Researchers Look to Solar Power to Make Dialysis Greener

By Tracy Hampton

Solar power can help offset the high utility costs of hemodialysis, making the treatments more environmentally friendly, report scientists in Australia. The findings, published recently in the Clinical Journal of the American Society of Nephrology, point the way to a “green dialysis” future when resources are used and reused wisely.

Hemodialysis treatments for kidney failure patients require a considerable amount of basic utilities such as water and power, leaving a vast carbon footprint behind that is sure to grow as the incidence and prevalence of dialysis use inevitably rise worldwide. “As our planet’s population continues to grow, so does the sustainable growth rate of the dialysis patient population. This annual growth rate is now expected to be 6 percent, which will give us roughly 4 million patients by 2025,” said Faisal Tarass, MD, head of the department of hemodialysis at the Hospital Princessa Lala Meriem, in Morocco.

Demands of dialysis

Research indicates that each hemodialysis treatment uses more than one half the daily power consumption of an average Australian four-person home, and power prices are predicted to soar to two to three times the current rate over the coming decade in Australia. Yet little thought has yet been given to addressing the resource demands of dialysis.

To see whether solar energy might be used to help meet the power demands of dialysis equipment, John Agar, MBBS, Anthony Perkins, and Alwie Tjipto, MBBS, of Geelong Hospital, Barwon Health, in Victoria, Australia, established a solar-assisted dialysis program in Geelong (located in southeastern Australia) that included four home dialysis machines. For solar comparison, Geelong is comparable with St. Louis, Missouri.

Previously, the investigators conducted other resource conservation initiatives that addressed water reuse practices and recycling of reject water. They successfully developed interventions that have reduced water losses of up to 100,000 L per week across their facility and home hemodialysis sites. For example, reject water from the hospital-based dialysis unit provides

No Reduction from Paracalcitrol on Left Ventricular Mass in CKD Patients, but Other Outcomes Hint at Benefit

Forty-eight weeks of paracalcitol, the active hormonal form of vitamin D, doesn’t reduce left ventricular mass or most measures of cardiac function in patients with stage 3 or 4 chronic kidney disease (CKD), according to a study published in the Feb. 15 Journal of the American Medical Association. But there was one intriguing finding: treatment reduced left atrial volume and improved some clinical outcomes, setting the stage for larger studies to explore whether treatment with paracalcitol has a role in treatment of CKD patients.

“Cardiac hypertrophy is exceedingly common in patients with chronic kidney disease, both before and on dialysis,” according to Ravi Thadhani, MD, lead investigator and director for clinical research in nephrology at the Massachusetts General Hospital in Boston. CKD patients are “profoundly deficient” in vitamin D, and observational studies and animal models have suggested that vitamin D might reduce left ventricular hypertrophy. It was that hypothesis that Thadhani and colleagues set out to test.
What do those low cost labs really offer?

We believe a true lab partner should act like a partner, not a vendor.

Which is why we’ve decided not to slash our prices and strip away all of the services, support and expertise you’ve come to count on. Instead, we’re providing the same level of service you need to ensure the best outcomes possible for your patients. And that means offering our comprehensive laboratory testing services with no hidden fees, advanced billing systems, comprehensive reporting tools, and on-site clinical in-services. We believe that the more resources you have to take care of your patients, the easier it will be to take care of your business.
Solar Power

Continued from page 1

autoclave steam for instrument sterilization, ward toilet flushing, janitor stations, and garden maintenance. Satellite center reject water is tanker-trucked to community sporting fields, schools, and gardens. Home-based nocturnal dialysis patient reject water is used for home domestic utilities, gardens, and animals. A natural progression for the team was to move from water to power.

The group chose solar power above wind power for this study because solar radiation is silent and, because it penetrates clouds, more dependable. Wind is unpredictable, and harnessing its power can cause noise and visual pollution. This study represents the first known and reported solar project in dialysis.

For their study, the investigators used the simplest solar model: array donation to, and service draw from, the national grid. The power generated by the solar array was metered and recorded before being directed to the national grid, permitting weekly tracking of all grid-donated power and power drawn specifically for dialysis-related use.

Cutting costs, saving resources

After the first 12 months of the program (from July 26, 2010, to July 25, 2011), power costs were reduced by 76.5 percent. Interestingly, the authors report that from a "what has the weather been like" assessment of Geelong, the 12-month study period was one of the worst remembered; however, solar exposure is not entirely dependent on sunshine and sunlight.

"After several years, the system is expected to turn a profit in addition to generating effectively free power. A solar array is estimated to have a lifespan of approximatley 30 years.

"Geelong Hospital is showing that renewable power for dialysis is both practical and cost-effective," said Frances Mortimer, MRCP, who was not involved with the research and is the medical director of the Centre for Sustainable Healthcare in Oxford, UK.

"Professor Agar’s article provides a timely reminder of the environmental impact of hospital use of renal medicine in particular," said Andrew Conner, MD, who was the Centre for Sustainable Healthcare’s first Green Nephrology Fellow (2009–2010). "It’s inspiring to see practical measures being put into place to reduce these impacts and to realize financial benefits simultaneously."

Conner, who is in the department of renal medicine at Derriford Hospital, in Plymouth, UK, has published widely in the field of sustainable health care.

Directors of dialysis services may wish to investigate whether they can take similar steps toward greener dialysis, taking into account that charges for grid-provided power and reimbursement rates for grid-donated power from alternative sources such as the sun or wind will vary from place to place and from power company to power company.

"Although not all locations, purchasing environments, or local administration will be capable of supporting the twin issues of environmental degradation and climate change demand that simple ecoassessment is made and solutions sought," the authors wrote.

They encourage the dialysis community to assess the solar exposure records at their home geographic position, which can be done at http://www.wunderground.com/calculators/solar. With local latitude and longitude coordinates, investigators can obtain tables and graphs for the mean daily, weekly, monthly, or annual solar exposure of a particular location.

"Now, the expected local solar exposure, available solar arrays, local purchase and installation costs, power rates charged by local utilities, any predicted price changes, and local reimbursement rates for grid-contributed power, a simple calculation can determine whether solar-assisted power might be financially viable," the authors wrote.

The researchers also advocate for applying water conservation and improved waste management systems (such as those that use steam sterilization of post-dialysis plastic waste before shredding) to dialysis programs. "For too long, we have (ab)used but have not considered the environmental consequences of that (ab)

use. It is time to change that paradigm," they wrote.

Connor has worked to spread this same message in recent years by leading work to determine the carbon footprints of renal services and different dialysis regimens. In the UK, his work within the Green Nephrology Programme has included recruiting a network of Green Nephrology Local Representatives in over half of the nations’ kidney units, surveying the environmental practices of these units, and developing tools to reduce their impacts through case studies.

“One of the challenges for the future must now be to drive down the emissions generated in the production of dialysis consumables,” Conner said.

Protecting the environment is a worthy cause in itself, but there may be additional motivation to green nephrology because patients with kidney disease are particularly vulnerable to the effects of climate change. For example, extremes of weather can disrupt dialysis services and negatively affect the health of these patients, who are particularly at risk in very hot weather.

Disclosure: Fresenius Medical Care (Australia) provided the funding and secured the technical advice to resource the project.


Paracalcitol

Continued from page 1

in the study. He chose to use paracalcitol, rather than the dietary form of vitamin D, because the conversion to the hormono logical form takes place in the kidneys, and is impaired in CKD.

The primary endpoint in the study was left ventricular mass index (LVMI) as determined by cardiac MRI, “the gold standard,” Thadhani said. Prespecified secondary endpoints included changes in diastolic mitral annular relaxation velocity (E’), changes in B-type natriuretic peptide (BNP), and several measures of left ventricular function. The trial, known as PRIMO (Paracalcitol Capsule Benefits in Renal Failure-Induced Cardiac Myopathy) was investigator-initiated, and funded by Abbott Laboratories.

The study took place at 60 centers in 11 countries, which required a coordination and standardization effort. Thadhani characterized as “very labor-intensive.” It enrolled 227 patients, with a mean age of approximately 65. Most patients had hypertension, and many were receiving medication for it. Patients were randomized to receive either placebo or paracalcitol for 48 weeks. Early and sustained reduction in parathyroid hormone levels in the active-treatment group indicated good compliance throughout the study.

At the study’s end, there was no significant difference between the treatment arms in LVMI, even after a sensitivity analysis to account for patients with missing data or those lost to follow-up. While unexpected, Thadhani said, “I think it is an important result, because it gives us an idea of where the signal may not be,” and therefore will guide the design of future studies. There was also no difference in E’, a measure of left ventricular relaxation.

There were, however, clear differences between the groups on other secondary endpoints. B-type natriuretic peptide increased in both groups, but favored active treatment. While total hospitalizations did not differ between groups, there was only one cardiovascular event requiring hospitalization in the active treatment group, but eight in the placebo group, five of them for congestive heart failure.

Thadhani cautioned that therapy needs to be aware of these two consequences of the therapy, he said.

While unexpected, Thadhani said, “I think we have a signal, one that could explain perhaps: the PRIMO randomized controlled trial, JAMA 2012; 15:674–84.
By Grant Olan

ASN’s Geriatric Nephrology Advisory Group (GNAG) recently won a $25,000 grant from the Association of Specialty Professors (ASP) for improving competency in palliative end-of-life care among nephrology fellows.

GNAG is pleased to announce that the ASP grant will support the Dimitrios G. Oreopoulos Visiting Professor Program. This program, named in honor of the longtime GNAG chair and lifetime leader in the field of geriatric nephrology, will help foster exposure of fellows and faculty in Accreditation Council for Graduate Medical Education (ACGME)-certified nephrology fellowship training programs to issues related to palliative and end-of-life care.

Nephrology training programs have not traditionally emphasized training in end-of-life care, and research suggests that nephrologists are often not comfortable addressing the end-of-life needs of their patients. Nephrologists and other providers involved in the care of older patients with advanced kidney disease have a unique opportunity to improve the quality of end-of-life care for this population. Training a future generation of nephrologists how to manage the end-of-life needs of their older patients with kidney disease is a critical component in achieving this goal.

The program will provide $1425 in travel support for visits from a nationally recognized expert in end-of-life care for up to five nephrology fellowship programs ($7125 total). GNAG is now accepting applications. The deadline to apply is 11 p.m. ET on May 1, 2012. For more information, please visit www.asn-online.org.

The visiting professor program builds on GNAG’s longstanding commitment to advancing nephrologists’ understanding of end-of-life care, including GNAG’s development of the ASN Geriatrics Nephrology Online Curriculum in 2009. The curriculum addresses the most significant aspects of caring for aging patients with kidney disease (including assessing GFR in the elderly, drug dosing and renal toxicity, management of ESRD in elderly patients, and end of life decision making) and is free for all members of ASN and the renal community, physicians, students, and other providers at http://www.asn-online.org/education_and_meetings/palliative_care/end_of_life/education/curricula/geriatrics/

The ASP grant will also support GNAG’s efforts to update and enhance the end-of-life and palliative care content in the ASN Geriatrics Nephrology Online Curriculum, and to improve access to this resource and other online educational resources related to end-of-life care for fellows and faculty in ACGME-certified nephrology fellowship training programs.
The perfect complement to Kidney Week

For the Kidney Week sessions you missed
For a synopsis of key topics in nephrology
For critiques and perspectives by leaders in the field
Earn CME credits
- Acute Kidney Injury
- Clinical Nephrology
- End-Stage Renal Disease
- Hypertension
- Kidney Transplantation
- Parenchymal Disorders

Berlin, Germany
January 21 – 22, 2012

Dallas, TX
March 3 – 4, 2012

Chicago, IL
March 17 – 18, 2012

Cartagena, Colombia
April 18, 2012

Washington, DC
April 28 – 29, 2012

New York, NY
May 5 – 6, 2012
Many clinical guidelines—including a recent one on dialysis—recommend taking a patient’s life expectancy into account in selecting treatments, but accurate prognostic tools are hard to find and use, especially amid the time constraints of a busy practice. A new website could make life expectancy judgments for older patients easier and more accurate by offering automated calculators that provide patient-specific statistical likelihoods after a few clicks of a mouse. The calculators are backed up by a recent review article in the Journal of the American Medical Association (1).

“Ignoring prognosis and life expectancy can lead to poor care,” said study coauthor Sei Lee, MD. Patients are often treated with therapies that they will not live long enough to benefit from. Those with life-threatening conditions are often referred to hospice too late to appreciate its benefits. And age-based recommendations may withhold appropriate treatment from those who are unusually hale and hearty for their chronologic age.

“Life expectancy is often not accounted for in medical decision-making, so we tried to make it easier for doctors and other health-care providers by collecting all of the life-expectancy calculators that we could find in a systematic review and putting them in one place so that people could just go to one place and find what they needed,” Lee told ASN Kidney News. He is an assistant professor of medicine in the geriatrics division at the University of California, San Francisco.

After a literature search, the researchers screened some 20,000 prognostic indices. They ruled out disease-specific indices, focusing on all-cause mortality in patients over 60 years old. They found 16 indices that passed the test of being developed in one cohort and validated in another with a level of accuracy deemed “moderate” to “very good.” The indices apply to different populations, including those living at home, in nursing homes, and in hospitals.

The researchers then used the parameters delineated in each report to create automated calculators and published them at a website, Eprognosis.org. The researchers urge caution in their use because none of the prognostic indices has been completely tested for routine use, but they propose that the indices provide some objective information beyond a physician’s intuition and experience.

None is specific to nephrology, but measures of kidney health are important contributors to some. For example, the Inouye burden-of-risk illness score for nonterminal hospitalized persons 65 years and older has an accuracy rating of “good.” It gives a patient who on admission has chronic renal failure, an albumin level of 3.5 g/dL or lower, a creatinine level above 1.5 mg/dL, and no other risk factors (such as cancer, stroke, congestive heart failure, diabetes with end-organ damage, or dementia) a 32 percent 1-year mortality risk. The addition of a single additional risk factor raises this risk to 61 percent.

“I think that it is a very important review,” said Mark A. Swidler, MD, a nephrologist and associate professor of medicine, geriatrics, and palliative medicine at Mt. Sinai School of Medicine in New York City, who was not involved in the review.

“It draws attention to the importance of prognostic indices because we have an aging population that is living longer with a greater amount of comorbid conditions and geriatric syndromes, some of whom are facing dialysis decisions or are on dialysis. It is important to have methods to quantify the contributions of those conditions and syndromes to the patients’ survival. However, we’re not only talking about survival. Geriatric decision-making is also about quality of life, which is most reflected in optimizing mental function and functional status. Eprognosis is useful because it provides calculators, so all you have to do is put in the appropriate numbers and then you get an answer,” Swidler said. A clinician could bring up the calculator on a smart phone while talking to a patient but would be unlikely to perform the calculations required otherwise. Swidler agreed with the review authors, who noted that more work remains to make prognostic indices more helpful for routine use. Also, although prognostic information is important in a patient’s decision to choose or forego dialysis therapy, these indices have not been validated in dialysis or other nephrology populations.

Prognosis is especially relevant to high-impact treatments such as dialysis and transplantation. The 2010 edition of the Renal Physicians Association guideline on initiating and withdrawing dialysis emphasizes the need to estimate prognosis and survival time. The chair of the panel that drew up the guideline, Alvin H. Moss, MD, told ASN Kidney News, “The physician should learn the patient’s values, wishes, and goals for care and make a treatment recommendation, also taking into account the patient’s prognosis and overall condition. It is a shared decision-making process, about what course of treatment the patient would want given the patient’s condition. The prognostic information is very helpful in that process.”

Although some indices have been developed that are more applicable to nephrology patients than are those at Eprognosis.org, most are not as accessible as calculators. However, Moss helped create an easy-to-use calculator for patients already undergoing dialysis, “The Surprise Question—Dialysis Mortality Predictor.”

Rethinking dialysis in the elderly?
The consideration of prognosis could lead to some rethinking about dialysis, especially because the fastest-growing age group to start dialysis is made up of those 75 and older. The average life expectancy of a 75-year-old starting dialysis is 1.5–2 years, so the wisdom of the treatment was called into question by a study showing that the start of dialysis is associated with a substantial and sustained decline in functional status in nursing home residents with ESRD, published in 2009 in the New England Journal of Medicine by Manjula Kurella Tamura, MD, and associates (2).

An assistant professor of medicine at Stanford University, Kurella Tamura has a prognosis-oriented article coming out in Kidney International that provides a framework for individualizing ESRD management decisions in older patients by incorporating life expectancy and patient preferences to assess the risks and benefits of competing treatment strategies (3). “We tried to look at decisions like vascular access placement or referrals for kidney transplant, because life expectancy has a substantial effect on the potential benefits of those interventions,” she told ASN Kidney News.

Most guidelines recommend an arteriovenous (AV) fistula rather than an AV graft or a catheter as the first access type in patients beginning hemodialysis, but the recommendation may not apply equally to all. AV fistulas have...
fewer complications like access-related bloodstream infec-
tions than do AV grafts or catheters, but they take longer
to mature, so patients with limited life expectancies may
not realize the benefits. Kurella Tamura and her team esti-
ated that for the average 75-year-old patient, one would
need to treat 25 patients with an AV fistula rather than
an AV graft to prevent one episode of access-related in-
fec tion. “That to us seems like quite a large number of
patients. In contrast, you would only have to treat two
patients with an AV graft vs. a catheter in order to prevent
one bloodstream infection. That suggests that a fistula
may not be the access of first choice for some patients,”
she said.

The article says that perfectly accurate predictions of
life expectancy are not needed: “Reasonable estimates of
whether a patient is above or below the median life ex-
pectancy for his or her age will allow clinicians to make
better assessments of the risks and benefits of various
management strategies.”

The article also contains life expectancy estimates for
dialysis patients of different ages broken into quartiles.
For example, in the 75–79 age group, 25 percent of the
patients can be expected to live 1.7 years, and 25 percent
to live 6 months or less. Swidler said that the Eprognosis indices could be helpful
in placing patients into these quartiles and talking mean-
ingfully to them about how they want to optimize their
quality of life and spend their remaining time.

In an editorial in JAMA that accompanied the prog-
nostic indices review, Thomas M. Gill, MD, of Yale cau-
tions, “Despite the proliferation of prognostic indices
for mortality, there is currently no evidence that their routine
use improves patient outcomes. To determine whether use
of a previously validated prognostic index is better than
usual care, an impact study must be conducted.”

The review article agrees that “further research is need-
ed before general prognostic indices for elderly individuals
can be recommended for routine use.” But Lee said that
he would “absolutely encourage” clinicians to use the in-
dices “with a grain of salt” to improve on the use of clini-
cal experience alone.

Physicians too optimistic?

Studies have shown that physicians tend to be too opti-
mistic in estimating life expectancy. “When you compare
clinician intuition vs. an index vs. a combination of both,
the combination always wins, and so I would argue that
this piece of information is a valuable adjunct to clinical
intuition and has been shown to lead to more accurate
predictions,” Lee said.

A potentially controversial aspect of Eprognosis.org is
that its presence on the Internet makes it accessible to the
general public. Patients can access it simply by clicking
the button saying that they are health professionals. The
researchers left it accessible because anything that would
have made it harder for the public to use would have
made it less accessible to physicians. Lee acknowledged
that even sophisticated patients may not understand the
limitations of the indices.

Public accessibility can be seen as a part of the move-
ment toward shared decision-making, observers said.
“We’re moving toward an age where consumers are bet-
ter informed,” said Moss, a nephrologist and medical
ethicist at West Virginia University. “But drawing conclu-
sions from Eprognosis.org is not something that patients
should do independent of having a discussion with their
doctor.”

“I think families and patients have to be involved and
be given the choice of getting the information,” Swidler
said. “Dialysis in certain subgroups of the elderly ESRD
population is very challenging. You are signing up for a
treatment program that is a big commitment. And up
until now, I don’t think there has been enough available
information for the public to really know what the reality is and make good decisions.”

Lee said that he has been using prognostic indices for
years in his geriatrics and palliative care practice for discus-
sions with patients: “It really opens the door. Some patients
quickly let me know that they don’t want to talk about it,
and I recommend specific care incorporating life expect-
cy into my recommendations, but I don’t ever explicitly
talk about it. For other patients, they have been thinking
about it, and it feels like flood gates are opening.”

References
1. Yourman LC, Lee SJ, Schonberg MA, et al. Prognos-
tic indices for older adults: a systematic review. JAMA
al. Functional status of elderly adults before and after
1547.
3. Kurella Tamura M, Tan JC, O’Hare AM. Optimizing
renal replacement therapy in older adults: a frame-
work for making individualized decisions. Kidney Int
2011, in press.
FREE APP

Leading the fight against kidney disease

JASN

Available on the App Store

ASN
**FSGS’ Link to Neurologic Disorder Probed**

By Richard Robinson

The recent discovery of inverted formin 2 (INF2) as a major gene for focal segmental glomerulosclerosis (FSGS) focused the spotlight on this gene as important for understanding renal disease. New findings reveal that the same gene causes an uncommon neurologic disorder, Charcot-Marie-Tooth disease (CMT), in a subset of the same patients.

The finding has important clinical implications for FSGS patients, and it sheds light on the crucial role of the actin cytoskeleton in the structure and function of the podocyte, a property it appears to share with the Schwann cells that insulate axons.

“We do not know exactly why some mutations lead only to the renal disease, while others cause renal plus neurologic disease,” said Corinne Antignac, MD, PhD, lead author of the study and a researcher at the French National Institute of Health and Medical Research and the Necker Hospital in Paris. However, she said, it appears possible that the exact location of the mutation along the gene determines whether the kidneys and nervous system, or the kidneys alone, are affected.

The study was published late last year in the *New England Journal of Medicine*.

The clinical implication of the finding is quite clear, Antignac said. “If you have patients with familial-dominant FSGS, you have to check whether they might have a neurologic disorder.” Patients suspected of having peripheral neuropathy should be referred to a neurologist for further evaluation and treatment.

The CMT disease causes progressive weakness and atrophy of distal muscles and reduced tendon reflexes. Over time, patients typically experience deformities of the foot, including high arches and hammertoe, along with hand deformities.

Mutations in the *INF2* gene were originally linked to FSGS in 2010 by Marin Pollak, MD, and colleagues. In early 2011, Antignac and her team reported that out of 54 French families with autosomal-dominant FSGS, 17 percent carried *INF2* mutations. By contrast, only one patient in 84 sporadic cases carried a mutation. These results indicated that *INF2* mutations are a major cause of autosomal-dominant FSGS but are unlikely to account for a significant fraction of sporadic disease.

The gene encodes a formin protein, a family of proteins involved in remodeling of the actin and microtubule cytoskeleton. In fulfilling this role, INF2 interacts with myelin and lymphocyte protein (MAL), which, as its name implies, is found in both myelin and lymphocytes, along with podocytes. “When we read the literature, we saw that INF2 was interacting with MAL, and that reminded me that we had heard about patients with both FSGS and Charcot-Marie-Tooth disease,” Antignac said.

That led her to wonder whether the two diseases might have a common cause in these patients. She and her colleagues enrolled 16 patients with both FSGS and CMT from 16 unrelated families, including seven with autosomal-dominant FSGS and nine with sporadic disease. They also obtained DNA from an additional four families from previously published cases. They ruled out mutations in the two genes that account for the large majority of CMT cases, called PMP22 and MPZ, both of which are crucial for myelin stability in Schwann cells.

They found heterozygous mutations in *INF2* in 12 of the 16 patients. In most patients, though not all, symptoms of CMT developed earlier than or at the same time as proteinuria, in patients ranging from age 5 to age 28 (median, age 13). Several patients had both sensorineural hearing loss and muscle weakness. Patients were classified as having an intermediate CMT phenotype, with a combination of both axonal and demyelinating changes.

The nine different mutations were all located in exons 2 and 3 of the gene, which encode a protein domain crucial for interacting with multiple other proteins.

“All of the mutations for both CMT and FSGS are located in a more central part of the protein” compared with those causing FSGS alone, Antignac said. This may account for the more widespread clinical phenotype arising from these mutations, although much work remains to be done to test that hypothesis.

In the kidney, *INF2* is predominantly expressed in podocytes, where it interacts with MAL, among other targets, as it does in Schwann cells. In Schwann cells, the disease-causing mutations do not interrupt *INF2*-MAL binding but instead, Antignac showed, cause MAL to be mislocalized away from the nucleus and diffused throughout the cytoplasm. Cells with mutant INF2 had less cortical actin and a reduced number of long actin stress fibers, and their microtubule network was disorganized.

“INF2 is involved in polymerization and depolymerization of actin,” Antignac said, “and it is well known that the cytoskeleton is crucial for the shape of the podocyte. You can very well imagine if this system is interrupted, it could lead to abnormalities of the cytoskeleton, and to disease.”

Her group is currently investigating the role of the INF2-MAL complex in intracellular transport in the podocyte.

“It has been shown that the complex is involved in transport in lymphocytes, and we are trying to figure out whether it is critical for the podocyte. It is very important to try to understand how INF2 works,” she said, and how it goes awry when mutated, because it may give clues to the development of treatments for both primary and secondary FSGS.

“I think this is a fascinating finding,” said Pollak, who discovered the INF2-FSGS link. “It emphasizes the importance of taking a careful family history.” Pollak is chief of nephrology at Beth Israel Deaconess Medical Center in Boston.

“It’s a great paper,” Pollak said. “People have long noted there are certain similarities between podocytes and some cells of the nervous system, in terms of structure and biology, and this is consistent with that at a genetic level.” Those similarities are especially acute in the “architectural complexity” of the two cell types, made possible by actin and other cytoskeletal elements.

James Lupski, MD, PhD, professor and vice chairman of molecular and human genetics and professor of pediatrics at Baylor College of Medicine in Houston, who is an expert on CMT, agreed that the article is important.

“In both the neuropathy and the glomerular disorder, you are dealing with cells that have had to specialize, creating very unusual membrane structures. The Schwann cell wraps many times around the axon, while the podocyte must have a very large surface area to deal with filtration.” The remarkable thing, he said, “is that one protein is involved in solving this problem in both.”

**Suggested Reading**


---

In Advanced Renal Cell Carcinoma...

**Indication**

VOTRIENT is indicated for the treatment of patients with advanced renal cell carcinoma (RCC).

**Important Safety Information**

**WARNING: HEPATOTOXICITY**

Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. See “Warnings and Precautions,” Section 5.1, in complete Prescribing Information.

- **Hepatic Effects:** Patients with pre-existing hepatic impairment should use VOTRIENT with caution. Treatment with VOTRIENT is not recommended in patients with severe hepatic impairment. Increases in serum transaminase levels (ALT, AST) and bilirubin were observed. Severe and fatal hepatotoxicity has occurred. Transaminase elevations occur early in the course of treatment (92.5% of all transaminase elevations of any grade occurred in the first 18 weeks). Before the initiation of treatment and regularly during treatment, monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended.

- **QT Prolongation and Torsades de Pointes:** Prolonged QT intervals and arrhythmias, including torsades de pointes, have been observed with VOTRIENT. Use with caution in patients at higher risk of developing QT interval prolongation, in patients taking antiarrhythmics or other medications that may prolong QT interval, and those with relevant pre-existing cardiac disease. Baseline and periodic monitoring of electrocardiograms and maintenance of electrolytes within the normal range should be performed.

- **Hemorrhagic Events:** Fatal hemorrhagic events have been reported (all Grades [16%] and Grades 3 to 5 [2%]). VOTRIENT has not been studied in patients who have a history of hemoptysis, cerebral, or clinically significant gastrointestinal hemorrhage in the past 6 months and should not be used in those patients.

- **Arterial Thrombotic Events:** Arterial thrombotic events have been observed and can be fatal. In clinical RCC studies of VOTRIENT, myocardial infarction, angina, ischemic stroke, and transient ischemic attack (all Grades [3%] and Grades 3 to 5 [2%]) were observed. Use with caution in patients who are at increased risk for these events.

- **Gastrointestinal Perforation and Fistula:** Gastrointestinal perforation or fistula has occurred. Fatal perforation events have occurred. Use with caution in patients at risk for gastrointestinal perforation or fistula. Monitor for symptoms of gastrointestinal perforation or fistula.

- **Hypertension:** Hypertension, including hypertensive crisis, has been observed. Blood pressure should be well-controlled prior to initiating VOTRIENT. Monitor for hypertension and treat as needed. Hypertension was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks). In the case of persistent hypertension despite anti-hypertensive therapy, the dose of VOTRIENT may be reduced. VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite the use of antihypertensive medications.

- **Proteinuria:** Proteinuria was reported in 44/586 patients (8%) (Grade 3, 5/586 [<1%] and Grade 4, 1/586 [<1%]). Baseline and periodic urinalysis during treatment is recommended. Discontinue for proteinuria >3+ (Grade 4). Proteinuria has been observed in clinical studies as a common adverse reaction (≥5%) in the VOTRIENT arm versus placebo. In a phase 3, randomized, double-blind, placebo-controlled trial, VOTRIENT provided significant improvement in progression-free survival (PFS) in both treatment-naïve and cytokine-pretreated patients with advanced RCC (95% CI, 2.8-5.6) vs placebo (95% CI, 0.8-2.4) (P < 0.001) in treatment-naïve patients and (95% CI, 5.6-12.9) vs placebo (95% CI, 2.8-14.8) (P < 0.001) in cytokine-pretreated patients. The median PFS with VOTRIENT (n=290) was 9.2 months (95% CI, 7.4-12.9) vs 4.2 months (95% CI, 2.8-5.6) with placebo (n=78). Of patients with advanced RCC who experienced PFS events, 26/586 (4%) (Grade 3, 5/586 [<1%] and Grade 4, 1/586 [<1%]) were observed. Use with caution in patients with proteinuria. Discontinue for proteinuria >3+ (Grade 4).

- **Wound Healing:** VOTRIENT may impair wound healing. Temporary interruption of therapy with VOTRIENT is recommended in patients undergoing surgical procedures. VOTRIENT should be discontinued in patients with wound dehiscence.

- **Hypothyroidism:** Hypothyroidism was reported as an adverse reaction in the VOTRIENT arm. Most common adverse events observed with VOTRIENT were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting. Adverse reactions occurring in >10% of patients and more commonly (≥5%) in the VOTRIENT arm versus placebo included increases in transaminases (grade 3, 15%; grade 4, 3%); decreases in total bilirubin (36% vs. 10%); decreases in phosphorus (34% vs. 11%), glucose (41% vs. 33%), and potassium (38% vs. 21%). Grade 3 or 4 increases in WBC occurred in 11% of patients; grade 4, 2% of patients. No clinically relevant changes were observed in hematologic or coagulation parameters. Electrolytes within the normal range should be performed.

- **Drug Interactions:** CYP2C19, CYP2D6, or CYP2C8 is not recommended. VOTRIENT can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should not use VOTRIENT. Please see Brief Summary of Prescribing Information on www.nccn.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc 2011. All rights reserved. Accessed November 17, 2011. To view the most recent and complete version of the NCCN® Guidelines.

- **Hypertension:** Hypertension, including hypertensive crisis, has been observed. Blood pressure should be well-controlled prior to initiating VOTRIENT. Monitor for hypertension and treat as needed. Hypertension was observed in 47% of patients with RCC treated with VOTRIENT. Hypertension occurs early in the course of treatment (39% of cases occurred by Day 9 and 88% of cases occurred in the first 18 weeks). In the case of persistent hypertension despite anti-hypertensive therapy, the dose of VOTRIENT may be reduced. VOTRIENT should be discontinued if there is evidence of hypertensive crisis or if hypertension is severe and persistent despite the use of antihypertensive medications.
Move Forward With VOTRIENT

In a phase 3, randomized, double-blind, placebo-controlled trial, VOTRIENT provided significant improvement in progression-free survival (PFS) in both treatment-naïve and cytokine-pretreated patients with advanced RCC.1,2

NCCN Guidelines® Category 1 recommendation4
- As a first-line therapy for relapsed or Stage IV unresectable RCC of predominant clear cell histology. These Guidelines also include therapies other than VOTRIENT as first-line treatment options

WARNING: HEPATOTOXICITY
Severe and fatal hepatotoxicity has been observed in clinical studies. Monitor hepatic function and interrupt, reduce, or discontinue dosing as recommended. See “Warnings and Precautions,” Section 5.1, in complete Prescribing Information.

VOTRIENT: Safety Profile Summary1
- Most common adverse events observed with VOTRIENT were diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting
  - Grade 3/4 fatigue occurred in 2% of patients; all grades, 19% of patients
  - Grade 3/4 anemia occurred in 3% of patients; all grades, 14% of patients
- For any individual adverse reaction in the VOTRIENT arm, the rate of Grade 3/4 adverse events ≤5%

Most common laboratory abnormalities were ALT and AST increases1
- Grade 3 ALT increases occurred in 10% of patients; grade 4, 2% of patients
- In clinical trials, 92.5% of all transaminase elevations of any grade occurred in the first 18 weeks of treatment with VOTRIENT
- Monitor serum liver tests before initiation of treatment with VOTRIENT and at least once every 4 weeks for at least the first 4 months of treatment or as clinically indicated. Periodic monitoring should then continue after this time period

- Adverse Reactions: The most common adverse reactions (≥20%) for VOTRIENT versus placebo were diarrhea (52% vs. 9%), hypertension (40% vs. 10%), hair color changes (depigmentation) (38% vs. 3%), nausea (26% vs. 9%), anorexia (22% vs. 10%), and vomiting (21% vs. 8%). Laboratory abnormalities occurring in >10% of patients and more commonly (≥5%) in the VOTRIENT arm versus placebo included increases in ALT (53% vs. 22%), AST (53% vs. 19%), glucose (41% vs. 33%), and total bilirubin (56% vs. 10%); decreases in phosphorus (54% vs. 11%), sodium (31% vs. 24%), magnesium (26% vs. 14%), and glucose (17% vs. 3%); and leukopenia (37% vs. 6%), neutropenia (34% vs. 6%), thrombocytopenia (32% vs. 5%), and lymphocytopenia (31% vs. 24%).

VOTRIENT has been associated with cardiac dysfunction (such as a decrease in ejection fraction and congestive heart failure) in patients with various cancer types, including RCC. In the overall safety population for RCC (N=586), cardiac dysfunction was observed in 453 patients (≤5%). Please see Brief Summary of Prescribing Information on adjacent pages.


Votrient™
pazopanib tablets (200 mg)

anti-hypertensive therapy and dose reduction of VOTRIENT.
- Wound Healing: VOTRIENT may impair wound healing. Temporary interruption of therapy with VOTRIENT is recommended in patients undergoing surgical procedures. VOTRIENT should be discontinued in patients with wound dehiscence.
- Hypothyroidism: Hypothyroidism was reported as an adverse reaction in 26/586 (4%). Monitoring of thyroid function tests is recommended.
- Proteinuria: Monitor urine protein. Proteinuria was reported in 44/586 (8%) (Grade 3, 5/586 [1%] and Grade 4, 1/586 [0.1%]). Baseline and periodic urinalysis during treatment is recommended. Discontinue for Grade 4 proteinuria.
- Pregnancy Category D: VOTRIENT can cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant while taking VOTRIENT.
- Drug Interactions: CYP3A4 Inhibitors (eg, ketoconazole, ritonavir, clarithromycin): Avoid use of strong inhibitors. Consider dose reduction of VOTRIENT when administered with strong CYP3A4 inhibitors. CYP3A4 Inducers (such as rifampin): Consider an alternate concomitant medication with no or minimal enzyme induction potential or avoid VOTRIENT.

CYP Substrates: Concomitant use of VOTRIENT with agents with narrow therapeutic windows that are metabolized by CYP3A4, CYP2D6, or CYP2C8 is not recommended.
The ΔSCr was decreased by more than 10 percent of baseline in 52 percent of patients. Fourteen percent met the KDIGO criteria for AKI during their hospitalization. AKI risk associated with AKI at 0.8 days after the addition of ΔSCr. The risk of AKI was more than six times higher (odds ratio 6.38) for patients with a 10 percent or greater increase in serum creatinine. In contrast, AKI was significantly reduced (odds ratio 0.31) for patients with a 10 percent or greater increase in serum creatinine.

New approaches are needed to identify patients at increased risk of AKI after cardiac surgery. Recent studies suggest that changes in creatinine before and after cardiac surgery correlate better with patient proctively than any other baseline measurement.

Patients with an increase of more than 10 percent in serum creatinine measured within 6 hours after elective cardiac surgery are at high risk of AKI, the new research suggests. The ΔSCr shows increased predictive ability. The authors note that their study used a surrogate marker of AKI, rather than clinical events [Ho J, et al. Serum creatinine measurement immediately after cardiac surgery and prediction of acute kidney injury. Am J Kidney Dis 2012; 59:106-211].

Postoperative Change in Serum Creatinine Helps Predict AKI Risk

Measuring the change in serum creatinine immediately after cardiac surgery may help in predicting acute kidney injury (AKI), suggests a study in the American Journal of Kidney Diseases. The prospective study included 350 patients undergoing elective coronary artery bypass grafting or valve replacement in Winnipeg, Canada, from 2007 to 2009. Serum creatinine was measured at baseline and within 6 hours after the end of surgery, and then each day during the remaining hospital stay. The immediate postoperative change in serum creatinine (ΔSCr) was evaluated as a predictor of AKI, based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

[36x258]Predict AKI Risk
[37x92]the remaining hospital stay. The immediate after cardiac surgery may help
[38x351]angiotensin system on hyperkalemia and
[38x411]studies of the clinical role and safety of
[38x555]renin-angiotensin system, leading to cau-
[38x639]with aliskiren alone was also associated
[38x699]plus ARB versus ARB monotherapy.
[38x711]risk of hyperkalemia and acute kidney in-
[38x723]bined with ACEIs or ARBs versus ACEIs
[38x759]domized trials comparing aliskiren com-
[38x795]sis in the
[38x807]tion. The factors associated with AKI in
[38x819]criteria for AKI during their hospitaliza-
[212x775]creased from 0.69 in the base model to
[212x823]System for Cardiac Risk Evaluation score.

The ΔSCr was decreased by more than 10 percent of baseline in 52 percent of patients. Fourteen percent met the KDIGO criteria for AKI during their hospitalization. AKI risk associated with AKI at 0.8 days after the addition of ΔSCr. The risk of AKI was more than six times higher (odds ratio 6.38) for patients with a 10 percent or greater increase in serum creatinine. In contrast, AKI was significantly reduced (odds ratio 0.31) for patients with a 10 percent or greater increase in serum creatinine.

New approaches are needed to identify patients at increased risk of AKI after cardiac surgery. Recent studies suggest that changes in creatinine before and after cardiac surgery correlate better with patient proctively than any other baseline measurement.

Patients with an increase of more than 10 percent in serum creatinine measured within 6 hours after elective cardiac surgery are at high risk of AKI, the new research suggests. The ΔSCr shows increased predictive ability. The authors note that their study used a surrogate marker of AKI, rather than clinical events [Ho J, et al. Serum creatinine measurement immediately after cardiac surgery and prediction of acute kidney injury. Am J Kidney Dis 2012; 59:106-211].

Postoperative Change in Serum Creatinine Helps Predict AKI Risk

Measuring the change in serum creatinine immediately after cardiac surgery may help in predicting acute kidney injury (AKI), suggests a study in the American Journal of Kidney Diseases. The prospective study included 350 patients undergoing elective coronary artery bypass grafting or valve replacement in Winnipeg, Canada, from 2007 to 2009. Serum creatinine was measured at baseline and within 6 hours after the end of surgery, and then each day during the remaining hospital stay. The immediate postoperative change in serum creatinine (ΔSCr) was evaluated as a predictor of AKI, based on Kidney Disease: Improving Global Outcomes (KDIGO) criteria.

[36x258]Predict AKI Risk
[37x92]the remaining hospital stay. The immediate after cardiac surgery may help
[38x351]angiotensin system on hyperkalemia and
[38x411]studies of the clinical role and safety of
[38x555]renin-angiotensin system, leading to cau-
[38x639]with aliskiren alone was also associated
[38x699]plus ARB versus ARB monotherapy.
[38x711]risk of hyperkalemia and acute kidney in-
[38x723]bined with ACEIs or ARBs versus ACEIs
[38x759]domized trials comparing aliskiren com-
[38x795]sis in the
[38x807]tion. The factors associated with AKI in
[38x819]criteria for AKI during their hospitaliza-
[212x775]creased from 0.69 in the base model to
[212x823]System for Cardiac Risk Evaluation score.

The ΔSCr was decreased by more than 10 percent of baseline in 52 percent of patients. Fourteen percent met the KDIGO criteria for AKI during their hospitalization. AKI risk associated with AKI at 0.8 days after the addition of ΔSCr. The risk of AKI was more than six times higher (odds ratio 6.38) for patients with a 10 percent or greater increase in serum creatinine. In contrast, AKI was significantly reduced (odds ratio 0.31) for patients with a 10 percent or greater increase in serum creatinine.

New approaches are needed to identify patients at increased risk of AKI after cardiac surgery. Recent studies suggest that changes in creatinine before and after cardiac surgery correlate better with patient proctively than any other baseline measurement.

Patients with an increase of more than 10 percent in serum creatinine measured within 6 hours after elective cardiac surgery are at high risk of AKI, the new research suggests. The ΔSCr shows increased predictive ability. The authors note that their study used a surrogate marker of AKI, rather than clinical events [Ho J, et al. Serum creatinine measurement immediately after cardiac surgery and prediction of acute kidney injury. Am J Kidney Dis 2012; 59:106-211].
Voclosporin, a novel calcineurin inhibitor, compares well with tacrolimus in primary kidney transplant recipients—including a possible reduction in new-onset diabetes after transplantation (NODAT), reports a trial in the American Journal of Transplantation.

The phase 2, open-label trial included 334 low-risk patients undergoing initial renal transplantation. Patients were randomly assigned to receive low, intermediate, or high doses of voclosporin or standard-dose tacrolimus. At 6 months, the rates of biopsy-proven acute rejection were 10.7 percent, 9.1 percent, and 2.3 percent in the low- to high-dose voclosporin groups compared with 5.8 percent in the tacrolimus group. This was within the study margin of noninferiority.

Analysis of secondary outcomes found a reduction in NODAT with voclosporin: 1.6 percent, 5.7 percent, and 11.7 percent, compared with 16.4 percent with tacrolimus. The high-dose voclosporin group had a small but significant increase in estimated GFR compared with those receiving tacrolimus. Pharmacokinetic and pharmacodynamic studies showed excellent correlation between the voclosporin trough level and area under the curve. There were no significant differences in mycophenolic acid exposure.

Voclosporin was developed as a new cal-

cineurin inhibitor for organ transplantation that would reduce toxicity with similar or better efficacy. The new trial suggests that voclosporin is noninferior to tacrolimus in preventing acute rejection after de novo kidney transplantation. Further trials are needed to confirm these results, including the additional trials required to achieve statins to reduce mortality, according to a report in the Clinical Journal of the American Society of Nephrology.

The researchers analyzed data on nearly 26,000 patients from the Dialysis Outcomes and Practice Patterns Study (DOPPS). Morbidity and mortality were assessed at different levels of DNa, accounting for both IDWG and the risk of death associated with lower predialysis serum sodium levels.

At all levels of predialysis serum sodium, higher DNa was associated with increased IDWG. For each 2 mEq/L increase in DNa, there was a 0.17 percent increase in body weight. However, the final model—including adjustment for predialysis serum sodium—found no association between higher DNa and heart failure.

This remained so even after further adjustment for IDWG. In facilities where at least 90 percent of patients had the same DNa (56 percent), the association with mortality was significant: adjusted hazard ratio 0.88 per 2 mEq/L increase. Because of the nature of the data, confounding by indication was considered unlikely.

Recent studies have suggested that reducing DNa may reduce IDWG. Before any such change in clinical practice is made, it’s important to assess the impact on patient outcomes.

The new analysis of DOPPS data does not support the theory that lowering DNa to reduce IDWG will translate to better patient outcomes. The researchers write, “In the absence of randomized prospective studies, the benefit of reducing IDWG by decreasing DNa prescriptions should be carefully weighed against an increased risk for adverse outcomes” [Hecking M, et al. Dialysate sodium concentration and the association with interdialytic weight gain, hospitalization, and mortality. Clin J Am Soc Nephrol 2012; 7:922–1000].
Composite Biomarker Can Track Inflammation in Lupus Nephritis

A combination of three biomarkers may be useful for monitoring interstitial inflammation in patients with lupus nephritis, according to a report in *Kidney International*.

The researchers collected urine samples from 61 patients with lupus nephritis, at or around the time of renal biopsy. All patients met at least four American College of Rheumatology criteria for systemic lupus erythematosus, including immune complex glomerulonephritis. A renal pathologist graded interstitial inflammation and interstitial fibrosis in 64 biopsy specimens. Linear discriminant analysis was performed to evaluate various urinary biomarkers for inclusion in a “composite biomarker” of interstitial inflammation.

The composite biomarker of tubulointerstitial inflammation consisted of monocytic chemotactic protein-1; hepcidin, which reflects nephritis flares; and liver fatty acid-binding protein. Sensitivity was 100 percent, specificity 81 percent, positive predictive value 67 percent, and negative predictive value 100 percent. The composite biomarker had a misclassification rate of only 14 percent.

Renal biopsy is typically performed at diagnosis of lupus nephritis or for subsequent disease flares. An accurate, noninvasive indicator of kidney injury—particularly interstitial inflammation—would be helpful in planning and monitoring medical treatment.

The new composite biomarker shows promise for use in monitoring tubulointerstitial inflammation in lupus nephritis. Although further validation is needed, the authors believe that the biomarker could provide useful information about the renal interstitial in other kidney diseases as well [Zhang X, et al. A composite urinary biomarker for monitoring interstitial inflammation in lupus nephritis. *Kidney Int* 2012; 81:401–406].

Switching to Sirolimus Doesn’t Slow Chronic Changes after Transplantation

For kidney transplant patients going through rapid steroid withdrawal, switching from tacrolimus to sirolimus doesn’t reduce the rate of long-term changes on subsequent renal biopsy specimens, according to a study published in *Transplantation*. The randomized controlled trial included 122 kidney transplant recipients undergoing rapid steroid withdrawal. At 1 month, the patients were assigned to switch from tacrolimus to sirolimus or to remain taking tacrolimus. Protocol biopsy specimens were obtained at 1 month, 1 year, and 2 years for assessment of long-term changes, including interstitial fibrosis and tubular atrophy (IFTA) and the sum of Banff chronic scores (Total Score). The influence of previous rejection episodes on the long-term scores was assessed as well.

One-year biopsy specimens were obtained from 90 percent of patients in both groups. The two groups had similar and significant increases in long-term changes—i.e., proportion of biopsy specimens with IFTA scores of 2 or greater and Total Scores greater than 2. At 1 year, patients who had previous episodes of rejection and who continued to receive tacrolimus had higher IFTA scores and were more likely to have Total Scores greater than 2. Among those without previous rejection, both the IFTA and Total Score showed significant progression from 1 to 2 years.

Chronic calcineurin inhibitor nephrotoxicity contributes to the development of IFTA after kidney transplantation. In a previous report, the authors found no difference in 1-year kidney function among patients who were converted from tacrolimus to sirolimus 1 month after transplantation. The new analysis showed no reduction in the progression of IFTA and other long-term changes through 2 years in kidney recipients who switched to sirolimus, compared with those continuing with tacrolimus. This was so even in patients with no previous episodes of rejection. Further study of the progression of long-term changes after early steroid withdrawal is needed [Heilman RL, et al. Impact of early conversion from tacrolimus to sirolimus on chronic allograft changes in kidney recipients on rapid steroid withdrawal. *Transplantation* 2012; 93:47–53].
New Options for Advanced Kidney Cancer

Several kidney cancer drugs made the news lately. The U.S. Food and Drug Administration (FDA) recently approved Inlyta (axitinib) for treating advanced renal cell carcinoma (RCC) after treatment with a systemic therapy has failed. An oral drug made by Pfizer, Inlyta blocks certain receptors that can influence tumor growth and also the progression of kidney cancer. Forty percent to 65 percent of patients whose cancer progresses after first-line therapy go on to receive a second-line treatment, the company said.

In its January announcement, the FDA said that the safety and effectiveness of Inlyta were evaluated in a randomized, open-label, multicenter clinical study of 723 patients whose disease had progressed during or after treatment with an initial systemic therapy. The study was designed to measure the time a patient lived without the cancer progressing. The results showed a median progression-free survival period of 6.7 months, compared with 4.7 months with a standard treatment (sorafenib).

A study presented at the 2012 Genitourinary Cancers Symposium in early February showed that some patients with metastatic RCC may need a higher than standard dose of the newly approved axitinib to achieve optimal benefit, according to an analysis of data from the phase III AXIS trial.

A new combination therapy is also under development. An immunotherapy (AGS-003) agent from Argos Therapeutics combined with the drug sunitinib may help prolong the lives of men with unfavorable-risk, metastatic RCC, according to new data from an open-label, phase 2 study. The study found that the combination of AGS-003 plus sunitinib was linked with a longer survival period than that for sunitinib alone in these patients. The study enrolled 21 patients (16 men) with newly diagnosed metastatic clear-cell RCC.

Multiple partial responses were observed with this combination regimen: 11 of 15 patients (73 percent) who had immune assessments over time showed increases in their CD28+ memory T immune cells, according to Argos. These immune responses correlated directly with longer survival.

Overall, the median progression-free survival was 11.2 months, and the estimated median overall survival was 29.3 months, on the basis of follow-up through January 2012. The combination of immunotherapy and drug is designed to stimulate a patient’s immune response to the tumor. Each production of a patient’s fully personalized immunotherapy generates up to 5 years of treatment for each patient, said Argos.

Lead investigator Robert Figlin, MD, who directs the division of hematology/oncology at the Cedars-Sinai Samuel Oschin Comprehensive Cancer Institute in Los Angeles, and colleagues found that the combination was tolerated well. Observed adverse events were as expected with sunitinib toxicities, but a notable exception was injection site reactions in approximately 50 percent of study participants.

Preliminary data have been shared about the use of the drug cabozantinib in pretreated patients with metastatic refractory RCC. The patients participated in an ongoing phase Ib trial of cabozantinib, an inhibitor of both MET and VEGFR2 factors. The drug was developed to block metastasis and blood vessel growth in order to kill tumor cells while blocking their escape pathways, Drug Discovery News reported.

The investigators looked at data from patients enrolled in a drug interaction study of cabozantinib in patients with advanced solid tumors. The 25 RCC patients in the trial received 140 mg oral cabozantinib administered daily, and the study endpoints were safety, tolerability, and antitumor activity.

The rate of disease control at week 16 for all 25 patients was 72 percent. An estimated median progression-free survival was 14.7 months (95 percent confidence interval; lower limit 7.5 months; upper limit was not reached). Ten patients remain in the study and are progression-free, with treatment durations ranging up to 16.4 months, according to Drug Discovery News.

Ever since the Centers for Medicare and Medicaid Services (CMS) released the Accountable Care Organization (ACO) final rule in October 2011, the American Society of Nephrology (ASN) ACO Task Force has been analyzing the rule to determine how it may affect patients with kidney disease and the nephrologists who care for them. This Q & A with Amy Williams, MD, and Emily Robinson, MD, is the first in a series of Q & A articles with task force members about ACOs and other approaches to new health care delivery models.

### ASN Task Force Answers Questions about Accountable Care Organizations

**What were the biggest changes from the proposed rule that CMS made to the final ACO rule?**

**Amy Williams:** CMS received extensive feedback on the initial ACO rules, including comments from ASN related to the care of individuals with chronic kidney disease (CKD), ESRD, and kidney transplants. In response to the general comments, CMS made changes that will make it easier for some organizations to form and participate in ACOs. However, the task force was dismayed that CMS did not make any substantial changes to the rule based on the ASN’s recommendations. Table 1 summarizes the most important modifications. You may access a complete list of the 33 quality measures on the ASN website.

**What were the biggest nephrology-specific changes between the proposed and final rules?**

**Amy Williams:** Although the changes to the ACO rules may allow more entities to participate in ACOs, few changes to the rule will have a direct impact on nephrology or on individuals with nephrologic diseases. The goal of delivering patient-centered, collaborative, coordinated health care should improve the care of patients with CKD, but to accomplish this, the nephrology community must partner with the ACO primary care providers to provide appropriate guidance in the care of CKD patients and the primary prevention of renal disease.

Unfortunately, the quality measures, although decreased in number, do not reflect priority outcomes or quality measures for patients with advanced CKD, ESRD, or recent renal transplants. Educating the ACO providers in appropriate use of the routine health maintenance and cancer screening tests in patients with advanced CKD, ESRD, and limited life expectancy will prevent unnecessary testing, possible adverse events, and unnecessary costs.

**How are patients attributed to an ACO?**

**Amy Williams:** The final process of patient assignment to an ACO has two steps:

1. Patients are preliminarily assigned to an ACO on the basis of the historical (prior 12 months) plurality of primary care G-code charges associated with an annual wellness visit or Welcome to Medicare visit attributed to the patient by a primary care provider.
2. If the patient has not had any primary care services from any primary care provider, he or she will be assigned to the specialist and the specialist’s ACO that has provided the plurality of primary care services. This ‘preliminary prospective assignment’ allows ACOs to know which patients they are likely responsible for managing and should help them identify high-risk patients, such as those with advanced CKD and renal transplants, and facilitate early implementation of evidence-based management to improve patient outcomes and manage the cost of care. Final reclassification of patient assignments will occur at the end of the performance period and will be based on which ACO provided the plurality of the patient’s primary services.

**What are the potential positive developments for my dialysis patients if they are attributed to an ACO?**

**Emily Robinson:** There would be pros and cons for a dialysis patient attributed to an ACO. ACOs are charged with developing processes to promote evidence-based medicine, promote beneficiary engagement, and coordinate care, all of which could help all patients, including dialysis patients. ACOs also are mandated to have systems in place to identify high-risk individuals and develop individualized care plans.

Dialysis patients specifically may benefit from improved efforts to coordinate care and efforts at medication reconciliation, one of the quality measures, because they often have medical records in many different locations and different physicians who prescribe their medications. Other quality measures, including vaccination for influenza and pneumonia as well as screening for risk of falling, may be helpful for these patients, although likely they are already being done in the dialysis units.

**Amy Williams:** Partnering with ACO providers to develop and implement patient education materials and best practices for treating patients with CKD, ESRD, and renal transplants could prevent adverse patient and renal outcomes from nephrotoxic medications, polypharmacy complications, and missed opportunities for renal-preserving interventions. Such co-

### Table 1. Modifications to ACO proposed rule

<table>
<thead>
<tr>
<th>Aspect of ACO program</th>
<th>Detailed changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Financial provisions</td>
<td>The final rule reduces financial risk and allows for all ACOs to earn savings from the first dollar saved. CMS initially proposed a rule that only ACOs that shared financial risk in the “two-sided” model could share in savings from the first dollar their ACO saved Medicare. The final rule also eliminates a 25 percent withhold of savings for all participants.</td>
</tr>
<tr>
<td>Application and structural changes</td>
<td>The final rule eliminates the initial application requirement to obtain a mandatory Antitrust Agency review and instead provides a voluntary expedited review. The requirement to undergo an Antitrust Agency review each time an ACO adds a provider or supplier was also eliminated.</td>
</tr>
<tr>
<td>Eligible entities</td>
<td>The proposed rule listed the four groups outlined in the Affordable Care Act, and stated that critical access hospitals paid through Method II were eligible to apply as ACOs. The final rule added Federally Qualified Health Centers and Rural Health Clinics to the list of eligible entities. For all entities, the beneficiaries of established ACO will be assigned on the basis of use of primary care services. Thus, all entities applying must provide a list of practitioners who provide primary care services in their facilities.</td>
</tr>
<tr>
<td>Patient assignment</td>
<td>The initial proposal assigned patients retrospectively on the basis of the plurality of primary services. This approach was changed to incorporate a hybrid of preliminary prospective assignment with quarterly beneficiary identification and reconciliation of assignment at the end of each performance year, based on the patient’s plurality of primary care during that year. This allows for the identification of beneficiaries after the initial ACO application, not waiting until after 1 year of management as initially proposed. The final rule outlined not only assignment based on plurality of primary care services rendered by a primary care physician, but also assignment for beneficiaries who have not had care from any primary care physician. These patients will be assigned on the basis of plurality of primary services provided by the ACO professional (i.e., nephrologists). CMS will monitor avoidance of high-risk patients and, as stated in the proposed rule, will terminate ACO agreements if this behavior is revealed.</td>
</tr>
<tr>
<td>Beneficiary data sharing</td>
<td>In addition to sharing limited patient data (name, date of birth, sex, and health insurance claim number) at initiation of application, the frequency of beneficiary data reports to the ACO was increased from yearly to quarterly. Established ACOs will have the opportunity to ask CMS for additional patient-specific data after receiving a patient’s consent. The ACOs are required to notify the beneficiaries of data sharing and give them the opportunity to decline. If the assigned beneficiary declines data sharing with the ACO, the ACO is still responsible for his or her care (quality, cost, outcomes).</td>
</tr>
<tr>
<td>Quality measures</td>
<td>The initial 65 quality measures in five domains have been decreased to 33 measures in four domains. Unfortunately, the only measure with significant impact on CKD management, microalbuminuria screening, was eliminated. During the first year, CMS will pay for reporting the measures and, during the second and third years of the agreement period, will pay for both reporting and performance. Although declaring that 50 percent of the primary care physicians as meaningful users of the electronic medical record (EMR) is no longer a condition for participation, the EMR remains a quality measure now weighted higher than the other measures. This change will allow practices to apply for inclusion in the ACO program while developing the EMR tools.</td>
</tr>
</tbody>
</table>
ordination may lead to better preparation and appropriate referral for renal replacement therapy or conservative care, ultimately achieving better patient outcomes.

**What are the potential risks or downsides for my dialysis patients if they are attributed to an ACO?**

Emily Robinson: Some aspects of the ACO program may not be so positive for dialysis patients. Some of the quality measures, such as mammograms, colonoscopies, aggressive lipid management, or even aggressive blood pressure control, may not apply to dialysis patients. We may find that instead of careful consideration of the risks and benefits of these interventions in each individual patient based on specific evidence in dialysis patients, these patients may be given the interventions only to satisfy quality measures, even if they are unnecessary and potentially harmful.

If a patient is in a dialysis unit that is not associated with the primary care physician’s ACO, it is possible that the primary care physician will encourage a change of dialysis unit to one within the ACO for better control of costs and savings, even if it is not close to the patient’s home. There may be perverse incentives to hold off on access planning with CKD patients as long as possible to avoid unnecessary costs, thus increasing catheter rates among patients who are beginning dialysis.

Amy Williams: The rule states that difficult patients must be included in the ACO, and an ACO can be terminated for discriminating against these patients. However, the potential for ACOs to avoid assignment of high-risk patients is a concern. Most individuals with advanced CKD and ESRD have multiple comorbidities and require complex care. It is unclear how successful CMS will be in detecting ACOs that avoid enrolling these patients. Nephrologists will need to continue to be advocates for these patients and have a significant role in their medical management.

Emily Robinson: We hope that CMS’s efforts truly safeguard against cherry-picking of patients, and that individuals receiving dialysis, whose care is often complex, will not have a harder time finding a primary care physician willing to accept them as patients.

In the next issue the ASN ACO Task Force will address more questions, including these: Can my nephrology practice join an ACO? What will it mean for me as a nephrologist if my dialysis patients are attributed to an ACO? What other kinds of new care delivery models exist?

If you have questions about ACOs you’d like the task force to address, please email the ASN Manager of Policy and Government Affairs, Rachel Shaffer, at rshaffer@asn-online.org.

Amy Williams is affiliated with the Mayo Clinic in Rochester, NY, and Emily Robinson is affiliated with the Brigham and Women’s Hospital in Boston.
Detective Nephron, world-renowned for his expert analytic 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 master consultant.

Detective Nephron

I am craving a good case today. Wonder what Henle has in store for me.

L. O. Henle enters the room.

What do you want?

I… have a case for us.

Is it another electrolyte disorder?

Hyperphosphatemia.

Hmm…well, let’s take that one, then.

A 67-year-old man with multiple myeloma presents with acute kidney injury secondary to obstruction. They placed a Foley catheter in the emergency room, and his renal function is improving. Initially he had a creatinine level of 4.0 mg/dL, and over the past 2 days it is down to 1.3 mg/dL. Interestingly, the phosphorus level is rising. It was 6 mg/dL on presentation and now it is up to 15 mg/dL.

Near-normal renal function and elevated phosphorus…always an interesting combination.

The medical team wants to start binders as soon as possible.

Aha! This is going to be exciting.

Just some more information, if you will allow, sir.

Sure—I hope it is the information I am looking for.

The calcium and magnesium levels are normal. The patient doesn’t have any signs of tumor lysis syndrome, or acidosis of any kind. Lactate was normal. Also, he has not been getting any vitamin D supplementation or any phosphate enemas.

Wow, you really are taking the fun out of this by giving me a laundry list of differential diagnoses that can cause elevated phosphorus. It seems that you have already ruled out the major common causes. What bothers me is that this is rising in the setting of improving renal function.

We repeated the tests multiple times.

I believe you!

To me this is very confusing. What could be causing such high levels of phosphorus?

Is it the kidney?

The kidneys, I know, are highly efficient in maintaining phosphate balance even when the dietary intake of phosphorus is increased severalfold. If, however, there is an acute phosphate load (i.e., an increase in phosphate concentration over a few hours rather than days), then the entry of phosphate into the extracellular compartment exceeds the rate at which it is excreted, and hyperphosphatemia results.

Exactly! So, think of the causes of hyperphosphatemia in three ways. (1) You gave him too much (we caused it) (i.e., a phosphate load sufficient enough to overwhelm the ability of the kidney to excrete it), (2) His kidneys stopped working (acute renal or chronic renal injury). (3) The kidney is deciding to enhance proximal tubular phosphate reabsorption (very rare).

Seems like we had ruled out causes of acute phosphate load.

Well, the phosphate load can be endogenous or exogenous. No exogenous causes (i.e., ingestion of phosphate-containing laxatives) were found in your case. Endogenous causes can be from cell breakdown—so tumor lysis, rhabdomyolysis, and marked hemolysis can do it. In your particular case, the myeloma history does concern me a bit. Hmmmm!

But with normal calcium, potassium, creatine kinase, and uric acid, less likely any of the above.

Fascinating!

The other causes of mobilization of intracellular phosphate into the extracellular fluid are lactic acidosis and diabetic ketoacidosis. Severe metabolic acidosis can cause cellular phosphate utilization because of inhibition of glycolysis. There is no tissue hypoxia in this case, to our knowledge.

And it’s not renal failure; this man’s GFR is actually improving and most likely will be normal soon. Now, let’s look at the third set of causes and perhaps come up with a diagnosis. What in this patient’s history might have warranted a medication that can have direct effects on phosphorus absorption?

You mean bisphosphonates? No, he didn’t get that one. I know—they can cause mild hyperphosphatemia because they stimulate phosphate transport directly. His parathyroid hormone (PTH) is around 50 pg/mL, so hypoparathyroidism is less likely, and he has no signs of clinical acromegaly. Thought you might like that one, given your prior cases.

Good work, my apprentice. Either deficient PTH secretion or renal resistance to PTH
(pseudohypoparathyroidism) results in increased phosphate reabsorption and leads to hyperphosphatemia. Usually in this case the calcium is low, too. Tumoral calcinosis might be rare in this case because that is more of a genetic disease. Hmm… tough case, but I think I might have just thought of the answer. Like I said, the myeloma history bothers me.

Henle (puzzled)  
What could this possibly be, given that the renal function is getting better and the phosphorus level is getting worse?

Nephron  
How controlled is his myeloma? And what light chain is it?

Henle  
Hmm… Not so well controlled. A multiple regimen is failing, and it’s IgM kappa type.

Nephron (confident)  
All right, then, go ahead and reassure the team to do nothing, and make sure they don’t start any binders because that might be harmful.

Henle exits without questioning.

Nephron (to himself)  
Wonder why he just left without asking me “why”?

Before Detective Nephron can go down to get coffee, Henle returns to the office.

Nephron  
You’re back.

Henle  
I am puzzled. I think you are getting at pseudohyperphosphatemia from paraproteins? Is that right? Should I ask the lab to de-proteinate?

Nephron  
Good work!

Henle  
So this is all a factitious result.

Nephron  
Spurious hyperphosphatemia due to interference with analytic methods may occur in patients with hyperglobulinemia, hyperlipidemia, hemolysis, and hyperbilirubinemia. Phosphate can be determined accurately by reanalysis of the specimen after removal of protein by ultrafiltration. Classically this can be seen with IgM-related diseases rather than IgG, but even in IgG-related paraprotein diseases, this has been recorded. Paraproteins can cause Na, creatinine, CO₂, and Ca values to be spurious. When dealing with large molecules like IgM, one has to be extremely careful about these spurious results.

Henle  
Yes, you are correct.

Nephron (with confidence)  
Henle exits, and Detective Nephron starts reading ASN Kidney News. A few days later, the detective is sipping away at his coffee when Henle enters the office.

Nephron  
Nothing is better than a cup of warm coffee. And a great case.

Henle  
After removal of the proteins, a phosphorus level came back 4.0 mg/dL, and the regular blood work still reads 13–14 mg/dL. This is fascinating.

Nephron  
Great work, Henle (with a smirk). Again, my dear apprentice, never underestimate the power of the nephrologist. Not every electrolyte disorder is real, and not every number should be treated. By not treating here, you prevented harm. Pseudoelectrolyte disorders are a common finding in paraproteinemias. 😊

Detective Nephron was developed by Kenar Jhaveri, MD, assistant professor of medicine at Hofstra North Shore LI School of Medicine. Thanks to Dr. Riniita Wachoe, clinical instructor, division of nephrology, Weill Cornell Medical Center, New York, for her editorial assistance. Send correspondence regarding this section to kjhaveri@nshs.edu or kdj200@gmail.com.
COMMUNI•K — making connections that matter

Takeda and Affymax are teaming up with the renal community to target the relevant issues in patient care for chronic kidney disease (CKD). We want to listen to you, learn about your challenges, and leverage your wisdom to work toward developing smart solutions.

COMMUNI•K  
You talk. We listen. Patients win.