The presence of donor-specific antibodies in kidney recipients is a significant hurdle to successful organ transplantation with good long-term outcomes. Although this is a well-accepted fact, the clinical significance of different levels of these antibodies has been unclear. Now, new research indicates that recipients who have even very low levels of preformed antibodies directed against a donated kidney have a significantly increased risk of acute rejection and graft failure. The findings, which are published in the Journal of the American Society of Nephrology, could help physicians determine better donor-recipient matches and tailor recipients’ immunosuppressive therapy after transplantation.

“Our study reviews disparate findings across different patient cohorts of varying levels of immunological risk and for the first time demonstrates a universally applicable risk stratification using the results of the various currently available immunological testing,” said first author Sumit Mohan, MD, of Columbia University.

Detecting antibodies
Transplant recipients who have had previous transplants, blood transfusions, and other sensitizing events often have antibodies directed against a particular donor’s kidney. Many studies have examined the risks associated with the presence of such donor-specific antibodies in transplant recipients, and there are conflicting reports of the clinical significance of antibodies detected by newer, more sensitive solid-phase assays, especially when the results of more traditional tests such as flow cytometry crossmatching are negative.

“This has been confusing and has limited our ability to understand and develop standard clinical management for patients with donor-specific antibodies at the time of transplantation while at the same time potentially preventing transplantation of certain donor-recipient pairs,” said Mohan. Understanding the true level of risk in patients with antibodies detected by different techniques is essential to optimizing outcomes after transplantation.

Even Low Levels of Donor-Specific Antibodies Adversely Affect Kidney Allograft Outcomes

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The recently released Government Accountability Office (GAO) report, "End-Stage Renal Disease: Reduction in Drug Utilization Suggests Bundled Payment is Too High," has generated controversy within the kidney community. Focused on erythropoiesis-stimulating agent (ESA) utilization, the report comes at a time when a potential rebasing of the bundled payment rate is already creating uncertainty and concern. The report introduces additional controversy by recommending reducing that payment rate quickly and dramatically.

“As the Medicare ESRD Prospective Payment System—more commonly known as “the bundle”—and the Quality Incentive Program (QIP) enter their third year of operation, rebasing the bundle is a front-and-center issue for the nephrology community. At press time, it was not entirely clear which part of the federal government—Congress or the Centers for Medicare & Medicaid Services (CMS)—will drive that process, or when. It remains to be seen to what extent CMS’s slated 2014 addition of oral-only drugs to the bundle, recommendations from government entities such as the GAO and the
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GAO Report

Continued from page 1

Medicare Payment Advisory Commission (MedPAC), or congressional efforts to find broad savings propositions, or some combination thereof, could influence a potential rebasing in 2013. CMS implemented the new bundled payment system and the QIP—the first-ever mandatory value-based purchasing program in Medicare—in 2011. The transitional implementation phase will be completed on January 1, 2014, when the bundle will be expanded to include payment for certain “oral-only” drugs that do not have injectable equivalents, which are currently covered under Medicare Part D. In theory, next January’s deadline means that the methodology for calculating the base payment rate should be adjusted and a new bundled payment value set to account for these additional drugs before 2014 begins.

To date, however, CMS has not determined the methodology it will use to incorporate oral-only drugs into the bundled payment, and it is unclear whether the agency has the legal authority to do so. The December GAO report highlighted CMS’s statement that “did not have immediate plans to rebase the rate and that the statute does not provide CMS with explicit authority to do so.” Although the Medicare Improvements for Patients and Providers Act of 2008 (MIPPA) did not explicitly authorize CMS to rebase the payment rate to account for changes over time in the utilization of dialysis and related items and services, such as ESRD drugs, it did not explicitly prohibit CMS from doing so.

MIPPA does require CMS to update the payment amount to account for changes in the prices of items and services already included in the bundle and for changes in productivity. CMS increased the rate by 2.1 percent in 2012 and recently announced its intention to increase it by 2.3 percent in 2013.

Who actually has the authority to order a rebasing of the bundle is not the only debatable issue. Generating considerable controversy are GAO’s finding that ESRD drug utilization in 2013 was about 23 percent lower than in 2007, that the bundle will include drugs reimbursed at rates that are currently covered under Medicare Part D. In theory, next January’s deadline means that the methodology for calculating the base payment rate should be adjusted and a new bundled payment value set to account for these additional drugs before 2014 begins.

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GAO posited that Medicare payments for dialysis services would have been about $550 million lower in 2011 if the bundled payment amount reflected average ESRD drug utilization in that year (rather than utilization in 2007, the year used for calculating the current bundled payment rate). GAO stated “our findings suggest that the current bundled payment rate is excessive given recent changes in ESRD drug utilization.” The GAO report was narrowly focused, examining just one aspect of care—anaemia management—rather than the complete scope of products and services that go into providing dialysis that the bundle encompasses.

“By examining only one component of care, we concluded that because there are many other components that are necessary to deliver the highest quality care for dialysis patients,” said Robert Sepucha, senior vice president for policy and business development at Fresenius Medical Care North America. He added the report “also failed to take the true cost of a given component has two variables: price and utilization. In focusing solely on declination utilization without any regard to the rising costs of ESAs, the report provided an incomplete and ultimately inaccurate view of the bundle.

The finding that ESRD drug utilization has declined in the past 5 years is not new. Several studies—including those from the Dialysis Outpatient Practice Monitor System (DOPPS) and the United States Renal Data Service (USRDS)—have recently found that ESRD drug utilization, particularly ESA use, has declined since 2007. MedPAC also reported in December 2012 that ESA use had declined in recent years. Nonetheless, MedPAC, which assessed ESAs as well as many other components of dialysis care, concluded that the payment system is too new to consider rebasing at this time.

“MedPAC actually reviewed a more complete set of data for dialysis facilities than the GAO and is not recommending any of the dramatic cuts GAO is proposing,” said Katrina Russell, president of the National Renal Administrators Association (NRAA).

The reasons behind the decline in ESA use are complex and still not fully understood. “The cause of reduced ESA use is undoubtedly multifactorial,” observed ASN Public Policy Board Chair Thomas H. Hostetter, MD.

“In 2011, the Food and Drug Administration changed the ESA label, eliminating a safe lower target dose, and it appears that nephrologists acted accordingly by reducing ESA use,” Hostetter said. “Several studies showing the risk of targeting high hemoglobin in recent years also likely contributed to a decline in ESA use, and then you do have the bundled payment and the QIP. So it is very challenging, at least at the present time, to conclusively draw out what is really driving this reduction. Most important, it is still unclear what effect the reduction may have on long-term patient outcomes—beneficial, neutral, or harmful.”

The Dialysis Patient Citizens (DPC) is urging caution in implementing the report’s conclusions, according to DPC Executive Director Hrant Jamgochian.

“As noted in the report, the patient impact of this decline is unclear,” Jamgochian said. “While early evidence suggests that the incidence of stroke and heart attacks has declined with decreasing ESA use, there has been an increase in blood transfusion rates, which can adverse health effects on patients and can limit access to successful kidney transplant. Before knowing the full patient impact of these changes, we caution policymakers not to ask too hastily to reinforce this decreased utilization by adjusting reimbursement rates downward.”

NRAA’s Russell added that “making cuts of the magnitude GAO is recommending would impose great financial strain on small dialysis organizations and could lead to fewer choices and access to care problems for patients.”

While the nephrology community is in agreement that the exact causes of the decrease in ESA use and its effect on patients remain unknown, the notion that CMS may be paying for more ESRD drugs than are being used attracted the attention of some members of Congress, even ahead of the GAO report. The report’s release has likely increased the possibility that Congress would consider rebasing the bundle and claim any savings to help cover the cost of a year-end legislative package.

Given the vulnerable patient population the Medicare ESRD Program serves, there is considerable concern that legislative rebasing of the bundle—earlier than anticipated in the life cycle of the new payment system—could create serious unintended consequences for patients. “The ESRD bundled payment system is new, complex, and still in the implementation phase, with many changes, including adding oral medications into the bundle in 2014, making it even more complex,” said Allen Nissenson, MD, chief medical officer at DaVita.

“Complete, rigorous, and valid data are required to ensure that any adjustments to the payment system that are made in the future are justifiable, appropriate, and are in the best interests of patient clinical outcomes. Data meeting these requirements are not yet available.”

At press time, it remained possible that Congress could legislate a rebasing of the bundle and use the savings it prescribes as a budgetary offset as it attempts to address the fiscal cliff, the Sustainable Growth Rate, and other costly issues. Congress asked the Congressional Budget Office (CBO) to estimate how much savings could be obtained by rebasing the bundle at this time. CBO’s estimate will play a significant role in determining Congress’ appetite for pursuing rebasing, because the legislative branch is likely to focus on “big” savings rather than squanderer time and political capital negotiating smaller-ticket provisions.

“There is no question that Medicare’s reimbursement rate needs to accurately reflect the total cost of care,” said Fresenius’ Sepucha. “Should a rebasing occur, we believe the experts at CMS should lead the process so it is done thoughtfully and comprehensively. But that process should not be undertaken hastily, nor should it be done in a vacuum.”

Said Hostetter: “Any rebasing of the bundle needs to be thoughtful and transparent, examine every component of high-quality care, and provide opportunities for input from patients, health professionals, and other experts. ASN will continue to collaborate with other stakeholders in the nephrology community to advocate that any future rebasing be conducted through a CMS rulemaking process that meets these criteria. Rebasin the bundle in search of savings is not something that Congress should attempt based on one report that largely examined just one of the many, many components of care for our complex patients.”

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To determine this risk, Mohan and his colleagues sifted through the medical literature to find studies that assessed donor-specific antibodies and health outcomes in kidney transplant recipients. Their search identified seven retrospective cohort studies that included 1119 patients. These studies included patients who were shown to be negative for donor-specific antibodies by flow cytometry crossmatching. They compared patients with and without donor-specific antibodies detected by solid-phase assays at the time of transplantation. The analysis allowed the investigators to define the level of risk for acute antibody-mediated rejection and allograft failure in patients with donor-specific antibodies relative to patients without.

Determining risk

After analyzing the results of these studies, the investigators determined that the detection of donor-specific antibodies by newer solid-phase assays—despite negative results from older tests—nearly doubles the risk for acute antibody-mediated rejection and increases the risk of graft failure by 76 percent. (The absolute risk of failure in the first year in the United States is currently about 8.2 percent for first-time recipients and about 10.7 percent for recipients of repeated transplants.)

Previously reported cohorts of patients who were tested only with the most recent solid-phase assays were more heterogeneous than previously thought, the authors found. These cohorts included patients who would have been identified as being at risk by flow cytometry; as a result, these cohorts have tended to have a much higher risk of acute antibody-mediated rejection and allograft failure than patients who were tested only with the older tests. The investigators determined that the most recent solid-phase assays were better at identifying patients who were at risk by flow cytometry crossmatching.

“The article is an important reminder that donor-specific antibodies are clinically relevant, the treatment protocols are heterogeneous, and the available evidence is limited,” said Dorry Segev, MD, PhD, who was not involved with the research and is a transplant surgeon at the Johns Hopkins School of Medicine. Segev is an expert in issues related to incompatibility kidney transplantation and organ allocation. “The problem of sensitization to donor-specific antibodies is not going away, but rather is getting worse, and will not be solved by paired donation alone. The findings provide strong motivation for the creation of large multicenter cohorts to better study treatment protocols and center-specific effects in kidney transplantation across donor-specific antibody barriers,” he added.

Nearly 17,000 kidney transplantations take place each year in the United States.

Study coauthors include Demetra Tsapapas, PharmD, Bekir Tantirov, MD, R. John Crew, MD, Geoffrey Dube, MD, Lloyd E. Ratner, MD, David Cohen, MD, and Jai Radhakrishnan, MD.

Disclosures: The authors reported no financial disclosures.


Donor-Specific Antibodies

Continued from page 1

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Regenerative Medicine and Bioartificial Kidneys Could Aid Shortage of Donor Kidneys

For Giuseppe Orlando, MD, and Shuro Roy, PhD, 2012 was a year of milestones for their respective research programs that ultimately will help combat the critical shortage of donor organs for kidney transplantation. The year 2013 promises to bring their work to further fruition. Scientiﬁc advances suggest that bioengineered and artificial kidneys may not be far in the future. Falling prices for genetic sequencing may bring a brave new world of individualized medical care sooner than we thought. From policy to practice, nephrology is changing. Here are some of the things we will be watching in 2013.

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2013: The Year Ahead

The new year promises to be filled with change. As the Affordable Care Act unfolds, healthcare will move toward accountable care organizations and medical homes. The Food and Drug Administration considers new endpoints for kidney drugs, perhaps facilitating entry into the market. Scientific advances suggest that bioengineered and artificial kidneys may not be far in the future. Falling prices for genetic sequencing may bring a brave new world of individualized medical care sooner than we thought. From policy to practice, nephrology is changing. Here are some of the things we will be watching in 2013.

Regenerative Medicine and Bioartificial Kidneys Could Aid Shortage of Donor Kidneys

For Giuseppe Orlando, MD, and Shuro Roy, PhD, 2012 was a year of milestones for their respective research programs that ultimately will help combat the critical shortage of donor organs for kidney transplantation. The year 2013 promises to bring their work to further fruition. Orlando, a transplant surgeon and scientist, headed the Wake Forest Institute for Regenerative Medicine research team that succeeded in creating acellular renal extracellular matrix (ECM) scaffolds through decellularization-recellularization technology. The scaffolds were applied to whole porcine kidneys. “These kidneys maintained their innate three-dimensional architecture as well as their vascular system and may represent the ideal platform for kidney engineering,” said Orlando, who reported the research in the journal Annals of Surgery. His goal is a bioengineered kidney that could be manufactured from the patient’s own cells.

For Roy, a bioengineer in the University of California at San Francisco’s (UCSF) Department of Bioengineering and Therapeutic Sciences, the goal is not to generate new renal tissue but to design reliable implantable renal assist devices—bioartificial kidneys—for end stage renal disease (ESRD) patients. Last year, the U.S. Food and Drug Administration (FDA) selected the UCSF bioartificial kidney for its Innovation Pathway 2.0, because of the device’s “transformative potential” in ESRD and “its potential to benefit from early interactions with the FDA in the approval process,” according to the university.

Roy and the project’s medical director, William H. Fissell, MD, associate professor of clinical medicine, Vanderbilt University Medical Center, have been working for about 10 years with a multidisciplinary team of 40 researchers in nine U.S. laboratories to develop the bioartificial kidney, aiming for clinical trials by 2017.

Could donated kidneys produce scaffolds for populating ESRD patients’ own cells?

Orlando, who was an invited lecturer in the “Bioengineering and Informatics: Curating Renal Disease with Cells and Devices” session at Kidney Week 2012, implanted the acellular scaffolds in pigs and one
Reducing the burden of ESA administration

Consider the first once-monthly, non-EPO ESA offering less-frequent dose administration.

INDICATION AND LIMITATIONS OF USE
OMONTYS® (peginesatide) Injection is indicated for the treatment of anemia due to chronic kidney disease (CKD) in adult patients on dialysis.

OMONTYS is not indicated and is not recommended for use in patients with CKD not on dialysis, in patients receiving treatment for cancer and whose anemia is not due to CKD, or as a substitute for red blood cell (RBC) transfusions in patients who require immediate correction of anemia. OMONTYS has not been shown to improve symptoms, physical functioning, or health-related quality of life.

IMPORTANT SAFETY INFORMATION

WARNING: ESAs INCREASE THE RISK OF DEATH, MYOCARDIAL INFARCTION, STROKE, VENOUS THROMBOEMBOLISM, THROMBOSIS OF VASCULAR ACCESS AND TUMOR PROGRESSION OR RECURRENTE. Chronic Kidney Disease:

• In controlled trials, patients experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered erythropoiesis-stimulating agents (ESAs) to target a hemoglobin level of greater than 11 g/dL.
• No trial has identified a hemoglobin target level, ESA dose, or dosing strategy that does not increase these risks.
• Use the lowest OMONTYS dose sufficient to reduce the need for RBC transfusions.

Contraindications
OMONTYS is contraindicated in patients with uncontrolled hypertension and in patients who have had serious allergic reactions to OMONTYS.

Warnings and Precautions
Increased mortality, myocardial infarction, stroke, and thromboembolism:

• Using ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and stroke. Patients with CKD and an insufficient hemoglobin response to ESA therapy may be at even greater risk for cardiovascular reactions and mortality. A rate of hemoglobin rise of ≥1 g/dL over 2 weeks may contribute to these risks.

• In controlled clinical trials of ESAs in patients with cancer, increased risk for death and serious adverse cardiovascular reactions including myocardial infarction and stroke was observed.

• There is increased mortality and/or increased risk of tumor progression or recurrence in patients with cancer receiving ESAs.

• In controlled clinical trials of ESAs, ESAs increased the risk of death in patients undergoing coronary artery bypass graft surgery (CABG) and deep venous thrombosis (DVT) in patients undergoing orthopedic procedures.

• In 2 trials of OMONTYS, patients with CKD not on dialysis who had experienced increased specific cardiovascular events.

Hypertension (see Contraindications): Appropriately control hypertension prior to initiation of and during treatment with OMONTYS. Reduce or withhold OMONTYS if blood pressure becomes difficult to control.

Serious allergic reactions (see Contraindications): Serious allergic reactions have been reported with OMONTYS. Immediately and permanently discontinue OMONTYS and administer appropriate therapy if a serious allergic reaction occurs.

Lack or loss of response to OMONTYS: Initiate a search for causative factors. If typical causes of lack or loss of hemoglobin response are excluded, evaluate for antibodies to peginesatide.

Dialysis management: Patients receiving OMONTYS may require adjustments to dialysis prescriptions and/or increased anticoagulation with heparin to prevent clotting of the extracorporeal circuit during hemodialysis.

Laboratory monitoring: Evaluate transferrin saturation and serum ferritin prior to and during OMONTYS treatment. Administer supplemental iron therapy when serum ferritin is less than 100 mcg/L or when serum transferrin saturation is less than 20%. Monitor hemoglobin every 2 weeks until stable and the need for RBC transfusions is minimized. Then, monitor monthly.

Adverse reactions
Most common adverse reactions in clinical studies in patients with CKD on dialysis treated with OMONTYS were dyspnea, diarrhea, nausea, cough, and arteriovenous fistula site complication.

Please see accompanying Brief Summary.
models. Multiple models could help facilitate the participation of a diverse range of provider types and locations so that it may be possible to encourage participation in different care environments to benefit. ASN and other patient and health professional organizations have also advocated that at least one pilot or demonstration project should include “upstream” patients with late-stage chronic kidney disease (CKD) in addition to patients with end stage renal disease (ESRD). Also unknown is how “prescriptive” an RFP might be; would CMMI specifically delineate the components it wants to see in a pilot or demo, or will applicants be encouraged to innovate independently, proposing a diversity of care delivery strategies?

• How many entities respond to the RFP and, ultimately, how many patients have the opportunity to receive care in these cutting-edge new care delivery pilots or demos.

Table 2

<table>
<thead>
<tr>
<th>Time Period of Trial</th>
<th>Nitrendipine</th>
<th>Diltiazem</th>
<th>Placebo</th>
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<td>1993 to 1996</td>
<td>14.0 (11.0)</td>
<td>13.5 (11.3)</td>
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<td>13.5 (11.3)</td>
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<tr>
<td>2004 to 2009</td>
<td>14.0 (11.0)</td>
<td>13.5 (11.3)</td>
<td>13.0 (11.3)</td>
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Regarding what a final pilot or demonstration project will look like, there is considerable excitement within the nephrology community as well as within the Innovation Center that a nephrology-specific integrated nephrology care delivery model could foster transformative improvements in patient care and produce valuable lessons for other areas of medicine—such as oncology—that may look to develop integrated care delivery models in the future.
Genomic Medicine: the Trek Toward the Clinic

Significant advances will occur in genomic medicine to monitor and treat diseases over the next few years, predicts Eric D. Green, MD, PhD, director of the National Human Genome Research Institute (NHGRI). After 2020, those advances will have an impact on improving the effectiveness of health care, but it will be a "long, hard process," Green said.

"We have a long way to go to fully understand the human genome," Green said. The Human Genome Project was "a starting line and by no means the end." Unraveling the genetic risk factors for common complex diseases like diabetes, heart disease, and cancer will continue to be a priority because these diseases represent a major health care burden. "The lowest hanging fruit is cancer genomics," Green said.

Green gave a state-of-the-art lecture, "Entering the Era of Genomic Medicine: Research Opportunities and Challenges," at Kidney Week 2012 in San Diego. The scientific community currently has only a Cliff Notes view of the functional landscape of the human genome. To change the view from Cliff Notes to encyclopedic, NHGRI sponsors the ENCODE (ENCyclopedia Of DNA Elements) project to compile a comprehensive catalog of functional elements that control the expression of genetic information in a cell.

ENCODE was launched just a few months after the 2003 completion of the Human Genome Project. During the post-Human Genome Project era, scientists have learned that the "whole story" cannot be told by the primary DNA sequence alone, Green said. Epi-genetic factors that "decorate the DNA sequence," to modify the expression, or activity, of specific genes are another major player in the genome.

Less than 2 percent of the human genome contains the 20,000 genes that encode proteins. The remaining 98 percent encode transcription factors and other elements, not all of which are known. The "non-protein parts" are not as well understood as the protein-coding genes, Green said. But they will continue to attract more attention because mutations in the non-protein parts, not the protein-coding genes, are the main DNA contributors to risk for developing commonly occurring, non-Mendelian, multi-genetic diseases such as kidney disease, diabetes, hypertension, cardiovascular disorders, and cancer.

In contrast, the rare, single-gene Mendelian disorders such as cystic fibrosis are caused by mutations in the protein-coding genes, Green said.

To jumpstart the discovery of risk variants for commonly occurring diseases, NHGRI has funded several large research programs, including the Genome Wide Association Study (GWAS), the HapMap Project, and the 1,000 Genomes Project.

Yet scientists' ability to store, analyze, and interpret data has not advanced as quickly as the sequencing technologies that can decipher exomes, the protein-coding genes, and whole genomes.

"The numerous DNA sequences that have been deciphered since 2003 combined with new information about the genomic architecture of disease is massive," Green said, and "is the largest current bottleneck" in genomic medicine.

"We have a big data problem," he said. "We are victims of our own success." Less than a decade ago it took 3 to 4 months and $10 million to $50 million to decipher the human genome. Today an individual's genome can be sequenced in three to four days for $4000 to $8000. Soon it will cost $1000, Green said, enabling the widespread application of DNA sequencing in the clinic as well as the lab.

A second bottleneck likely to be addressed in coming years is information dissemination. Including clinical genomics information systems in electronic health records systems may be one approach.

"Physicians are still a long way from submitting their patients' full genomes for sequencing, not because the price is high, but because the data are difficult to interpret," wrote Nobel laureate Harold Varmus, MD, a former Director of NIH and now head of the National Cancer Institute in Genome Medicine.
The 2013 Outlook for Research Funding

By Grant Olan

Current federal deficit reduction efforts could lead to more cuts to U.S. medical research funding. Since the November 2012 election, Congress has been consumed with averting the “fiscal cliff” on January 2, 2013.

As of press time, Congress and President Obama had not reached a deal, but most experts agree that one would be made either before or after the January deadline. If before, the agreement would most likely employ a two-step process whereby Congress would agree with the president to allow the 2003 tax cuts to expire for the top 2 percent of wage earners and postpone the automatic $1.2 trillion across-the-board cuts to federal discretionary programs for the first 6 or 9 months in 2013 to allow time to identify areas in the federal budget for savings or cuts and to revise the tax code.

If the United States goes over the fiscal cliff before Congress and the president reach a deal, other issues will come to the forefront that must be dealt with: principally, funding the remainder of the Fiscal Year (FY) 2013 budget that expires on September 30, 2013, and raising the “debt ceiling” before the United States reaches the legal limit of how much debt the federal government can assume. Congress will also take up FY 2014 budget and appropriations bills in the spring.

As Congress and the president deal with all of these issues, ASN will be on the front lines to remind lawmakers that medical research has already done its part and that more cuts to research funding will not balance the budget.

“ASN is greatly concerned that more cuts are on the horizon for the National Institutes of Health (NIH) and medical research at other federal agencies as talks intensify on the U.S. budget and debt ceiling,” said ASN Research Advocacy Committee Chair John Sedor, MD.

The White House Office of Management and Budget (OMB) projected NIH would see another cut of $2.5 billion, or 8.2 percent, and the loss of up to 2,300 research grants if there is no deal to avert the fiscal cliff. National Cancer Institute Director Harold Varmus, MD, claims cancer research would actually sustain cuts closer to 40 percent since NIH has decided to fund administrative costs and current obligations before new grants in the event the United States goes over the fiscal cliff.

Whether 8.2 percent or 40 percent, NIH Director Francis Collins, MD, PhD, declared that the cuts “would be devastating for many investigators who are seeking to continue programs that they have had funded in the past and are back for their competing renewal, or who are starting things that are entirely new; and I think the burden would hit particularly heavily upon first-time investigators who are seeking to get their programs up and going.”

Today, only one in six applications (18 percent) are approved for NIH research funding—an all-time low—and the average age of a scientist receiving their first grant is 40 years. More cuts to medical research would not only mean the loss of promising research, they could jeopardize the position of the United States as the global leader in research, with countries such as China doubling down on investment in this area. For these reasons, ASN has been aggressively advocating for a balanced approach to deficit reduction that does not rely on further cuts to research.

Funding for patient outcomes at risk?

Cuts would also hamper other research agencies like the Patient-Centered Outcomes Research Institute (PCORI) established by the 2010 Affordable Care Act (ACA). PCORI’s mission is to help “fund research that will provide patients, their caregivers, and clinicians with the evidence-based information needed to make better-informed health care decisions.”

Although the Supreme Court upheld the constitutionality of the ACA last June, funding for PCORI would still be subject to sequestration (the technical term for the fiscal cliff). The White House OMB estimated in September that the Patient-Centered Outcomes Research Trust Fund, which funds PCORI, would be subject to a 7.6 percent cut, amounting to $90 million from the $390 million fund in FY 2013. Despite the uncertainty, PCORI continues to forge ahead. After laying groundwork and selecting research priorities in 2011 and 2012, PCORI is poised to begin tackling its mission in earnest in 2013 if its funding is not decimated by sequestration.

In May of 2012, PCORI adopted a revised “National Priorities for Research and Research Agenda” after considerable public input from many different stakeholders during a 54-day comment period. ASN recommended that PCORI consider kidney disease as a model for chronic disease research because kidney disease affects individuals throughout the human lifespan, as well as racial and ethnic minority populations. The care of pediatric and adult patients with CKD provides a model for care of patients with common diseases who have complex medical histories, multiple comorbidities, and are cared for in a variety of settings at a high cost. The full letter is available at http://www.asn-online.org/policy/.

PCORI adopted several of ASN’s suggestions, including a recommendation to make disparities in the development and progression of chronic illnesses, including CKD, a core research priority. In addition to addressing disparities, PCORI’s five national priorities include assessment of prevention, diagnosis, and treatment options; improving health care systems; communication and dissemination research; and accelerating patient-centered outcomes research and methodological research. The complete PCORI report is available at http://www.pcori.org/news-room/.

In November 2012, PCORI adopted 47 revised methodology standards to guide the conduct of patient-centered outcomes research. A full report, providing context for the revised methodology standards, will be available in the spring. Researchers conducting PCORI-funded studies will be required to adhere to the methodology outlined in this report.

Signaling a shift from planning-related activities to more research-oriented activities, PCORI also authorized the development of three research funding announcements in November. PCORI will support studying treatment options for uterine fibroids, the safety and benefits of interventional procedures, and the safety and benefits of treatment options for severe asthma, and fall prevention in the elderly. The agency is also currently considering input from the public on two additional topics for funding that it will announce in early 2013. More information about funding opportunities is available at http://www.pcori.org/funding-opportunities/.

As PCORI moves ahead with or without a fully funded budget, ASN will continue to advocate the importance of investments in research by all federal agencies that improve the health of kidney patients.
ASN and FDA Form the Kidney Health Initiative

ASN and the U.S. Food and Drug Administration (FDA) have joined forces to form the Kidney Health Initiative (KHI). Established through a memorandum of understanding signed in September 2012, KHI’s mission is to “advance scientific understanding of the kidney health and patient safety implications of new and existing medical products and to foster development of therapies for diseases that affect the kidney by creating a collaborative environment in which FDA and the greater nephrology community can interact to optimize evaluation of drugs, devices, biologics, and food products.”

“KHI represents an exciting undertaking by ASN and FDA to bring about long-needed interactions between all of the different health care stakeholders who are responsible for developing, delivering, and monitoring care for patients with kidney disease,” said ASN President Bruce Molitoris, MD, FASN. “Bringing together the different, often fractured, components of the health care industry into interdisciplinary interactions will promote innovation, hasten translation, and improve the quality of patient care and outcomes. As KHI begins operations in 2013, KHI will benefit stakeholders, including payers, but most importantly our patients.”

KHI has attracted attention from a diverse range of stakeholders in the kidney community, and at press time comprised nearly 20 member organizations. As KHI begins operations in 2013, how do stakeholders view its potential and what impact could KHI have on kidney research and patient safety?

KHI structure and scope

With up to 26 million Americans living with kidney disease, and given the disease’s serious health implications and economic burden, KHI’s creation is timely. During his President’s Address at ASN Kidney Week 2012, Ronald Falk, MD, FASN, introduced KHI to the kidney community by stating that the ASN-FDA partnership would “help write a new and exciting chapter in our fight against kidney disease.” KHI seeks to address the lack of new medications for kidney disease and improve patient safety by facilitating dialogue, developing efficient trial designs, drafting white papers, and creating a transparent infrastructure to facilitate communication and collaboration among the greater kidney community and the FDA. To learn more about KHI’s mission and objectives, please visit http://www.asn-online.org/khi/KHI_Mission.pdf. KHI is open to a wide variety of stakeholders, including patient and health professional organizations, pharmaceutical and biotechnology companies, device manufacturers, dialysis providers, foundations, research institutes, and U.S. and international government agencies. And because nephrologists collaborate with many other medical specialties, organizations representing these professionals (such as cardiovascular disease or diabetes) are eligible for KHI membership.

KHI’s public-private framework is a byproduct of FDA’s Critical Path Initiative (CPI), a blueprint to foster innovation in the development and evaluation of medical products. Other CPI partnerships include the Clinical Trials Transformation Initiative, the Medicare Device Innovation Consortium, and the Cardiac Safety Research Consortium (CSRC), which served as the template for KHI. A partnership between FDA and the Duke Clinical Research Institute, CSRC evaluates the cardiac safety profiles of new drugs and devices. Since 2006, CSRC has authored nine white papers, convened several think tanks, and created the CSRC ECG Warehouse—a database of electrocardiogram data that is an important resource for cardiac researchers.

“Although similar to CSRC, KHI differs in its structure and scope. ASN will serve as an equal partner with FDA on the KHI board of directors, which is headed by two co-chairs—one each from ASN and FDA. The board will also include voting members from each branch of FDA, as well as non-voting members from other federal agencies, including the National Institutes of Health, Centers for Disease Control and Prevention, and the Centers for Medicare & Medicaid Services. The inaugural KHI co-chairs are Prabir Roy-Chaudhury, MD, PhD, FASN, of the division of nephrology at the University of Cincinnati College of Medicine, and Patrick Archdeacon, MD, of the FDA’s Center for Drug Evaluation and Research. Roy-Chaudhury views KHI as an opportunity to improve nephrology’s “orphan status” in the areas of randomized controlled clinical trials and bringing new therapeutics to market. “This requires having all of the stakeholders—physicians, patient advocacy groups, industry, and, critically, FDA—at the same table working together to open pathways for getting the right drug, biologic, or device to the right patient in the right way,” he said.

“KHI is a forum where FDA can be more responsive to the nephrology community,” said Archdeacon, “and we’re looking forward to hearing from KHI members about what they perceive are the important issues and priorities.”

KHI focuses on bringing patients to the table distinguishes it from other CPI partnerships. “Having patients involved is absolutely critical,” said ASN co-chair Roy-Chaudhury. “They give KHI a different and much-needed perspective, because patients and patient advocacy groups often have the ability to quickly focus down on the key obstacles to better care, in a way that health care professionals may not be able to,” he added. The FDA co-chair Archdeacon agrees, noting “FDA, industry, and the entire nephrology community need to better understand the issues facing kidney patients, as experienced by the patients themselves. KHI will allow us to hear from the patients directly.”

In launching KHI, ASN and FDA personnel worked proactively to develop a strong and transparent policy regarding conflict of interest (COI) management and disclosure. KHI board members and working group participants are required to disclose and update COI disclosures for the duration of their involvement. Because some members will possess competitive interests, KHI has a clearly delineated plan for disclosing and managing COIs in the selection of, and participation in, KHI projects and activities, which is available at http://www.asn-online.org/khi/coi.aspx.

Stakeholder perspectives

Reaction among stakeholders in the kidney space to KHI’s creation has been uniformly positive. “I’m really excited to see this true collaboration between industry, practitioners, FDA, and patients—the end users who have the most important voice,” said Karen E. Ryals, executive director of the American Association of Kidney Patients. She views KHI as an opportunity to address patient safety issues, explore new avenues in treatment, and most importantly to improve communication not only between patients and kidney professionals but within care settings. “The kidney community can become segmented, but if we work in a collaborative spirit I believe a lot more will get done, which will benefit patients tremendously,” Ryals said.

“I believe those of us in industry are quite excited about KHI,” said Mark T. Houser, MD, of Abbott Laboratories. “From a drug development perspective, anything that improves dialogue and communication between the FDA and the pharmaceutical industry and, additionally, adds an important resource for cardiac researchers.”

These interactions should help identify areas where the needs for new therapies are the greatest, and also provide additional clarity to industry regarding a regulatory path which always reduces risk in drug development. However, given that drug development is a global process it will clearly be important to include other global regulatory agencies as KHI matures.”

Continued on page 12
Kidney Health Initiative

Continued from page 17

of retrospective or prospective data, as well as to establish data standards, offers an opportunity to maximize the information available from clinical trials conducted on these relatively small patient populations,” she said.

As a KHI pioneer member, the American Society of Diagnostic and Interventional Nephrology (ASDIN) has an opportunity to collaborate with ASN and FDA to nurture novel therapeutic strategies that meet patient care goals that all three entities share,” said Alexander S. Yezli, MD, ASDIN president-elect. "Interventional nephrology focuses primarily on vascular access, and ASDIN would like to be involved in the development of new care via novel therapeutic solutions and increased knowledge of vascular disease processes, he said.

Could KHI benefit FDA as well, in facilitating cross-talk among FDA’s different branches? Absolutely, said Archdeacon. "Because of the wide range of products and breadth of diseases that impact the kidney, there are numerous FDA review divisions that regulate products affecting kidney health that may not regularly interact with one another. "Having a single forum where we’re able to talk about nephrology and ways to facilitate innovation and renal safety also provides a good opportunity for the FDA to facilitate intramural interaction,” he said.

Moving research forward

What will KHI’s role be in the promotion and advancement of kidney research? Molitoris believes "KHI represents an opportunity to delineate the clinical aspects and quality measures that will be used to evaluate drugs, devices, biologics, and food products. This will help researchers—whether academics or industry, basic or clinical—target specific undertakings thereby facilitating development and delivery of new diagnostic and therapeutic advances. Once a specific disease aspect is identified as being a therapeutic endpoint, then efforts to hasten and approve diagnostic capabilities will be involved, whether with industry or FDA, and if the correct steps to rule out renal toxicity are identified, the review process can be accelerated because compounds could be vetted beforehand."

"In the area of patient safety, the scope and impact of KHI can extend well beyond the renal space.”

The next steps for KHI

KHI will appoint board members in 2013 who will be charged with reviewing candidate projects and activities, with the eye toward selecting one or two key projects that will be completed in a short timeframe, said Archdeacon. Roy-Chaudhury believes that the initial project(s) should be enablers of future, larger projects, for example, endpoints for clinical trials. "It would be wonderful to have one set of endpoints for clinical trials in a particular area of nephrology (vascular access or transplant, for example) that everybody—physician groups, FDA, and industry—all agree on.

How can ASN members become involved in KHI? "ASN members will play an important role in setting the course for the near term with regard to important undertakings for KHI,” said Molitoris. "In addition to serving on the board of directors, ASN members will be involved in subcommittees and working subgroups developing the informational material and approaches necessary to answer specific project questions.”

Roy-Chaudhury also sees KHI as a venue for ASN members to "channel their wealth of knowledge to facilitate the bench-to-bedside development of novel drugs, devices, and biologics, and also to provide direction, substance, and prestige to KHI.”

To learn more about KHI and how your organization can join, please visit http://www.asn-online.org/khi/, or contact the project director for KHI, Melissa West, at mwest@asn-online.org.

KHI Objectives

1. Facilitate dialog and research that informs regulatory processes with regard to the kidney health of patients being treated for kidney-related as well as other diseases.
2. Assess current medical therapies and diagnostics to identify areas in need of greater innovation and/or better defined regulatory pathways.
3. Develop innovative and efficient trial designs appropriate to answer the most important questions related to kidney health.
4. Establish expert consensus around common terminology and key definitions related to kidney health.
5. Develop approaches to the systematic collection of retrospective or prospective data, such as registries and/or global databases, and establishment of data standards.
6. Coordinate “think tanks,” public forums, educational exchanges, and other events to promote discussion and updates on topics in kidney health pertaining to drug, device, biologics, and food product development and evaluation.
7. Create transparent infrastructure and processes that facilitate collaboration and communication among the greater nephrology community and the FDA, including:
   - Seeking input from all stakeholders (including the FDA, industry, nephrologists and other health professionals, the public or patient groups, the National Institutes of Health, the Centers for Medicare and Medicaid Services, the Health Resources and Services Administration, and other federal agencies),
   - Leveraging previously conducted and ongoing clinical studies, research infrastructure, and databases,
   - Creating an open and efficient mechanism for encouraging and evaluating potential projects submitted to KHI and ensuring objective evaluation.
   - Involving consortium members in the selection and execution of projects.
8. Establish systems to optimize post-market surveillance of products that affect kidney health, either intentionally or via adverse drug reactions.
9. Draft white papers regarding key issues, describing opportunities and challenges and proposing solutions, as well as promoting execution of these solutions.
ASN Highlights 2013
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Topics covered include:
- Acute Kidney Injury
- Clinical Nephrology
- End-Stage Renal Disease
- Hypertension
- Parenchymal Disorders
- Transplantation

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Lower Blood Pressure Doesn’t Reduce Mortality in Type 2 Diabetes

Aggressive blood pressure reduction in the year after diagnosis of type 2 diabetes does not lead to a reduced risk of death, according to a study of primary care data in the British Medical Journal.

The researchers analyzed data from nearly 127,000 adult patients with type 2 diabetes newly diagnosed at U.K. general practices between 1990 and 2005. Systolic and diastolic blood pressures during the subsequent year were analyzed for association with mortality. Comparisons were made for patients with and without established cardiovascular disease—present in 9.8 percent of patients at baseline. Median follow-up was 3.5 years.

With adjustment for a wide range of baseline characteristics, “tight” control of blood pressure to less than 130/80 mm Hg was not associated with increased survival in patients with cardiovascular disease. For patients with systolic blood pressure of 110 mm Hg, the hazard ratio

For renal transplant patients...

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myfortic REFILL CALENDAR

- Multiple companies offer a generic version of CellCept® (mycophenolate mofetil)
  - Presently, there are 11 manufacturers of generic CellCept®
  - 11 different MMF tablets (500 mg) and 10 different MMF capsules (250 mg) are available
- myfortic is the only patent-protected MPA
  - Produced only by Novartis
  - 1 manufacturer in 1 facility

When you prescribe myfortic, your patients get myfortic... consistent from refill to refill

Consistency also comes with savings:

Start your patients with a 30-day free trial by visiting www.myfortic.com/jr2 or by calling the Novartis Monthly Co-pay Card® for eligible patients.

Help support your patients throughout their transplant experience by having them visit www.myfortic.com/jr2 where they can sign up to receive relevant educational information.

myfortic and CellCept or MMF should not be used interchangeably without physician supervision because the rate of absorption following the administration of these products is not equivalent.

myfortic®, CellCept® (mycophenolate mofetil), MPA, mycophenolic acid.

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Product coverage and program subject to change without notice.

Based on data from the myfortic Co-pay Savings Program. Initial prescription or refills based on 1-year (2011) transaction data for cash payment and insured patients combined.

Program is available to eligible patients taking myfortic® and is subject to change without notice. Not valid for patients whose prescriptions are paid for by Medicare, Medicaid, or other federally subsidized health care program, or for Massachusetts residents.

Indication: myfortic® (mycophenolic acid) delayed-release tablet is indicated for the prophylaxis of organ rejection in patients receiving allogeneic renal transplants, administered in combination with cyclosporine and corticosteroids.

Important Safety Information:

WARNING: EMBRYOFOetal TOXICITY, MALIGNANCIES, AND SERIOUS INFECTIONS

- Use during pregnancy is associated with increased risks of first trimester pregnancy loss and congenital malformations. Females of reproductive potential (FRP) must be counseled regarding pregnancy prevention and planning
- Immunosuppression may lead to increased susceptibility to infection and possible development of lymphoma and other neoplasms. Only physicians experienced in immunosuppressive therapy and management of organ transplant recipients should prescribe myfortic® (mycophenolic acid) delayed-release tablet. Patients receiving myfortic® should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient

myfortic® is contraindicated in patients with hypersensitivity to mycophenolate sodium, mycophenolic acid (MPA), mycophenolate mofetil (MMF), or to any of its excipients.

Please see additional Important Safety Information and Brief Summary of Prescribing Information, including Boxed WARNINGS, on adjacent pages.
for death was 2.79, compared to those with ‘usual control’—systolic blood pressure 130 to 139 mm Hg. For diastolic blood pressure, hazard ratios for death were 1.32 at 70 to 74 mm Hg and 1.89 at less than 70 mm Hg, compared to usual control of 80 to 84 mm Hg.

Lower blood pressure targets were also associated with increased mortality among patients without cardiovascular disease. Similar patterns were found on analysis of patients receiving treatment for diagnosed hypertension.

Aggressive blood pressure reduction has been recommended for high-risk patients with diabetes, cardiovascular disease, or kidney disease. The new data suggest that lowering blood pressure to less than 130/80 mm Hg may be associated with increased, rather than decreased, all-cause mortality. The risk may be greatest at blood pressures less than 110/75 mm Hg [Vamos EP, et al: Association of systolic and diastolic blood pressure and all-cause mortality in people with newly diagnosed type 2 diabetes: retrospective cohort study. BMJ 2012; 345: e5567].

Can ICU Chloride Restriction Lower AKI Risk?

A “chloride-restrictive” approach to fluid management may reduce the risk of acute kidney injury (AKI) in critically ill patients, according to a preliminary communication in The Journal of the American Medical Association.

In two sequential six-month periods, the researchers compared a chloride-restrictive versus a standard, “chloride-liberating”, strategy to intravenous fluid management. In the first treatment period, adults in a university ICU received standard intravenous fluids. This was followed by a six-month phase-out period. Then in the second treatment period, chloride-rich fluids were given only with approval of the attending specialist, with alternative fluids specified. Cases of AKI were defined by the injury and failure class of the risk, injury, failure, loss, end-stage (RIFLE) classification.

The standard strategy was used in 760 patients and the chloride-restrictive strategy in 773. Total chloride administration decreased from 694 to 496 mmol, per patient. The mean increase in serum creatinine was 22.6 µmol/L during the control period versus 14.8 µmol/L during the intervention period.

The incidence of RIFLE-defined AKI decreased from 14.0 percent during the control period to 8.4 percent during the intervention period. Use of renal replacement therapy (RRT) decreased from 10.0 to 6.3 percent. These effects remained significant on covariate adjustment: odds ratio 0.52 for both AKI and RRT. In hospital death, lengths of stay, and need for RRT after discharge were similar between groups.

Administration of chloride-containing intravenous fluids might contribute to the risk of AKI in critically ill patients. The new trial suggests that the use of a chloride-restrictive strategy might decrease this risk. While emphasizing the need for further study, the authors believe their results suggest the need to exert prudence in the administration of fluids with supra-physiological concentrations of chloride, especially in critically ill patients with evidence of early acute renal dysfunction or at risk of acute dysfunction [Yunos NM, et al: Association between a chloride-liberating vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. JAMA 2012; 308: 1556–1572].
Tacrolimus is approved for use in children with steroid-resistant nephrotic syndrome.

Questions are being raised about the effectiveness of asixtinib as a life-prolonging second-line treatment for patients with advanced cancer.

Manufactured by Pfizer and marketed as Intinta, asixtinib was approved in the United States in January 2012 and in Europe in September 2012. The U.K.’s National Institute for Health and Clinical Excellence (NICE), which provides guidance to the National Health Service (NHS), recently released a preliminary report recommending against the use of asixtinib as a second-line therapy for the treatment of advanced kidney cancer because of how comparisons with other treatments were conducted.

The preliminary decision by the independent Appraisal Committee of NICE was that asixtinib should not be recommended for kidney cancer treatment after first-line treatment failure with sunitinib (another kidney cancer drug from Pfizer marketed as Sutent) or a cytokine drug.

For children with nephrotic syndrome that does not respond to steroids, the combination of tacrolimus and prednisolone is preferable to cyclophosphamide, concludes a trial in Kidney International.

The randomized trial included 131 consecutive children with idiopathic steroid-resistant nephrotic syndrome at five pediatric nephrology units. Diagnoses included minimal change disease, focal segmental glomerulosclerosis, or mesangio proliferative glomerulonephritis. Patients were stratified for initial or late steroid resistance.

They were then assigned to tacrolimus, 0.1 to 0.15 mg/kg/day for 12 months; or cyclophosphamide. The two groups received equal doses of alternate-day prednisolone.

Defined according to spot urine protein-to-creatinine ratios, the rate of complete or partial remission at 6 months was 82.5 percent with tacrolimus versus 45.9 percent with cyclophosphamide: hazard ratio 2.64. Complete remission rates were 52.4 versus 14.8 percent, respectively. The tacrolimus group also had a higher 12-month rate of sustained remission or steroid-sensitive relapse.

More children withdrew in the cyclophosphamide group, mainly because of infections. To achieve one additional remission, the number needed to treat with tacrolimus was three.

There is no agreed-upon approach to the management of idiopathic steroid-resistant nephrotic syndrome in children. This multicenter trial strongly supports the combination of tacrolimus and prednisolone over cyclophosphamide.

The authors note that tacrolimus may cause acute nephro毒性, but this usually responds to dose reduction [Gulati A. et al: Treatment with tacrolimus and prednisolone is preferable to intravenous cyclophosphamide as the initial therapy for children with steroid-resistant nephrotic syndrome. Kidney Int 2012; 82: 1130-1135].

Myfortic® (mycophenolic acid®) delayed-release tablets * as mycophenolic acid sodium

INDICATIONS AND USAGE

Mycophenolic acid (mycophenolic acid) delayed-release tablets are indicated for the prophylaxis of organ rejection in patients receiving allocellular renal transplants, administered in combination with corticosteroids and azathioprine.

CONTRAINDICATIONS

Mycophenolic acid (mycophenolic acid) delayed-release tablets are contraindicated in patients with a hypersensitivity to mycophenolic acid, mycophenolic acid sodium, mycophenolate mofetil, or to any of its excipients.

WARNING: EMERGENCY TOXICITY, MALOCCLUSION AND SERIOUS INJURIES

The rate of lymphoproliferative disease or lymphoma in Myfortic-treated patients was comparable to rates of lymphoproliferative disease or lymphoma in patients treated with cyclophosphamide. The authors note that tacrolimus is a risk factor for lymphoid malignancies.

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CONTRAINDICATIONS

Mycophenolic acid (mycophenolic acid) as an isolate of an immunosuppressive regimen are all increased risk of development of lymphomas and lymphoid neoplasms (see Postmarketing Experience), Mycophenolic acid (mycophenolic acid) administration and placebo. These risks appear to be related to the intensity and duration of immunosuppression rather than to the specific choice of immunosuppressive drug.

Allergic reactions, including angioedema, fever, malaise, and rash, have been reported with both Myfortic and Myfortic® delayed-release tablets.

Neutropenia, a risk factor for opportunistic infections, has been observed in patients receiving Myfortic. Some patients have developed infections, including pneumocytomegalovirus, that are usually associated with neutropenic patients. Neutropenia has been associated with increased risk for hospitalization. Myfortic should be used with caution in patients with a history of neutropenic infections.

Patients getting Myfortic should be monitored for blood dyscrasias (e.g. neutropenia or anemia). Neutropenia was found to be reversible with dose reduction or cessation of therapy with MPA derivative.

Cases of pure red cell aplasia (PRCA) have been reported in patients treated with mycophenolic acid (MPA). In patients treated with Myfortic, MPA has been associated with neutropenia, anemia, and thrombocytopenia.

Patients treated with Myfortic should be monitored for blood dyscrasias, neutropenia, anemia, and thrombocytopenia, and should be advised that vaccinations may be less effective. Influenza vaccination should be avoided and patients should be advised that vaccinations may be less effective. Influenza vaccination should be avoided and patients should be advised that vaccinations may be less effective. Influenza vaccination should be avoided and patients should be advised that vaccinations may be less effective.

Patients getting Myfortic should be monitored for blood dyscrasias (e.g. neutropenia or anemia). Neutropenia was found to be reversible with dose reduction or cessation of therapy with MPA derivative. Mycophenolate mofetil had no effect on male rat fertility at daily oral doses as high as 18 mg/kg.

Mycophenolic acid was genotoxic in the mouse lymphoma/thymidine kinase assay, the micronucleus test in rats and human lymphocytes, the sister chromatid exchange test in human lymphocytes, and the mouse lymphoma/multitest system. The genotoxic activity of MPA is probably due to the depletion of the amidine nitrogen required for binding to DNA.

PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivative. Mycophenolate mofetil had no effect on male rat fertility at daily oral doses as high as 18 mg/kg.

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The risk appears to be related to the intensity and duration of immunosuppression rather than to the specific immunosuppressive regimen. Patients receiving immunosuppressive regimens involving combinations of drugs, including Myfortic (mycophenolic acid), as part of an immunosuppressive regimen are at increased risk of developing PML and PVAN. Myfortic (mycophenolic acid) is contraindicated in patients with a hypersensitivity to mycophenolate sodium and mycophenolate mofetil (MMF) and mycophenolate sodium. The pharmacology of mycophenolate mofetil (MMF) and mycophenolate sodium is similar. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for more detailed information.)

Pregnancy Planning During treatment with Myfortic, the use of live attenuated vaccines should be avoided and patients must use acceptable contraception methods. Patients must use contraceptive counseling and use appropriate methods, and the patient must be informed of the potential serious risks to the fetus if Myfortic is used during pregnancy. The practitioner should strongly encourage the patient to enroll in the pregnancy registry. The information group for the Registry will help the patient find Health Care Community (not certified) alternatives to PML and PVAN.

Contra-indications: Drug Interactions: Oral Contraceptives: Myfortic (mycophenolic acid) is a competitive inhibitor of dihydropyrimidine dehydrogenase (DPD). DPD is responsible for converting fluoropyrimidines, e.g., 5-fluorouracil, to inactive metabolites. Use of fluoropyrimidines must be avoided when Myfortic is used. Clinical studies of Myfortic did not include sufficient numbers of subjects aged 65 years of age or older to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Gastrointestinal System Disorders Adverse events reported in clinical studies of Myfortic in adult renal transplant patients and in the long-term observation of both de novo renal transplant patients and maintenance renal transplant patients (up to 4 years) with Myfortic are listed below and are also listed in the following severity tables.

Oral Contraceptives: Myfortic (mycophenolic acid) is a competitive inhibitor of dihydropyrimidine dehydrogenase (DPD). DPD is responsible for converting fluoropyrimidines, e.g., 5-fluorouracil, to inactive metabolites. Use of fluoropyrimidines must be avoided when Myfortic is used. Clinical studies of Myfortic did not include sufficient numbers of subjects aged 65 years of age or older to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Contraceptive sponge Female condom Diaphragm with spermicide Tubal sterilization Condoms Intrauterine devices (IUDs) Systemic steroids

The pharmacology of mycophenolate mofetil (MMF) and mycophenolate sodium is similar. (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for more detailed information.)
Baxter
Continued from page 17

industry Spotlight

unit manufactures equipment for injecting various fluids and drugs, according to the WSJ.

Gambro, a company held by two Scandinavian private-equity firms, positions itself as “the leader in blood perfusion therapies in the hospital setting.” Sales of its products—including hemodialysis devices such as advanced monitors, dialyzers, bloodlines, cyclers, and dialysis solutions—total $1.6 billion in 2011, Forbes reported.

Baxter’s Parkinson said the Gambro deal is a good fit for Baxter overall, and would provide a platform for additional deals and growth in developing regions.

Reuter reported that Baxter posted sales of $13.89 billion in 2011. At the end of the third quarter of 2012 Baxter had $3.19 billion in cash, and announced it would spend $1 million in cash from overseas operations and accrue an additional $3 billion in debt to complete the deal. Baxter had about $3 billion in cash flow in 2011, according to the WSJ.

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Table 5. Adverse Events (%) in Controlled de novo and Maintenance Renal Studies Reported in >20% of Patients

<table>
<thead>
<tr>
<th>Condition</th>
<th>de novo Renal Study</th>
<th>Maintenance Renal Study</th>
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<tr>
<td>Infections and Infections</td>
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<tr>
<td>CMV Infection</td>
<td>20.2</td>
<td>18.1</td>
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<td>Urinary Tract Infection</td>
<td>29.1</td>
<td>33.3</td>
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<td>Gastrointestinal Disorders</td>
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Table 6. Summary of the incidence of opportunistic infections in de novo and maintenance transplant patients, which were similar in both treatment groups.

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Table 7. Adverse Events Reported in >20% of Patients Treated with Myfortic® in Combination with Cyclosporine® and Corticosteroids

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Table 8. Summary of the incidence of opportunistic infections in de novo and maintenance transplant patients, which were similar in both treatment groups.

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ASN Recently released a five-part video series, “Improving Dialysis Rounds for Geriatric Patients,” produced by the ASN Nephrology Advisory Group and made possible with support from the Association of Specialty Professors.

The publicly available, free video series, accessible online at http://www. asnrounds.org, reflects ASN’s dedication to providing resources related to geriatric care in response to increasing interest in individualizing care for geriatric patients. Each video covers critical aspects of care for aging patients, including patient assessment, dialysis care, recognition of physical and mental decline, quality-of-life issues, and sharing crucial decision-making information with patients and caregivers.

“The ASN Geriatric Nephrology Advisory Group and I believe these exceptional videos go a long way to providing the most optimal care for kidney patients,” said ASN President Bruce Molitoris, MD, FASN. ASN encourages all nephrology health professionals to watch the videos and share them with their networks of peers and trainees.”
Kidney Week On-Demand: online access to more than 350 hours of educational content from the meeting. This resource in the ASN Learning Center is complimentary to fully paid Annual Meeting participants with access codes or is available for purchase.

For more information on sessions captured or how to purchase, visit www.asn-online.org/dl/kw.

CME credit will not be awarded for these materials.
CJASN for iOS and Android

Access the latest research and commentary published in the Clinical Journal of the American Society of Nephrology from anywhere in the world.

Download these and other ASN apps at www.asn-online.org/media.