To practicing nephrologists, few drugs are more familiar than sodium polystyrene sulfonate (SPS) (Kayexalate). Generally given in a premixed preparation with sorbitol, Kayexalate is widely used for the treatment of elevated potassium levels, with millions of doses prescribed every year. Despite recent safety concerns—including reports of colonic necrosis, leading to a safety warning from the U.S. Food and Drug Administration—SPS plus sorbitol continues to be available and prescribed.

Prompted by this new attention to an old drug, Richard Sterns, MD, of Rochester General Hospital, University of Rochester School of Medicine and Dentistry, NY, reviewed 50 years of published data on the use of SPS for hyperkalemia and reached some surprising conclusions.

“We found no rigorous scientific evidence showing that ion exchange resins are effective in ridding the body of excess potassium,” said Sterns. “We also found some evidence showing that, on rare occasions, they can be harmful.

“We suspect that if ion exchange resins were introduced today, they would not be approved.” The invited commentary by Sterns—with co-authors Maria Rojas, MD, Paul Bernstein, MD, and Sreedevi Chennupati, MD—appears in the May *Journal of the American Society of Nephrology*.

**Grandfathered drug predates modern drug approval process**

Sodium polystyrene sulfonate is an ion exchange resin designed to exchange sodium for potassium in the colon. It may be given orally or by enema. Because of its poten-

Continued on page 4
Before you start, stop.
Because the benefits should accumulate.
Not the risks.

Renvela® (sevelamer carbonate) tablets or for oral suspension is an effective first-line monotherapy for controlling serum phosphorus in dialysis patients – without calcium or metal accumulation. Renvela is the only phosphate binder available in both tablet and powder dosing options.

Indication: Renvela® (sevelamer carbonate) is indicated for the control of serum phosphorus in patients with chronic kidney disease (CKD) on dialysis.

Important Treatment Considerations
Renvela is contraindicated in patients with bowel obstruction • Caution should be exercised in patients with dysphagia, swallowing disorders, severe gastrointestinal (GI) motility disorders including severe constipation, or major GI tract surgery • Uncommon cases of bowel obstruction and perforation have been reported • Serum bicarbonate and chloride levels should be monitored • Vitamins D, E, K (coagulation parameters), and folic acid levels should be monitored • The most frequently occurring adverse reactions in a short-term study with sevelamer carbonate tablets were nausea and vomiting • In a short-term study of sevelamer carbonate powder dosed three times daily, adverse events were similar to those reported for sevelamer carbonate tablets • In long-term studies with sevelamer hydrochloride, which contains the same active moiety as sevelamer carbonate, the most common adverse events included vomiting, nausea, diarrhea, dyspepsia, abdominal pain, flatulence, and constipation • Cases of fecal impaction and, less commonly, ileus, bowel obstruction, and bowel perforation have been reported • Drug-drug interactions may occur with some medications and should be taken into consideration when instructing patients how to take Renvela • Patients should be informed to take Renvela with meals and to adhere to their prescribed diets.

Please see Brief Summary of Prescribing Information on adjacent page.

New Questions

Continued from page 1

tial to cause severe constipation, SPS is usually given with sorbitol, a widely used laxative for that purpose.

The Kayexalate name is still widely used, even though generic preparations are most commonly given. "Kayexalate be- comes synonymous with SPS—it's kind of like Kleenex or Xerox," said Sterns. "When Kayexalate is written, what's given is a premixed preparation of the SPS resin in sorbitol." Because it has FDA approval, one would assume that adequate evidence supporting its effectiveness. However, Kayexalate was approved in 1958—four years before passage of Kefauver-Harris Drug Amendment. Until recently, administering SPS in sorbitol was viewed as "a pretty benign treatment," according to Michael Emmett, MD, of Baylor University Medical Center in Dallas. "Sorbitol is a very convenient vehicle for suspending the SPS. It became the standard operating procedure years ago, with very little data. I think many people assumed that even if the combination was not particularly effective for reducing potassium, it wasn't hurting anything either."

But over the past few years, the FDA has received several reports of serious bowel injury, or intestinal necrosis, in patients receiving SPS plus sorbitol. Sterns, like other nephrologists, was aware of the reports of bowel injury. "The perception, mine included, was that this occurred primarily in very sick people—often in transplant patients, or following surgery, or after Kayexalate in sorbitol enemas—because the combination product remained on the market. Sterns spoke to the manufacturers in Dallas. "Sorbitol is a very convenient vehicle for suspending the SPS. It became the standard operating procedure years ago, with very little data. I think many people assumed that even if the combination was not particularly effective for reducing potassium, it wasn't hurting anything either."

What about sorbitol?

The efficacy evidence on sorbitol is even more sketchy—another 1961 paper concluded that "sorbitol alone is as effective as a combination" in lowering serum potassium. Yet for decades, the FDA-approved combination remained on the market. Sterns commented that this was quite disturbing in the Southern Medical Journal, which suggested that this was more common than had been previously thought.

The report has prompted a re-evaluation of the risks versus benefits of Kayexalate in sorbitol enemas—considering the point now where people have really begun to question if this drug is potentially dangerous," said Emmett. "If it doesn't do much, then why are we using it?"

In September 2009, the FDA issued a warning against concomitant administration of Kayexalate with sorbitol—although the combination product remains on the market. Sterns spoke to the manufacturers of the most widely used generic preparation of SPS plus sorbitol. "They actually made some good points," said Sterns. "They have received very few reports, actually just one report, of colon necrosis. But we now have a smaller concentration of sorbitol than previously used, and it still causes harm."

What should we do? Sterns commented that this was an area for further research: "I think it's safe to say that we just don't really know for sure."

The following adverse events have been identified during postmarketing use of sorbitol, which has the same additional adverse reactions as柚alate products: abdominal pain, diarrhea, vomiting, dizziness, headache, and respiratory distress.

Production of Experiments

The FDA's review process required for drugs introduced after 1962. Sterns and colleagues looked at the historical data on Kayexalate, including the FDA files. "The Agency did go back and review Kayexalate and rule that it was ef- effective, but it was based on what today would be considered anecdotal evidence," said Sterns. The evidence included a 1961 paper by Scherr et al (N Engl J Med 1961; 264:115–119), which reported that 23 of 30 patients had at least a 0.4 mEq/L drop in plasma potassium during the first 24 hours on Kayexalate. To this day, the paper by Scherr et al remains the largest published experience with Kayexalate. Based on the Scherr report and a few others—including observations of patients who actually became hypokalemic while receiving Kayexalate—the FDA concluded that the drug was effective.

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High Hopes

Continued from page 1

only in combination with diet, exercise, and other diabetes medicines. The Novo Nordisk drug was not approved as a first-line treatment because of “safety concerns”; the FDA described clinical trial data suggesting that the drug may be associated with pancreatitis. Laboratory animal data indicated that rare type medullary thyroid cancer may be associated with liraglutide. In addition to requiring additional studies to better understand the risks associated with liraglutide, the FDA called for a Risk Evaluation and Mitigation Strategy to include a patient medication guide and a communication plan.

Novo Nordisk’s phase III clinical trials evaluated liraglutide as monotherapy and in combination with commonly prescribed treatments. According to the company, liraglutide achieved better or equivalent lowering of blood glucose than drugs such as sulphonylureas and thiazolidinediones. Weight gain was not associated with liraglutide use. GLP-1 analogues stimulate the release of insulin from the pancreatic beta cells only when blood sugar levels are high. Byetta, marketed by Amylin and GlaxoSmithKline, is a member of this family of diabetes medications that requires twice-daily dosing. A longer-acting form of Byetta is under FDA review, with a decision expected later this year.

Dapagliflozin: potential first in class SGLT2 inhibitor

In the pipeline is another type 2 diabetes drug, Dapagliflozin, a sodium-glucose cotransporter-2 (SGLT2) inhibitor that targets an insulin-independent pathway. Inhibiting SGLT2 forces the kidneys to put glucose into urine, where it is excreted, thereby lowering blood glucose. If given the green light by FDA, Dapagliflozin will be first in class SGLT2 inhibitor for the treatment of diabetes.

AstraZeneca and Bristol-Myers Squibb reportedly are on track to seek the agency’s approval to market the drug. According to BioCentury, Dapagliflozin is not the only SGLT2 inhibitor in the pipeline for type 2 diabetes therapy. Dapagliflozin, however, is the first SGLT2 inhibitor to reach clinical testing, and is the first for which phase III data have been publicly reported. At the European Association for the Study of Diabetes (EASD) annual meeting last October, scientists said that the drug produced early and substantial reductions in blood glucose and body weight when added to metformin therapy. After 24 weeks of treatment, glycated hemoglobin levels declined 0.7 percent to 0.8 percent with dapagliflozin. In the placebo group, the decline was 0.3 percent (p < 0.05). According to MedPage Today, Han-
New Questions
Continued from page 3
“We need to be more rigorous in looking for this complication.”

Amid safety concerns, efficacy still unknown
Meanwhile, there are still no convincing data to answer the most pressing question: Does Kayexalate lower high potassium levels? When they started their review, Sterns and colleagues knew that Kayexalate was a grandfathered product that hadn’t been subjected to the rigorous efficacy evaluations required for today’s new drugs. “But what I had not realized was that there’s no evidence this preparation increases fecal potassium losses—even in animals,” said Sterns. “And in humans, there are no controlled data.”

Emmett’s group has performed research showing no change in serum potassium levels in end stage renal disease patients with normokalemia or mild hyperkalemia receiving SPS alone or SPS plus sorbitol. “This really casts doubt that Kayexalate was doing very much at all,” according to Emmett.

Another review (Nephrol Dial Transplant 2003; 2215–2218) has questioned the theoretical basis of Kayexalate’s potassium-lowering effect. “Based on in vitro binding characteristics of Kayexalate, the only favorable location for this exchange of Na+ for K+ in the gastrointestinal tract is in the colon,” according to Kamel, MD, of the University of Toronto. However, the amount of K+ that is delivered to the colon is small—about 5 mmol/day.

“In humans, active secretion of potassium in the gastrointestinal tract occurs in the recto-sigmoid portion of the colon,” said Kamel. “One possible theoretical benefit to the use of cation-exchange resins is that, if they were to lower the potassium concentration in luminal fecal water, the net secretion of potassium by the colon would be enhanced.” However, Emmett points out that several other cations are available in the colon to exchange for resin-bound sodium. “Even if patients with ESRD had an adaptive increase in colonic potassium secretion, and if resins were effective in lowering the potassium concentration in fecal water and hence stimulate this process, stool volume would be limiting,” Kamel added.

“There are data to show that the addition of resins does not significantly enhance the excretion of potassium beyond the effect of diarrhea induced by osmotic or secretory cathartics.”

Research needed—but other options available
Despite the lack of data, Kayexalate continues to be prescribed and administered. “We’ve looked at our local practice patterns, and I don’t think they’re unique,” said Sterns. “The administration of Kayexalate has become a pretty monosynaptic reflex to the finding of hyperkalemia—even in patients who have only mild renal impairment and would be better managed with just diuretic and by stopping potassium-sparing agents.”

Emmett agrees that giving Kayexalate is still a reflex for many physicians. “You see a potassium level that’s very high, and you generally throw the whole kitchen sink at the patient … three or four different things, one of which is Kayexalate. And then the potassium comes down, and nobody knows exactly which of these various therapies was most important in achieving that result.”

“The risk to a single patient is unlikely to be very high,” according to Sterns. “But because of the large number of Kayexalate doses given every year, I think we’re exposing an awful lot of people to potential risk.” Sterns and colleagues recommend that physicians “exhaust other alternatives” for treatment of hyperkalemia before turning to ion exchange resins.

Emmett noted that there are other good options for the acute treatment of hyperkalemia, including intravenous insulin and glucose, inhaled beta-2 agonists, and even sodium bicarbonate—“which may or may not be very effective but is probably safe,” according to Emmett. “Diuretics are also useful, if the patient has reasonable kidney function. If kidney function is very poor, then dialysis is the most effective way to reduce the potassium concentration urgently.”

A randomized trial would be needed to demonstrate the safety and efficacy of Kayexalate, and SPS plus sorbitol, in the treatment of hyperkalemia—although it is unclear who would perform such a study. “A good start might be a study in experimental animals, which has never been done,” said Sterns. “And of course, a controlled trial to show increased fecal excretion.”

Given the other effective options, Emmett questions whether the issue of Kayexalate effectiveness is really all that pressing. Of the various options for acutely lowering potassium, “Kayexalate is clearly the least powerful,” he said. “I don’t think patients would be harmed or physicians would be very upset if a recommendation came out that it should not be a component of the treatment regimen to acutely reduce plasma potassium levels.”

Kayexalate Timeline
• Late 1940s to early 1950s: Initial studies of medical applications of synthetic cation-exchange resins.
• 1958: Kayexalate approved for treatment of hyperkalemia under the FD&C Act.
• 1961: Study by Scherr et al in 30 patients—still the largest published experience with Kayexalate. Recommendations to give Kayexalate with sorbitol because of potential for severe constipation.
• 1962: Kefauver-Harris Amendments passed; Kayexalate receives “grandfathered” drug designation.
• 1982: Premade preparation of Kayexalate plus sorbitol approved for commercial distribution—still the most widely used preparation.
• 2005: Reports of serious bowel injuries associated with Kayexalate plus sorbitol. FDA recommendation for administration with sorbitol removed.
• 2009: FDA issues warning against giving Kayexalate with sorbitol. Premixed product (containing 33% sorbitol) remains on market.
Since the beginning, we’ve delivered comprehensive testing, analysis, and reporting with the reliability and personal service you require to ensure the best outcomes possible for your patients.

Our trusted team of clinical experts, paired with our patient-centric tools and resources help you comply with new industry guidelines—so you can navigate unprecedented change with the utmost confidence and ease.
The impact of diabetic kidney disease on the health of the U.S. population is staggering. More than 23 million Americans have diabetes, which is the leading cause of chronic kidney disease and end stage renal disease in this country.

In this issue, we review our current understanding of the physiologic, epidemiologic, and genetic factors that influence the pathogenesis and susceptibility to the early stages of tissue injury related to diabetes. Also discussed are the goals of conservative therapy in patients with established diabetic kidney disease and a review of the principles related to dialysis modality selection for those with advanced disease requiring renal replacement therapy. Finally, we review the issues and challenges of managing new-onset diabetes after kidney transplantation and other solid organ transplant groups of patients.

Ira Davis, MD, is medical director, global clinical affairs, Baxter Healthcare Corp. Renal Division in McGaw Park, IL.

Does dialysis modality matter in diabetic patients with end stage renal disease?

By Anjali Bhatt Saxena and Rajnish Mehrotra

The basic question of whether dialysis modality per se affects the survival of ESRD patients has been debated since the introduction of peritoneal dialysis (PD) for the treatment of ESRD. This issue is particularly important for diabetics because several observational studies have shown a higher risk for death among older diabetic patients treated with PD. Indeed, based on the results of some observational studies, some have questioned whether it is ethical to offer PD as an option for older diabetics.

There are many theoretical advantages and disadvantages to both hemodialysis (HD) and PD (Table 1). Special consideration should be given to diabetics with ESRD since these patients have more severe vascular disease and a higher risk for infection than their nondiabetic counterparts. For diabetics with ESRD, PD may provide certain advantages over HD (Table 2). On the other hand, valid concerns about the adverse effects of glucose-based peritoneal dialysis solutions, including the risks of weight gain and worsened hyperglycemia, may limit PD utilization in diabetics.

Many researchers have sought to answer the question of which dialysis modality is superior. A randomized controlled trial (RCT) would most reliably examine whether any differences in outcomes of patients treated with HD or PD are attributable to the dialysis modality per se, but the existing body of literature is unfortunately lacking in RCTs. The Netherlands Cooperative Study of Dialysis (NECOSAD) is the most recent attempt to perform such an RCT. In this study, 735 of 773 eligible patients refused to be randomized to either HD or PD, thus leaving a study group of only 38 patients—far too few from which to make meaningful conclusions. In the absence of RCTs, data examining the effects of dialysis modality are limited to those originating from either observational or prospective cohort studies.

The observational studies examining survival differences between HD and PD patients over the past two decades are heterogeneous in design but manifest a common theme: PD provides an early survival advantage that varies in magnitude and duration depending on patients' age, diabetic status, and presence of co-morbidities. Interestingly, during the same period of time, eight prospective cohort studies have been published on this topic, five of which report no difference in survival outcomes between the two modalities. Specifically with regard to diabetics with ESRD, most studies suggest that younger

### Table 1. Potential advantages and disadvantages of in-center hemodialysis and peritoneal dialysis

<table>
<thead>
<tr>
<th>Advantage</th>
<th>In-center hemodialysis</th>
<th>Peritoneal dialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages</td>
<td>Effective removal of waste products</td>
<td>Schedule flexibility, easier to travel</td>
</tr>
<tr>
<td></td>
<td>Care given by trained professionals</td>
<td>Few risks of dialysis-associated cramps</td>
</tr>
<tr>
<td></td>
<td>Regular contact with other patients</td>
<td>Clinic visits limited to 1–2x a month</td>
</tr>
<tr>
<td></td>
<td>Rapid correction of electrolyte imbalances</td>
<td>Patient and/or family involved in care</td>
</tr>
<tr>
<td></td>
<td>No equipment to store at home</td>
<td>No need for needles or vascular access</td>
</tr>
<tr>
<td></td>
<td>Treatment usually occurs only three times a week</td>
<td>Steady-state therapy, gentler ultrafiltration</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Vascular access surgery required</td>
<td>Permanent external catheter, &quot;body-image&quot; problems</td>
</tr>
<tr>
<td></td>
<td>Use of large needles</td>
<td>No &quot;off&quot; days</td>
</tr>
<tr>
<td></td>
<td>Schedule inflexibility</td>
<td>Risk of peritonitis</td>
</tr>
<tr>
<td></td>
<td>Must travel to center three times a week</td>
<td>Risk of weight gain from glucose in dialysate</td>
</tr>
<tr>
<td></td>
<td>Cramping with ultrafiltration</td>
<td>Must store dialysis equipment and supplies at home</td>
</tr>
<tr>
<td></td>
<td>Risk of bacteremia (with tunnel catheter)</td>
<td>Need for self-monitoring of care</td>
</tr>
</tbody>
</table>
Dialysis modality

Continued from page 7

Table 2
Potential benefits of peritoneal dialysis in diabetics who suffer from more severe vascular disease

- Gentler and more gradual ultrafiltration, greater hemodynamic stability
- Vascular surgeries not required for dialysis access
- Better preservation of residual kidney function
- Minimal rapid shifts in electrolytes (potassium, calcium)

diabetics with no additional co-morbidity have a survival advantage while older diabetics with additional co-morbidity have a survival disadvantage when treated with PD. In other subgroups of diabetics, there appears to be no difference in outcomes between patients treated with either of the two dialysis modalities. In these studies, however, the reported statistical differences in hazard ratios translates into small differences in more clinically relevant measures such as life expectancy of patients treated with HD or PD.

It must also be mentioned that most published studies examining the effect of dialysis modality on survival have drawn their cohorts from patients incident before the year 2000. These older cohorts lacked the benefits of more recent advances in PD such as improvements in connectecoty, catheter exit-site antibiogenic prophylaxis protocols to reduce infection risk, and increased awareness of the importance of solute clearances and careful volume management. All of these PD advances have probably contributed to improvements in PD outcomes, but their benefit has not been well captured in the literature.

A comparison of patient and technique survival in incident HD and PD from 1996 to 2003 has shown that the outcome of incident PD patients progressively improved whereas that of HD patients remained unchanged during the same time period. These improvement trends have continued over the past five years, and a more recent analysis of patients starting dialysis in 2002–04 in the United States shows no significant differences in outcomes between modalities, even among older diabetics treated with either HD or PD.

What can we learn from this varied literature? One must first remember that observational studies, although having the advantage of large patient numbers and therefore excellent statistical power, depend on information gathered from previously existing patient databases that contain limited details about the clinical condition of individual patients. This limitation makes it difficult to know whether reported differences in these studies are truly an effect of dialysis modality or whether they result from uncounted differences between the patient groups (HD and PD). Such observation studies are also subject to inaccuracies as a result of nonrandom allocation of patients into two dialysis groups and in most parts of the world, do not necessarily reflect patient choice. Thus, despite the use of advanced statistical analyses, one has to be careful in attributing any differences in outcomes of patients treated with different therapies to the dialysis modality itself.

Given the lack of strong and conclusive data favoring one dialysis modality over another plus the differential changes in outcomes of patients treated with HD and PD over time in the United States, it appears reasonable that neither dialysis modality should be automatically excluded for any diabetic patient with advanced CKD; rather, careful evaluation of medical factors are likely best addressed on an individual level.

The diabetic patient who ultimately starts HD should take care to limit intradialytic fluid gains and rapid electrolyte shifts, and venous dialysis catheters should be avoided as far as possible. A diabetic starting PD should be prescribed a regimen that minimizes the use of hypertonic glucose-based solutions. Perhaps more importantly, patient preference should play a major role in the decision-making process, but it necessarily requires dialysis education to be provided in a timely and complete manner. Ultimately, the life-saving benefits of dialysis are of no use if the patient is miserable for lack of being given a choice in their dialysis lifestyle.

Anjali Bhatt Saxena, MD, is with the Santa Clara Valley Medical Center in San Jose, CA, and Stanford University School of Medicine, Palo Alto, CA. Rajnish Mehrotra, MD, is with the division of nephrology and hypertension at Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center in Torrance, CA, and the David Geffen School of Medicine at UCLA in Los Angeles, CA.

Disclosures: Rajnish Mehrotra has received research grant support, served as an ad hoc consultant, and received honoraria from Baxter Health Care. Anjali Saxena has served as an ad hoc consultant to Baxter Health Care.

Goals of Therapy for Patients with Diabetic Nephropathy

By Jamie P. Dwyer

Many therapies exist to treat diabetic kidney disease (DKD). Some have been proven to delay the progression of chronic kidney disease (CKD), while others have not been rigorously tested in a controlled way. This article summarizes the major clinical findings that direct DKD treatment and outlines the progress of ongoing trials whose results will direct care.

Glycemic control

Intensive glycemic control reduces albuminuria in type 1 diabetes. The Diabetes Complications and Control Trial (DCCT) randomized 1441 type 1 diabetics (age 13–39) without cardiovascular (CV) disease and with normal kidney function to intensive (A1c < 6.0%) versus conventional (A1c >9.0%) glycemic control. Only 73 individuals had microalbuminuria at the start of the study.

Participants were followed for a mean of 6.5 years. Intensive glycemic control reduced the occurrence of microalbuminuria by 39 percent and overt proteinuria by 54 percent. There were nearly three times as many severe hypoglycemic episodes in the intensive control arm as in the conventional arm. There was no reduction in CV events in the DCCT (probably a result of the cohort’s youth), but these same subjects were followed in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study. EDIC showed a 42 percent reduction in any CV event 10 years after both groups had similar glycemic control (implying that the CV effect of intensive glycemic control persisted after control was loosened).

In type 2 diabetes, however, the results are not as clear. An early study by the University Group Diabetes Program (UGDP) tested the efficacy of tolbutamide, insulin, phenformin, or placebo, and showed no renal, microvascular, or CV benefit, with increased CV death in the tolbutamide arm. The much larger UK Prospective Diabetes Study (UKPDS) tested sulphonylurea or insulin versus dietary control, and showed no renal benefit, a 25 percent microvascular benefit, and no CV effect, although some subgroups showed a possible effect at 10 years. Three large trials (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation [ADVANCE], and the VA Diabetes Trial [VADT]) (Table 1) have collectively studied nearly 23,000 individuals. CV effects ranged from no benefit to increased risk, and there was variable renal benefit and a significant proportion of hypoglycemia in the intensive groups.

Evidence supports intensive glucose control as renoprotective therapy in type 1 diabetes. The therapy may also benefit patients with type 2 diabetes who are early in the course of disease, who can achieve glycemic control easily, and who are less prone to hypoglycemia. Current evidence does not support extremely aggressive control of hyperglycemia in all patients with type 2 diabetes.

Single-agent inhibition of the renin-angiotensin system (RAS)

Treatment of type 1 diabetic nephropathy with angiotensin converting enzyme inhibitors (ACE-I) clearly protects against deterioration in renal function. Captopril 25 mg TID was shown to reduce the composite outcome of death, dialysis, or kidney transplantation by 50 percent (relative risk reduction [ARR]; absolute risk reduction [ARR] 9.7 percent, number needed-to-treat [NNT] 10 subjects, for four years). This trial included 409 patients with baseline urinary protein excretion ≥ 500 mg/day and serum creatinine ≥ 2.5 mg/dL.

Treatment of patients with type 2 diabetes and early nephropathy (in this case, microalbuminuria) with the angiotensin receptor blocker (ARB) irbesartan has been shown to prevent progression to overt proteinuria. Irbesartan 300 mg daily versus placebo reduced the onset of overt


Table 1. Intensive glucose control in type 2 diabetes, showing no compelling benefit

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td>n = 10,205</td>
<td>n = 1,140</td>
<td>n = 1,791</td>
</tr>
<tr>
<td>Age (y, mean)</td>
<td>62</td>
<td>66</td>
<td>60</td>
</tr>
<tr>
<td>DM duration (y)</td>
<td>10</td>
<td>8</td>
<td>11.5</td>
</tr>
<tr>
<td>On insulin at baseline (%)</td>
<td>30 / 8.1</td>
<td>1.5 / 7.2</td>
<td>54 / 9.4</td>
</tr>
<tr>
<td>Hemoglobin A1C, baseline (%)</td>
<td>8.1%</td>
<td>7.2%</td>
<td>9.4%</td>
</tr>
<tr>
<td>Al-T target (%)</td>
<td>&lt;6.0% vs. 7.9%</td>
<td>&lt;6.5% vs. 1.7% (achieved 6.3% vs. 1.7%)</td>
<td>6.9% vs. 8.4% (1.5% difference)</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Increased total and CV mortality in intensive group</td>
<td>No benefit on CV outcomes, reduction in microvascular events</td>
<td>No benefit</td>
</tr>
<tr>
<td>Renal outcome</td>
<td>No benefit</td>
<td>Albuminuria reduced 21%</td>
<td>No benefit</td>
</tr>
<tr>
<td>Hypoglycemia (%)</td>
<td>16.2</td>
<td>2.7</td>
<td>21.2</td>
</tr>
</tbody>
</table>

Many combinations are limited by hyperkalemia, which is more problematic in the “real world” than in a clinical trial.

Future studies

Several ongoing studies may address current uncertainties in the management of diabetic nephropathy. The Department of Veterans Affairs NEPHRON-IV Diabetes (VA NEPHRON-IV) Study is testing whether the combination of the ACE-I losartan and ARB losartan is superior to losartan alone to delay the progression of CKD. Approximately 1900 patients will be recruited until 2013.

The ALiskiren Trial In Type 2 Diabetes Using Cardio-Renal Endpoints (ALTITUDE) Study is testing whether dual RAS blockade with aliskiren and an ACE-I or ARB reduces CV and renal morbidity and mortality. It aims to recruit 8600 patients followed for four years.

Finally, the BP companion study to ACCORD will help elucidate the target BP for diabetic nephropathy caused by type 2 diabetes.

Conclusions

The cornerstone of the treatment of diabetic nephropathy is delaying the progression of CKD. Control of hyperglycemia and blood pressure, and use of RAS blockade are accepted therapies. Combination therapies and very strict BP control are not, as yet, entirely proven, but ongoing trials will address the limitations of currently completed studies.

Jamie P. Dwyer, MD, is with the division of nephrology and hypertension and the Nephrology Clinical Trials Center, both at Vanderbilt University Medical Center in Nashville, TN. The material in this article was originally presented as part of renal grand rounds at Drexel University Division of Nephrology in Philadelphia, PA, in 2009.

Disclosures: Jamie P. Dwyer reports research support from Keryx Biopharmaceuticals, Inc.

Table 2. Landmark “single-agent” clinical trials in type 2 diabetic nephropathy with overt proteinuria

<table>
<thead>
<tr>
<th></th>
<th>IDNT</th>
<th>RENAI</th>
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<tbody>
<tr>
<td>Population</td>
<td>n = 1715, with hypertension and urinary protein excretion ≥0.5g/d</td>
<td>n = 1513, with urinary protein excretion ≥0.5g/d</td>
</tr>
<tr>
<td>Age, years (mean [range])</td>
<td>58.9 (30–70)</td>
<td>60.1 (31–71)</td>
</tr>
<tr>
<td>Uinary albumin excretion (g/d, median)</td>
<td>1.9</td>
<td>1.2</td>
</tr>
<tr>
<td>SMD (mean, mg/dL)</td>
<td>1.7</td>
<td>1.9</td>
</tr>
<tr>
<td>Hemoglobin A1C, baseline (%)</td>
<td>8.2%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Primary outcome (RRR*, %)</td>
<td>20 (Iberasert vs. control)</td>
<td>16 (Losartan vs. control)</td>
</tr>
<tr>
<td>DoubleU of S0 (RRR, %)</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>ESRD (RRR, %)</td>
<td>28</td>
<td>23</td>
</tr>
</tbody>
</table>

*RRR: relative risk reduction.
Genetics of Diabetic Nephropathy

By John R. Sedor

Are common causes of progressive kidney disease regulated by genes?

Many common diseases, including nephropathy, cluster in families, and genetic variants seem likely to regulate disease pathogenesis (1). Until recently, convincing evidence that common disease genes exist has been lacking. Much of the difficulty in identifying genes for common diseases, such as diabetic nephropathy, sporadic FSGS, and nephrosclerosis, arises from the genetic architecture responsible for common diseases, which differs from that of Mendelian disorders.

Most of us learned about Mendel and his peas in medical school. The success of gene mapping for Mendelian disorders, such as polycystic kidney disease, is common knowledge to nephrologists and other physicians. Mendelian traits have a simple correspondence between the gene and the disease phenotype, and mapping strategies have been highly successful in identifying genetic causes of disease with understandable patterns of inheritance.

In contrast, complex traits, like chronic kidney disease, do not have recognizable inheritance patterns, a finding that has made gene mapping more difficult. The frequency of the causal variant in the population and the size of its contribution to the disease phenotype (the effect size) determine optimal gene mapping strategies (Figure 1). Investigators exploring genetic causes of common diseases still have not reached consensus on the underlying genetic architecture for these disorders.

Two models are dominant. The “common disease, common variant” hypothesis proposes that common diseases are caused by genetic variants harming a frequency greater than 5 percent in the population. The functional effects of these variants impair but do not prevent protein function. An illustrative analogy would be that these common variants cause a light bulb to dim, but not go out. Case-control mapping strategies should be successful in identifying causal variants if this hypothesis is correct.

The competing hypothesis is that common diseases are caused by rare variants with moderate effect sizes that generate dysfunctional proteins with little or no wild type function. In this model, common diseases would be caused by a multitude of rare variants in multiple genes. Current mapping strategies are unlikely to identify these gene variants but new technologies—such as exon and whole genome microarrays—may allow for the identification of these gene variants.

The functional effects of these variants may be pleiotropic effects at the protein level or effects on cellular signaling. For example, the gene that encodes the enzyme whose subunit inhibits ACE activity and advanced glycation end product formation, as a diabetic nephropathy susceptibility gene. Variants within the engulfment and motility 1 (ELMO1) gene, whose protein regulates cell migration and matrix and TGF-β expression, have been associated with diabetic nephropathy phenotypes and are located within the linkage signal on 7p. The linkage signal on 7q has been attributed to variants with adiponectin (ADIPOQ), which encodes an adipose-tissue-derived protein with anti-inflammatory functions, and NCK1 (3), a gene that encodes an adapter protein NCK1 that links actin and nephrin in podocyte foot processes.

More recently, genome-wide association studies (GWAS), another unbiased strategy, has been applied to gene mapping for common disease. This approach uses a group of patients with disease and controls numbering in the thousands and takes advantage of the technical advances in genotyping platforms, which incorporate genetic variants from the International HapMap Project. An atlas of common genetic similarities and differences in human beings of differing ancestors. These studies have reproducibly identified common variants with highly statistically significant associations with common disease phenotypes, although the underlying biology responsible for the association can be obscure.

The first GWAS data for diabetic nephropathy have now been reported by the Genetics of Kidneys in Diabetes (GoKinD) consortium, which included over 800 patients with Type 1 diabetic nephropathy as cases and 800 diabetic patients without nephropathy as controls (4). In this study, the most significant associations were with the following genes: common disease genes CHN2 (encodes chimerin 2 located on chromosome 7p, a region identified in linkage analyses, noted above, FRMD3 (encodes a FERM domain-containing protein), and CAR5 (encodes cysteinyl-cRNA synthetase). An intergenic region on chromosome 1p was also associated with diabetic nephropathy.

The GOKinD results highlight a strength of the GWA approach: the results point to novel pathways not previously considered as causal for diabetic nephropathy. Although the biology responsible for the action of these genes with diabetic nephropathy has yet to be discovered, these results were replicated in a prospective cohort from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EPIC) Group. Results from ongoing association studies from the Family Investigation of Non-insulin Dependent Diabetes Mellitus (FIND) and Finnish Diabetic Nephropathy Study consortia should be available soon.

Genes and other causes of chronic kidney diseases

Using ancestry mapping, two consortia—the U.S. National Institutes of Health (NIH) FSGS Genetic Study and FIND—reported that common variants in MYH9, a gene that encodes a ubiquitous intracellular motor protein, myosin 9, are associated with nondiabetic but not diabetic nephropathy in African American patients (5). The NIH patient sample included individuals with idiopathic or HIV-1-associated FSGS; the FIND group included African American nondiabetic ESRD patients. Much of the excess risk for kidney disease in African American patients can be explained by four genetic variants within MYH9 noncoding regions, suggesting these common variants have large effect size (Figure 1). The findings have been replicated in multiple, independent African American populations. The mechanism(s) by which MYH9 gene variants cause nondiabetic kidney diseases in African American patients is under intense study, as are approaches to apply this finding to patient care.

Finally, the Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) consortium reported that all-cause CKD, defined as estimated GFR less than 60 ml/min, was associated with common gene variants in noncoding regions of the gene that encodes Tamm-Horsfall protein (THP) (6). Uromodulin/THP provides a protein scaffold for the urinary casts used to diagnose kidney diseases in the clinic. Patients with diabetes were included in this sample. Interestingly, UMOD mutations cause medullary cystic disease and familial hyperuricemic nephropathy, suggesting both common and rare variants with the same gene may regulate different phenotypic presentations of kidney diseases. However, in contrast to MYH9 variants, UMOD variants only explain a small percentage of the variability in the CKD phenotype (Figure 1). A subsequent study from CHARGE has shown urinary uromodulin levels can predict development of nephropathy.

Will studies of common kidney disease genetics impact patient management?

The last seven years have been a time of breathtaking discovery and technical advancement in human genetics: The human genome sequence was reported in 2003. The atlas of common genetic variation in individuals of different ancestries—the Hap Map—was completed in 2005. The 1000 genomes project, which will expand our understanding of the range of human genetic variation, is about to publically release its first data set. The kidney community is actively applying the most advanced gene mapping strategies to understand the underlying...
The Risk of Posttransplant Diabetes Mellitus in Renal Transplant Recipients

By James T. Lane

New-onset diabetes after transplantation (NODAT) affects up to 50% of nondiabetic patients post-kidney transplant depending on the type of study (retrospective versus prospective), the patient population, frequency of sampling, posttransplantation complications, the immunosuppression regimen, duration of follow-up, and diagnostic criteria. The 2003 International Consensus Guidelines (1) unified the diagnosis and brought NODAT in line with the more commonly used American Diabetes Association (ADA) criteria for diabetes diagnosis, namely more than one fasting glucose ≥126 mg/dL. Although this brief review focuses on NODAT after kidney transplantation, this condition follows all forms of organ transplantation.

Pretransplant risk factors for NODAT similar to those for type 2 diabetes, include older age, increased body mass index, positive family history of type 2 diabetes, hypercholesterolemia, cytomegalovirus (CMV) infection, and genetic factors. No conclusive gender differences have been demonstrated. NODAT was also associated with TCF7L2 polymorphism, another factor shared with type 2 diabetes. Autosomal dominant polycystic kidney disease associates with insulin resistance and hyperinsulinemia, and may increase risk. Children also experience NODAT, although not at the same adult rates.

Several posttransplant factors increase risk for NODAT including the use of certain types of drugs for immunosuppression, marked weight gain after transplant, and the inflammatory response surrounding transplant. It was hoped that movement away from glucocorticoids as a cornerstone of immunosuppression would reduce glucose intolerance; however, nonsteroidal alternatives produce additional risk. Calcineurin inhibitors, including both cyclosporine and tacrolimus, are strongly associated with NODAT (2). These agents impair insulin secretion and damage pancreatic islets, increasing apoptosis of β-cells. Tacrolimus increases insulin resistance in animal studies. Sirolimus is also diabetogenic with insulin resistance as the likely cause.

NODAT produces more than long-term microvascular risks; it also increases cardiovascular death and decreases graft survival (3). Cardiovascular risk is not related to degree of hyperglycemia; even mild levels of hyperglycemia increase risk above and beyond what is seen with chronic kidney disease alone.

Given the need for renal replacement therapy, but soared by the risk of NODAT to patient and graft survival, how should we proceed? Patients first need to know about NODAT. Very often patients anticipate the benefits of renal transplantation without considering the risks and are not necessarily willing to think about negative outcomes. Patients appropriately informed about NODAT may be able to minimize weight gain following the transplant through appropriate counseling. A thorough history can identify the mentioned risk factors for NODAT. An oral glucose tolerance test prior to transplant will identify patients with preexisting impaired glucose tolerance. There should be an ongoing strategy to monitor glucose, especially the fasting glucose, posttransplant. Monitoring one to two times per week is not unreasonable. Elevated glucose levels early in the posttransplant period predict NODAT later on. In our patient population, NODAT peaked at three months after kidney transplant; monitoring has to be in place to address this time course. When NODAT is diagnosed, early referral to a diabetes educator for counseling and glucose monitoring is essential.

Patients with the highest risk of NODAT may warrant immunosuppressive regimens with less diabetogenic potential while weighing the risk of acute rejection. Antibody induction therapy, an area of interest at our center, may allow for lower levels of diabetogenic immunosuppressive drugs and less immunosuppression at the time of transplantation (4). A recent retrospective study investigated NODAT, type of immunosuppression, and observed hypomagnesemia in renal transplant recipients (5). Hypomagnesemia occurs in the immediate posttransplant period in association with calcineurin-inhibitor therapy and was an independent predictor of NODAT. It is not known whether more aggressive magnesium replacement may prevent NODAT.

The use of HbA1c has recently been adopted by the ADA to diagnose diabetes, but its utility in the transplant population remains unclear. Posttransplant HbA1c levels may be falsely decreased related to uremia. Because it reflects hyperglycemia over several months, it is not sensitive posttransplant, especially for onset of disease within the first few months. HbA1c remains a helpful test to follow patients after three to six months. Medical therapy for NODAT is similar to that for type 2 diabetes, with some exceptions. Unlike usual type 2 diabetes, metformin as a first-line single agent is controversial because of the risk of lactic acidosis in patients with reduced renal function or in patients at risk for rapid decline in renal function. Sulfonylureas have been used with success, but they have the potential to increase weight and cause hypoglycemia. Thiazolidinediones (TZDs) have been used with success, less hypoglycemia potential as monotherapy than other agents, but should be used with caution in patients with congestive heart failure or in patients with increasing edema. TZDs can also cause marked weight gain. Exenatide is not an ideal drug in the post-kidney transplant patient since it may cause nausea. However, we have used DPP-IV inhibitors in patients with mild hyperglycemia with good results. Finally, many of these patients require insulin therapy.

HbA1c goals recommended by the ADA should be followed. Additional cardiovascular risk factors, such as hypertension, hyperlipidemia, and obesity need to be concomitantly addressed.

Challenges remain for the prevention of NODAT and the threat it poses to patients and their transplanted organs, but we can reduce risk and ensure early diagnosis. Potential interventions undergoing prospective study may prevent NODAT. Until that time, NODAT is a formidable opponent in the quest to improve the lives of patients requiring transplantation.

References

Type 1 Diabetes Mellitus: The Relationship of Clinical and Renal Structural Changes

By Julia Steinke

Diabetic nephropathy (DN)—the progressive decline in renal function usually accompanied by proteinuria, hypertension, and declining glomerular filtration rate (GFR)—is a major complication of longstanding diabetes. After 15–25 years of diabetes, approximately 25–40 percent of patients with type 1 diabetes mellitus (T1DM) will develop overt signs of renal involvement. According to the USRDS database, diabetic nephropathy is the single most important cause of end stage renal disease (ESRD) in the United States, Japan, and Europe. Most importantly, much of the renal injury from diabetes occurs in clinical silence before the majority of symptoms or laboratory findings suggestive of DN become evident.

Early abnormalities such as microalbuminuria or hypertension may occur as early as seven years after onset of diabetes but typically take longer to develop. The first detectable renal structural change is an increase in glomerular basement membrane (GBM) width and is followed by an increase in the fraction of the glomerulus occupied by the mesangium, composed of mesangial matrix and cells (Table 1). GBM width has been found to be one of the earliest changes that occur in patients with T1DM, even prior to the onset of overt clinical signs of renal injury, such as microalbuminuria. GBM widening is not only the earliest and most obvious abnormal finding among renal structural parameters, but the most prevalent abnormal finding among morphometric parameters regardless of duration of diabetes (Table 1). On the other hand, there is very little change in the mesangial measures for the first 10–15 years of diabetes duration with a rapid increase thereafter (Figure 1).

The expansion of the mesangium is predominantly due to accumulation of mesangial matrix with less contribution from the mesangial cells. With advanced disease, progressive renal functional loss ensues due to glomerular collapse and sclerosis, and by capillary lumen obliteration resulting from massive mesangial expansion. Interstitial fibrosis and tubular atrophy at these later stages of the disease process may also contribute to functional loss. Other renal lesions include afferent and efferent arteriolar hyalinosis and capular drops that are virtually pathognomonic of diabetes and have been reported rather early in the disease process. The combined effects of glomerular basement membrane thickening, mesangial expansion, glomerular sclerosis, tubular atrophy, and interstitial fibrosis all contribute to eventual loss of renal function in progressive stages.

The typical clinical course of diabetic nephropathy has been described as the initial onset of microalbuminuria and hypertension with the later development of overt proteinuria and finally decline in renal function. The first clinical signs of renal injury can be expressed by changes within “normal limits” of measurable parameters. For example, subtle increases in blood pressure—within the range of normal detected by 24-hour blood pressure monitoring—often precede the development of microalbuminuria. Further blunting of the normal 10 percent decline, commonly referred to as “dipping,” in nocturnal blood pressure becomes more pronounced as microalbuminuria and proteinuria develop. Blood pressure changes may develop in parallel or even precede rises in albumin excretion. Hypertension is a predictor of GFR decline in patients with diabetic nephropathy. Although the prevalence of hypertension in patients with T1DM and normal albumin excretion is no different than that in the general population, it is significantly higher in T1DM patients with either microalbuminuria or overt proteinuria. Higher prevalence of elevated systolic and diastolic blood pressure has even been reported in the adolescent population with T1DM and microalbuminuria compared to age-matched normalalbuminuric patients. However, even subtle increases in nocturnal mean arterial blood pressure, detected with 24-hour ambulatory blood pressure monitoring, in normalalbuminuric T1DM patients are an important indicator of renal structural injury. The current literature certainly supports the use of renin angiotensin blockade in patients with microalbuminuria to slow progression to proteinuria, but there is a lack of support for such treatment in those without any clinical evidence for renal injury such as elevated albumin excretion.

Type 1 diabetes is associated with early and prolonged glomerular hypertension, i.e., a glomerular filtration rate (GFR) above normal limits. The presence of hypertension in young patients with type 1 diabetes has been reported to increase the risk of developing microalbuminuria later on, independent of glycemic control and blood pressure. However, this relationship of GFR and microalbuminuria remains controversial as reduced GFR below the lower limit of normal (<90 mL/min/1.73 m²) has been reported to be associated with more advanced glomerular lesions despite normal urinary albumin excretion. Therefore, it appears that the reliability of GFR as an indicator of clinically detectable injury without the use of a renal biopsy to compare is debatable.

Morphometry studies have demonstrated the importance of renal biopsy data when clinicians are evaluating microalbuminuria and renal function. It appears that mesangial changes are most closely correlated with renal function. The disproportionate increase in mesangium relative to the expansion in glomerular volume is closely correlated with a decrease in the GBM filtration surface density and thereby is related to a decline in GFR. This mesangial expansion is closely related not only to diminished GFR but to the development of microalbuminuria and hypertension.

Improvement in glycemic control, measured by glycated hemoglobin (HbA1c), in as little as three years has also shown to be correlated with slowed renal injury. The beneficial results of optimal glycemic control clearly have a sustained effect in the reduction of renal injury. There have been tremendous strides in our understanding of the progression of renal disease in type 1 diabetes mellitus as well as the risks that may impact this rate of progression, such as the profound importance of maintaining strict glycemic control. However, there are other considerations such as gender, genetics, and renal hemodynamics that clinicians should also consider when evaluating a young person with diabetes and renal structural changes. We have only begun to understand the multitude of factors that may influence the varying trajectories of renal injury.

Table 1. Percentage of abnormal morphometric parameters in relation to duration of diabetes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Abnormal value*</th>
<th>2–8 years</th>
<th>8–14 years</th>
<th>14–20 years</th>
<th>All durations</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td>144</td>
<td>74</td>
<td>25</td>
<td>243</td>
</tr>
<tr>
<td>GBM (nm)</td>
<td>&gt;445</td>
<td>23</td>
<td>50</td>
<td>68</td>
<td>36</td>
</tr>
<tr>
<td>Vv(Mes/glom)</td>
<td>&gt;0.25</td>
<td>10</td>
<td>16</td>
<td>48</td>
<td>16</td>
</tr>
<tr>
<td>Vv(MM/glom)</td>
<td>&gt;0.11</td>
<td>15</td>
<td>31</td>
<td>68</td>
<td>25</td>
</tr>
<tr>
<td>Vv(MC/glom)</td>
<td>&gt;0.13</td>
<td>3</td>
<td>3</td>
<td>12</td>
<td>4</td>
</tr>
</tbody>
</table>

Duration data are percent. * >95th percentile of normal, nondiabetic control subjects.

By Julia Steinke, MD, is with the division of pediatric nephrology, dialysis, and transplantation at the Helen Devos Children's Hospital and Clinics in Grand Rapids, MI.
August 28–September 3, 2010
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ASN Launches Distance Learning

The American Society of Nephrology (ASN) continues to broaden its commitment to education and to the kidney professionals who help ASN lead the fight against kidney disease. ASN now offers distance learning opportunities that make it possible for nephrologists to advance their professional education anytime, anywhere.

ASN’s Board Review Course & Update (BRCU) online mirrors the BRCU offered annually in San Francisco. Internationally renowned speakers lecture and participate in case presentations and panel discussions that blend physiology and pathophysiology with clinical discussions. BRCU is the primary preparatory course for the American Board of Internal Medicine’s (ABIM) initial certification and maintenance of certification examinations in nephrology; each section is patterned after the ABIM nephrology examination blueprint (maximum 70 AMA PRA Category 1 credits).

These new offerings are just the beginning. ASN will expand its distance learning education programs and offer opportunities for members to update their professional skills at their convenience and pace. Check the ASN website for announcements about new distance learning programs. To access all ASN’s distance learning opportunities, visit the ASN website at http://www.asn-online.org/education_and_meetings/distance-learning.

On April 14, 2010, ASN launched ASN Renal WeekEnds (RWE) Online. This comprehensive overview of Renal Week 2009 presents breakthroughs in research, as well as clinical and translational medicine summarized by experts in the field. Now ASN members can access key presentations on acute kidney injury, kidney transplantation, hypertension, end stage renal disease, glomerular disorders, and clinical nephrology from the office, at home, or while traveling (maximum 9.5 AMA PRA Category 1 credits).

ASN Presents Remarks at Key CMS Meeting on ESA Usage

ASN was among a small group of invited presenters at the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) meeting to review available evidence on use of erythropoietin-stimulating agents (ESAs) to manage anemia in patients with chronic kidney disease (CKD). MEDCAC provides independent guidance and expert advice to CMS on specific clinical topics.

Presenting on behalf of ASN, Wolfgang Winkelmayer, MD, ScD, FASN, delivered remarks at Centers for Medicare and Medicaid Services (CMS) headquarters in Baltimore last month.

“We derive from the available evidence that current ESAs may be dangerous if used for overly aggressive treatment targets compared with practices that are compatible with current treatment guidelines,” Winkelmayer said. “Continued access to these medications is required, however, to give patients with CKD a fair chance at first receiving and then maintaining the function of a kidney transplant. Swift action is needed to support comparative effectiveness research that closes the evidence gap in the optimal role of ESAs in the treatment of relatively severe anemia and to more modest treatment targets while maintaining these patients transfusion-free.”

ASN members Rajiv Agarwal, MD, MBBS, FASN; Daniel Coyne, MD; and Joseph Messana, MD, served as a guest panelists on the MEDCAC panel considering presenters’ remarks and reviewing evidence.


State Initiatives to Manage Diabetes on the Rise

States have taken several steps to ensure that diabetes patients are appropriately managed by private and public insurers alike. Forty-six states require insurers to have some sort of coverage for diabetes management. Typically this coverage includes direct treatment, as well as diabetes equipment and supplies. The National Conference of State Legislatures has put together an interactive map to highlight private insurance mandates, public insurance coverage, and state-based public prevention programs. The map and associated tables can be accessed at http://tiny.cc/nclsi. The site also includes related legislation and links to state laws and regulations.

Looking for diabetes prevention and control programs in your state? The Centers for Disease Control has a list of links to state programs that can be accessed at http://tiny.cc/cdc249.

Want to know how much diabetes is costing your state? The American Diabetes Association can tell you at http://tiny.cc/statecost.

The Centers for Medicare and Medicaid Services included diabetes prevention for the Quality Improvement Organization’s (QIO) 9th Statement of Work. QIOs work on a state level to improve health care services delivered to Medicare beneficiaries. Five states or jurisdictions were chosen to participate in the “Every Diabetic Counts” Program, an initiative to reduce health disparities among diabetes patients through diabetes self-management education: the District of Columbia, Georgia, Louisiana, Maryland, and New York. QIOs in these states are responsible for monitoring statewide diabetes rates and education efforts, and must submit the number of patients who complete self-management training on a monthly basis. To follow the progress of these and other Medicare Quality Improvement state initiatives, check out: www.cms.hhs.gov/qualityimprovementorgs/. To view and download the “Every Diabetic Counts” toolkit, visit http://tiny.cc/EDC.


Policy Update

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Please see Brief Summary of Full Prescribing Information on adjacent page.

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CONTRAINDICATIONS
None known.

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Diagnosis Tests:
Abdominal x-rays of patients taking lanthanum carbonate may have a radio-opaque appearance typical of an imaging agent.

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There were no differences in the rates of fracture or mortality in patients treated with FOSRENOL® compared to alternative therapy for up to 3 years. The duration of treatment exposure and time of observation in the clinical program are too short to conclude that FOSRENOL® does not affect the risk of fracture or mortality beyond 3 years.

Information for the Prescriber:
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Drug Interactions:
Lanthanum is not metabolized.

The absorption and pharmacokinetics of FOSRENOL® are unaffected by co-administration with citrate-containing compounds (see CLINICAL PHARMACOLOGY: In Vitro/Vivo Drug Interactions).

An in vitro study showed no evidence that FOSRENOL® forms insoluble complexes with warfarin, digoxin, furosemide, phenytoin, metoprolol and enalapril in simulated gastric fluid. In studies in healthy volunteers, FOSRENOL®, when administered 30 minutes in advance, in did not alter the pharmacokinetics of warfarin, digoxin, or metoprolol. However, it is recommended that concurrent administration to reduced absorption when co-administered with antacids (e.g. aluminum-magnesium-, or calcium-based) should not be taken within 2 hours of dosing with FOSRENOL®.

Examples of relevant classes of compounds where antacids have been demonstrated to reduce bioavailability include antibiotics (such as quinolones, ampicillin and tetracyclines), thyroid hormones, ACE-inhibitors, statin lipid regulators and anti-migraine drugs.

The bioavailability of oral ciprofloxacin was decreased by approximately 50% when taken together with FOSRENOL® in a single-dose study in healthy volunteers. It is recommended that oral quinolone antibiotics are not taken simultaneously with FOSRENOL®.

The bioavailability of levothyroxine was decreased by approximately 40% when taken together with FOSRENOL®. Consequently, thyroid hormone replacement therapy should not be taken simultaneously with FOSRENOL® and monitoring of TSH levels is recommended in patients receiving both medicinal agents.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Oral administration of lanthanum carbonate to rats for up to 104 weeks, at doses up to 1500 mg/kg/day (2.5 times the maximum recommended daily human dose (MRHD) of 5725 mg/m²/day, on a mg/m² basis, assuming a 65-kg patient) revealed no evidence of carcinogenic potential in the mouse. Oral administration of lanthanum carbonate for up to 99 weeks, at a dose of 1500 mg/kg/day (1.3 times the MRHD) was associated with an increased incidence of glandular stomach adenomas in male mice.

Lanthanum carbonate tested negative for carcinogenic activity in an in-vitro Ames assay using Salmonella typhimurium and Escherichia coli strains and in vitro HGPRT gene mutation and chromosomal aberration assays in Chinese hamster ovary cells. Lanthanum carbonate also tested negative in an oral mouse micronucleus assay at doses up to 2000 mg/kg (1.7 times the MRHD), and in micronucleus and unscheduled DNA synthesis assays in rats given lanthanum chloride at doses up to 0.1 mg/kg, a dose that produced decreased plasma lanthanum concentrations >2000 times the peak human plasma concentration.

Lanthanum carbonate, at doses up to 2000 mg/kg/day (3.4 times the MRHD), did not affect fertility or mating performance of male or female rats.

Pregnancy:
Pregnancy Category C. No adequate and well-controlled studies have been conducted in pregnant women. The effect of FOSRENOL® on the absorption of vitamins and other nutrients has not been studied in pregnant women. FOSRENOL® is not recommended for use during pregnancy.

In pregnant rats, oral administration of lanthanum carbonate at doses as high as 2000 mg/kg/day (3.4 times the MRHD) resulted in no evidence of harm to the fetus. In pregnant rabbits, oral administration of lanthanum carbonate at 1500 mg/kg/day (5 times the MRHD) was associated with a reduction in maternal body weight gain and food consumption, increased post-implantation loss, reduced fetal weights, and delayed fetal ossification. Lanthanum carbonate administered to rats from implantation through lactation at 2000 mg/kg/day (3.4 times the MRHD) caused delayed eye opening, reduction in body weight gain, and delayed sexual development (preputial separation and vaginal opening) of the offspring.

Labor and Delivery
No lanthanum carbonate treatment-related effects on labor and delivery were seen in animal studies. The effects of lanthanum carbonate on labor and delivery in humans is unknown.

Nursing Mothers:
It is not known whether lanthanum carbonate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSRENOL® is administered to a nursing woman.

Geriatric Use:
Of the total number of patients in clinical studies of FOSRENOL®, 32% (538) were ≥ 65, while 9.3% (159) were ≥ 75. No overall differences in safety or effectiveness were observed between patients ≥ 65 years of age and younger patients.

Pediatric Use:
While growth abnormalities were not identified in long-term animal studies, lanthanum was detected in developing bone including growth plate. The consequences of such deposition in developing bone in pediatric patients are unknown. Therefore, the use of FOSRENOL® in this population is not recommended.

ADVERSE REACTIONS
The most common adverse events for FOSRENOL® were gastrointestinal events, such as nausea and vomiting and they generally abated over time with continued dosing.

In double-blind, placebo-controlled studies where a total of 180 and 95 ESRD patients were randomized to FOSRENOL® and placebo, respectively, for 4-6 weeks of treatment, the most common events that were more frequent (≥5% difference) in the FOSRENOL® group were nausea, vomiting, dysphagia, flatulence, and abdominal pain (Table 1).

Table 1. Adverse Events That Were More Common on FOSRENOL® in Placebo-Controlled, Double-Blind Studies with Treatment Periods of 4-6 Weeks.

<table>
<thead>
<tr>
<th>Event</th>
<th>FOSRENOL®%</th>
<th>Placebo%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=180)</td>
<td>(N=95)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Dysphagia flatulence</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

The safety of FOSRENOL® was studied in two long-term clinical trials, which included 1215 patients treated with FOSRENOL® and 943 with alternative therapy. Fourteen percent (14%) of patients in these comparative, open-label studies discontinued in the FOSRENOL®-treated group due to adverse events. Gastrointestinal adverse events, such as nausea, diarrhea and vomiting were the most common type of event leading to discontinuation.

The most common adverse events (≥5% in either treatment group) in both the long-term (2 year), open-label, active controlled, study of FOSRENOL® vs. alternative therapy (Study A) and the 6-month, comparative study of FOSRENOL® vs. calcium carbonate (Study B) are shown in Table 2. In Table 2, Study A events have been adjusted for mean exposure differences between treatment groups (with a mean exposure of 0.9 years on lanthanum and 1.3 years on alternative therapy). The adjustment for mean exposure was achieved by multiplying the observed adverse event rates in the alternative therapy group by 0.71.

Table 2. Incidence of Treatment-Emergent Adverse Events That Occurred in ≥5% of Patients (in Either Treatment Group) and in Both Comparative Studies A and B

<table>
<thead>
<tr>
<th>Event</th>
<th>Study A %</th>
<th>Study B %</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 682)</td>
<td>(N=533)</td>
<td>(N=267)</td>
</tr>
<tr>
<td>FOSRENOL®</td>
<td>Alternative Therapy Adjusted Rates</td>
<td>FOSRENOL® Calcium Carbonate</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Diarrhea flatulence</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Headache</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>Rash</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

OVERDOSAGE
There is no experience with FOSRENOL® overdose. Lanthanum carbonate was not acutely toxic in animals by the oral route. No deaths and no adverse effects occurred in mice, rats or dogs after single oral doses of 2000 mg/kg. In clinical trials, daily doses up to 4718 mg/day of lanthanum were well tolerated in healthy adults when administered with food, with the exception of GI symptoms. Given the topical activity of lanthanum in the gut, and the excretion rate of the majority of the dose, supportive therapy is recommended for overdose.

DOSEAGE AND ADMINISTRATION
The total daily dose of FOSRENOL® should be divided and taken with meals. The recommended initial total daily dose of FOSRENOL® is 1500 mg. The dose should be titrated every 2-3 weeks until an acceptable serum phosphate level is reached. Serum phosphate levels should be monitored as needed during dose titration and on a regular basis thereafter.

In clinical studies of ESRD patients, FOSRENOL® doses up to 3750 mg were evaluated. Most patients required a total daily dose between 1500 mg and 3300 mg to reduce plasma phosphate levels to less than 6.0 mg/dL. Drugs were generally titrated in increments of 750 mg/day.

Tablets should be chewed completely before swallowing. To aid in chewing, tablets may be crushed. intact tablets should not be swallowed.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

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Does Soda Intake Affect Kidney Disease Risk?

High consumption of sugar-sweetened soft drinks is associated with an increased prevalence—but not incidence—of hyperuricemia and chronic kidney disease (CKD), according to a study in the Journal of the American Medical Association.

The study included 17,745 participants in the Atherosclerosis Risk in Communities study, who provided baseline data on their consumption of sugar-sweetened sodas. About 5 percent reported drinking more than one soda per day. Based on serum creatinine and uric acid measurements, 37 percent of participants met sex-specific criteria for hyperuricemia while 3.1 percent had prevalent CKD.

On multivariate analysis, individuals who drank more than one soda per day had an increased prevalence of hyperuricemia, compared to those who drank less than one soda per day: odds ratio 1.31. The prevalence of CKD was increased for participants who drank more than one soda per day and who had a serum uric acid level of greater than 9.0 mg/dL: odds ratio 2.59.

A longitudinal analysis was performed using three- and nine-year follow-up data. The results showed no association between soda consumption and the incidence of hyperuricemia or CKD. Soda consumption was unrelated to incident CKD risk, regardless of whether hyperuricemia was present at baseline or developed during follow-up. Consumption of diet soda was unrelated to prevalent or incident hyperuricemia or CKD.

Rising rates of obesity, metabolic syndrome, and CKD have occurred at a time of increasing consumption of high-fructose corn syrup—most of it in soft drinks. Two recent studies have linked sweetened soda consumption to albuminuria and elevated serum creatinine. Both of these studies focused on prevalence and neither looked at the effects of elevated uric acid.

The new study finds increased rates of prevalent hyperuricemia among Americans who drink more than one sugar-sweetened soda per day. Prevalence of CKD is increased for heavy soda drinkers with hyperuricemia. However, there are no similar associations on longitudinal analysis of incident hyperuricemia and CKD. "[O]ur findings add to but in no way close the heated discussion over the potential dangers of sugar-sweetened soda," the investigators conclude [Bomback AS, et al. Sugar-sweetened soda consumption, hyperuricemia, and kidney disease. Kidney Int 2010; 77:609–616].

No Increase in Mortality for Living Kidney Donors

At medium-term follow-up, there is no increase in the overall risk of death for Americans who become living kidney donors, concludes a study in the Journal of the American Medical Association.

The study included 80,347 people who became live kidney donors in the United States between 1994 and 2009, reported to the Organ Procurement and Transplantation Network through the United Network for Organ Sharing. Donors were followed up for a median of 6.3 years. Survival was compared with a cohort of 9364 matched participants from the third National Health and Nutrition Examination Survey (NHANES III), excluding those with contraindications to kidney donation.

The number of live kidney donors increased significantly over the years—in 2008, there were 5968 donors. The rate of death within 90 days after nephrectomy was 3.1 per 10,000 donors, and remained stable throughout the 15 years covered by the registry. This was so despite an increased number of donors over age 50.

Surgical mortality was higher for men than women, 5.1 versus 1.7 per 10,000 donors; and for black donors than white donors, 7.6 versus 2.6 per 10,000. The strongest risk factor for mortality was hypertension: 36.7 versus 1.3 per 10,000 donors.

Despite the increase in 90-day mortality, live kidney donors had long-term mortality similar to or lower than that in the matched NHANES III cohort: at 12-year follow-up, mortality was 1.5 percent versus 2.9 percent, respectively. This remained so on stratification by age, sex, and race.

Living kidney donation is an increasingly important source of organs for transplantation. Although donor appears safe, continued follow-up is essential to gather accurate information on the expected outcomes.

This registry study finds no increase in mortality among living kidney donors at a median follow-up of 6.3 years, compared to a closely matched population cohort. Certain groups have increased surgical mortality; potential donors should be counseled accordingly. While calling for more research on the physiologic changes after nephrectomy, the authors conclude that living kidney donation is a "reasonable and safe" approach to increasing the number of kidneys for transplantation [Seger DL, et al. Perioperative mortality and long-term survival following live kidney donation. JAMA 2010; 170:959–966].
Cholesterol Drug Tied to Rhabdomyolysis

At high doses, the drug simvastatin (Merck, also known as Zocor), puts patients at risk of developing rhabdomyolysis, a severe breakdown of muscle that can result in acute kidney injury, dysfunction, and even death.

In mid-March, the Food and Drug Administration issued a warning message that patients taking the highest allowable dose of Zocor, 80 mg, had an increased risk for muscle injury. The FDA issued the news partly in response to findings from the trial Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).

Known risk factors for developing rhabdomyolysis include age above 65 years old, low thyroid hormone levels (hypothyroidism), and poor kidney function.

According to the FDA, myopathy is a known side effect of all statin medications. In fact, Merck said warnings about myopathy have always been part of the drug information package. “The labeling for simvastatin has reflected information about potential muscle effects since approval,” according to a Merck statement about the FDA announcement.

“Simvastatin, when used as a supplement to a healthy diet, can help reduce LDL cholesterol and reduce the risk of death from cardiovascular disease in patients at high risk of coronary events,” said Michael Rosenblatt, MD, Merck’s chief medical officer. “We support the FDA’s recommendation that patients continue taking their medication as prescribed by their physicians, and that patients speak to their physician if they have symptoms or questions.”

The company is working with regulatory agencies to update the drug’s labeling as needed.

The FDA recommends that health care professionals:

• be aware of the potential increased risk of muscle injury with the 80 mg dose of simvastatin compared to lower doses of simvastatin and possibly other statin drugs.
• review patients’ medical history and medications to determine whether simvastatin is clinically appropriate for each patient.
• discuss with patients the benefits and risks, including the risk of myopathy and rhabdomyolysis, of simvastatin therapy.
• be aware of potential drug-drug interactions with simvastatin.
• report any adverse events associated with the use of simvastatin to FDA’s MedWatch program. Visit www.fda.gov for more information.

Dialysis Company Owes U.S. $19.4 Million

In deciding a “whistleblower” case originally filed in St. Louis in 2005, a federal court in Nashville on March 23 awarded the United States $19,366,705, plus interest, says the U.S. Department of Justice. The U.S. District Court concluded that Renal Care Group, Renal Care Group Supply Company (RCGSC), and Fresenius Medical Care Holdings, which acquired Renal Care Group in 2005, “recklessly disregarded federal law when billing the Medicare program for home dialysis supplies and equipment from 1999 to 2005.”

U.S. District Judge William J. Haynes, Jr., held that defendants disregarded the mandates of the applicable Medicare statutes and regulations. He said that Renal Care Group employees raised complaints and concerns about the operation and Medicare billing activity of the RCGSC.

According to Nashville Business Journal, in October 1998, the company’s chief operating officer for the south central region protested a corporate request that “encouraged some dialysis patients to switch from primarily facility care to much more at-home care—in which they used fluids and a machine or catheter to provide their own treatment,” because of higher federal reimbursement.

The court scrutinized Renal Care Group and RCGSC in light of the two tiers of payments that Medicare gives to dialysis companies. Companies that operate dialysis facilities are supposed to bill Medicare using “Method I,” which applied to Renal Care Group. Companies that supply patients with dialysis at-home supplies but don’t run dialysis facilities, like RCGSC, are paid under Medicare “Method II,” which pays 30 percent more.

The court’s order noted that Renal Care Group did not follow the advice of the company’s lawyers when operating the supply company, and discussed an internal audit of the supply company that found that 100 percent of the company’s files were missing information that Medicare required for billing the government program.

The court held that “reckless disregard is sufficient for liability” under the federal False Claims Act, and that specific intent to defraud was not a standard that had to be met.

Fresenius has appealed the District Court decision. “We disagree with the court’s conclusion that payment by the government (Medicare program) of claims by Renal Care Group’s Method II company constituted ‘unjust enrichment,’” Fresenius spokeswoman Terry Morris said in a statement.

Industry Spotlight

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