immunosuppressants.[19–21] Patients maintained on belatacept have a higher incidence of post-transplant lymphoproliferative disorder (PTLD) and progressive multifocal leukoencephalopathy.[12,13] Finally, the cost of belatacept as compared with that of other agents also must be justified, and the regulatory environment/burden associated with use of the drug in the United States must be navigated.[18]

Evidence of acute rejection from the BENEFIT study[12] showed that neither the more-intensive nor less-intensive belatacept treatment groups achieved a threshold of noninferiority when compared with the cyclosporine control group. In

the BENEFIT-EXT study,[13] this 20% noninferiority threshold was reached, and it nearly matched the low rate of acute rejection seen with cyclosporine. The types of graft rejections encountered were in no way innocuous, but patients who did not suffer graft rejection while on belatacept therapy seemed to do better long term. This finding is unlike that seen with the use of many immunosuppressants in transplantation, suggesting that another mechanism may be involved.

In terms of risk of post-transplant infection, there seems to be little difference between the rates of infection with CMV, BK polyomavirus, or herpes virus between belatacept-treated patients and those receiving other immunosuppressants; however, the rate of tuberculosis (TB) is higher with belatacept.[12,13] Although the rate of TB infection is inherently low in the United States, the increased risk of TB infection on belatacept must be considered in areas where TB is endemic.

PTLD rates, although more frequent with use of belatacept, are not that different from those noted with the use of new immunosuppressants. Reported PTLD cases have ranged from those limited to the allograft to disseminated disease that involves the central nervous system. Secondary analyses have shown that more PTLD cases occur among Epstein-Barr virus (EBV)-naïve patients who received an organ from an EBV-positive patient.[12,13] In patients who have had EBV infections, PTLD rates are similar to those to which we have become accustomed. Thus, the US Food and Drug Administration has reflexively labeled belatacept to be used only in transplant recipients who are EBV seropositive at the time of surgery.

Unresolved Issues

Beyond any obvious advantages/disadvantages to the use of belatacept are other issues that ultimately will decide where the drug fits into the mix of available drugs for post-transplant immunosuppression. Clinical investigators must determine how belatacept therapy compares with the current standard of care (tacrolimus and MMF). In addition, use of the drug in alternative protocols (eg, with mTOR inhibitors, CNIs, or steroid-free maintenance therapy) must be assessed. Lastly, the effects and long-term outcomes of conversion to belatacept from other maintenance immunosuppressive protocols must be considered.

Ongoing clinical trials are investigating some of these issues. Immunosuppression with belatacept-based, steroid-sparing regimens in de novo kidney transplant recipients recently was evaluated by Ferguson and others.[19] All patients received rabbit antithymocyte globulin induction therapy and then were randomized into one of three treatment arms: the first one received belatacept and MMF, the second one received belatacept and sirolimus, and a third (control) arm received tacrolimus and MMF. In the belatacept/MMF arm, the rate of acute rejection was 12% at 12 months, compared with only 3% in the tacrolimus/MMF arm. Patients in the belatacept/sirolimus arm, however, did reasonably well, with only a 4% rate of acute rejection at month 12. In both belatacept-containing arms, a significant increase in GFR was observed when compared with the tacrolimus/MMF arm.[19]

> Belatacept is a novel immunosuppressant agent that may change current paradigms, but its acceptance as an alternative to the present standard of care is limited by uncertainties over a variety of issues.

Grinyó and others[22] reported that when transplant recipients were switched from cyclosporine or tacrolimus to belatacept, the GFR showed significant improvement 1 and 2 years after the switch. When compared with cyclosporine, the conversion to belatacept resulted in the same mean change in GFR as seen in early phase II and phase III trials of belatacept. The consequence of conversion, however, was a higher rate of acute rejection. Further trials to evaluate the feasibility and safety of conversion from CNI to belatacept therapy are ongoing and planned.

In conclusion, belatacept is a novel immunosuppressant that may change current paradigms. Distinct advantages and disadvantages are associated with its use. Its acceptance as an alternative maintenance immunosuppressant is limited by uncertainties about various issues. The ultimate impact of the drug will be determined by the results of further studies.

TOFACITINIB

Based on a presentation by Stephan Busque, MD, MSc, FRCSC, Professor of Surgery and Director of the Adult Kidney and Pancreas Transplant Program, Stanford University School of Medicine, Palo Alto, California

Janus kinase (JAK), a family of intracellular, nonreceptor tyrosine kinases, is named after the two-faced Roman god of gates and doors, beginnings and endings. Currently, there are four known Janus kinases—JAK1, JAK2, JAK3, and TYK2. JAK3 is restricted to the immune system and is involved in signal transduction of cytokines via signal transducers and activators of transcription. Scientists became interested in JAK3 as a target for immunosuppression when a mutation in the γ protein of the receptor was associated with a form of severe combined immunodeficiency disease (SCID).[23]

Tofacitinib, a JAK3 inhibitor originally known as CP-690,550, initially was believed to be highly selective to JAK3[24]; however, it also is effective in the signaling of JAK1 and, to a much lesser extent, of JAK2. New findings of a beneficial synergistic and additive effect from blocking both JAK1 and JAK3 have led investigators to believe that this broader form of JAK inhibition may be advantageous.

Several phase II trials are evaluating tofacitinib therapy in the immunosuppressive management of renal transplantation, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and dry eye syndrome. With regard to kidney transplantation,

the drug was developed and tested as an alternative to CNI-based therapy. After a phase I study involving 28 patients,[25,26] two phase II trials (IIa and IIb) have been completed.[27,28]

The phase IIa study was carried out in a population of renal transplant recipients at low immunologic risk, the majority receiving a living-donor kidney.[27] Less-intensive (15 mg twice daily) and more-intensive (30 mg twice daily) regimens of tofacitinib were compared with tacrolimus. All study patients received induction with an interleukin-2 receptor blocker (basiliximab or daclizumab). Maintenance therapy included MMF and a steroid taper to 5–10 mg/d of prednisone by week 12.

Tofacitinib was noninferior to tacrolimus in regard to the percentage of patients with biopsy-proven acute rejection. However, early in the study, it became apparent that tofacitinib was associated with a higher rate of infectious complications, when compared with tacrolimus. In particular, four patients on tofacitinib 30 mg twice daily developed polyomavirus-associated nephropathy; this led to amendment of the initial protocol to eliminate the use of MMF in this arm and reduce the aggregate level of immunosuppression.

These early results demonstrate that clinical JAK3 inhibition is effective in preventing acute rejection of kidney allografts in CNI-free regimens. Use of tofacitinib at 30 mg twice daily plus MMF may be associated with overimmunosuppression, resulting in a higher incidence of transplant-associated infections, in particular, CMV and BK polyomavirus infections, as well as PTLD. Renal function was excellent through month 6 and was similar among all three treatment arms. Trends toward increased neutropenia and anemia and mild increases in serum lipid levels were noted in the tofacitinib treatment arms.

In the phase IIb study, the same two doses of tofacitinib were compared with cyclosporine in 331 renal transplant recipients, with ~ 60% of the organs coming from deceased donors.[28] Induction and maintenance therapies were similar to the regimens used in the phase IIa study. In these low- to moderate-risk patients, tofacitinib was equivalent to cyclosporine in preventing acute rejection at 6 months; was associated with improved renal function, as measured by GFR at month 12 ($P < 0.01$); and led to significantly fewer ($P < 0.05$) patients developing chronic allograft nephropathy at month 12 (24% for 15 mg of tofacitinib twice daily; 25% for 30 mg twice daily) compared with cyclosporine (48%). However, serious infections, anemia, neutropenia, and PTLD occurred more frequently in the tofacitinib arms of the study than in the cyclosporine arm.

Based on these early data, further evaluation of tofacitinib in patients who have received renal transplants appears to be warranted.

IMMUNOSUPPRESSIVE AGENTS IN PHASE I/II CLINICAL TRIALS

Based on a presentation by Diane M. Cibrik, MD, MS, Clinical Associate Professor of Internal Medicine, Division of Nephrology, University of Michigan Medical School, Ann Arbor

New potential therapeutic agents for kidney transplantation have emerged in three categories: ischemic-reperfusion injury (IRI), induction therapy, and maintenance immunosuppression.

Diannexin

The two-hit insult hypothesis of tissue injury is fundamental to the understanding of diannexin's mechanism. The ischemic insult from hypoxia that occurs during organ procurement results in an overall proinflammatory state. Reperfusion is essential to halt ongoing ischemic damage, but it also results in additional graft injury. Also involved are necrotic and apoptotic pathways, including recruitment of inflammatory mediators, Toll-like receptors (TLR2/TLR4), reactive oxidative species, cellular infiltration, complement, and the coagulation system.

In the first insult of the IRI cascade, hypoxia results in increased inducible nitric oxide synthase, impaired oxidative metabolism, and depletion of adenosine triphosphate (ATP). In addition, increases in anaerobic glycolysis, inhibition of the sodium/potassium ATPase pump, and decreased expression of cytoprotective genes occur. All of these insults collectively result in tissue injury and ultimately harm transplanted allografts.

When organs are reperfused in the second insult, leukocytes are recruited into the graft with activation of chemokines and inflammatory cytokines. Increased oxygenation at the cellular level leads to the generation of reactive oxygen species, thereby damaging cellular components and injuring tissues.

Diannexin is a recombinant homodimer of the endogenous human annexin V protein. Annexin V functions as a coagulation inhibitor by competing with phosphatidylserine (PS) binding sites for prothrombin. The binding of diannexin to exteriorized PS on the surface of endothelial cells/platelets blocks the leukocyte/platelet attachment and subsequent activation of the inflammatory cascade. Secretory phospholipase A2 activity is inhibited, and factor XII activation is prevented. The combined effects of blocking the IRI cascade at its beginning lead to less inflammation, thrombosis, and vasoconstriction.

The first phase IIa study of diannexin analyzed its impact on outcomes in marginal kidney donors.[29] This study included extended-criteria donors, donors after cardiac death, and standard-criteria donors with cold ischemic times > 24–36 hours. Delayed graft function occurred in 33% of patients given 400 μg/kg of diannexin and 56% of patients given placebo. In addition to these immediate effects, statistically significant, long-term improvement in GFR was observed at 12 months in patients given 400 μg/kg of diannexin.

QPI-1002

An IRI agent known as QPI-1002 (I5NP) is a synthetic, double-stranded, small-interfering RNA, 19 base-pair oligonucleotide against p53 messenger RNA (mRNA). The tumor suppressor protein p53 can activate proteins involved in DNA repair, induce growth arrest during the cell cycle, and initiate apoptosis. The antisense strand of QPI-1002 is incorporated into the RNA-induced silencing complex. In

the presence of QPI-1002, this complex destroys p53 mRNA, thereby decreasing production of p53. This mechanism allows proximal tubule cells the necessary time to repair cellular damage and avoid apoptosis.

There are no data on the use of QPI 1002 in human transplantation. However, animal autotransplantation data[30] pointed to significant decreases in serum creatinine levels at 24 hours when the drug was given 15 minutes before organ removal and eventual reperfusion.

ASKP1240

ASKP1240 is a fully human monoclonal antibody directed against CD40. It inhibits both humoral and cellular immune responses by blocking the CD40/CD40 ligand complex between T cells, B cells, APCs, and endothelial cells. Exposure to the drug also inhibits proliferation of CD40 ligand-induced B cells and mature dendritic cell cytokines in vitro. Other studies have pointed to prolonged allograft survival (kidney, liver, islets) in nonhuman primates given ASKP1240.[31] More recently, a phase IIa, single-dose study in de novo renal transplant recipients has been completed; a phase IIb study currently is in development.

TOL101

TOL101, a murine monoclonal immunoglobulin M antibody against the αβ subunit of the T-cell receptor of $CD3^+$ T cells, has not been shown to be active against the γδ T-cell receptor. TOL101 downregulates the αβ T-cell receptor to induce minimal T-cell proliferation and proinflammatory cytokine release in vitro. In addition, by not inhibiting the γδ T-cell receptor, TOL101 preserves the tolerogenic and protective effects of γδ T cells.[32] This is noteworthy, because the human αβ T-cell receptor protein sequence is conserved only in higher primates; in vivo animal models of pharmacologic activity/outcomes have not been performed. TOL101 is currently in phase I/II development.

Sotrastaurin

Sotrastaurin is a novel, small-molecular-weight molecule that inhibits protein kinase C (PKC)-dependent T-cell activation. Sotrastaurin selectively blocks a CNI-independent pathway downstream from both signals 1 and 2. The drug is hepatically metabolized.

In the A2207 study,[33] investigators compared the use of sotrastaurin plus MMF with the use of tacrolimus/MMF (control group). Patients given the study drug showed significantly poorer graft survival. The composite efficacy failure that led to the early termination of the study was driven by the high rate of biopsy-proven acute rejection (26%) in the sotrastaurin group. The company developing sotrastaurin recently decided to forego further investigation of it based upon efficacy and other concerns.

LCP-Tacro

This extended-release form of tacrolimus is given once daily. It uses the MeltDose drug delivery technology to improve bioavailability, providing improved systemic absorption and reduced peak/trough fluctuation and food-effect variability.

Polvino and others[34] revealed a consistent maximum plasma concentration of LCP-Tacro when compared with a baseline tacrolimus control group. Data on the area under the curve reflected minimal variability in drug concentration over 24 hours in liver transplant patients.[35]

REFERENCES

1. Keogh A, Richardson M, Ruygrok P, et al. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. *Circulation.* 2004;110:2694–2700.

2. Ekberg H, Tedesco-Silva H, Demirbas A, et al. Reduced exposure to calcineurin inhibitors in renal transplantation: ELITE-Symphony Study. *N Engl J Med.* 2007;357:2562–2575.

3. Lorber MI, Mulgaonkar S, Butt KM, et al. Everolimus versus mycophenolate mofetil in the prevention of rejection in de novo renal transplant recipients: a 3-year randomized, multicenter, phase III study. *Transplantation.* 2005;80:244–252.

4. Tedesco Silva H, Cibrik D, Johnston T, et al. Everolimus plus reduced-exposure CsA versus mycophenolic acid plus standard-exposure CsA in renal-transplant recipients. A2309 Study. *Am J Transplant.* 2010;10:1401–1413.

5. Webster AC, Lee VW, Chapman JR, Craig JC. Target of rapamycin inhibitors (sirolimus and everolimus) for primary immunosuppression of kidney transplant recipients: a systematic review and meta-analysis of randomized trials. *Transplantation.* 2006;81:1234–1248.

6. Holdaas H, Rostaing L, Serón D, et al. Conversion of long-term kidney transplant recipients from calcineurin inhibitor therapy to everolimus: a randomized, multicenter, 24-month study. ASCERTAIN Investigators. *Transplantation.* 2011;92:410–418.

7. Budde K, Becker T, Arns W, et al. Everolimus-based, calcineurin-inhibitor-free regimen of de-novo kidney transplants: an open-label, randomized, controlled trial. ZEUS Study Investigators. *Lancet.* 2011;377:837–847.

8. Johnston O, Rose CL, Webster AC, Gill JS. Sirolimus is associated with new-onset diabetes in kidney transplant recipients. *J Am Soc Nephrol.* 2008;19:1411–1418.

9. Schena FP, Pascoe MD, Alberu J, et al. Conversion from calcineurin inhibitors to sirolimus maintenance therapy in renal allograft recipients: 24-month efficacy and safety results from the CONVERT Trial. Sirolimus CONVERT Trial Study Group. *Transplantation.* 2009;87:233–242.

10. Kauffman HM, Cherikh WS, Cheng Y, Hanto DW, Kahan BD. Maintenance immunosuppression with target-of-rapamycin inhibitors is associated with a reduced incidence of de novo malignancies. *Transplantation.* 2005;80:883–889.

11. Campbell SB, Walker R, Tai SS, Jiang Q, Russ GR. Randomized controlled trial of sirolimus for renal transplant recipients at high risk for nonmelanoma skin cancer. *Am J Transplant.* 2012;12:1146–1156.

12. Vincenti F, Larsen CP, Alberu J, et al. Three-year outcomes from BENEFIT, a randomized, active-controlled, parallel group study in adult kidney transplant recipients. *Am J Transplant.* 2012;12:210–217.

13. Pestana JO, Grinyo JM, Vanrenterghem Y, et al. Three-year outcomes from BENEFIT-EXT: a phase III study of belatacept versus cyclosporine in recipients of extended criteria donor kidneys. *Am J Transplant*. 2012;12:630–639.

14. Mannon RB, Matas AJ, Grande J, et al. Inflammation in areas of tubular atrophy in kidney allograft biopsies: a potent predictor of allograft failure. DeKAF Investigators. *Am J Transplant*. 2010;10:2066–2073.

15. Lerut E, Naesens M, Kuypers DR, Vanrenterghem Y, Van Damme B. Subclinical peritubular capillaritis at 3 months is associated with chronic rejection at 1 year. *Transplantation* 2007;83:1416–1422.

16. Naesens M, Lerut E, Damme BV, Vanrenterghem Y, Kuypers DR. Tacrolimus exposure and evolution of renal allograft histology in the first year after transplantation. *Am J Transplant.* 2007;7:2114–2123.

17. Lerut E, Kuypers DR, Verbeken E, et al. Acute rejection in non-compliant renal allograft recipients: a distinct morphology. *Clin Transplant.* 2007;21:344–351.

18. Gabardi S, Halloran PF, Friedwald J. Managing risk in developing immunosuppressive agents: the new regulatory environment. *Am J Transplant*. 2011;11:1803–1809.

19. Ferguson R, Grinyó J, Vincenti F, et al. Im-

munosuppression with belatacept-based, corticosteroid-avoiding regimens in de novo kidney transplant recipients. *Am J Transplant.* 2011;11:66–76.

20. Vincenti F, Grinyó JM, Charpentier B, et al. Primary outcomes from a randomized, phase III study of belatacept vs cyclosporine in kidney transplant recipients (BENEFIT study). Presented at the 2009 American Transplant Congress; May 30–June 3, 2009; Boston, Massachusetts. *Am J Transplant.* 2009;9(suppl 2):191. Abstract 4.

21. Durrbach A, Larsen C, Medina-Pestana D, et al. Primary outcomes from a randomized, phase III study of belatacept vs cyclosporine in ECD kidney transplants (BENEFIT-EXT study). Presented at the 2009 American Transplant Congress; May 30–June 3, 2009; Boston, Massachusetts. *Am J Transplant.* 2009;9(suppl 2):199. Abstract 27.

22. Grinyó J, Mainan G, del Carmen Rial M, et al. Renal function at 2 years in kidney transplant recipients switched from cyclosporine or tacrolimus to belatacept: results from the long-term extension of a phase II study. Presented at the 2011 American Transplant Congress; April 30–May 4, 2011; Philadelphia, Pennsylvania. *Am J Transplant.* 2011;11:99. Abstract 226.

23. Pesu M, Candotti F, Husa M, Hofmann SR, Notarangelo LD, O'Shea JJ. Jak3, severe combined immunodeficiency, and a new class of immunosuppressive drugs. *Immunol Rev.* 2005;203:127–142.

24. Flanagan ME, Blumenkopf TA, Brissette WH, et al. Discovery of CP-690,550: a potent and selective Janus kinase inhibitor for the treatment of autoimmune diseases and organ transplant rejection. *J Med Chem.* 2010;53:8469–8484.

25. van Gurp E, Weimar W, Gaston R, et al. Phase 1 dose-escalation study of CP-690 550 in stable renal allograft recipients: preliminary findings of safety, tolerability, effects on lymphocyte subsets and pharmacokinetics. *Am J Transplant.* 2008;8:1711 –1718.

26. van Gurp EA, Schoordijk-Verschoor W, Klepper M, et al. The effect of the JAK inhibitor CP-690,550 on peripheral immune parameters in stable kidney allograft patients. *Transplantation.* 2009;87:79 –86.

27. Busque S, Leventhal J, Brennan D, et al. CP-690,550, a JAK3 inhibitor, in de novo kidney transplant recipients: 6-month results of a phase 2 trial. *Am J Transplant.* 2007;7:304. Abstract 601.

28. Vincenti F, Tedesco Silva H, Busque S, et al. Randomized phase 2b trial of tofacitinib (CP-690,550) in de novo kidney transplant patients: efficacy, renal function and safety at 1 year. *Am J Transplant.* 2012 June 8. Epub ahead of print.

29. Cooper M, Kapur S, Stratta R, et al. Diannexin, a novel ischemia/reperfusion therapeutic agent, reduces delayed graft function (DGF) in renal transplant recipients from marginal donors. *Am J Transplant.* 2010;10(suppl 4):83. Abstract 145.

30. Imamura R, Isaka Y, Sandoval RM, et al. Intravital two-photon microscopy assessment of renal protection efficacy of siRNA for p53 in experimental rat kidney transplantation models. *Cell Transplant.* 2010;19:1659–1670.

31. Pearson TC, Trambley J, Odom K, et al. Anti-CD40 therapy extends renal allograft survival in rhesus macaques. *Transplantation.* 2002;74:933–940.

32. Getts D, Mulgaonkar S, Melton L, et al. TOL101—anti-αβTCR monoclonal antibody immune monitoring during initial phase 2 renal transplant trials. Presented at the 2012 American Transplant Congress; June 2–6, 2012; Boston, Massachusetts. Abstract 192.

33. Friman S, Arns W, Nashan B, et al. Sotrastaurin, a novel small molecule inhibiting protein-kinase C: randomized phase II study in renal transplant recipients. *Am J Transplant.* 2011;11:1444–1455.

34. Polvino WJ, Melkus TC, Nigro V. Reduction in tacrolimus C_{max} by conversion from twice-daily tacrolimus capsules (Prograf) to once-daily extended release MeltDose tacrolimus tablets (LCP-Tacro): phase II randomized trial in stable kidney transplant patients. Presented at the 2012 American Transplant Congress; June 2–6, 2012; Boston, Massachusetts. Abstract 1295.

35. Feng S, Chapman WC, DuBay D. A phase 2 randomized study of the pharmacokinetics, safety and efficacy of LCP-Tacro tablets once-a-day vs Prograf capsules twice-a-day in de novo liver transplants. Presented at the 2012 American Transplant Congress; June 2–6, 2012; Boston, Massachusetts. Abstract 709.

Current Status of Risk Evaluation and Mitigation Strategies (REMS) in Organ Transplantation

Satish N. Nadig, MD, DPhil

University of Michigan Medical School, Ann Arbor, Michigan

Abstract Risk Evaluation and Mitigation Strategies (REMS) are a set of policies put into practice by the US Food and Drug Administration (FDA) Amendments Act of 2007. These strategies provide postmarketing oversight of pharmacotherapeutics to avoid potential or known risks. At this year's American Transplant Congress (ATC), leaders in pharmacology and medicine provided an overview of the past, present, and future of the drug-approval process and the impact REMS likely will have on the field of solid-organ transplantation. Experts reviewed the elements of REMS and requirements that healthcare providers and patients must meet when these strategies are imposed. Speakers also discussed specific strategies related to current immunosuppressive regimens.

Risk management is of utmost importance in prescribing pharmacologic therapeutics and monitoring their use. Drugs approved by the US Food and Drug Administration (FDA) that are later found to have serious or sometimes fatal ramifications are removed from the market. Thereafter, FDA officials intensely reevaluate the approval process for such products.[1] However, some medications that may cause grave side effects are nevertheless granted FDA approval because they provide specific therapeutic benefits or are effective in certain medical situations where no safer therapeutic options are available. Nowhere in medicine is this truer than in organ transplantation.

Despite the carcinogenicity and toxicity of immunosuppressive therapies, they are routinely prescribed to prevent organ rejection. To minimize their deleterious side effects, the need for and risk/benefit ratio of such drugs and biologic agents are continually reviewed by the physicians, pharmacists, and nurses in the transplant community. Since Risk Evaluation and Mitigation Strategies (REMS) were introduced in 2007, each new immunosuppressive medication has carried a set of professional and patient literature by which healthcare workers abide to minimize any risks associated with its use.[2]

At this year's American Transplant Congress, experts in the field of REMS research reviewed the history of pharmaceutical regulation and postmarketing surveillance, discussed the impact REMS have had on the prescription and use of immunosuppressive medication, and provided insight on controversies related to their implementation.

WHAT ARE REMS AND WHY ARE THEY IMPORTANT?

Based, in part, on a presentation by Rita Alloway, PharmD, Research Professor of Internal Medicine, Division of Nephrology and Hypertension, University of Cincinnati College of Medicine, Cincinnati, Ohio

Legislative efforts to protect people in the United States from substances that may harm them date back more than a century.

An Historic Perspective

Pure Food and Drug Act of 1906. The first of over 200 laws passed over the years to regulate the development, manufacture, and distribution of drugs was the Pure Food and Drug Act of 1906.[3] This legislation ordered federal inspection of meat products and prevented the use of poisonous and/or habit-forming patent medicines.

Federal Food, Drug, and Cosmetic Act of 1938. Over the ensuing 3 decades, it became increasingly clear that the Pure Food and Drug Act of 1906 needed to be revamped. In 1938, more than 100 people died after using a medicinal product called Elixir Sulfanilamide; the product contained diethylene glycol as a solvent and was never tested in animals or humans for toxicity. Federal, state, and local agencies worked together to recover over 234 of the 240 gallons manufactured.[4]

The public outrage stemming from this incident led to enactment of the Federal Food, Drug, and Cosmetic Act of 1938, which outlined a new system of drug control to stimulate medical progress and better protect the public.[4] Among new powers given to the FDA were the abilities to demand evidence that new drugs are safe, to regulate processing of food, and to inspect factories.[5]

Kefauver-Harris Amendments of 1962. Use of the sedative thalidomide in the 1950s and 1960s was linked to

Dr. Nadig is a Clinical Lecturer/Fellow in the Section of Transplantation Surgery, Department of Surgery, University of Michigan Medical School, Ann Arbor, Michigan.

thousands of birth defects among infants in Western Europe. News of this horrific problem and efforts to keep the drug off the US market resulted in the Kefauver-Harris Amendments of 1962, which mandated that companies submit the results of adequate, well-controlled studies proving the safety and effectiveness of a drug before it could be marketed. This legislation required the FDA to provide premarketing approval of all new or amended drug applications, that patients give informed consent before taking part in clinical studies, that companies follow good manufacturing practices, and that physicians report adverse events to the government. In addition, power to regulate the advertising of prescription drugs was transferred from the Federal Trade Commission to the FDA.[6]

Other Federal legislation. Over the years, a number of other Federal laws have been passed to help protect the public and speed approval of new drugs. For example, in 1970, passage of the Controlled Substance Act sought to regulate narcotics and other controlled substances in terms of manufacturing, importation, possession, use, and distribution.[7] In 1976, the same year that the Medical Device Amendment mandated safety and efficacy standards for new devices,[5] patient package inserts were introduced for distribution with oral contraceptives.[8]

During the 1980s, the FDA implemented Risk Management Plans to include the standard package insert with a prescription drug; in addition, patients might receive a medication guide or patient package insert with information written for the consumer. For drugs posing more significant risks, various risk-management steps (education; redistricted drug distribution) could be imposed.[9,10]

In 1992, the Prescription Drug User Fee Act authorized the FDA to collect funds from companies that were developing some human drug and biologic products.[11] These funds could only be used to speed the preapproval process; timelines then were set for regulatory reviews, and drugs were approved and marketed more quickly. As a result, the postmarketing safety system used in the United States gained greater responsibility for detecting safety problems early.[11]

Recent initiatives. Between 1997 and 2004, 12 drugs were removed from the US market because of safety concerns, resulting in legislative and regulatory initiatives to better ensure the safety of drug therapy.[9] In 2005, Risk Minimization Action Plans (RiskMAPS) were initiated to minimize the potential hazards of products posing a clinically important or unusual level of risk when compared with their benefits.[7,8,10,12] The FDA issued a guidance recommending methods to develop RiskMAPS, to select tools to minimize risks, to evaluate the use of RiskMAPS and associated monitoring tools, and to provide the FDA with feedback about these plans.[13]

> The FDA Amendments Act effectively established REMS as a method of controlling the investigation of real or potential adverse outcomes related to the use of pharmaceuticals and biologics.

By 2007, the FDA had learned of many adverse events related to the use of certain heavily prescribed medications, including the nonsteroidal anti-inflammatory drug rofecoxib and the antidiabetic drug rosiglitazone. The Agency teamed with the Institute of Medicine to develop and implement methods for minimizing the risk of drug therapy while preserving its benefits.[1,11] In addition, the agencies needed ways to evaluate and improve these tools.[14]

FDA Amendments Act of 2007. With enactment of a new section of the Food, Drug, and Cosmetics Act known as the FDA Amendments Act of 2007 (FDAAA; Public Law 110-85),[15] the FDA could require submission of proposed REMS as part of the application process for any drug or biologic product to ensure that the benefits of the product outweighed its risks. This legislation applied to new drug applications, abbreviated new drug applications, and biologics license applications. In addition, if any new safety information on an established product came to light, companies that already received approval for a drug or biologic agent were required to submit proposed REMS for use of that drug or biologic agent within 120 days of notification. Companies also could voluntarily submit REMS for a drug or biologic during the application process; the FDA would approve the plan only if the strategy was needed.

Thus, the FDAAA effectively established REMS as a method of controlling the investigation of real or potential adverse outcomes related to the use of pharmaceuticals and biologics. These strategies are intended to inform patients about the serious risks related to use of a drug or biologic product, to minimize the chance that such a product might interact adversely with another drug or biologic product or with a disease entity, and to prevent the risk of fetal exposure to certain pharmaceutical or biologic products.[12] A fundamental difference between the postmarketing strategies of REMS and previous strategies is that the FDAAA enabled and empowered the FDA to sanction noncompliant drug manufacturers.

Development of REMS

When considering whether REMS must be developed for a particular product, the FDA analyzes the number of patients likely to need the drug or biologic, the severity of the disease being treated with it, the expected treatment duration, the degree of known or potential adverse reactions, and the novel nature of the substance. The company must submit a timetable to assess REMS; it also must present an evaluation of the effectiveness of the REMS at a minimum of 18 months, 3 years, and 7 years after its approval, although the FDA can require additional assessments. For

TABLE 1
Requirements for Risk Evaluation and Mitigation Strategies (REMS)

Professional label and package insert
Inserts included with medications that are intended to provide patients with an instructional framework for safe use of a drug or biologic
Medication guides
Guides that allow patients and physicians to review the current safety guidelines for a given medication
Communication plan for healthcare providers
Letters that provide information to healthcare providers on the correct and safe ways to administer any given drug or biologic
Elements To Assure Safe Use (ETASU)
FDA-approved requirements for additional safeguards (eg, certification of the healthcare worker to administer the drug or biologic) when the safe use of a drug or biologic is not sufficently covered by other elements of the REMS
Implementations systems
Mechanisms developed by the drug sponsor to monitor the implementation of REMS

FDA = US Food and Drug Administration
Source: Childs et al[14]

assessment purposes, all REMS also must have a goal.[10] The specific components of REMS are listed in Table 1.[14]

Elements To Assure Safe Use (ETASU). REMs may specifically require an ETASU component. In such cases, healthcare providers prescribing the drug or biologic must have particular training, experience, or certifications. Special training and certification also is needed for pharmacies, practitioners, or healthcare facilities that dispense the agent, and the drug may be dispensed only in certain healthcare settings and to patients who present evidence of safe-use conditions.

Certified physicians working with the patient must understand how to use the drug or biologic agent safely, keep up with required patient monitoring, and diagnose and treat possible adverse effects; likewise, certified pharmacists dispensing the drug or biologic must be familiar with the agent's safe use and risks and agree to seek authorization before filling prescriptions. Every patient using such a drug must be monitored and enrolled in a registry.[10]

IMPACT OF REMS ON ORGAN TRANSPLANTATION

Based, in part, on a presentation by Steven Gabardi, PharmD, BCPS, Abdominal Organ Transplant Clinical Specialist, Departments of Transplant Surgery and Pharmacy Services, Brigham and Women's Hospital, and Assistant Professor of Medicine, Harvard Medical School, Boston, Massachusetts

As of June 2012, 92 FDA-approved drugs and biologics were accompanied by REMS. At this time, however, belatacept and everolimus are the only FDA-approved immunosuppressants having REMS.[16] Interestingly, sirolimus, a mammalian target of rapamycin inhibitor, had approved REMS as of November 23, 2010, but that REMS later was rescinded. On June 6, 2011, the FDA determined that a medication guide incorporated in the labeling of the drug, independent of REMS, was sufficient and necessary to provide adequate information to patients using this immunosuppressive agent.[17]

In September 2008, the FDA mandated that manufacturers of mycophenolate mofetil and mycophenolic acid submit REMS to ensure that the benefits of using these drugs outweighed the risks and that any unexpected problems could be managed in an organized fashion. Specifically, this mandate was a response to a boxed warning that highlighted the increased risk of pregnancy loss and congenital malformations that may occur when these drugs are taken during pregnancy (eg, cleft lip and palate; abnormalities of the distal limbs, heart, esophagus, and kidneys).[16] A medication guide for these products was approved in December 2008; the full REMS will include other elements, including physician training and certification, patient education, a pregnancy registry, an implementation plan, and a timetable for assessing the REMS.[16] This REMS currently is being reviewed.[16,18]

The issuing of REMS for mycophenolic acid and mycophenolate mofetil may have a tremendous effect on transplant-specific healthcare professionals. Some healthcare personnel believe that implementation of these strategies will impose new obstacles to transplantation, whereas others believe they will improve patient safety and are justifiable.

IMPLICATIONS OF REMS FOR HEALTHCARE PROVIDERS

Based, in part, on a presentation by Diane M. Cibrik, MD, MS, Clinical Associate Professor of Internal Medicine, Division of Nephrology, University of Michigan Medical School, Ann Arbor

Administrators at regulatory agencies do not hold sole responsibility for assessing the safety of prescription drugs and biologic agents. Healthcare providers and patients must be diligent in using these products according to recommendations outlined by the REMS.

Everolimus

The REMS for everolimus were approved by the FDA on April 20, 2010. They consist of a medication guide and communication plan, offering both "Dear Pharmacist" and "Dear Healthcare Provider" letters. In May 2012, the FDA determined that the medication guide could be maintained as part of the approved labeling and no longer was required as an element of the approved REMS.[19]

Currently, the healthcare provider letter for everolimus discusses the potential risks of impaired wound healing, hyperlipidemia, proteinuria, and renal allograft thrombosis related to its use.[19] It also mentions that possible nephrotoxicity may occur in everolimus-treated patients taking standard doses of cyclosporine adjunctively.

When healthcare professionals receive these informative letters, they are expected to follow the medication guide, heed the warnings in the letters, and dutifully report serious adverse events related to use of the medication. Importantly, all serious adverse events must be reported

to both the FDA and the product's manufacturer, even if they may not be directly related to its use.

Belatacept

Belatacept therapy is indicated only for use in transplant patients who are seropositive for Epstein-Barr virus infection. Its use is associated with the serious and potentially fatal risk of posttransplant lymphoproliferative disorder (PTLD) and progressive multifocal leukoencephalopathy (PML). Patients given belatacept have a greater risk for developing PTLD, which predominantly involves the central nervous system. PML has been noted among patients given higher doses of belatacept than recommended as part of an immunosuppressive regimen.[20]

The REMS for belatacept—a medication guide and a communication plan with a timetable for implementation—were approved in June 2011. The communication plan for this drug is extensive and includes a Web site (http://www.nulojix.com/hcp/index.aspx) and a "webinar" slide presentation (http://www.nulojix.com/pdf/NulojixApprovalPlus/REMS%20Educational%20Deck.pdf) specifically intended for healthcare providers. Along with letters to healthcare professionals and fact sheets, the REMS mandate use of an infusion specialist letter and preinfusion checklist. Finally, to disseminate information among all groups of transplant providers, a review of guidelines for safely administering belatacept was published in various transplant-specific journals.

Controversies

REMS are intended to protect patients from serious complications related to drug or biologic therapy. However, they also can prove challenging to healthcare personnel. Some professionals become concerned about enrolling in various programs, needing different certifications, and complying with prescription requirements. The cost of healthcare is currently a hot topic, and many physicians and pharmacists have voiced concerns that REMS may interfere with medical practice and impose costs without supplying a source for reimbursement. In addition, patients worry that they may not be able to obtain particular medicines from any healthcare provider who refuses to participate in REMS. Many professionals also believe that the implementation of REMS may widen the time lapse between drug prescription and delivery to a patient.[12]

For these and other reasons, officials at the FDA are gathering input from healthcare personnel and patients about developing and implementing REMS. The Agency is planning to hold at least one public meeting by the end of fiscal year 2013 to scrutinize methods of standardizing REMS and reduce the burden imposed upon patients and the healthcare community.[12]

SUMMARY

At the outset, REMS were intended to benefit patients without burdening the transplant practitioner. On the whole, that goal seems to have been met.[1] However, the development of newer, more potent immunosuppressant drugs and the imposition of more REMS for established transplant-related medications—including the imminent approval of REMS for mycophenolate mofetil and mycophenolic acid—may increase the healthcare practitioner's burden. Further, this burden may increase greatly if ETASUs are added to REMS and healthcare practitioners need certification to administer specific immunosuppressants. Ultimately, healthcare facilities would have to increase staffing and vigilance to ensure that certifications remain up-to-date.[1]

On the other hand, the increased oversight imposed by REMS makes it easier to obtain regulatory approval for potent, potentially harmful medications that might otherwise not reach the marketplace, such as immunosuppressants. The use of REMS also allows such medications to remain on the market.[6] Overall, these strategies benefit transplantation medicine, although they cause compliant healthcare professionals to navigate a number of obstacles. The advent and popularity of electronic health records among hospitals nationwide hopefully will ease, or even solve, these problems in the future.[22]

REFERENCES

1. Shane R. Risk evaluation and mitigation strategies: impact on patients, health care providers, and health systems. *Am J Health Syst Pharm.* 2009;66:S6–S12.

2. Gabardi S, Halloran PF, Friedewald J. An update on risk evaluation and mitigation strategies in transplantation [letter to the editor]. *Am J Transplant.* 2012;12:257–258.

3. United States. Pure Food and Drug Act (1906). United States Statutes at Large (59th Congress, Session I, Chapter 3915, pp 768–772; cited as 34 U.S. Stats 768). In: *History of Medicine Division. Medicine in the Americas: Historical Works.* Bethesda, MD: National Library of Medicine; 2004. http://www.ncbi.nlm.nih.gov/books/NBK22116/. Accessed June 25, 2012.

4. Ballentine C. Taste of raspberries, taste of death: the 1937 elixir sulfanilamide incident. *FDA Consumer.* June 1981. http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/SulfanilamideDisaster/default.htm. Accessed June 25, 2012.

5. Regulatory information: Legislation. US Food and Drug Administration Web site. http://www.fda.gov/RegulatoryInformation/Legislation/default.htm. May 4, 2011. Accessed June 25, 2012.

6. Meadows M. Promoting safe and effective drugs for 100 years. FDA Consumer. January–February 2006. US Food and Drug Administration Web site. June 8, 2009. http://www.fda.gov/AboutFDA/WhatWeDo/History/ProductRegulation/PromotingSafeandEffectiveDrugsfor100Years/default.htm. Accessed June 25, 2012.

7. Regulatory information: Controlled Substances Act. US Food and Drug Administration Web site. http://www.fda.gov/regulatoryinformation/legislation/ucm148726.htm. June 11, 2009. Accessed June 25, 2012.

8. Leiderman DB. Risk management of drug products and the U.S. Food and Drug Administration: evolution and context. *Drug Alcohol Depend.* 2009;105:S9–S13.

9. Gabardi S, Halloran PF, Friedewald J. Managing risk in developing transplant immunosuppressive agents: the new regulatory environment. *Am J Transplant.* 2011;11:1803–1809.

10. Choe LY. Food and Drug Administration. Risk Evaluation and Mitigation Strategies (REMS). US Food and Drug Administration Web site. http://www.fda.gov/downloads/AboutFDA/WorkingatFDA/FellowshipInternshipGraduateFacultyPrograms/PharmacyStudentExperientialProgramCDER/UCM276838.pdf. Accessed June 25, 2012.

11. Psaty BM, Korn D. Congress responds to the IOM drug safety report—in full. *JAMA.* 2007;298:2185–2187.

12. Dal Pan GJ. A short tutorial on REMS: the FDA perspective. Medscape Web site. April 27, 2012. http://www.medscape.com/viewarticle/762240. Accessed June 25, 2012.

13. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics

Evaluation and Research. Guidance for industry: development and use of Risk Minimization Action Plans. US Food and Drug Administration Web site. March 2005. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071616.pdf. Accessed July 25, 2012.

14. Childs L, Alexander E, Duong MT. Risk evaluation and mitigation strategies: assessment of a medical center's policies and procedures. *Am J Health Syst Pharm.* 2012;69:885–889.

15. US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. Guidance for Industry: format and content of proposed Risk Evaluation and Mitigation Strategies (REMS), REMS assessments, and proposed REMS modifications. US Food and Drug Administration Web site. September 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm184128.pdf. Accessed June 25, 2012.

16. Risk Evaluation and Mitigation Strategy under review for CellCept and Myfortic. US Food and Drug Administration Web site. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm148735.htm. Accessed June 25, 2012.

17. Belen O. Supplement approval: remove REMS element. [correspondence on Rapamycin (sirolimus)]. US Food and Drug Administration Web site. June 6, 2011. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021083s050,021110s060ltr.pdf. Accessed June 25, 2012.

18. Gabardi S. Understanding risk evaluation and mitigation strategies in organ transplantation. *Pharmacotherapy.* 2011;31:714–722.

19. Belen O. Supplement approval: remove REMS element [correspondence on Zortress (everolimus)]. US Food and Drug Administration Web site. November 21, 2011. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021560s004ltr.pdf. Accessed June 25, 2012.

20. Zortress (everolimus) important drug warning. Novartis Pharmaceuticals Corporation Web site. May 6, 2009. http://www.pharma.us.novartis.com/assets/pdf/REM/zortress_HCP_letter.pdf. Accessed July 25, 2012.

21. Safety: Nulojix (belatacept): Risk Evaluation and Mitigation Strategy (REMS). US Food and Drug Administration Web site. July 7, 2011. http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm262210.htm. Accessed June 25, 2012.

22. Fotsch EJ. Electronic health records: the new vehicle for drug labeling, safety, and efficacy. *Clin Pharmacol Ther.* 2012;91:917–919.

Long-Term Primary Care Issues in the Transplant Population

Jared Brandenberger, MD

University of Washington Medical Center, Seattle, Washington

Abstract As posttransplant patients live longer with healthy grafts, primary care issues are becoming more important. Along with longstanding transplant issues such as maintaining graft function and managing infections, concerns about cardiovascular health, diabetes, and cancer screening and detection are hot topics among transplant physicians striving to improve the longevity of their patients. Open communication and an individualized approach are crucial as we await the results of important research to help us better treat our patients.

The 2012 American Transplant Congress showcased many innovations in the field of organ transplantation. From the bench to the clinic to the operating room and beyond, the field of transplantation continues to evolve, improving the lives of our patients and the longevity of their grafts. Now more than ever, the entire patient must be considered, not just the transplanted organ. Unfortunately, long-term care of the transplant patient is often overlooked. Transplant surgeons easily can fail to notice the unique problems often encountered by patients in the years after surgery.

This panel session explored some of the most common issues faced by our patients, touching on key issues, treatment, and misconceptions by the medical community at large. Among topics covered were the management of hypertension, diabetes, and infection in transplant patients. In addition, speakers discussed cancer prevention and screening in this population. These experts discussed each issue in terms of the transplant patient and the general population.

Dr. Brandenberger is Acting Instructor and Senior Fellow in Transplant Surgery, University of Washington Medical Center, Seattle, Washington.

TAILORING TREATMENT IN THE MANAGEMENT OF HYPERTENSION

Based on a presentation by Alan G. Jardine, BSc, MBChB, MD, FRCP, MRCP, Professor of Renal Medicine, University of Glasgow School of Medicine, Scotland

As transplant patients are living longer with healthy grafts, management of hypertension is becoming a crucial issue. Cerebrovascular and cardiovascular events are among the most common causes of death among patients having a functioning graft. Aside from increasing the risk of myocardial infarction and sudden cardiac death, hypertension also has implications for the health of the graft.

The most common factors associated with refractory hypertension among the transplant population are vasoconstriction related to use of calcineurin inhibitors (CNIs), sodium retention related to corticosteroid therapy, a decrease in glomerular filtration rate (GFR) resulting from activation of the renin-angiotensin pathway, and the presence of preexisting comorbidities such as pretransplant hypertension.

Controlling Blood Pressure

Opelz and Döhler[1] showed that a drop in systolic blood pressure, even in patients having hypertension for years after kidney transplantation, was associated with improved survival of both patients and grafts. Although this trend was more pronounced in graft recipients < 50 years of age, the authors concluded that improving blood pressure control in all age groups would improve outcomes. With continuing insights into managing immunosuppression, graft loss, and infectious issues, the handling of cardiovascular issues will continue to be important to the long-term health of transplant recipients of all ages.

The most current and widely recognized recommendations are the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines,[2] which recommend that blood pressure be measured during each office visit *(Grade 1C)* and maintained at < 130 mm Hg systolic and < 80 mm Hg diastolic *(Grade 2C)* for patients 18 years of age and older and for those under 18 who fall below the 90th percentile for gender, age, and height.

Physicians are not limited by the guidelines to any class of antihypertensive agent but should monitor their patients for adverse effects and drug interactions. If proteinuria is detected, use of an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-receptor blocker (ARB) is recommended as first-line therapy (not graded). The KDIGO guidelines also recommend that healthcare personnel identify ideal blood pressure targets, measure the effect that minimizing proteinuria has on progression of chronic renal disease, and determine the effects of ACE inhibitors and ARBs on patient and graft survival.

A recent study of 183 renal transplant patients by Agena et al[3] showed that home

blood pressure measurements agreed to a significantly greater degree with ambulatory blood pressure monitoring than with blood pressure measurements taken in the office. Further, hypertension was controlled in significantly more patients who underwent home and ambulatory blood pressure monitoring than in those who had office monitoring.

Avoiding and Managing Hypertension

For years, physicians have believed that lifestyle modifications may improve hypertension; this theory extended to the transplant population. In a study of 660 renal transplant patients, van den Berg et al[4] found that a reduction in sodium intake to the recommended maximum of 70 mmol/d could lower systolic blood pressure by 4–5 mm Hg. They concluded that restricting sodium intake could prevent graft failure and mortality resulting from hypertension in this population.

When it comes to medical treatment of hypertension, there is no consensus and somewhat scarce data about optimal therapy. For years, amlodipine has been the backbone of treating the posttransplant patient because the drug mitigates CNI-related vasoconstriction and lowers blood pressure effectively. Emerging evidence suggests that other drug classes may have promise in the transplant population

Heinze et al[5] found an increase in both patient and graft survival with the use of ACE inhibitors. Likewise, Weir[6] reported a decrease in proteinuria with the use of ACE inhibitors and ARBs. However, in a 2009 Cochrane Database review, Cross et al[7] showed that treatment with calcium channel blockers diminished graft loss and improved GFRs; use of ACE inhibitors was associated with a decrease in proteinuria, but it also was linked to an increase in hyperkalemia and a decrease in GFR. Currently, dihydropyridine calcium channel blockers remain a mainstay of antihypertensive treatment for transplant recipients with hypertension.

Maintaining Immunosuppression

Another factor in managing hypertension in the organ transplant population is the type of immunosuppressant used. Minimization or withdrawal of corticosteroids post transplant leads to lower blood pressure at the cost of an increased risk of acute rejection, yet overall graft and patient survival do not suffer.[8,9]

Maintenance therapy with a low dose of corticosteroids may avoid some immunologic risk while improving hypertension.[10] CNI withdrawal with conversion to rapamycin may lead to decreased blood pressure in the stable posttransplant patient over the long term; in addition, conversion from cyclosporine to tacrolimus may benefit some renal transplant patients.[11,12] Results from the BENEFIT and BENEFIT-EXT trials also showed a decrease in hypertension with use of CNI-sparing regimens in patients who underwent kidney transplantation.[13]

Summary

When following renal transplant patients, ambulatory and home blood-pressure monitoring may best reflect the patient's real hypertensive status. Blood pressure goals of 125–130 mm Hg systolic and 75–80 mm Hg diastolic are reasonable and may reduce left ventricular hypertrophy, a significant risk factor for sudden cardiac death. Calcium channel blockers (eg, amlodipine) and, in certain cases, ACE inhibitors and ARBs are the most effective antihypertensive choices; however, use of thiazide diuretics also may be acceptable. Decreasing immunosuppression to improve hypertension and modifying lifestyle choices may improve outcomes, as well.

In short, "we are doing all right," but there is much room for continued study of the risk factors and treatment of hypertension in organ-transplant recipients.

DIABETES MANAGEMENT IN TRANSPLANTATION: HOW TIGHT FOR HOW LONG?

Based on a presentation by Steven J. Chadban, PhD, FRACP, Clinical Professor of Medicine, The University of Sydney Medical School, Sydney, Australia

Treatment of the diabetic patient before and after organ transplant is challenging. Diabetes mellitus greatly contributes to end-stage organ dysfunction in the transplant population, and many patients waiting for an organ have undiagnosed diabetes. The prevalence of type 2 diabetes among the general population of Australia jumps after age 45; it is estimated that there is one case of undiagnosed diabetes for each one known.[14] Among Australian patients waiting for a kidney, there is one diabetic patient for every five, representing a significant portion of the pretransplant population, according to Dr. Chadban.

Overall, diabetes is extremely common among the renal transplant population—30%–60% of patients with end-stage renal disease and 15%–40% of patients on transplant waiting lists are diabetic. Further, 10%–40% of patients will develop new-onset diabetes after transplant (NODAT), a phenomenon seen more commonly in recent years and especially in the renal transplant population. Many unique factors of the posttransplant patient affect both insulin production and insulin resistance (Table 1). The prevalence of NODAT, along with a greater tendency for labile blood sugar levels after transplant, is responsible for the common need for antidiabetic treatment among patients who have undergone renal transplant.

The clinical importance of diabetes among renal transplant patients from an endocrine standpoint is obvious. Wiesbauer et al[15] linked glucose control with survival post transplant. Likewise, Valderhaug et al[16] noted the relationship between NODAT and death with a functioning graft. In addition, immunologic consequences may be involved. Thomas and others[17] reported a possible link be-

TABLE 1
Risk Factors for New-Onset Diabetes After Transplant (NODAT)

- Insulin resistance
- Corticosteroid use
- Calcineurin inhibitor therapy
- Inflammation
- Hepatitis C virus infection
- Cytomegalovirus infection
- Obesity
- Inactivity

tween hyperglycemia and a predisposition to acute allograft rejection.

Monitoring Blood Glucose Levels

Important differences to keep in mind when monitoring and treating patients who have undergone organ transplant are the inaccuracy of fasting blood glucose levels as compared with preprandial measurements, the inaccuracy in hemoglobin A_{1c} (Hb_{A1c}) values, and the importance of the oral glucose tolerance test in screening efforts.

Monitoring blood glucose levels is somewhat different for transplant recipients than for the general population. In posttransplant patients, preprandial blood glucose levels may be a more sensitive indicator of insulin requirements than fasting levels, possibly because blood glucose levels rise continuously and additively throughout the day after each meal. This effect improves somewhat at 3 and 6 months after surgery, but preprandial measurements are a much better gauge of glucose control than postprandial levels. This is an area where continuous blood glucose monitoring may be of help in the future.

Because the immediate posttransplant period is so volatile with regard to blood glucose levels, Hb_{A1c} values also are not accurate in this population; further, they have not been studied long term in renal transplant recipients. The standard diagnostic for NODAT remains the oral glucose tolerance test. In all, the accurate measurement of blood glucose levels in the posttransplant population remains challenging.

Managing Diabetes

Effective treatment of diabetes mellitus in the posttransplant population continues to evolve. Few data regarding the optimal antidiabetic regimen in renal transplant recipients are available, and insulin remains the mainstay of treatment. Use of sulfonylureas or thiazolidinediones is safe in renal transplant patients, but these drug classes may not be as widely used as insulin due to the prevalence of refractory diabetes in this population. For the most part, biguanides are contraindicated for use in patients who have received a kidney transplant.[2]

Modification of immunosuppression to improve control of blood glucose levels also has been explored. Results from the Symphony study showed both an increase in diabetes that was related to immunosuppression and an association between tacrolimus therapy and NODAT.[18] Unfortunately, corticosteroid-free immunosuppression does not impact NODAT greatly; further, it is associated with an increase in acute rejection. Thus, many transplant programs are now choosing to pursue minimization of corticosteroids in immunosuppressive regimens to improve glucose tolerance.

Zelle et al[19] reported an increase in survival among renal transplant patients who took part in exercise. This intuitive finding is difficult to attribute to the effect of physical exercise on blood glucose levels and requires further study.

The optimal treatment for patients with NODAT remains a moving target. The KDIGO guidelines suggest that physicians consider modifying immunosuppression when NODAT is diagnosed while weighing the risks of graft rejection and subsequent treatment.[2] In addition, physicians should help patients to achieve a target Hb_{A1c} level < 7.5%.

Summary

Development of NODAT is related to early concerns about a possible association with and an increased risk of acute rejection; late concerns include end-organ damage, vascular disease, and the risk of death, most commonly from cardiovascular causes. To treat patients with NODAT, physicians may consider modification of immunosuppressive regimens in selected individuals, improvement in diet and exercise, and judicious control of blood glucose levels, taking care to avoid hypoglycemia. No pharmacologic treatment is firmly recommended, but insulin-based therapeutic regimens remain the mainstay of antidiabetic management in this population.

AVOIDING INFECTION: VACCINES AND LIFESTYLE AFTER TRANSPLANTATION

Based on a presentation by Robin K. Avery, MD, Professor of Medicine, Cleveland Clinic Foundation, Cleveland, Ohio

The prevention of infection in transplant patients is extremely important. It is also a source of considerable confusion among providers. In many cases, use of vaccinations in transplant patients, especially when there are infants and young children in the household, is a major quandary, and physicians must help dispel some of the myths surrounding immunization as they pertain to our patients.

One common fear is that immunizations are related to acute rejection. However, there is no compelling evidence in the literature showing an increased risk of rejection with immunization. Likewise, any concerns about using immunizations in the early posttransplant period are related to the vaccines' lack of efficacy, not patient safety.

Recommendations for Immunization

Current recommendations for immunization can be divided into pre- and posttransplant guidelines.

Pretransplant guidelines. Patients may receive pneumococcal vaccine within 5 years of transplant surgery and influenza vaccine annually. Patients awaiting transplant also should receive tetanus-diphtheria-pertussis (Tdap) immunization (especially if they are at risk for developing pertussis) and hepatitis A and B vaccine (if they are seronegative). Pretransplant patients also may receive varicella vaccination, but not within 4 weeks of transplant surgery and not if they have started taking immunosuppressants.

Some population-specific recommendations for immunizing pretransplant patients also have been issued. For example, administration of the herpes zoster vaccine may be considered for wait-listed patients over 60 years of age; this product is indicated for patients over 50 years of age and often is not covered by insurance. For young men and women awaiting transplant, administration of the human papillomavirus vaccine may be considered. If patients may undergo splenectomy during the operation, *Haemophilus influenzae* type B vaccine and meningococcal vaccine may be given;

in addition, if possible, pneumococcal vaccine may be given at least 2 weeks before transplant surgery. It is important to immunize pretransplant patients as soon as possible, since vaccination is less effective once the patient has progressed to end-organ disease.

Posttransplant guidelines. Recommendations for immunizing patients who already have undergone renal transplant include pneumococcal vaccination every 5 years, hepatitis A and B immunization (if the patient was not immunized before surgery), and any other indicated vaccination. However, measles-mumps-rubella vaccine, oral polio vaccine, and yellow-fever vaccine are contraindicated for renal transplant patients.

Maintaining Health and Everyday Activities

Employment. Job-related safety is a concern for transplant patients when it comes to infectious issues. Most patients can return to work with little risk. However, individuals employed in agriculture and the construction industry need to avoid contact with soil if they are not wearing gloves. Pet stores are also an area of concern; patients working with animals should discuss their employment with an infectious disease specialist before returning to work.

Likewise, healthcare personnel who receive a transplant also should discuss their return to work with an infectious disease specialist. Those returning to work should practice strict hand hygiene and avoid exposure to patients infected with cytomegalovirus, hepatitis C virus, respiratory viruses, tuberculosis, fungi, or multidrug-resistant organisms. They should be careful to wear gloves when treating patients in wound-care or intensive care units and avoid working in walk-in clinics, urgent care facilities, homeless shelters, or jails.

Home and hobbies. Gardening and activities such as caving pose the same risk and involve similar precautions for soil-borne pathogens as do jobs related to soil exposure. Hunting and cleaning of game also should be accomplished with gloves. These and other high-risk activities, such as scuba diving, should be discussed with an infectious disease specialist before transplant recipients take part in them.

Specific recreational exposures to avoid include marijuana use and contact with untreated water, caves, hot tubs, and chicken coops. At home, in the workplace, or during recreational activities, fastidious hand hygiene is indispensable.[20]

Travel is of particular concern; a study showed that 17% of patients reviewed felt ill enough to seek medical attention during or immediately after travel. A dedicated travel clinic is a particularly valuable resource for patients who wish to visit other areas. Further, individuals who undergo transplant surgery and plan to travel should receive appropriate immunizations and prophylaxis and consult with their transplant surgeons. Such individuals should refrain from traveling out of the country immediately after surgery or during times of increased immunosuppression.[21]

Pets also are associated with infections. Toxoplasmosis and cat scratch disease are related to contact with cats; psittacosis, histoplasmosis, and cryptococcosis are linked to contact with birds; mycobacterial infections are related to contact with aquariums; and *Salmonella* infection is linked to contact with reptiles.[22] During the first year after transplant surgery or during periods of increased immunosuppression, patients should follow compulsive hand hygiene and not acquire new pets or clean bird cages or litter boxes.

Summary

Education is crucial to prevent infection following kidney transplant. The availability of a dedicated transplant infectious disease service and a travel clinic is valuable for active individuals. When seeking answers to infection-related questions, physicians must consider the patient's total burden of immunosuppression, periods of increased immunosuppression (eg, during treatment for rejection, neutropenia), and the presence of appropriate support. Common sense, caution, and above all communication are essential to preventing infection in our patients.

CANCER PREVENTION AND SCREENING: HOW BIG IS THE RISK?

Based on a presentation by Bryce A. Kiberd, MD, FRCPC, Professor of Medicine and Medical Director of the Division of Nephrology, Dalhousie University, Halifax, Nova Scotia, Canada

Transplant recipients have a twofold to fourfold higher cancer rate than does the general population. As organ recipients live longer, mortality from malignancy may be increasing; in particular, young females have a higher relative risk of cancer than do males < 45 years of age. All transplant recipients carry a risk of malignancy that is comparable to that of the members of the general population who are 20–30 years their senior.[23] However, whereas young patients have an increased overall cancer risk, transplant recipients > 55 years of age have a lower all-cancer mortality than do people of the same age in the general population.[24]

Although overall cancer risk increases among young transplant recipients, the incidence of all cancers is not increased; in fact, the incidence of certain malignancies differs widely between transplant recipients and the general population. Common posttransplant malignancies, such as skin cancer, renal cell carcinoma, and lymphoma, are five times more likely to develop in transplant patients. The incidence of other cancers, including melanoma; multiple myeloma; and colon, cervical, lung, stomach, hepatocellular, bladder, and endometrial cancers, is two to four times more common among transplant recipients. However, the posttransplant population does not have an increased risk of developing two very common cancers—prostate cancer and breast cancer.[23]

Screening

Screening for cancer has had a proven impact in the general population. In the posttransplant population, the considerations are slightly different. Transplant recipients have a somewhat lower life expectancy and develop certain malignancies much more commonly, which changes the risk-benefit ratio for some types of screening. Table 2 outlines proposed

TABLE 2
Proposed Screening Recommendations and Grading for Transplant Patients (Txp) Compared with the General Population

Malignancy	Grade	Increased risk in Txp	Txp grade[a]
Colon	A	2.0–2.3 times	A
Cervix	A	2.2 times	A
Breast	B	No increased risk	< B
Prostate	No screening	No increased risk	Not recommended
Lung	Inconclusive	2.3 times	Inconclusive

[a] Per Bryce A. Kiberd, MD, FRCPC

screening recommendations and grading for transplant patients as compared with the general population.

For cancers that develop more commonly in the transplant population, there are no firm recommendations for screening. The KDIGO guidelines for renal transplant recipients call for individualized cancer screening on a case-by-case basis.[2] They also recommend annual skin cancer screening by healthcare professionals and patient self-screening for skin malignancies, minimization of sun exposure, and use of sunblock.[2] Nonmelanomatous skin cancers contribute more to the mortality of transplant recipients than does melanoma. However, melanoma also carries a significant risk in this population.

Transplant recipients have a significant risk of developing lymphoma (incidence, 1.6 cases/100 patient-years; 25% mortality). This is especially relevant in high-risk populations (children, patients infected with Epstein-Barr virus [EBV]). Since EBV is a predisposing factor, some physicians have suggested following EBV titers and potentially lowering patients' immunosuppression when titers are high. This, of course, must be balanced against the risk of rejection. More study is needed in this area.

Renal cell cancer is another common posttransplant malignancy, and screening is a topic of debate. Some centers screen for this malignancy routinely. Advantages include the availability of noninvasive tests and increased effectiveness if the cancer is detected early. Disadvantages of routine screening include the relatively high incidence of incidental lesions found and the minimal proven benefit of most analyses. Screening may be worthwhile in high-risk populations or transplant recipients with previous disease, but, again, more study is needed.

Overall, transplant recipients should be screened for cancer using an individualized approach. Physicians should pay special attention to younger patients and to older patients having good function and fewer comorbidities. In older patients or individuals having multiple comorbidities, physicians should focus more on active issues and less on screening for low-yield malignancies. In all, medical personnel should emphasize the prevention of cancer deaths, not the prevention of cancer itself.

REFERENCES

1. Opelz G, Döhler, B. Improved long-term outcomes after renal transplantation associated with blood pressure control. *Am J Transplant.* 2005;5:2725–2731.

2. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant.* 2009;9(suppl 3):S1–S155.

3. Agena F, Prado E, Souza P, et al. Home blood pressure (BP) monitoring in kidney transplant recipients is more adequate to monitor BP than office BP. *Nephrol Dial Transplant*. 2011;26:3745–3749.

4. van den Berg E, Geleijnse JM, Brink E Jr, et al. Sodium intake and blood pressure in renal transplant recipients. *Nephrol Dial Transplant*. 2012;27:3352–3359.

5. Heinze G, Mitterbauer C, Regele H, et al. Angiotensin-converting enzyme inhibitor or angiotensin II type 1 receptor antagonist therapy is associated with prolonged patient and graft survival after renal transplantation. *J Am Soc Nephrol.* 2006;7:3889–3899.

6. Weir MR. Hypertension and the kidney: perspectives on the relationship of kidney disease and cardiovascular disease. *Clin J Am Soc Nephrol.* 2009;4:2045–2050.

7. Cross N, Webster A, Masson P, O'Connell P, Craig J. Antihypertensives for kidney transplant recipients: systematic review and meta-analysis of randomized controlled trials. *Transplantation.* 2009;88:7–18.

8. Knight S, Morris P. Steroid avoidance or withdrawal after renal transplantation increases the risk of acute rejection but decreases cardiovascular risk: a meta-analysis. *Transplantation.* 2010;89:1–14.

9. Matas AJ. Minimization of steroids in kidney transplantation. *Transplant Int.* 2009;22:38–48.

10. Steiner R, Awdishu L. Steroids in kidney transplant patients. *Semin Immunopathol.* 2011;33:157–167.

11. Lightenberg G, Hene R, Blankestijn P, Koomans H. Cardiovascular risk factors in renal transplant patients: cyclosporin A *versus* tacrolimus. *J Am Soc Nephrol.* 2001;12:368–373.

12. Artz M, Boots J, Lightenberg G, et al. Improved cardiovascular risk profile and renal function in renal transplant patients after randomized conversion from cyclosporine to tacrolimus. *J Am Soc Nephrol.* 2003;14:1880–1888.

13. Vanrenterghem Y, Bresnahan B, Campistol J, et al. Belatacept-based regimens are associated with improved cardiovascular and metabolic risk factors compared with cyclosporine in kidney transplant recipients (BENEFIT and BENEFIT-EXT studies). *Transplantation.* 2011;91:976–983.

14. Diabetes Australia: Awareness, prevention, detection, management, and a cure. Diabetes Australia Web site. March 15, 2012. http://www.diabetesaustralia.com.au/Understanding-Diabetes/Diabetes-in-Australia/. Accessed June 28, 2012.

15. Wiesbauer F, Heinze G, Regele H, et al. Glucose control is associated with patient survival in diabetic patients after renal transplantation. *Transplantation.* 2010;89:612–619.

16. Valderhaug TG, Hjelmasaeth J, Hartmann A, et al. The association of early post-transplant glucose levels with long-term mortality. *Diabetologia.* 2011;54:1341–1349.

17. Thomas MC, Moran J, Mathew TH, Russ GR, Rao MM. Early peri-operative hyperglycaemia and renal allograft rejection in patients without diabetes. *BMC Nephrol.* 2000;1:1–1.

18. Frei U, Daloze P, Vitko S, et al. Acute rejection in low-toxicity regimens: clinical impact and risk factors in the Symphony study. *Clin Transplant.* 2010;24:500–509.

19. Zelle D, Corpeleijin E, Stolk R, et al. Low physical activity and risk of cardiovascular and all-cause mortality in renal transplant recipients. *Clin J Am Soc Nephrol.* 2011;6:898–905.

20. Avery RK, Michaels MG. Strategies for safe living following solid organ transplantation. *Am J Transplant.* 2009;9:S252–S257.

21. Kotton CJ, Ryan ET, Fishman JA. Prevention of infection in adult travelers after solid organ transplantation. *Am J Transplant*. 2005;5:8–14.

22. Steele RW. Should immunocompromised patients have pets? *Ochsner J.* 2008;8:134–139.

23. Webster AC, Craig JC, Simpson JM, Jones MP, Chapman JR. Identifying high risk groups and quantifying absolute risk of cancer after kidney transplantation: a cohort study of 15,183 recipients. *Am J Transplant.* 2007;7:2140–2151.

24. Kiberd BA, Rose C, Gill JS. Cancer mortality in kidney transplantation. *Am J Transplant.* 2009;9:1868–1875.

CME/CE Post Test

Using this page as a worksheet, select the best answer to each question based on your reading of the articles in this issue of *The Immunology Report,* then complete the evaluation on page 29 and see the instructions below it to obtain CME/CE credit.

1. The most sensitive and specific assay for detecting antibodies in renal transplant recipients is the:
   a. Solid-phase assay (eg, ELISA)
   b. Flow cytometry cross-matching
   c. Cytotoxicity assay (eg, CDC test)
   d. Latex agglutination test

2. Which of the following statements is *true?*
   a. Biopsy is useless in detecting antibody-mediated rejection (AMR) among patients with donor-specific antibodies (DSA).
   b. Baseline DSA levels correlate with the risk of early and late alloantibody-mediated allograft injury.
   c. Elevated DSA levels persist more rarely in patients who experience graft loss than in those with preserved renal function.
   d. Production of panel reactive lymphocytic antibodies in renal transplant patients is associated with long-term graft outcome.

3. Treatment with _____ has been shown to be effective against AMR and acute cellular rejection with minimal toxicity and results in sustained reduction in both immunodominant and non-immunodominant DSA levels.
   a. Intravenous immune globulin
   b. Cyclosporine
   c. Rituximab
   d. Bortezomib

4. Transplant patients currently taking a calcineurin inhibitor and _____ would likely benefit from a switch to an mTOR inhibitor such as everolimus.
   a. At risk for new-onset diabetes
   b. Having poor graft function
   c. Having a history of leukemia
   d. At high risk of cytomegalovirus disease

5. When compared with control patients taking cyclosporine, patients in the BENEFIT and BENEFIT-EXT trials who were treated with belatacept showed increases in:
   a. Serum lipids and triglycerides
   b. Glomerular filtration rate
   c. Systolic blood pressure
   d. Diastolic blood pressure

6. A fundamental difference between Risk Evaluation and Mitigation Strategies (REMS) put forward by the 2007 US Food and Drug Administration (FDA) Amendments Act (FDAAA) and previous postmarketing safety programs is:
   a. The FDA approves REMS for every drug marketed.
   b. The REMS do not require drug manufacturers to report potential adverse reactions that occur after drug approval.
   c. The FDAAA enabled and empowered the FDA to sanction drug manufacturers who do not comply with REMS requests.
   d. The REMS apply to new drug applications only.

7. A component of REMS that requires healthcare providers prescribing a drug to have particular training, experience, or certifications is:
   a. Elements to Assure Safe Use
   b. Risk-Benefit Ratio Assessment
   c. Risk Minimization Action Plans
   d. Professional Development and Accountability Licensing

8. Currently, the mainstay of antihypertensive treatment for patients who have undergone organ transplantation is:
   a. Angiotensin-converting enzyme inhibitors
   b. Dihydropyridine calcium-channel blockers
   c. Angiotensin receptor blockers
   d. Thiazide diuretics

9. Which of the following types of antidiabetic drugs generally are contraindicated for use in transplant patients?
   a. Insulins
   b. Sulfonylureas
   c. Biguanides
   d. Thiazolidinediones

10. Patients awaiting organ transplant may receive varicella vaccine if they:
   a. Already have received measles-mumps-rubella vaccine
   b. Already received tetanus-diphtheria-pertussis vaccine
   c. Are taking sirolimus or belatacept for immunosuppression
   d. Are vaccinated more than 4 weeks before transplant surgery

Evaluation

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

	Strongly agree	Agree	Disagree
1. As a result of this activity, I am more knowledgeable about …			
a. Antibody-mediated rejection, its early detection and diagnosis, and current trends in its management in renal transplant patients at risk.	❑	❑	❑
b. The advantages and disadvantages of conventional and novel immunosuppressants for preventing graft rejection.	❑	❑	❑
c. The background and clinical implications of the FDA's development of Risk Evaluation and Mitigation Strategies (REMS) to minimize the risks of drug therapy.	❑	❑	❑
d. The key issues involved in long-term care of transplant patients in regard to avoiding infection, maintaining cardiovascular health, managing diabetes, and cancer prevention and screening.	❑	❑	❑

	Strongly agree	Agree	Disagree
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.	❑	❑	❑

	Yes	No	Don't know
3. Did the information you received from this CME/CE 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?	❑	❑	❑

	Patient management	Board review	CME/CE credit
4. I used the information in this CME/CE activity for … *(check all that apply)*	❑	❑	❑

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

Instructions for Obtaining CME/CE Credit or Contact Hours

To receive CME/CE credit or contact hours for this free educational activity and a certificate from the CME/CE provider:

- Study the educational material presented in this issue of *The Immunology Report.*
- Using page 28 as a worksheet, answer all of the post-test questions based on the content of the articles in this issue.
- Visit **www.ImmunologyReport.com** on the Web by September 15, 2013 (for pharmacists, September 14, 2015), click CME/CE Credit, read the information provided, and then click the appropriate link for physicians, nurses, pharmacists, or case managers to apply for credit or contact hours and take the post test and evaluation.
- The full text of each article is available at the ImmunologyReport.com Web site, should you need to refer to it again.