“Missing heritability” has become the holy grail in the search for genetic variants underlying type 2 diabetes. Genome-wide association studies have linked over 60 commonly occurring susceptibility loci to type 2 diabetes, but the impact of each of these variants is modest. These commonly occurring variants represent only about 10 percent of overall risk for developing the disease, said Mark McCarthy, MD, professor of diabetic medicine at the University of Oxford. McCarthy is one of the leaders of an international research consortium with a unique approach to identifying missing heritability, that is, the genetic variants that rarely occur in the population but that may have much stronger effects on type 2 diabetes disease risk than do the common variants thus far identified.

The consortium’s approach is to sequence and analyze the whole exomes—or coding portions of genes—of 10,000 individuals of five major ancestry groups: African American, East Asian, European, Hispanic, and South Asian.

The search for the variants that influence an individual’s genetic predisposition for developing type 2 diabetes and renal disease requires such large population studies and often many years of work, said Arlene Chapman, Continued on page 4

Losartan Fails to Prevent Allograft Fibrosis and Loss in Transplant Recipients

By Tracy Hampton

Angiotensin II blockade can slow the progression of chronic kidney disease, but how effective is it in kidney transplant recipients? Investigators recently completed a large, randomized placebo-controlled clinical trial that looked at this very question.

“Contrary to what has been observed in native kidney disease, angiotensin II blockade did not demonstrate a statistically significant benefit in lessening fibrosis or terminal kidney failure from severe fibrosis,” said first author Hassan Ibrahim, MD, professor in the division of renal diseases and hypertension at the University of Minnesota, Twin Cities campus. “Nevertheless, angiotensin II blockade was safe and well tolerated.”

The study, which is published in the Journal of the American Society of Nephrology, provides valuable information that can be used to design future interventional trials to treat kidney transplant recipients.

Trial design and results

Immunosuppressants help prolong the function of transplanted organs, but thera-

Continued on page 2
Losartan

Continued from page 1

pies that target non-immunological damage to these organs—such as elevated blood pressure and tissue fibrosis—have not been studied. Because angiotensin II blockade, which causes blood vessels to dilate, can slow the progression of kidney disease in the nontransplant setting, Ibrahim and his colleagues reasoned that the strategy should also be tested in transplant recipients.

“To our knowledge this is the first randomized placebo-controlled trial of angiotensin II blockade in these patients,” Ibrahim said.

The rationale for the trial rested on the hypothesis that blocking the fibrogenic effects of angiotensin II and ameliorating the hemodynamic consequences of reduced nephron number would reduce structural damage in transplanted kidneys.

The trial included 153 kidney transplant recipients who received either 100 mg of losartan per day or placebo within 3 months of transplantation. Treatment continued for 5 years. Losartan blocks the receptor for angiotensin II, an important factor involved in the renin-angiotensin-aldosterone system, which is a complex hormone system that regulates blood pressure and fluid balance.

A key premise of the trial was that losartan would exert a beneficial effect independently of its blood pressure-lowering properties, so every effort was made to keep blood pressure levels similar in the two treatment groups. This involved treating patients with calcium-channel blockers, followed by diuretics as second-line therapy and ß-blockers as third-line therapy.

The primary outcome of the trial was a composite of doubling of the cortical interstitial compartment (a precursor of fibrosis) from baseline to 5 years or end stage renal disease from interstitial fibrosis and tubular atrophy, previously termed chronic allograft nephropathy. In the intention-to-treat analysis of patients with adequate structural data, the primary end point occurred in six of 47 patients who received losartan and 12 of 44 patients who received placebo, but the investigators found no significant effect of losartan on time to a composite of end stage renal disease, death, or doubling of creatinine level. In a secondary analysis, losartan seemed to reduce the risk of a composite of doubling of interstitial volume or all-cause end stage renal disease by 64 percent, but this finding requires validation.

Additional studies warranted

Although losartan was not associated with a statistically significant benefit in the primary outcome, it was well tolerated. Despite a higher level of serum potassium, only one case of severe hyperkalemia (potassium level greater than 6 mEq/L) occurred. Serum potas-
sium levels were consistently 0.1 to 0.3 mEq/L higher in the losartan group, and hyperkalemia was observed intermittently in 17 of 77 (22.1 percent) patients in the losartan group and 5 of 76 (6.6 percent) patients in the placebo group. A total of 291 adverse events were reported, averaging 1.71 per participant in the losartan group and 2.09 in the placebo group.

According to the authors, a possible explanation for the lack of a clear and robust benefit of losartan, which has been observed in relatively advanced native kidney disease, is that this study was a primary prevention trial that included many relatively low-risk patients, mostly white recipients of live-donor kidney transplants who had low immunologic risk.

They also noted that the degree of interstitial expansion in the patients in this study was less than what has been described in the literature. The study’s original sample size estimate and power calculations predicted that 60 percent of placebo-treated patients would double their cortical interstitial fractional volume or develop end stage renal disease from interstitial fibrosis and tubular atrophy, but at the end of the trial, fewer patients than expected reached that end point.

“The event rate in the trial was much lower than what was expected, which affected the statistical power of our findings,” Ibrahim said.

The investigators concluded that the trend toward a treatment benefit from losartan and the lack of clear harm supports the performance of a larger clinical trial. In this regard, the findings...
provide valuable information for future studies of non-immunological therapies for kidney transplant recipients.

**Consensus among experts**

“Although the study had a negative result on the primary prevention of interstitial fibrosis and tubular atrophy, it showed the excellent tolerance of losartan in these patients with a good control of blood pressure,” said Joseph Campistol, MD, director of the Clinical Institute of Nephrology and Urology at the Hospital Clinic in Barcelona. “With these results in mind, the antihypertensive treatment in transplant patients could be re-evaluated.”

Ibrahim noted that results from a similar ongoing trial in Canada should provide additional information on the potential role of angiotensin II blockade in these patients.

Study co-authors include Scott Jackson, MS, Jeffrey Connaire, MD, Arthur Matas, MD, Arthur Ney, MD, Ann West, RN, Nicole Lentsch, RN, Jensina Erickson, Jenny Bodnez, RN, Bertram Kasiske, MD, FACP (Hennepin County Medical Center); Behzad Najafian, MD (University of Washington); and Michael Mauer, MD (University of Minnesota).

**Disclosures:** The study was sponsored by NIDDK (grant #U01 DK060706-09). The drug and placebo were provided by Merck Pharmaceuticals.


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atypical Hemolytic Uremic Syndrome (aHUS) is a chronic, genetic, lifelong disease of systemic, complement-mediated thrombotic microangiopathy (TMA) with catastrophic consequences.1,6

- 33% to 40% of patients die or progress to end-stage renal disease (ESRD) with the first clinical manifestation3,6
- 65% of all patients die, require dialysis, or have permanent renal damage within the first year after diagnosis despite plasma exchange or plasma infusion6

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Genetic Variant
Continued from page 1

MD, professor of medicine at Emory University. “This research has to be conducted in various stages and must be replicated,” she said.

Including patients and controls representing the major ancestry groups strengthens the likelihood that variants may be discovered that either characterize all ancestries or just one group, said Chapman. Variants may include those that reduce risk and thereby are protective as well as those that increase risk for developing the disease, she said.

Genomics studies in the past have focused on individuals of Northern European ancestry, said leading genomics researcher Nicholas Katsanis, PhD. However, the variants identified in any one group “may be invisible in other populations,” he said. Katsanis is the Jean and George Brunmly Jr., MD, professor of developmental biology, and professor of pediatricians and cell biology at Duke University.

Because each ancestry group in the whole-exome studies includes equal numbers of controls and patients with type 2 diabetes, the researchers should be able to determine whether there are variants that increase or reduce an individual’s predisposition for developing diabetes, said Tanya M. Teslovich, PhD, who spoke about the research at a recent meeting of the American Society of Human Genetics in San Francisco. Teslovich, a research fellow in statistical genetics at the University of Michigan, and McCarthy are among the 75 scientists at 27 universities and other institutions participating in the Type 2 Diabetes—GENES (Type 2 Diabetes Genetic Exploration by Next-generation sequencing in multi-Ethnic populaations) collaboration.

Although the commonly occurring loci already identified by genome-wide sequencing confer only a moderate risk, Teslovich and the other researchers regard them as beacons. “We hypothesize that genes underlying the common signals identified in genome-wide sequencing also harbor low-frequency and rare variants,” she said.

“Screening the exomes in a range of diverse ethnic groups increases the range of variants of each gene surveyed, and thereby improves our ability to detect genes showing differences in the patterns of the DNA codes for proteins between individuals with type 2 diabetes and controls,” Teslovich said.

Initial analysis of the sequence data of 3500 African American, East Asian, and South Asian individuals identified about 1.6 million single nucleotide variants (SNVs), 71.5 percent of which were previously unknown. “About only 89,000, or 5.6 percent, of these 1.6 million variants are present in all three ancestry groups,” she said. About 35.4 percent of the SNVs are unique to African Americans, while 35.4 percent and 30.6 percent, respectively, occur only in East Asians and South Asians. The analysis is too preliminary to state that these population-specific variants are associated with type 2 diabetes and contribute to disease risk in a single population, Teslovich said.

During the analysis of the sequence data on the participants with East Asian ancestry, Teslovich and her colleagues found that a variant in the PAX4 gene is associated with type 2 diabetes. Previous studies have shown that the gene is involved in pancreatic islet development and is linked to early diabetes onset.

In early 2013, the researchers will complete the exome sequencing of the 10,000 individuals in the study population. About 5300 individuals, half with type 2 diabetes and half controls, have been sequenced thus far, Teslovich said.

The study’s design should yield a catalog of variations, including alleles that are common in the general population as well as those that are observed in only a small number of individuals. “We will then examine each of the variants to determine which ones may affect an individual’s risk of developing type 2 diabetes,” she said.

Even if the Type 2 Diabetes—GENES collaboration does not identify any rarely occurring variants with a strong effect on risk for type 2 diabetes, the group’s findings will add to researchers’ and clinicians’ knowledge of diabetes.

“To some extent that doesn’t matter because we can still learn a lot about the biology of diabetes from such variants, and that has always been our primary motivation,” McCarthy said. ☺
Turn your dialysis rounds into incentive payments.

Falcon EHR’s integration of real-time dialysis data can help you document encounters more completely and efficiently for Meaningful Use.

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Journal View

Teen Overweight and Obesity Increase Long-Term ESRD Risk

Very-long-term follow-up shows elevated rates of ESRD for overweight and obese adolescents, according to a report in the Archives of Internal Medicine.

The study included approximately 1.2 million adolescents undergoing examination for compulsory military service in Israel from 1967 through 1997. Linkage to a national ESRD registry was performed to identify incident cases of ESRD between 1980 and 2010, at a mean follow-up time of 25 years. Body mass index at age 17 was evaluated as a predictor of ESRD developing in adulthood.

Treated ESRD was recorded during follow-up in 874 individuals, for an incidence rate of 2.87 per 100,000 person-years. The risk was significantly elevated for participants with overweight or obesity in adolescence. The incidence rates per 100,000 person-years were 6.08 for those in the 85th to 95th percentile of body mass index and 13.40 for those in the 95th percentile or higher.

With adjustment for blood pressure and other variables, the risk for the development of ESRD during follow-up was increased threefold for the overweight group and sevenfold for the obese group; hazard ratio 3,00 and 6.89, respectively. The risk was especially high for diabetic ESRD, HR 5.96 for overweight and 19.37 for obese adolescents, but was also elevated for nondiabetic ESRD, HR 2.17 and 3.41, respectively.

With rising rates of pediatric overweight and obesity, it is important to evaluate the implications for future risk of chronic diseases, including ESRD. The new study shows that overweight and obese adolescents are at increased risk of ESRD, including nondiabetic ESRD, at 25 years’ follow-up. The authors call for further investigation of possible mechanisms, especially because the risk is increased for causes of ESRD apparently unrelated to obesity (Vivante A, et al. Body mass index in 1.2 million adolescents and risk for end-stage renal disease. Arch Intern Med 2012; 172:1644–1650).

In Canada, Similar Outcomes with HD and PD

Nationwide data on Canadian patients with ESRD show similar outcomes for those given peritoneal dialysis (PD) versus hemodialysis (HD), reports a study in Nephrology Dialysis Transplantation.

Using the Canadian Organ Replacement Register, the researchers identified 46,839 patients who started renal replacement therapy from 1991 through 2004. Of these, 69.5 percent were incident on HD and 30.5 percent on PD. Patients were followed up for survival through 2007, with outcomes compared for patients starting dialysis in 1991–1995, 1996–2000, and 2001–2004.

On intention-to-treat analysis across the study period, overall survival was better with PD through the first 18 months but was better with HD after 36 months. For the 2001–2004 cohort, survival was better with PD for the first 2 years, after which there was no significant difference between PD and HD. Peritoneal dialysis was associated with a 27 percent increase in mortality for elderly women (older than 65) with diabetes. As expected, technique survival was lower with PD than with HD, although it improved slightly from the 1991–1995 cohort to the 2001–2004 cohort.

In Canada, the use of PD as the initial dialysis modality has remained relatively stable over time but has decreased in recent years: from 57 percent in 1991 to 18 percent in 2007. The authors used newer statistical models to compare PD and HD survival in a contemporary cohort of incident dialysis patients in Canada.

The results show overall similar survival for ESRD patients receiving PD versus HD. Survival is higher with PD for the first 2 years but is similar thereafter. The authors conclude that “PD and HD should be seen as complementary modalities” offering a choice of treatment approaches for the individual patient (Nutes K, et al. Hemodialysis and peritoneal dialysis are associated with similar outcomes for end-stage renal disease treatment in Canada. Nephrol Dial Transplant 2012; 27:3568–3575).

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Patients with moderate renal impairment have a sharply increased risk of major bleeding during treatment with enoxaparin, suggests a report in the Archives of Internal Medicine.

From June through November 2009, 164 patients at the authors' Veterans Administration Medical Center were treated with enoxaparin sodium (1 mg/kg every 12 hours or 1.5 mg/kg once daily). On the basis of a creatinine clearance of 30–50 mL/min, 59 patients were classified as having moderate renal impairment. Episodes of major bleeding—causing death, hospitalization, longer hospital stay, or emergency department visit—were compared for patients with moderate renal impairment versus normal renal function (creatinine clearance over 80 mL/min).

Twenty-two percent of patients with moderate renal impairment had major bleeding episodes while taking enoxaparin, compared with 5.7 percent of those with normal renal function. The odds ratio for major bleeding in the moderate renal impairment group was 4.7, decreasing to 3.9 on multivariable adjustment for other risk factors. Independently of renal function, the risk of major bleeding was higher in patients receiving enoxaparin as bridge therapy: 13.7 percent, compared with 8.1 percent for those receiving new anticoagulation, thromboembolism, evaluated as a secondary outcome, was similar between groups.

Enoxaparin, a low-molecular-weight heparin, allows simplified dosing without the need for laboratory monitoring. Even though enoxaparin is excreted by the kidneys, there is no recommended dose adjustment for patients with moderate renal impairment. This study finds a fourfold increase in major bleeding in enoxaparin in patients with moderate renal impairment. More research is needed to establish appropriate dosing of this important and widely used anticoagulant in patients with reduced kidney function [DeCarolis DD, et al. Enoxaparin outcomes in patients with moderate renal impairment. Arch Intern Med 2012; 172:1713–1718].

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 RECURRANCE.

**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 has not been shown to provide additional benefit. Use caution in patients with persistent cardiovascular disease 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 on dialysis 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 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.

**CCB plus ARB Improves Outcomes in Hypertension and CKD**

In high-risk older adults with hypertension and chronic kidney disease (CKD), adding a calcium channel blocker (CCB) to high-dose angiotensin II receptor blocker (ARB) yields further reductions in cardiovascular events, reports a trial in *Kidney International*.

The multicenter “Olmesartan and Calcium Antagonists Randomized” (OSCAR) trial included 1078 older Japanese adults with hypertension and baseline cardiovascular disease and/or diabetes. In the main trial, patients were randomly assigned to upward titration of ARB or to the addition of a CCB to ARB therapy. The current study was a prespecified subgroup analysis assessing treatment responses according to baseline estimated GFR (eGFR).

On the basis of an eGFR of less than 60 mL/min/1.73 m², 355 patients had CKD; in almost all, eGFR was 30–59 mL/min/1.73 m². In patients with or without CKD, blood pressure was lower with CCB plus ARB than with high-dose ARB.

Among CKD patients, the primary composite outcome of cardiovascular events and noncardiovascular death was about twice as high in the high-dose ARB group: 30 versus 16 events, hazard ratios 2.25. In particular, the rates of cerebrovascular and heart failure events were higher in CKD patients receiving high-dose ARB, compared with CCB plus ARB. By contrast, for patients without CKD, the primary event rate was similar between treatment groups. The subgroup interaction was significant, with high-dose ARB being an independent prognostic factor for primary events among...
patients with CKD. High-dose ARB therapy lowers the rate of cardiovascular and renal events in certain high-risk groups of patients with hypertension. The combination of an ARB with a CCB is a recommended treatment for the general hypertensive population. This OSCAR subgroup analysis suggests that CCB plus ARB is more effective than high-dose ARB for elderly high-risk patients with CKD. In this group, the combination yields a lower risk of cardiovascular events, particularly stroke and heart failure. The results lend new insights for decisions about antihypertensive therapy for older adults with CKD (Kim-Matsuyama S, et al. Annals of Internal Medicine 2012; 157:152-160).

### ACEIs Linked to Increased Angioedema Risk

The risk of angioedema appears higher for patients taking angiotensin-converting enzyme inhibitors (ACEIs) compared with other drugs targeting the renin-angiotensin-aldosterone system, according to a study in the *Annals of Internal Medicine*. The retrospective analysis included adult patients from 17 health plans contributing data to the Mini-Sentinel program. From 2001 through 2010, more than 1.8 million patients started treatment with an ACEI, 467,313 with an angiotensin receptor blocker (ARB), and 486,766 with the direct renin inhibitor aliskiren. A propensity score approach was used to compare the risk of angioedema between these three groups and with 1.6 million patients starting treatment with a β-blocker. The “real-world” study showed an overall low rate of angioedema, with a total of 4511 events during follow-up. However, risk was elevated with ACEIs or aliskiren. The cumulative incidence per 1000 patients was 1.79 with ACEIs and 1.44 with aliskiren, compared with 0.62 with ARBs and 0.58 with β-blockers. The incidence rates per 1000 person-years were 4.38 for ACEIs and 4.67 for aliskiren, compared with 1.66 for ARBs and 1.67 for β-blockers. The adjusted hazard ratio for angioedema (compared with β-blockers) was 3.04 with ACEIs and 2.85 for aliskiren. The risk of serious angioedema causing airway obstruction was low, but higher with ACEIs.

Some reports have linked drugs targeting the renin-angiotensin-aldosterone system to an increased risk of angioedema, but few have addressed the magnitude of this risk or the differences in risk between drug classes. The new study suggests that angioedema risk, though low overall, is elevated threefold in patients taking ACEIs compared with β-blockers. Aliskiren may also increase risk, according to studies based on a small number of cases; risk may differ for individual ARBs as well (Tobías S, et al. Comparative risk for angioedema associated with the use of drugs that target the renin-angiotensin-aldosterone system. *Arch Intern Med* 2012; 172:1582-1589).

### Vaccines Improve Survival in Dialysis Patients

Influenza and pneumococcal vaccination are associated with improved survival for patients receiving dialysis and are recommended in the *American Journal of Kidney Diseases*. The study included data from 903 of 1033 dialysis facilities in ESRD Networks 6, 11, and 15. The centers provided information on health status at the start of dialysis, receipt of influenza and pneumococcal vaccination, and mortality associated with the 2005–2006 influenza season. The analysis included data on 36,066 patients who had been receiving dialysis for at least 1 year as of the end of 2005. All-cause mortality was compared for vaccinated versus unvaccinated patients.
During the 2005–2006 season, 41.8 percent of patients were vaccinated against influenza and pneumococcal disease. Vaccinated patients were older, in worse health, more likely not to be black, and more likely to be receiving hemodialysis. The 1-year mortality was 17.1 percent overall, 15.9 percent for patients receiving both vaccinations, and 20.3 percent for those receiving neither vaccination. Mortality was even higher for patients who refused vaccination for “other reasons” or whose vaccination status was unknown.

Both vaccinations, alone and together, were associated with lower mortality. In adjusted models, the odds ratios for death were 0.71 for patients with influenza vaccination alone, 0.76 for those with pneumococcal vaccination alone, and 0.61 for those with both vaccinations. These patterns were supported on survival analysis.

Dialysis patients are a high-priority group for vaccination against influenza and other vaccine-preventable diseases. Because of their frequent interactions with health professionals, they have repeated opportunities for vaccinations and other preventive care.

This large analysis demonstrates “significant, strong, and independent” improvement in survival among dialysis patients who receive influenza and pneumococcal vaccination. The investigators conclude, “Every dialysis visit can be a preventive health opportunity for those not yet immunized.” [Bend TC, et al. Mortality of dialysis patients according to influenza and pneumococcal vaccination status. Am J Kidney Dis 2012; 60:959–965].

CKD Prediction Models Are “In Their Infancy”

Although much more work is needed in development and clinical application, risk models to predict chronic kidney disease (CKD) and its progression show “acceptable” discrimination, concludes a systematic review in PLOS Medicine.

The investigators performed a critical assessment of CKD risk models. A literature search identified 26 publications reporting on the development, validation, or impact assessment of models to predict the risk of CKD occurrence or progression. Discrimination, recalibration, and reclassification performance were assessed, along with validation and impact assessment.

In derivation samples, most of the CKD risk models showed acceptable to good discriminatory performance, with area under the receiver operating characteristics curve values greater than 0.70. Calibration was generally acceptable, although less frequently evaluated. External validation was performed for only eight out of 30 occurrence models and five out of 17 progression models, with modest-to-acceptable discrimination.

The studies provided little information on the predictive value of newer circulatory or genetic CKD biomarkers, or on the clinical utility of risk prediction models. In addition to a lack of validation studies, the derivation samples were limited by a lack of ethnic diversity. Limitations of the review included the lack of a consensus approach to rating prediction models and the difficulty of assessing publication bias.

Risk assessment of CKD has important implications for prevention and early detection. Although risk factors for CKD development and progression have been identified, their value in CKD risk stratification through clinical prediction models has yet to be established.

“These findings suggest that the development and clinical application of CKD risk models is still in its infancy,” the investigators conclude. Although published models show acceptable discriminatory performance, their value in clinical practice remains to be demonstrated. More work on calibration and external validation is needed before the models are incorporated into clinical guidelines [Echouffo-Tcheugui JB, Kengne AP. Risk models to predict chronic kidney disease and its progression: a systematic review. PLOS Med 2012; 9(11):e1001544; doi:10.1371/journal.pmed.1001544].

Table 3

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>Patients Treated with OMONTYS (N = 842)</th>
<th>Patients Treated with Epoetin (N = 842)</th>
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<tbody>
<tr>
<td>Nausea</td>
<td>18.4%</td>
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<tr>
<td>Vomiting</td>
<td>13.3%</td>
<td>13.3%</td>
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<td>Constipation</td>
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<tr>
<td>Cough</td>
<td>15.6%</td>
<td>16.6%</td>
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<tr>
<td>Injury, Prophylaxis and Proliferation of Red Blood Cells</td>
<td>16.5%</td>
<td>16.8%</td>
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<tr>
<td>Procedural Hypotension</td>
<td>10.9%</td>
<td>12.5%</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Nausea, Vomiting</td>
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<td>Nasal Obstruction</td>
<td>12.2%</td>
<td>14.0%</td>
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<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>11.4%</td>
<td>11.8%</td>
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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 mg/L or when serum transferrin saturation is less than 20%. The majority of patients with CKD will require supplemental iron during the course of ESA therapy. Following initiation of therapy and after each dose adjustment, monitor hemoglobin every 2 weeks until the hemoglobin is stable and sufficient to minimize the need for RBC transfusion. Thereafter, hemoglobin should be monitored at least monthly provided hemoglobin levels remain stable.

ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Increased Mortality, Myocardial Infarction, Stroke, and Thromboembolism
- Hypersensitivity (see Warnings and Precautions)
- Serious allergic reactions (see Warnings and Precautions)

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of OMONTYS cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice. Patients with Chronic Kidney Disease (CKD)

Adverse reactions were determined based on pooled data from two active controlled studies of 1066 dialysis patients treated with OMONTYS and 542 treated with epoetin including 938 exposed for at least 6 months and 825 exposed for greater than one year to OMONTYS. The population for OMONTYS was 20 to 85 years of age, 58.3% male, and the percentages of Caucasian, Black (including African Americans), and Asian patients were 51.7%, 31.4%, and 2.1%, respectively. The median weight adjusted dose of OMONTYS was 10.7 mg/kg and 112 U/kg of epoetin.

Table 3 summarizes the most frequent adverse reactions in dialysis patients treated with OMONTYS.

Postmarketing Experience

Because postmarketing reports of adverse reactions in voluntary and from a population of uncertain size, it is not always possible to determine their frequency of adverse reactions related to drug exposure.

Serious allergic reactions have been reported during postmarketing use of OMONTYS (see Warnings and Precautions).

Immunogenicity

Of the 237 patients tested during clinical trials, 29 (12%) had detectable levels of peginesatide-specific binding antibodies. There was a higher incidence of peginesatide-specific binding antibodies in patients dosed subcutaneously (1.5%) compared to those dosed intravenously (0.7%). Peginesatide neutralizing antibodies were detected in all patients in the no-stopping study. An increase in serum levels of antibodies was noted in VAD-continuous and VAD-discard patients. No patients with positive VAD-stopping assay results were noted in VAD-discard patients. In approximately half of all antibody-positive patients, the presence of antibodies was associated with declining hemoglobin levels, the requirement for increased doses of OMONTYS to maintain hemoglobin levels, and/or transmission for access of CKD. No cases of pure red cell aplasia (PRCA) developed in patients receiving OMONTYS during clinical trials.

DRUG INTERACTIONS

No formal drug interaction studies have been performed. Peginesatide does not bind to serum albumin or lipoproteins as demonstrated in in vitro protein binding studies in rat, monkey and human sera. In vitro studies conducted with human hepatocytes or microsomes have shown no potential for peginesatide to induce or inhibit CYP3A4 enzymes.

Use in SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Peginesatide was teratogenic and caused embryolethality when administered to pregnant animals at doses and/or exposures that resulted in polyhydramnios. OMONTYS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Administration of peginesatide by intravenous injection to rats and rabbits during organogenesis was associated with embryolitic toxicity and malformations. Dosing was every third day for rats for a total of 5 doses and every fifth day in rabbits for a total of 4 doses (0.01 to 0.05 mg/kg). In rats and rabbits, embryolethal effects included reduced fetal weight, increased resorption, embryolethal, fetal palate defects (rat only), ventricle anomalies, unossification of sternebrae and metatarsals, and reduced ossification of some bones. Embryolethal toxicity was evident in rats at peginesatide doses of 0.01 mg/kg and the no-stopping study and in rabbits at peginesatide doses of 0.05 mg/kg. In rats, in a separate embryofetotoxicity study in cisplatin treated pregnant rats, NOAEL was 0.1 mg/kg and there was no effect at 0.01 mg/kg.

In rabbits, litters were observed at doses lower (0.05 mg/kg) than the dose of 0.35 mg/kg in patients.

Hemoglobin

It is not known whether peginesatide is excreted in human milk. Because many drugs are excreted into human milk, caution should be exercised when OMONTYS is administered to a nursing woman.

Pediatric Use

The safety and efficacy of OMONTYS in pediatric patients have not been established.

Geriatric Use

Of the total number of dialysis patients in Phase 3 clinical studies of OMONTYS, 32.5% were age 65 and over, while 13% were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

OVERDOSAGE

OMONTYS overdose can elevate hemoglobin levels above the desired level, which should be managed with discontinuation of or reduction of OMONTYS dosage and/or with phlebotomy, as clinically indicated. Cases of severe hyperviscosity have been observed following overdose with ESAs (see Warnings and Precautions).

Marketed by:

Affymax, Inc.
Palo Alto, CA 94304

Distributed and Marketed by:

Takeda Pharmaceuticals America, Inc.
Overland Park, KS 66211

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References:

Indications for Use: The HeRO Graft is indicated for end stage renal disease patients on hemodialysis who have exhausted all other access options. See Instructions for Use for full indication, contraindication and caution statements. Rx only.

HeRO Graft is classified by the FDA as a vascular graft prosthesis.
Policy Update

Fiscal Cliff Deal a Mixed Bag

By Rachel Shafter and Grant Olan

The worst outcomes of the “fiscal cliff” were averted for now with President Barack Obama’s signing into law the American Taxpayer Relief Act (ATRA) on January 2. In addition to permanently extending most of the 2001 and 2003 temporary tax cuts, the new law includes spending cuts to prevent a nearly $27 billion cut to Medicare physician reimbursement rates in 2013, and delays sequestration—automatic across-the-board spending cuts to federal discretionary spending and a 2 percent cut to other Medicare services initially scheduled to take effect January 2, 2013—for 2 months until March 2013.

The new March deadline enacted for dealing with sequestration also coincides with two other major deadlines. The U.S. government faces a possible government shutdown in March (when current appropriations for government expire) unless Congress approves appropriations for the remainder of Fiscal Year (FY) 2013. Moreover, the United States government will default on its debt soon unless Congress raises the “debt ceiling,” the legal limit of how much debt the United States can assume.

Dialysis-specific provisions bring challenges, opportunities for 2013

For patients with kidney disease and the nephrologists who treat them, the fiscal cliff deal Congress brokered was a mixed bag. To pay for the tax cut extension, Medicare physician payments in 2013 (see box, page 12), and other costly components of the deal, Congress had to identify savings from government operations to “offset” those costs.

A Government Accountability Office (GAO) report released in December 2012 described significant potential savings in the Medicare End-Stage Renal Disease (ESRD) Program and caught Congress’ attention. In a nutshell, the GAO report suggested that Medicare had been paying for more erythropoiesis-stimulating agents (ESAs) than it was being administered. GAO concluded that by “rebasing,” the base bundled payment rate, the Centers for Medicare & Medicaid Services (CMS) would reduce its ESA costs considerably. As described in the January issue of ASN Kidney News, many in the kidney community—including ASN—expressed concerns about a congressionally-mandated rebasing based on a report that focused on just one element of ESRD care.

Despite these concerns, when the Congressional Budget Office estimated that rebasing could save nearly $5 billion over 10 years, Congress moved forward with using it as an “offset” in the fiscal cliff deal. However, it is critical to note that this figure is an estimate only; Medicare is not legally mandated to actually achieve that level of savings. Thus far, some estimates floating around Washington have “guessed” rebasing could result in an approximately $10 reduction in the base rate (about 4 percent) of each payment.

1. Granted CMS authority to rebase the bundled payment rate. Prior to the passage of ATRA, CMS did not actually believe that it had the legal authority to rebase the bundle—an important detail the GAO report clarified. Through ATRA, Congress specified that CMS not only has the authority to rebase, but also now has a mandate to do so. It is likely that CMS will begin the rebasing process in the 2013 rulemaking cycle.

2. Specified data years to inform rebasing calculations. ATRA instructs the secretary of the Department of Health and Human Services (HHS) to compare base biologic rates in the 2007 rule with 2012 utilization rates, and to use data from the most recent year available—2012—in rebasing calculations. Importantly, the Secretary must also use the most recently available Average Sales Prices (ASP) and examine other changes in prices for drugs and biologics.

3. Mandated an analysis of case-mix adjustments by 2016. ATRA further instructs the HHS secretary to conduct an analysis of the current case-mix adjustments to the bundled payment system and make necessary revisions by 2016. Given that case-mix adjustments—established in 2010—have been viewed as a particularly flawed element of the bundled payment system by some, the possibility for improvement is now on the table.

4. Delayed addition of oral-only drugs to the bundled payment system. Oral-only drugs with no injectable equivalents were slated to be added to the bundled payment system beginning in 2014—a date that ATRA delayed by 2 years to January 1, 2016. While the reasons for that delay were not immediately clear from a financial perspective, it may come as welcome news to units that were not entirely prepared to make the transition.

5. Asked GAO to submit a report on oral-only drug addition. ATRA requires GAO to submit a report to Congress regarding the HHS secretary’s plans to add oral-only drugs to the bundle no later than December 31, 2015. Because ATRA also mandated that the oral-only drugs be added to the bundle no later than the following day—January 1, 2016—it remains somewhat unclear how the timing of GAO’s and HHS’s activities will play out.

To summarize, nephrologists have seen Medicare physician payments sustained in recent years. The Budget Control Act, signed during the summer of 2011, raised the federal debt ceiling and enacted $2.1 trillion in cuts to federal spending in several stages. Phase one cut $21 billion from several discretionary programs in the FY 2012 budget, and cuts budget levels for FY 2013–2021 by about $900 billion (Table I).

Table I

<table>
<thead>
<tr>
<th>2011 Budget Control Act Cuts</th>
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<td>FY 2012: $21 billion cut from several discretionary programs</td>
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<td>FY 2013–2021: $908 billion of budget level cuts</td>
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<td>FY 2013–2021: $1.2 trillion in automatic across-the-board cuts to all discretionary programs if Congress does nothing to avert sequestration</td>
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Continued on page 12

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The fiscal cliff continued from page 11.

During phase two, the Budget Control Act provisions empowered a Joint Committee on Deficit Reduction to present a plan for making the remaining $1.2 trillion in cuts, but the committee failed to come up with a plan. That failure would have triggered $1.2 trillion in automatic across-the-board cuts to all federal discretionary spending beginning January 2, 2013. But Congress and the president delayed sequestration by 2 months, thereby delaying the “fiscal cliff” to March 2013.

In response to the threat of sequestration, ASN in July joined a new coalition of 3000 national, state, and local organizations—including other medical specialty societies and research organizations—and has been advocating for a balanced approach to deficit reduction that does not rely on further cuts to non-defense discretionary (NDD) spending, which includes funding for medical research, transportation, education, public safety, public health, and other important government services.

 ASN’s collaborations with the NDD community include:

- A “Rally to Restore Balance and Protect America’s Families” on Capitol Hill to launch the NDD campaign with key members of Congress.
- NDD community-wide national days of action, congressional briefings, and Capitol Hill meetings during the fall of 2012.
- An ASN member campaign targeting members of Congress with nearly 450 emails, letters, calls, and meetings.

These activities built support for NDD programs that in part helped delay the implementation of sequestration until March 1, 2013, and give Congress and the president more time to avert it. Otherwise, $1.2 trillion in cuts will come on top of the more than $900 billion already cut. That would equate to a cut of about 6.5 percent for federal medical research and other NDD programs in FY 2013.

The current outlook for a deal to

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For renal transplant patients...

**myfortic®**: Consistent From Refill to Refill to Refill

Potential MMF REFILL CALENDAR

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**myfortic** REFILL CALENDAR

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- 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 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 Savings Program at 1-877-952-1000.

More than 81% of myfortic prescriptions® had a $0 co-pay with 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 regular 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, and MMF are not substitutable.

- Myfortic® (mycophenolate mofetil), MPA, mycophenolic acid.

**CellCept** is a registered trademark of Hoffmann-La Roche Inc.

*As of January 13, 2012.

†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: EMBRYOFETAL 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 counselled 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.
avert sequestration in March is grim. Congress has thus far proven incapable of agreeing on how to apply the remaining $1.2 trillion of cuts mandated by the 2011 Budget Control Act, and Senate Minority Leader Mitch McConnell (R-KY) says additional revenue as an offset is off the table. It is hard to imagine how a deal can come together to avert sequestration without revenue offsets or a complete repeal. And having delayed sequestration once, it is unlikely Congress would kick the can down the road again.

“ASN shares concerns about the growing national debt and supports responsible federal deficit reduction measures. But federal NDD programs like medical research are not the main drivers of our nation’s debt and have already done a fair share for deficit reduction,” said ASN Research Advocacy Committee Chair John R. Sedor, MD.

“I urge everyone to join ASN’s campaign in support of medical research and other NDD programs. Visit http://www.asn-online.org/policy/ to learn how.”

Important Safety Information: (cont)

- Embryofetal Toxicity: myfortic® can cause fetal harm when administered to a pregnant female. Use of myfortic® during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital anomalies.

- Pregnancy Prevention and Planning: FRP must be made aware of the increased risk of first trimester pregnancy loss and congenital malformations, and must be counseled regarding pregnancy prevention and planning. (See additional Important Pregnancy Testing, Contraception, and Pregnancy Planning information below.)

- Lymphoma and Other Malignancies: Patients receiving immunosuppressive regimens involving combinations of drugs, including myfortic®, as part of an immunosuppressive regimen are at increased risk of developing lymphomas and other malignancies, particularly of the skin.

- Infections: Overuse of the immune system can also increase susceptibility to infection, fatal infections, and sepsis.

- Polyomaviruses: Infections: Immunosuppressed patients are at increased risk for opportunistic infections, including Polyomavirus infections. Polyomavirus infections in transplant patients may have serious and sometimes fatal outcomes. These include cases of JC virus-associated progressive multifocal leukoencephalopathy (PML) and Polyomavirus-associated nephropathy (PVAN), especially due to BK virus infections, which have been observed in patients receiving myfortic®. PVAN, especially due to BK virus infection, is associated with serious outcomes, including deteriorating renal function and renal graft loss. Patient monitoring may help detect patients at risk for PVAN.

- Cases of PML have been reported in patients treated with MPA derivatives including MMF and mycophenolate sodium. PML, which is sometimes fatal, commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia. Risk factors for PML include treatment with immunosuppressant therapies and impairment of immune function. In immunosuppressed patients, physicians should consider PML in the differential diagnosis in patients reporting neurological symptoms, and consultation with a neurologist should be considered as clinically indicated. Reduction in immunosuppression should be considered for patients who develop evidence of PML or PVAN. Physicians should also consider the risk that reduced immunosuppression represents to the graft.

- Blood Dyscrasias Including Pure Red Cell Aplasia: Cases of pure red cell aplasia (PRCA) have been reported in patients treated with MPA in combination with other immunosuppressive agents. In some cases, PRCA was found to be reversible with dose reduction or cessation of therapy with MPA derivatives. In transplant patients, however, reduced immunosuppression may place the graft at risk. Patients receiving myfortic® should be monitored for blood dyscrasias (eg, neutropenia or anemia). If blood dyscrasias occur (eg, neutropenia develops [ANC <1.0 x 10⁹/L] or anemia), dosing with myfortic® should be interrupted or the dose reduced, appropriate diagnostic tests performed, and the patient managed appropriately.

- Pregnancy Testing: To prevent unplanned exposure during pregnancy, FRP should have a serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL immediately after starting myfortic®. Another pregnancy test with the same sensitivity should be done 8 to 10 days later. Repeat pregnancy tests should be performed during routine follow-up visits. Results of all pregnancy tests should be discussed with the patient. In the event of a positive pregnancy test, female patients should be counseled with regard to whether the maternal benefits of mycophenolate treatment may outweigh the risks to the fetus in certain situations.

- Contraception: FRP taking myfortic® must receive contraceptive counseling and use acceptable contraception during the entire myfortic® therapy, and for 6 weeks after stopping myfortic®, unless the patient chooses abstinence. Patients should be aware that myfortic® reduces blood levels of the hormones in the oral contraceptive pill, and could theoretically reduce its effectiveness. (Please see package insert for acceptable contraceptive methods for females.)

- Pregnancy Planning: For patients who are considering pregnancy, consider alternative immunosuppressants with less potential for embryofetal toxicity. Risks and benefits of myfortic® should be discussed with the patient.

- Gastrointestinal Disorders: Gastrointestinal bleeding (requiring hospitalization) has been reported in de novo renal transplant patients (1.0%) and maintenance patients (1.3%) treated with myfortic® (up to 12 months).

- Patients with Renal Impairment: Subjects with severe chronic renal impairment (GFR <25 mL/min/1.73²m²) may present higher plasma MPA and MPAG AUC relative to subjects with lesser degrees of renal impairment or normal healthy volunteers. No data are available on the safety of long-term exposure to these levels of MPAG.

- Concomitant Medications: Caution should be used with drugs that interfere with enteroglucagon reuptake because of the potential to reduce efficacy.

- Hypoxanthine-guanine phosphoribosyl-transferase (HGPT) Deficiency: myfortic® should be avoided in patients with HGPT deficiency such as Lesch-Nyhan and Kelley-Seegmiller syndrome.

- Immunizations: Use of live attenuated vaccines should be avoided.

- The principal adverse reactions associated with the administration of myfortic® include constipation, nausea, and urinary tract infection in de novo patients and nausea, diarrhea, and nasopharyngitis in maintenance patients.


Please see Brief Summary of Prescribing Information, including Boxed WARNINGS, on adjacent pages.
20 years of age or older in the United States with diabetes. Clinical trials in these populations demonstrate that antihypertensive interventions reduce the risk of both CKD progression and cardiovascular complications.

For these reasons, ASN recommended to the USPSTF continued screening of patients with hypertension and diabetes for CKD. Existing guidelines from a number of professional organizations, including the American Diabetes Association, the National Kidney Foundation, and the Joint National Commission on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, also recommend screening these high-risk populations for CKD.

In addition to screening patients who have comorbid conditions that cause CKD, ASN’s response to the USPSTF highlighted other patient characteristics that confer increased risk and may also warrant screening, including family history of kidney failure as a strong risk factor for kidney disease. The National Kidney Disease Education Program (NKDEP) at the National Institutes of Health has advocated for screening patients who have a family history of kidney disease.

Moreover, ASN noted that screening individuals with a family history of kidney disease may also help address disparities among racial and ethnic minority populations in the United States. African Americans and Native Americans are up to four times more likely than Caucasians to progress to kidney failure, while Hispanics are twice as likely. The elevated risk of developing CKD and kidney failure in these groups is not well explained by the higher prevalence of diabetes and hypertension. (African Americans, for example, are at disproportionate risk for developing focal segmental glomerulosclerosis and primary glomerulopathy, due in part to an increased risk of high-grade polynuromatous polymorphisms in the Apolipoprotein L1 gene.) However, recent findings indicate that CKD screening and treatment of African Americans may be more cost-effective than CKD screening and treatment of non–African Americans.

ASN also pointed out that NKDEP and the American Heart Association also recommended CKD screening for patients with a clinical diagnosis of cardiovascular disease, who are also at high risk of kidney disease. CKD is common among patients with cardiovascular disease and is a strong independent risk factor for cardiovascular events and death. As such, screening for CKD has been recommended for all patients with cardiovascular disease, including those with coronary artery disease or congestive heart failure.

The thorough evaluation of CKD screening among asymptomatic adults without diabetes or hypertension completed by AHRQ and USPSTF led to the convening of new, unanswering questions for public health. ASN recommends ongoing screening of high-risk groups for CKD, both good for patients and good economic sense, and applauds the USPSTF recommendation to Congress for further research on CKD screening to fill evidence gaps.

Ian H. de Boer, MD, is affiliated with the division of nephrology at the Kidney Research Institute, University of Washington, Seattle.

Granit Olani, is a policy associate with ASN. Uptal Patel, MD, is an associate professor of medicine and pediatrics, an investigator in the Health Services Research and Development Unit at the Durham Veterans Affairs Medical Center, and core faculty at the Duke Clinical Research Institute.
Kidney TREKS: ASN’s New Initiative to Increase in Nephrology Careers

By Lauren Stern and Mark Parker

Kidney Treks begins with a one-week, fully funded lab-based course in June 2013 at Mount Desert Island Biologic Laboratories in Bar Harbor, Maine. Med students may apply online at www.asn.org/education/training/kidney-treks.aspx until May 15.

In recent years much attention has been focused on medical students' and residents' declining interest in nephrology careers (1,2). The numbers of candidates, especially U.S. medical graduates (USMGs), applying to nephrology fellowship programs have dwindled over the past decade. In the 2012 fellowship appointment year there were only 1.1 applicants for each nephrology position in the National Residency Matching Program and only 24.2% of matched applicants were USMGs (3). This decline seems unjustified since nephrology remains an intellectually challenging and rewarding field. Some of the reasons being reported include limited nephrology exposure during medical school and internal medicine residency, uncompelling research projects, lack of mentorship, and perceived perception of SNPs in the United States [SNPs in American English].

In response to these concerns, the ASN’s new Kidney Treks (Turing Research and Education for Kidney Scholars) program is aimed at trainees at the medical school level. It begins with a unique laboratory experience at Mount Desert Island Biologic Laboratories (MDIBL) in Bar Harbor, Maine. This 1-week, fully funded, lab-based hands-on course will take place June 8–14, 2013. Modeled on the highly successful “Origins of Renal Physiology” course for fellows and junior faculty at MDIBL, and directed by Mark Zeidel, MD, FASN, Chair of the Department of Medicine at Beth Israel Deaconess Hospital in Boston, the week will feature renowned investigators in the field. Students will participate in modules that allow them to perform experiments and discuss and present results that will help them understand key concepts in nephrology, including water and salt homeostasis, acid–base homeostasis, glomerular function, personalized medicine, and genetics. Both classical experiments and modern molecular

Continued on page 16
Kidney TREKS

Continued from page 15

techniques will be explored.

Participants will then enter a longitudinal mentorship component of the program and will be paired with a nephrologist at their home institution. This mentor will serve to guide them through nephrology electives and additional research opportunities, such as application to the ASN Student Scholars Grants program. Finally, participants will be invited to attend ASN Kidney Week during their third or fourth years in medical school through the ASN Program for Medical Students and Residents. This successful initiative includes guided learning pathways and exposes trainees to the full spectrum of nephrology discovery at Kidney Week.

Applications for the Kidney TREKS program can be found online at www.asn-online.org/education/training/students/kidney-treks.aspx. Medical students of all levels are encouraged to apply and acceptance will be on a rolling basis with a final deadline of May 15, 2013.

Lauren Stern, MD, is affiliated with Boston Medical Center and Boston University School of Medicine, and Mark Parker, MD, is director of the division of nephrology and transplantation, Maine Medical Center, and associate clinical professor of Medicine, Tufts University School of Medicine.

References

ASN Highlights 2013
A closer look at the best of Kidney Week

Earn CME credits and view key presentations from Kidney Week 2012.

Topics covered include:
- Acute Kidney Injury
- Clinical Nephrology
- End-Stage Renal Disease
- Hypertension
- Parenchymal Disorders
- Transplantation

Registration now open
www.asn-online.org/highlights
Prepping for the Next Wave of Managed Care?

A health care industry analyst has made a prediction for 2013 that American companies like Denver-based DaVita, the second largest provider of dialysis services in the United States, may be best positioned to “benefit from changes in the health care market stemming from Obamacare.”

In early January, Martin Brunninger, head of the medical technology sector at Nomura Securities, told a CNBC cable audience that because 70 percent of the dialysis care market is dominated by two big players (DaVita and Germany’s Fresenius), “we have efficiency gains and there’s not much more earnings power in the U.S. sector.”

Brunninger said that if one company moves away strictly from dialysis care, however, that company likely would enjoy an advantage. “DaVita has diversified away and they have a broader approach now in saving managed dollars for broader patient populations,” he added. “I think that is the future.”

On November 1, 2012, HealthCare Partners merged into a subsidiary of DaVita’s parent company. The parent company changed its name to DaVita HealthCare Partners Inc. HealthCare Partners, now one of the two main operating divisions of DaVita HealthCare Partners, with operations in southern California, central Florida, southern Nevada, and northern New Mexico, assumes clinical and economic accountability and management responsibility for nearly all of the health care needs of a patient population. This includes offering professional services provided by primary care and specialty physicians as well as coordinating hospital and other services, the company noted.

In addition, the DaVita subsidiary runs the first and largest pharmacy dedicated to serving the unique needs of kidney patients. In 2012, DaVita Rx expanded its services to help manage patient medications and clinical outcomes. DaVita recently agreed to provide certain pharmacy services to Fresenius Medical Care, which will use DaVita Rx prescription drug services for its Medicare patients in the United States.

DaVita also announced in an unrelated transaction that it will extend its supply agreement with Fresenius Medical Care for certain dialysis supplies including hemodialysis machines and disposable products.

DaVita Rx also focuses on patient compliance by providing refill reminders, reviews for possible drug interactions, and other services, with the aim of healthier patients who have an improved quality of life.

With provisions of the Affordable Care Act slated to take effect within the coming year, DaVita’s move toward serving broader populations may help the firm capitalize on moves toward managed care.

As health care systems around the world keep moving toward lower spending on increasing numbers of patients, “it doesn’t necessarily mean the quality needs to be diminished,” Brunninger said. “It’s about management and where the profits are going.”

Companies Collaborate to Produce Wearable Dialysis Technology

A WAK Technologies has signed an agreement with Baxter International Inc. to develop wearable dialysis technology. The agreement lets AWAK continue developing its investigational peritoneal dialysis-based automated wearable artificial kidney, the company said.

AWAK Technologies is a research-focused, medical technology company dedicated to the development and commercialization of sorbent-based dialysis regeneration technology.

“Our agreement with Baxter is part of our overall strategy to bring innovative technologies for dialysis treatment to market that include collaborations and licensing agreements with academia including the University of California, Los Angeles (UCLA) and Temasek Polytechnic, Singapore, as well as working cooperatively with government agencies in the United States and Singapore; such as the U.S. Veteran Affairs Innovation Initiative (VAI2), SPRING Singapore and International Enterprise (IE) Singapore,” said NEO Kok-Beng, President & CEO of AWAK Technologies.

The agreement will provide Baxter with exclusive global manufacturing and a distribution license for AWAK’s investigational peritoneal dialysis-based automated wearable artificial kidney, a minority ownership stake in the company, and the option to purchase additional equity in the company.

Dialysis Businesses Attractive Targets

J ust after Baxter bid $4 billion to purchase Gambro, a maker of dialysis-related products, in the hope of being a dominant force in the dialysis marketplace, there is another news item out of Gambro’s Brentwood, Tennessee home base. Ambulatory Services of America (ASA), of Brentwood, has bought a majority interest in six dialysis centers and an acute dialysis program in the Los Angeles area.

The terms of the purchase were not disclosed, but the facilities were purchased from Kidney Centers Inc. (KCI), and the six dialysis centers currently serve 700 patients. The acute dialysis program serves eight hospitals.

“Given the strong presence of Innovative Dialysis in the Los Angeles area, we had long known of KCI, and we appreciated its physician joint venture model, which is much like ours,” said Timothy Martin, the chief executive officer of ASA and its subsidiary, Innovative Dialysis. “At Innovative Dialysis, we prefer to operate in joint ventures with physicians where our nephrologist-partners can take the lead in providing high-quality care to patients with ESRD, and we can support them by taking care of the business aspects of running dialysis facilities. We look forward to working with the staff at these facilities as well as their physician partners.”

Through this acquisition, ASA now provides care to 7000 patients through 85 dialysis programs, ASA announced in December 2012.

The ASA vision is to become the first national clinical enterprise to treat ESRD patients and avoid hospitalization from multiple medical specialties. The company plans to do this through deals with differing specialties that provide high-quality, evidence-based services that help demonstrate improved clinical outcomes. The initial focus is on both radiation oncology and renal dialysis.

Industry Spotlight

Fresenius Dialyzes in Wee Hours, Offloads Biotech Biz

Dialysis takes numerous hours of patients’ time per week, which can greatly interfere with family, work, and recreational schedules. Now Fresenius Medical Care North America (FMCNA), the largest provider of dialysis services in the United States, has established more than 140 nighttime dialysis center sites...

FMCNA, the nation’s leading network of dialysis facilities, established programs across the country, including recently opened programs in Weymouth, Massachusetts; Waco, Texas; Coeur d’Alene, Idaho; and Santa Fe, California. More are scheduled to open this year.

FMCNA’s nighttime dialysis option offers the same level of supervised care as traditional daytime, in-center treatments, but patients receive their dialysis at night, usually over a longer time, the company reported.

“Night-time dialysis is a more gradual process, and at night, patients typically receive treatments three times a week but over an 8-hour period (versus a typical 3- to 4-hour period for daytime dialysis). When dialysis is provided over a longer time, fluids are removed more slowly, which results in a more gentle treatment for most patients, the company reported.

“In-center, nocturnal dialysis is a viable alternative to standard in-center dialysis for patients who require greater fluid and phosphorus removal and who are amenable to spending 3 nights a week in the dialysis facility,” said Eduardo Lacoen, Jr., MD, FMCNA’s vice president for clinical science, epidemiology, and research. He recently published a study that demonstrated the health benefits of nighttime dialysis, among them improved clearance of phosphorus and ferritin on both FMCNA patients who switched from daytime to nighttime dialysis. Studies also suggest that nighttime dialysis patients may be able to better control their blood pressure and mineral levels, allowing them to eat a wider variety of foods, according to Fresenius.

Overall, parent company Fresenius Medical Care is focusing on its core strengths of delivering dialysis and transfusion services, as seen recently when Fresenius floated its biotech arm for sale, Reuters reported. Fresenius reported in December 2012 that it planned to discontinue the Fresenius Biotech subsidiary, which posted sales of about 26 million Euros (about $34 million) in the first 9 months of 2012. Fresenius may retain some dialysis-related drugs.

At the same time, Fresenius said that it had “successfully closed the acquisition of blood-transfusion-technology company Fenwal Holdings, Inc….as part of the company’s strategy to expand in the medical-devices/transfusion-technology segment,” Fox Business News reported.
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NIH Glomerular Disease Conference Leads to New Opportunities for Advancing Knowledge and Treatments

By Charles E. Alpers

Major research advances in the past 2 decades have provided a greatly enhanced understanding of mechanisms underlying glomerular disease. These include the identification of proteins specific to podocytes and the slit diaphragm, and the diseases that may develop as a consequence of mutation or dysfunction of these proteins. Research has also demonstrated the pathogenic contribution of abnormally galactosylated immunoglobulin A (IgA) to the development of IgA nephropathy; pinpointed SpeB as the major inciting antigen of acute poststreptococcal glomerulonephritis; and identified the phospholipase A2 receptor (PLA2R) as the principal antigen in most cases of idiopathic membranous nephropathy.

Other studies have provided evidence that a specific circulating factor (soluble urokinase receptor [suPAR]) is implicated in the pathogenesis of focal and segmental glomerulosclerosis (FSGS), and that another factor (the hypogalactosylated form of angiotensin-like-protein 4 [ANGPTL4]) may be involved in the pathogenesis of minimal change disease (MCD). However, the extent to which these factors may be causative remains to be established. Despite these and other major accomplishments in understanding their pathogenesis, there has been a lack of corresponding advances in therapeutics for these diseases.

Given this background, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), in conjunction with the ASN Glomerular Disease Advisory Group, organized the “Glomerular Disease Pathophysiology, Biomarkers, and Strategies for Facilitating Translational Research” conference, which was held at the National Institutes of Health (NIH) campus in Bethesda, MD, on April 17 and 18, 2012. The conference goals were to identify approaches to build upon this body of knowledge; develop an infrastructure that would facilitate implementation of clinical trials of new therapeutics in glomerular disease; and foster a dialogue between academic researchers, private-sector entities (including biotechnology companies and major pharmaceutical companies), and the U.S. Food and Drug Administration (FDA) that would ultimately serve to reduce the obstacles in bringing new agents for treatment of glomerular diseases to clinical trials.

The conference began with presentations by leaders of clinical trial networks from outside the glomerular disease field, including Frank Accurso, MD, of the University of Colorado on behalf of the Cystic Fibrosis Foundation Therapeutics Development Network, which now supports phase III trials conducted at 77 sites, and Neil Solomon, MD, of Vifor Pharma, speaking on behalf of the Aspreva Lupus Management Study (ALMS).

Discussion subsequently focused on specific disease entities and the potential for therapeutic interventions in each category. The keynote overview speaker, former ASN President William Couser, MD, reviewed both areas of progress made in the past 4 decades—including the identification of key pathogenic molecules described above—and the residual critical gaps in our understanding. The latter include insufficient knowledge of the initiating events in most glomerular diseases and of the best targets for therapeutic intervention. A major problem in the care of patients with glomerular diseases is that most therapies in current use were developed for application in other medical fields, such as transplantation and rheumatology, that require systemic therapy and do not target specific glomerular processes. An advantage of more tightly targeted therapeutics is that they offer the possibility of reduced toxicities and off-target effects.

Other presentations, followed by breakout discussion groups, focused specifically on the MCD/FSGS spectrum of diseases, IgA nephropathy, membranous nephropathy, vasculitis, and the recently emerging entity C3 glomerulopathy. Discussion centered on clinical trial assessment, and the need for a durable multi-institutional clinical trials infrastructure with the necessary bioinformatics and biorepository support akin to what has been accomplished with the cystic fibrosis network and the large oncology group study networks, such as the Southwest Oncology Group (SWOG). Such an infrastructure would enable the recruitment of a sufficient number of patients for meaningful trial results and obviate the need to create a trial network anew for each potential clinical study of a glomerular disease therapeutic.

A topic discussed at length, but not resolved at this meeting, was achieving agreement between representatives of the FDA on acceptable surrogate biomarkers for progressive glomerular disease. This has been a particularly challenging issue because end points, such as development of ESRD or death, are neither inevitable nor necessarily early events in the evolution of glomerular disease. The most obvious surrogate marker for glomerular disease—proteinuria—has too many vagaries to be currently acceptable to the FDA as a biomarker across different glomerular disease categories. The identification of specific pathogenic moieties, such as anti-PLA2R antibodies in membranous nephropathy and circulating suPAR in FSGS, may allow development of future assays that could be disease specific and fulfill a biomarker function for monitoring disease progress in future clinical trials.

There were several important outcomes from this conference. First was the issuance of a request for applications from the NIDDK (RFA-DK-12-014, application due date February 27, 2013) to fund consortium sites that will establish and longitudinally follow cohorts of patients with common glomerular diseases (MCD, FSGS, IgA nephropathy, and idiopathic membranous nephropathy) who can then be entered into clinical trials and studies that validate biomarkers of disease progression and other relevant clinical and translational studies. Second, as highlighted in the ASN President’s Address by Ronald Falk, MD, FASN, at Kidney Week 2012, this conference furthered a dialogue that contributed to the development of the Kidney Health Initiative (KHI), a partnership of ASN and the FDA.

The mission of KHI 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 nephrology community can interact to optimize evaluation of drugs, devices, biologics, and food products. For more information about KHI, please visit http://www.asn-online.org/khi/.

Charles E. Alpers, MD, is a member of the ASN Glomerular Diseases Advisory Group. Alpers is associated with the department of pathology at the University of Washington Medical Center in Seattle.
Detective Nephron, world-renowned for expertise in analytical skills, trains budding physician-detectives in the diagnosis and treatment of kidney diseases. L.O. Henle, a budding nephrologist, presents a new case to the consultant.
Henle: This is very revealing. In other words, in this case, she likely has MGUS that hasn't been diagnosed.

Henle leaves, and returns a few days later.

Nephron: Fine work, Detective!

Podocyte: It's always nice to drop in and discuss a good case of glomerular disease.

Henle: Her serum free light chains suggested an elevated free kappa-to-lambda ratio of 5. Her bone marrow biopsy specimen showed 5 percent plasma cells, which is consistent with MGUS. Greater than 10 percent and she would have a myeloma. So now we are left with MGUS and MPGN. Do we treat or not? And what do we treat with?

Podocyte: This is a tough question you are asking, Henle.

To me it seems that if damage is happening in an organ, particularly in the kidney, because of the monoclonal nature of this light chain kappa, how can we call this “undetermined significance”? It is clear to me that it is significant. Unfortunately, the hematology community needs to learn more about this entity and perhaps not call it MGUS when there is end-organ damage. Some cases of this have been successfully treated with anti-B cell agents such as rituximab. However, it makes more sense to treat this entity as a paraprotein, targeting agents such as those used in multiple myeloma. But, until we have more data, we might not be able to do anything.

Nephron: We prescribe medications all the time, and we have to be careful regarding the potential drastic effects they can have on the body. My dear apprentice, MGUS is a chronic entity, and so is MPGN, and it is possible that she might need treatment for now. Conservative management is reasonable, given the lack of data.

Podocyte: I disagree. I would give her rituximab if B lymphocytes were responsible for the monoclonal gammapathy. Rituximab would not be effective if plasma cells were responsible for the monoclonal gammapathy. This raises the question whether drugs such as bortezomib would be of benefit in such cases.

Henle watches them argue.

Nephron: Henle, as you can see, we don't have a final answer for you. That is perfectly reasonable and the main reason why ongoing research in nephrology is critical. The current status of nephrology research is grim. It needs more energy and enthusiasm from residents, students, and fellows to move the field forward. Nevertheless, from a single entity of MPGN, you diagnosed a potential premalignancy state in this patient. Never underestimate the power of the nephrologist.

Detective Nephron was developed by Kesar Jha, MD, assistant professor of medicine at Hofstra Medical School and an attending nephrologist at Long Island Jewish Medical Center in Great Neck, New York. Thanks to Dr. Ritu Madan of the Weill Cornell Medical Center, New York, and Dr. Sunjee Sethi of the Mayo Clinic, Minnesota, for their editorial assistance. Send correspondence regarding this section to kjha@msn.com or kcf200@gmail.com.
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