Less Specialist Care Could Mean More Hospitalizations and Higher Mortality, Study Finds

By Karen Blum

A recent report in *Health Affairs* provides a sobering reminder of the importance of specialty medical care in improving health outcomes (1). The study of 11,581 rural and urban Medicare beneficiaries with one or more complex chronic conditions found that living in rural areas with fewer opportunities for seeing a specialist was associated with a 40% higher rate of preventable hospitalizations and a 23% higher rate of death compared to living in urban areas.

Preventable hospitalization rates per 100 beneficiaries ranged from 14.9 in rural areas to 10.6 in metropolitan areas in the study, while annual mortality rates ranged from 8.6% in rural areas to 7% in metropolitan areas. Diving deeper, researchers found that having one or more specialist visits during the previous year was associated with a 15.9% lower preventable hospitalization rate and 16.6% lower mortality rate. The supply of specialists overall was 31% lower in rural areas.

The initial pass rate for the nephrology certification exam dropped by 9% in 2019, setting off concerned discussions on Twitter and a search for explanations by many in the nephrology community.

The decline in the pass rate to 74% represents a precipitous drop from the 90% rate of 2016. The rates in both 2017 and 2018 were 83%. For the 15 subspecialties tested under the aegis of the American Board of Internal Medicine (ABIM) in 2019, the average pass rate was 90.5%.

Although the size of the decline raised questions about a problem with the test, ABIM is steadfast in defending the reliability of its psychometric methods for holding the test difficulty steady from year to year. Given that, other proposed explanations include a change in the quality of the test-taking pool, a failing in the quality of education trainees are receiving, and a mismatch between the test material and the clinical experience of fellows.

By the numbers

Although scores temporarily recovered from a similar drop in the past, it’s unlikely that this drop is a single-year aberration. The scores dropped 7 percentage points to 80% in 2014, only to bounce back to 89% in 2015 and 90% in 2016. But that recovery was followed by another decline to 83% in both 2017 and 2018. The nephrology pass rates reflect a long-term decline: in the five-year period from 2006 to 2010, the pass rates averaged 94%; from 2010 to 2014, they averaged 88%; and from 2015 to 2019, they averaged 84% (and for the past three years, 80%).

During that recent five-year period, the only other ABIM-tested subspecialties with pass rates averaging under 90% were geriatric medicine at 86% (and 88% for the past three years) and endocrinology, diabetes, and metabolism at 89% (89% for the past three years).

A sampling of other 5-year averages include: rheumatology, 92%; gastroenterology, 97%; infectious disease, 97%; and cardiovascular disease, 93%.

Although several observers raised the statistical possibility that nephrology, with fewer exam takers, would be subject to larger swings than some larger subspecialties, subspecialties such as rheumatology and infectious disease have...
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lower in rural areas.

Even after controlling for primary care visits, lack of access to specialists was still the primary driver of higher mortality and preventable hospitalizations among those in rural areas, said lead study author Kersten J. Johnston, PhD, MPH, an assistant professor of health management and policy at Saint Louis University, in Missouri.

“I was surprised to see how much of an impact seeing a specialist had on rural beneficiaries in terms of explaining the gap in mortality rates,” she said. “I thought it would be more even with social risk factors like income, poverty, and education.”

Johnston and colleagues used information from the Medicare Current Beneficiary Survey linked to respondents’ fee-for-service Medicare claims and administrative data for the years 2006 to 2013. They also linked data on healthcare supply at the level of Hospital Service Area provided by the Dartmouth Institute for Health Policy and Clinical Practice, and county-level rural-urban classifications from Area Health Resources Files provided by the US Department of Health and Human Services Health Resources and Services Administration.

Investigators limited the study sample to beneficiaries with heart failure, ischemic heart disease, and chronic obstructive pulmonary disease or asthma, and at least two years of continuous enrollment in fee-for-service Medicare Parts A and B. Rural beneficiaries were more often white, had a higher burden of heart failure and ischemic heart disease, and had lower incomes and less education than did those in the suburbs or cities.

While the study did not look specifically at beneficiaries with kidney disease, given that some of the participants studied had diabetes and heart failure, “it’s pretty likely that a lot of them have comorbid kidney disease,” Johnston said.

Some 3.3% of rural beneficiaries had a visit with a nephrologist, compared with 5.3% of urban beneficiaries.

The authors recommended several strategies: the Centers for Medicare & Medicaid Services could use to improve access to specialty care for rural residents, such as expanding telemedicine programs, workforce reforms to increase the supply of specialists, and partnerships between rural and urban hospitals for the provision of specialty care, at least on an intermittent basis.

Nephrologists interviewed for this story said they were not surprised by the findings.

Several studies have shown that people in rural areas who have kidney disease have limited access to nephrologists than those living in suburbs and small cities.

“Lack of early referral to nephrologists has been shown time and again to be strongly associated with faster progression to ESKD, and to lower rates of arteriovenous fistula placement and kidney transplant listing,” Golestaneh said. A number of patients “crash into dialysis,” she said, needing emergency dialysis by the time of diagnosis.

Nephrology is amenable to telemedicine and e-consults, said Golestaneh. “By utilizing these tools, primary care doctors can get guidance on blood pressure medication adjustment, how to prioritize patients with regard to follow-up, how to risk stratify patients according to the likelihood of progression, and probably most importantly, when to assist their CKD patients to go to bigger medical centers for vascular access placement and transplant evaluations.”

The emphasis on increasing access to home dialysis in the Advancing American Kidney Health Initiative, established by executive order in July 2019, also could be of benefit to rural residents, said Sumit Mohan, MD, MPH, FASN, an associate professor of medicine and epidemiology at Columbia University, New York.

But complicating the issue, fewer physicians are choosing to go into nephrology, Mohan said. Some 40% of fellowship training positions were unfilled in 2017 and 2018, according to an ASN Data Brief (3). “We now estimate that one in seven adults has CKD in the US—about 40 million people—and the overwhelming majority are unaware that they have it,” Mohan said.

Primary care providers may not be as skilled at identifying patients with CKD for a multitude of reasons, he said, including how lab tests are reported. In addition, patients frequently are not symptomatic in the early stages; when they do have symptoms, they include signs like weight loss, decreased appetite, or fatigue, which could be attributable to a range of conditions. “If you don’t have enough exposure to physicians who are providers in the care of CKD, you can see how those people will do worse,” Mohan said.

With the growing burden of CKD there is a need for more nephrologists, and for primary care providers to get better at recognizing and managing early CKD, Mohan said. “We simply don’t have the bandwidth as a specialty to manage all of them,” he said.

References
Nephrology Certification Exam
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fewer examinees than nephrology and have not experienced swings greater than 3 or 4%.

A drop in candidate numbers
Perhaps the leading explanation for the drop in scores is a change in the quality of the trainee pool. “It is public knowledge that over the last several years, nephrology programs in the US have had difficulty filling their positions,” said Gary Singer, MD, a senior partner at Midwest Nephrology Associates in St. Peters, Mo., and a member of the ABIM nephrology board. Ten to 15 years ago, nephrology training programs saw 1.5 candidates applying for every position. Currently, only six of every 10 positions are filled directly through the National Resident Matching Program match. And nephrology is not the first choice of a significant number of fellows matching into it.

Nephrology also has a higher proportion of international medical graduates now than in the past—and also more than many other subspecialties—and international graduates do not perform as well as US graduates on the nephrology certification exam.

Evidence of a change in the candidate pool comes from their performance on the internal medicine certification exam taken before they enter into nephrology training. “Candidates who completed the nephrology certification exam had the lowest scores on the internal medicine certification exam compared to other subspecialties,” said Bradley Brossman, PhD, vice president of psychometrics at ABIM.

“Ten years ago, candidates who completed the nephrology certification exam had among the highest scores on the internal medicine certification exam compared to other subspecialties.”

Scott Gilbert, MD, of Tufts Medical Center and chair of the ASN Workforce and Training Committee, said: “Given the declining interest in nephrology, it raises the concern we are accepting trainees into our program through the match and the subsequent scramble who we might not have considered in earlier years in order to fill our complement. This highlights the need to maintain our standards even if it means not filling all of our positions.”

Another factor could be that some fellows are not pursuing nephrology certification because their ultimate goal is the higher-paying field of being a hospitalist—perhaps with special expertise in nephrology—according to ASN Executive Vice President Tod Ibrahim. The number of fellows taking the test for the first time has declined in the past two years, from a rough average of around 420 in the prior decade to 365 in 2018 and 375 in 2019.

Further evidence for the candidate-pool argument is that the other subspecialty with the lowest pass rates is geriatrics—another field that has had trouble attracting a sufficient number of applicants.

Need for better education?
Regardless of any change in the candidate pool, the drop in the pass rate is “tough to see,” said Matthew Sparks, MD, assistant professor of medicine at Duke University and associate director of its fellowship program. “The most counterintuitive aspect of this is whether we are letting individuals into our field that have more deficits to fill. But all these people passed the internal medicine boards, and we should be able to get them to pass the nephrology boards on the first attempt. We should be able to identify those that need more help and utilize resources to help them. The individuals taking the test represent more than just themselves. They represent the program in which they trained, the educational opportunities they have, and the emphasis of their education.”

Sparks said that the low pass rate “is a hard pill to swallow when the nephrology community has put a lot more effort into education recently by including educational sessions at ASN Kidney Week and by more grassroots efforts to start online educational websites.”

Training program challenges
As long ago as 2014, Christina Yuan of Walter Reed National Military Medical Center and two co-authors wrote an editorial in the American Journal of Kidney Disease wondering whether “training programs are not providing adequate education,” and concluding that, based on calculations from the general pass rates, many nephrology training programs “are perilously close to or have fallen below” the minimum pass-rate threshold required by the Accreditation Council for Graduate Medical Education (ACGME) to remain accredited. Despite repeated requests to confirm or deny this conclusion, ACGME declined to respond, instead referring questions to ABIM, which is not involved in program accreditation.

Prediabetes After Kidney Transplant Increases Cardiovascular Risk
Prediabetes after kidney transplantation is associated with an increased risk of cardiovascular events, similar to that seen with posttransplant diabetes mellitus (PTDM), reports a study in Kidney International.

The researchers present long-term follow-up data on 603 kidney transplant recipients, enrolled in a multicenter study of the clinical evolution of prediabetes and PTDM. Patients underwent serial oral glucose tolerance tests for up to 5 years; median follow-up was 8.38 years.

The presence of prediabetes and PTDM was determined at 12 months after transplantation, due to the reversibility of these conditions at earlier times. The association of prediabetes with later fatal or nonfatal cardiovascular events was assessed.

At 12 months, 27% of patients were classified as having prediabetes and 16% as having PTDM. Patients with these conditions were older, more likely to be men, and more likely to be obese. Of the total 116 cardiovascular events, 73 occurred more than 12 months after transplantation.

The incidence of events after 12 months was 17% in patients with prediabetes and 20% in those with PTDM, compared to 7% in patients with normal glucose metabolism. Incidence rates were 0.023, 0.028, and 0.0095 events/person-year, respectively. On multivariate analysis, both abnormalities were associated with a two-fold increase in cardiovascular events: hazard ratio 2.41 for prediabetes and 2.24 for PTDM. Prediabetes at 3 months and glycosylated hemoglobin at 12 months were unrelated to cardiovascular events. Neither prediabetes nor PTDM was a risk factor for total mortality.

Prediabetes or PTDM occurs in 20% to 30% of patients after renal transplantation. Although PTDM is a known risk factor for cardiovascular disease, less is known about the impact of prediabetes.

This cohort study finds a 27% incidence of prediabetes 12 months after kidney transplantation, along with a 16% incidence of PTDM. Both conditions are associated with an increased risk of fatal or nonfatal cardiovascular events, in a group of patients already at high risk.

“Since prediabetes is potentially a reversible condition, there is an opportunity to prevent cardiovascular disease in this population,” the researchers write. They add that the oral glucose tolerance test is “a simple tool” to identify patients at risk that “should be included in clinical practice.”

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Indication
Parsabiv™ (etelcalcetide) is indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on hemodialysis.

Limitations of Use:
Parsabiv™ has not been studied in adult patients with parathyroid carcinoma, primary hyperparathyroidism, or with CKD who are not on hemodialysis and is not recommended for use in these populations.

Important Safety Information
Contraindication: Parsabiv™ is contraindicated in patients with known hypersensitivity to etelcalcetide or any of its excipients. Hypersensitivity reactions, including pruritic rash, urticaria, and face edema, have occurred.

Hypocalcemia: Parsabiv™ lowers serum calcium and can lead to hypocalcemia, sometimes severe. Significant lowering of serum calcium can cause QT interval prolongation and ventricular arrhythmia. Patients with conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to Parsabiv™. Closely monitor corrected serum calcium and QT interval in patients at risk on Parsabiv™.

Significant reductions in corrected serum calcium may lower the threshold for seizures. Patients with a history of seizure disorder may be at increased risk for seizures if they develop hypocalcemia due to Parsabiv™. Monitor corrected serum calcium in patients with seizure disorders on Parsabiv™.

Concurrent administration of Parsabiv™ with another oral calcimimetic could result in severe, life-threatening hypocalcemia. Patients switching from cinacalcet to Parsabiv™ should discontinue cinacalcet for at least 7 days prior to initiating Parsabiv™. Closely monitor corrected serum calcium in patients receiving Parsabiv™ and concomitant therapies known to lower serum calcium.

Measure corrected serum calcium prior to initiation of Parsabiv™. Do not initiate in patients if the corrected serum calcium is less than the lower limit of normal. Monitor corrected serum calcium within 1 week after initiation or dose adjustment and every 4 weeks during treatment with Parsabiv™. Measure PTH 4 weeks after initiation or dose adjustment of Parsabiv™. Once the maintenance dose has been established, measure PTH per clinical practice.

Worsening Heart Failure: In Parsabiv™ clinical studies, cases of hypotension, congestive heart failure, and decreased myocardial performance have been reported. Closely monitor patients treated with Parsabiv™ for worsening signs and symptoms of heart failure.

Upper Gastrointestinal Bleeding: In clinical studies, 2 patients treated with Parsabiv™ in 1253 patient years of exposure had upper gastrointestinal (GI) bleeding at the time of death. The exact cause of GI bleeding in these patients is unknown and there were too few cases to determine whether these cases were related to Parsabiv™.

Patients with risk factors for upper GI bleeding, such as known gastritis, esophagitis, ulcers or severe vomiting, may be at increased risk for GI bleeding with Parsabiv™. Monitor patients for worsening of common Parsabiv™ GI adverse reactions and for signs and symptoms of GI bleeding and ulcerations during Parsabiv™ therapy.

Adynamic Bone: Adynamic bone may develop if PTH levels are chronically suppressed.

Adverse Reactions: In clinical trials of patients with secondary HPT comparing Parsabiv™ to placebo, the most common adverse reactions were blood calcium decreased (64% vs. 10%), muscle spasms (12% vs. 7%), diarrhea (11% vs. 9%), nausea (11% vs. 6%), vomiting (9% vs. 5%), headache (8% vs. 6%), hypocalcemia (7% vs. 0.2%), and paresthesia (6% vs. 1%).

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

IV = intravenous; sHPT = secondary hyperparathyroidism; PTH = parathyroid hormone; P = phosphate; cCa = corrected calcium.

Reference: 1. Parsabiv™ (etelcalcetide) prescribing information, Amgen.
for worsening signs and symptoms of heart failure. Closely monitor patients treated with PARSABIV.

Worsening Heart Failure

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV [see Adverse Reactions (6.1) in PARSABIV full prescribing information] and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Upper Gastrointestinal Bleeding

In clinical studies, two patients treated with PARSABIV in 1253 patient-years of exposure had upper gastrointestinal (GI) bleeding noted at the time of death while no patient in the control groups in 384 patient-years of exposure had upper GI bleeding noted at the time of death. The exact cause of GI bleeding in these patients is unknown, and there were too few cases to determine whether these cases were related to PARSABIV.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers, or severe vomiting) may be at increased risk for GI bleeding while receiving PARSABIV treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with PARSABIV [see Adverse Reactions (6.1) in PARSABIV full prescribing information] and for signs and symptoms of GI bleeding and ulcerations during PARSABIV therapy. Promptly evaluate and treat any suspected GI bleeding.

Adynamic Bone

Adynamic bone may develop if PTH levels are chronically suppressed. If PTH levels decrease below the recommended target range, the dose of vitamin D sterol and/or PARSABIV should be reduced or therapy discontinued. After discontinuation, resume therapy at a lower dose to maintain PTH levels in the target range [see Dosage and Administration (2.1) in PARSABIV full prescribing information].

ADVERSE REACTIONS

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

- Hypocalcemia [see Warnings and Precautions (5.1) in PARSABIV full prescribing information]
- Worsening Heart Failure [see Warnings and Precautions (5.2) in PARSABIV full prescribing information]
- Upper Gastrointestinal Bleeding [see Warnings and Precautions (5.3) in PARSABIV full prescribing information]
- Adynamic Bone [see Warnings and Precautions (5.4) in PARSABIV full prescribing information]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The data in Table 2 are derived from two placebo-controlled clinical studies in patients with chronic kidney disease and secondary hyperparathyroidism on hemodialysis. The data reflect exposure of 503 patients to PARSABIV with a mean duration of exposure to PARSABIV of 23.6 weeks. The mean age of patients was approximately 58 years, and 60% of the patients were male. Of the total patients, 67% were Caucasian, 28% were Black or African American, 2.6% were Asian, 1.2% were Native Hawaiian or Other Pacific Islander, and 1.6% were categorized as Other. Table 2 shows common adverse reactions associated with the use of PARSABIV in the pool of placebo-controlled studies. These adverse reactions occurred more commonly on PARSABIV than on placebo and were reported in at least 5% of patients treated with PARSABIV.

Table 2: Adverse Reactions Reported in ≥ 5% of PARSABIV-Treated Patients

<table>
<thead>
<tr>
<th>Adverse Reaction*</th>
<th>Placebo (N = 513)</th>
<th>PARSABIV (N = 503)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood calcium decreaseda</td>
<td>10%</td>
<td>64%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>7%</td>
<td>12%</td>
</tr>
<tr>
<td>Headache</td>
<td>9%</td>
<td>11%</td>
</tr>
<tr>
<td>Nausea</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>6%</td>
<td>8%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1%</td>
<td>6%</td>
</tr>
</tbody>
</table>

* Included adverse reactions reported with at least 1% greater incidence in the PARSABIV group compared to the placebo group

a Symptomatic reductions in corrected serum calcium between 7.5 and < 8.3 mg/dL (that required medical management)

b Symptomatic reductions in corrected serum calcium < 8.3 mg/dL

c Paresthesia includes preferred terms of paresthesia and hyposthesia
Other adverse reactions associated with the use of PARSABIV but reported in < 5% of patients in the PARSABIV group in the two placebo-controlled clinical studies were:

- Hypokalemia: 3% and 4% for placebo and PARSABIV, respectively.
- Hypertension: 1% and 2% for placebo and PARSABIV, respectively.
- Myalgia: 0.2% and 2% for placebo and PARSABIV, respectively.
- Hypophosphatemia: 0.2% and 1% for placebo and PARSABIV, respectively.

Description of Selected Adverse Reactions

Hypocalcemia

In the combined placebo-controlled studies, a higher proportion of patients on PARSABIV developed at least one corrected serum calcium value below 7.0 mg/dL (7.4% PARSABIV, 3.1% placebo), below 7.5 mg/dL (7.6% PARSABIV, 5.2% placebo), and below 8.3 mg/dL (7.9% PARSABIV, 19% placebo). In the combined placebo-controlled studies, 1% of patients in the PARSABIV group and 0% of patients in the placebo group discontinued treatment due to an adverse reaction attributed to a low corrected serum calcium.

Hypophosphatemia

In the combined placebo-controlled studies, 18% of patients treated with PARSABIV and 8.2% of patients treated with placebo had at least one measured phosphorus below the lower normal limit (i.e., 2.2 mg/dL).

QTc Interval Prolongation Secondary to Hypocalcemia

In the combined placebo-controlled studies, more patients treated with PARSABIV experienced a maximum increase from baseline of greater than 60 msec in the QTcF interval (0% placebo versus 1.2% PARSABIV). The patient incidence of maximum post-baseline predialysis QTcF > 500 msec in the placebo and PARSABIV groups was 1.9% and 4.6%, respectively.

Hypersensitivity

In the combined placebo-controlled studies, the subject incidence of adverse reactions potentially related to hypersensitivity was 4.4% in the PARSABIV group and 3.7% in the placebo group. Hypersensitivity reactions in the PARSABIV group were pruritic rash, urticaria, and face edema.

Immunogenicity

As with all peptide therapeutics, there is potential for immunogenicity. The detection of anti-drug binding antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to etelcalcetide with the incidence of antibodies to other products may be misleading.

In clinical studies, 7.1% (7 out of 99) of patients with secondary hyperparathyroidism treated with PARSABIV for up to 6 months tested positive for binding anti-etelcalcetide antibodies. Fifty-seven out of 71 had pre-existing anti-etelcalcetide antibodies.

No evidence of altered pharmacokinetic profile, clinical response, or safety profile was associated with pre-existing or developing anti-etelcalcetide antibodies. If formation of anti-etelcalcetide binding antibodies with a clinically significant effect is suspected, contact Amgen at 1-800-77-AMGEN (1-800-772-6436) to discuss antibody testing.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on the use of PARSABIV in pregnant women. In animal reproduction studies, effects were seen at doses associated with maternal toxicity that included hypocalcemia. In a pre- and postnatal study in rats administered etelcalcetide during organogenesis through delivery and weaning, there was a slight increase in perinatal pup mortality, delay in parturition, and transient effects on pup growth at exposures of 1.8 times the human exposure for the clinical dose of 1.5 mg three times per week. There was no effect on sexual maturation, neurobehavioral, or reproductive function in the rat offspring. In embryofetal studies, when rats and rabbits were administered etelcalcetide during organogenesis, reduced fetal growth was observed at exposures of 2.7 and 7 times exposures for the clinical dose, respectively.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

There were no effects on embryo-fetal development in Sprague-Dawley rats when etelcalcetide was dosed at 0.75, 1.5, and 3 mg/kg/day by the intravenous route during organogenesis (pre-mating to gestation day 17) at exposures up to 1.8 times human exposures at the clinical dose of 15 mg three times per week based on AUC.

No effects on embryo-fetal development were observed in New Zealand White rabbits at doses of etelcalcetide of 0.375, 0.75, and 1.5 mg/kg by the intravenous route (gestation day 7 to 19), representing up to 4.3 times human exposures based on AUC. In separate studies at higher doses of 4.5 mg/kg in rats (gestation days 6 to 17) and 2.25 mg/kg in rabbits (gestation days 7 to 20), representing 2.7 and 7 fold clinical exposures, respectively, there was reduced fetal growth associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption.

In a pre- and post-natal development study in Sprague-Dawley rats administered etelcalcetide at 0.75, 1.5, and 3 mg/kg/day by the intravenous route (gestation day 7 to lactation day 20), there was a slight increase in perinatal pup mortality, delay in parturition, and transient reductions in post-natal growth at 3 mg/kg/day (representing 1.8-fold human exposures at the clinical dose of 15 mg three times per week based on AUC), associated with maternal toxicities of hypocalcemia, tremoring, and reductions in body weight and food consumption. There were no effects on sexual maturation, neurobehavioral, or reproductive function at up to 3 mg/kg/day, representing exposures up to 1.8-fold human exposure based on AUC.

Lactation

Risk Summary

There are no data regarding the presence of PARSABIV in human milk or effects on the breastfed infant or on milk production. Studies in rats showed [14C]-etelcalcetide was present in the milk at concentrations similar to plasma. Because of the potential for PARSABIV to cause adverse effects in breastfed infants including hypocalcemia, advise women that use of PARSABIV is not recommended while breastfeeding.

Data

Presence in milk was assessed following a single intravenous dose of [14C] etelcalcetide in lactating rats at maternal exposures similar to the exposure at the human clinical dose of 15 mg three times per week. [14C] etelcalcetide-derived radioactivity was present in milk at levels similar to plasma.

Pediatric Use

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

Geriatric Use

Of the 503 patients in placebo-controlled studies who received PARSABIV, 177 patients (35.2%) were ≥ 65 years old and 72 patients (14%) were ≥ 75 years old.

No clinically significant differences in safety or efficacy were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old). No differences in plasma concentrations of etelcalcetide were observed between patients ≥ 65 years and younger patients (≥ 18 and < 65 years old).

OVERDOSAGE

There is no clinical experience with PARSABIV overdose. Overdosage of PARSABIV may lead to hypocalcemia with or without clinical symptoms and may require treatment. Although PARSABIV is cleared by dialysis, hemodialysis has not been studied as a treatment for PARSABIV overdose. In the event of overdose, corrected serum calcium should be checked and patients should be monitored for symptoms of hypocalcemia, and appropriate measures should be taken [see Warnings and Precautions (5.1) in PARSABIV full prescribing information].

PARSABIV™ (etelcalcetide)

Manufactured for:
KAI Pharmaceuticals, Inc., a wholly owned subsidiary of Amgen, Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799
Patent: http://pat.amgen.com/Parsabiv/

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The First Phone Call

By Joseph Mattana and James Gavin

The Nephrology Match yielded disappointing results again this year. At the same time, the current state of medical practice as a whole continues to suffer numerous problems, which are well described and largely obvious. Among them is a progressive degree of compartmentalization: Outpatient physicians are abandoning the hospital as a practice site, and hospitalists are quantitatively dominating inpatient medical care, with abandonment of the outpatient setting. This has afforded many efficiencies and advantages, including apparently favorable impacts on hospital metrics. It has also allowed for a form of subspecialization, a supporting argument being that this may better facilitate mastery and ongoing maintenance of competence in the increasingly complex domains of outpatient and inpatient practice.

From the perspective of many physicians, being limited to one or the other venue without additional responsibilities offers substantial quality-of-life advantages. Of course, this development is not without tradeoffs. From the standpoint of the patient it means discontinuity of care, with the hospitalized patient seeing a new and temporary physician, a hospitalist, who will ideally communicate regularly and effectively with the outpatient primary care physician and specialists. Such communications need to be bidirectionally effective. If these communications take place between a hospitalist and an outpatient intern who have never met (a not infrequent scenario now) and depend heavily on the faxing of voluminous and at times nearly incomprehensible templated printouts from electronic medical records, such communication is likely to suffer.

This compartmentalization has other consequences as well. The inpatient physician may lose touch with the outpatient domain of practice, especially the challenges faced by the outpatient physician, who receives the patient back after discharge and often scrambles to create an appointment while trying to determine what actually happened in the hospital and to come up with a plan after discharge. The outpatient physicians take on various risks as well, among them the potential for becoming somewhat disconnected from some of the potential life-threatening sequelae of the conditions they see—a concern recently shared with me by a senior primary care colleague, who for many years had navigated the inpatient and outpatient settings and was now taking on a fresh residency graduate for full-time outpatient primary care practice.

Now comes the nephrologist, whose practice is in many ways the antithesis of these models. As we all know, nephrology is truly one of the paradigms of medical practice. Nephrology is an ideal model of continuity, with nephrologists following up their patients in all domains including the inpatient unit, critical care unit, emergency department, and outpatient clinic. Nephrologists also oversee their patients’ procedural care in all settings, including inpatient and outpatient dialysis. For patients who undergo transplantation, the nephrologist continues to care for them in all settings and through all transitions, with numerous patients staying under our care for many years with immeasurable personal satisfaction.

We have extensive interactions with multiple medical and surgical specialties. We manage pediatric-to-adult transitions for patients with complex conditions. We work closely with nurses, social workers, nutritionists, and others in both inpatient and outpatient settings. The dialysis model is unique in that it entails especially close follow-up of patients, with thrice-weekly encounters between nurses and physicians throughout each month. Finally, aside from the intellectual and personal satisfaction that a career as a nephrologist provides, nephrology also affords a robust experience with continuous quality improvement—a longstanding part of nephrology practice—and the development of skills in navigating a complex regulatory environment and various payment models: skills that may be of great value in other domains.

As we all also know, nephrology is inseparable from general internal medicine; hence, the nephrologist’s scope is characteristically far beyond the kidney and typically includes taking ownership of many issues involving other organ systems. This is not lost among patients, who often see the nephrologist as their primary physician; hence, the nephrologist is in fact typically “the first phone call” for patients and other physicians when problems and questions arise. What should not be lost upon nephrologists is that this puts them in a remarkable position, including a vast spectrum of career options.

The structure of nephrology practice appears to be the ideal solution for much of what troubles us about current healthcare, including its fragmentation and discontinuity, and it also seems to have everything a physician would want in a career. However, this year’s Match results remind us that despite all that nephrology has to offer for patients and nephrologists, these offerings do not appear to be resonating with students and residents. The preferences of trainees regarding work–home balance, income, job availability within a geographically desirable location, and other items, and the trainees’ perception of various fields in how they align with those preferences, undoubtedly play a role in career choices for many. From this perspective, nephrology has fared less favorably for several years. The 2019 Nephrology Fellow Survey (1) reveals that these preferences hold true for nephrology trainees as well, with weekend call frequency, desired location, over-night call frequency, weekday length, and compensation being among the dominant factors in the consideration of various employment options. Changes in practice and reimbursement models are needed, and they may be able to address some of these issues.

Although improvements in perceived quality of life and job opportunities undoubtedly affect career choice, no career is likely to lead to long-term satisfaction without excitement about that field’s subject matter, including its intellectual challenge, the patients one cares for, the available therapeutic portfolio, and opportunities for growth in research, education, leadership, and other domains.

We must acknowledge that our field does have some current limitations, among them that after a half century dialysis remains the primary therapeutic modality for kidney failure. Nevertheless, rapid scientific advancement, new therapies for glomerular disease and for slowing the progression of chronic kidney disease, and advances in transplantation and many other areas hold great promise for improving care for our patients while providing great satisfaction for the nephrologist. Several residents have taken note of how the dearth of applicants for nephrology also provides a remarkable opportunity for a resident wishing to pursue a career in academic medicine to receive world-class training in nephrology as a pathway to that goal.

How can this excitement about all that nephrology has to offer be imparted to students and residents? Ongoing efforts by the American Society of Nephrology and the nephrology community will undoubtedly be essential to our success, but more is needed. Medical schools, department chairs, and internal medicine training program directors can help increase exposure to nephrologists not only as topical lecturers and consultants on innovative electives but also more often as medicine ward attendings and in other venues so that students and residents can better appreciate the vast scope of nephrology, its integration with all of internal medicine, and the vast spectrum of career pathways available to nephrologists.

With time, we can hope that more students and residents will appreciate that nephrology is in many ways a paradigm of medical practice. Being the first phone call is something any physician should be proud of.

Joseph Mattana is chair of the department of medicine at St. Vincent’s Medical Center, Bridgeport, CT, and Quinnipiac University Frank H. Netter MD School of Medicine and a member of the Kidney News Editorial Board. James Gavin is chief of nephrology at St. Vincent’s Medical Center and a member of Nephrology Associates, PC.

Reference
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Bringing a 2020 Focus to Clinical Trials in Kidney Health and Disease

A CALL FOR ACTION

By Richard Lafayette

This is a highly exciting year for nephrology. We will all need not only to watch but to participate in bringing about positive changes in healthcare for preventing and treating kidney diseases, hoping for strong support from the Advancing American Kidney Health initiative. One of the strongest reasons for enthusiasm, and one of the most important aspects, will be advancing clinical trials in nephrology. Clinical trials are the lifeblood of advancing medicine. To truly improve kidney care, we must be able to subject our treatments to rigorous high-quality trials in the appropriate patients and to evaluate them for the appropriate endpoints.

Only a few years ago, the status of clinical trials in kidney health and disease was quite disappointing (1). There was a long repeated history of multiple good ideas going by the wayside with unanticipated negative results (which is why trials are done) or underpowered incomplete trials. There are multitudes of examples. Hopes that fully corrective anemia therapy was safe and beneficial for our patients with advanced chronic kidney disease went unrealized; studies actually suggested harm. Preliminary data suggesting that more intensive dialysis would extend lives was similarly unsupported by clinical trials. Multiple studies failed to verify that seemingly promising interventions for acute kidney injury were indeed useful.

Beyond this, analyses suggested that despite the great need for validating and improving the care of patients with kidney disease—a very large, often ill, and cost-intensive population—there was relatively little in the way of documented clinical trial activity. Furthermore, the ongoing trials seemed to be relatively lacking in quality or potential impact. This was distinct from what was seen in other well-funded, high-visibility fields such as cardiology, oncology, and AIDS research. Limitations suggested to explain this scarcity included lack of federal funding for kidney disease, limited excitement by industry (fueld in part by frustration in the field from negative studies such as those above), and a limited infrastructure to carry out studies in an efficient and effective manner. These and other serious challenges were cited in a Kidney Disease—Improving Global Outcomes controversies conference (2) calling for desperate action to improve clinical trials in kidney disease.

These issues were further explored during a Global Kidney Health Summit in 2017 (3, 4). The participants reviewed and reported numerous factors responsible for the limited number and impact of clinical trials in kidney disease. These factors included limited knowledge of biologic targets, unclear relevant endpoints, lack of innovative trial designs, inadequate capacity to perform trials, uncertainty of what stage disease(s) to target, duplicative study designs, and a perception that trials are too expensive and high risk among kidney disease populations.

The participants expressed the aim of overcoming these limitations with a push toward funding more basic research, working on understanding and validating effective biomarkers as endpoints, engaging patients to be recruited for and participate in studies, including more kidney disease patients in active studies of general health trials (e.g., cardiology, oncology, diabetes), and engaging industry, advocacy groups, and physicians to substantially increase the number and size of clinical trials.

As an example of solutions, they advocated for innovative study design, moving somewhat from slow-moving, hard-to-recruit, and expensive prospective double-blind randomized control trials to more novel approaches such as randomized registry trials, cluster randomized trials, and adaptive trial designs. Most important, they endorsed the effort to increase the capacity for conducting clinical trials by developing networks nationally and internationally, cataloging sites whose personnel have the skill set to participate and to develop and provide more professional training in trial design and con-

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A Call for Action
Continued from page 9

duct. They targeted achieving the participation of 30% of patients with chronic kidney disease in trials by 2030. This action plan has great aspirations and merit, but it still requires huge coordination and funding to pull it off.

Reasons for optimism
Still, there are great reasons for optimism. A rudimentary evaluation of ClinicalTrials.org (5) today suggests 6380 trials in kidney disease. This suggests an uptick in activity as compared with just several years back (1). As opposed to decades ago, when late-breaking clinical trials were largely yielding negative results, recent years have brought some apparent successes in intervention (such as rituximab in membranous nephropathy, sodium-glucose co-transporter protein 2 inhibition and perhaps endothelin blockade in diabetes, tolvaptan in poly cystic kidney disease, and novel anemia therapies proving effective).

The US Food and Drug Administration has been active in evaluating and occasionally approving new endpoints for clinical trials, which is one suggestion that the efforts of the Kidney Health Initiative may be paying large dividends. Several examples suggest that nephrologists are indeed working together in broader collaborations to bring about meaningful guidelines and to spur interest in clinical trials. Patient advocacy groups have been successful in extolling the virtues and central importance of patient-reported outcomes as part of research studies, allowing for greater interest and participation of patients in ongoing and upcoming trials. Journals, guideline organizations, and regulatory bodies seem increasingly interested in using the results of innovative study designs to inform or determine clinical decision-making.

More effective and value-based care is an absolute necessity for maintaining kidney health and for treating patients with kidney disease. Not only is kidney disease a common issue affecting many millions of people, but also it is one that imposes tremendous suffering and a huge cost, both nationally and internationally. Advancements in care depend on the development of sound interventions for properly targeted populations that are each subjected to appropriate and well-designed clinical trials to allow the determination of their safety, efficacy, and impact on patients’ well-being. Progress is being made. Still, further efforts to increase clinical trials are desperately needed. We must build on caregiver interest, patient participation, stakeholders’ involvement, and funding, and we must develop increasing expertise in the design and execution of optimal clinical trials for our well-deserving population.

Richard Lafayette, MD, FACP, is Editor-in-Chief of Kidney News.

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Investment in Time, Resources Needed to Prepare Nephrology Nurses for Training Patients and Caregivers in Home Dialysis Delivery

By Glenda Payne and Tamara Kear

The World Health Organization has declared 2020, the 200th anniversary of the birth of Florence Nightingale, the Year of the Nurse. Nurses are encouraged by the exposure this will bring to the profession, as it promises to highlight their many roles. Further, nephrology nurses are cautiously excited about the recent focus on kidney health and the role nephrology nurses will play in implementing the Advancing American Kidney Health (AAKH) initiative launched in 2019. This executive order places a focus on kidney health by increasing patient choice with a focus on home dialysis therapy options, kidney disease prevention, and strategies to increase the number of transplantable kidneys. Nephrology nurses are concerned that the kidney community and dialysis industry are currently unprepared for the increased number of patients who might choose home therapy.

There is no evidence base to support the “right size” for training. According to the Medicare Conditions for Coverage for ESRD Facilities (CMS-5818-F), a nurse is required to have 12 months of experience as a registered nurse plus 3 months of experience in the modality (i.e., hemodialysis or peritoneal dialysis), and some state ESRD regulations impose more stringent requirements. Frequently, home programs are small, with a single nurse responsible for providing patient training with little to no support from other experienced nurses. The skills and training for patient education and care delivery for the in-center and home environments are not interchangeable. Nephrology nurses will require advanced training in home dialysis therapy.

The goals of the executive order connect to an area that is among the “top to watch” in 2020 and moving forward—the lack of nephrology nurses qualified to practice as home dialysis therapy nurses. With the final rules for the ESRD Treatment Choices (ETC) Mandatory Model coming in 2020 and the resultant changes in kidney replacement therapy, growth in home therapy will be a priority for many dialysis facilities. Nephrology nurses are concerned that the kidney community and dialysis industry are currently unprepared for the increased number of patients who might choose home therapy.

We must invest in the time and resources needed to educate nephrology nurses so they have the proper skill set to train patients and their caregivers for home therapy, as well as prepare additional nurses to be competent in delivering home dialysis training and therapy management. In addition, nephrology nurse practitioners will require additional training and education to transition in-center patients to home therapies, provide adequate dialysis prescriptions, and troubleshoot complications.

There is concern that the kidney community and dialysis industry are currently unprepared for the increased number of patients who will transition to home therapy, and this may become a significant barrier to successfully achieving the home therapy goals of the executive order.

Glenda Payne, RN, is a member of the Kidney News Editorial Board, and Principal, National Dialysis Accreditation Commission. Tamara Kear, PhD, RN, is Executive Director, American Nephrology Nurses Association.

Suggested Reading

The skills and training for patient education and care delivery for the in-center and home environments are not interchangeable. Nephrology nurses will require advanced training in home dialysis therapy.

The goals of the executive order connect to an area that is among the “top to watch” in 2020 and moving forward—the lack of nephrology nurses qualified to practice as home dialysis therapy nurses. With the final rules for the ESRD Treatment Choices (ETC) Mandatory Model coming in 2020 and the resultant changes in kidney replacement therapy, growth in home therapy will be a priority for many dialysis facilities. Nephrology nurses are concerned that the kidney community and dialysis industry are currently unprepared for the increased number of patients who might choose home therapy.
“Freedom” from Immunosuppression in Solid Organ Transplantation
By Uday Nori

The enduring success of solid organ transplantation over the past six decades is also accompanied by the need for immunosuppression regimens with their related systemic toxicity. Transplantation between immunologically diverse individuals led to shortened allograft survival for immunologic reasons (acute and chronic rejection) and nonimmunologic reasons (toxicity of the immunosuppressive medication regimens).

As a proof of concept, kidney transplantation between genetically identical twins without the requirement of immunosuppressive regimens was successful and ushered in a new era. However, for the larger majority of individuals undergoing allotransplantation, the concept that transplanting the donor’s immune system (bone marrow) along with the solid organ had existed for a long time. This can allow the development of mixed chimerism, the coexistence of donor and recipient lymphohematopoiesis, which in time obviates the need for long-term immunosuppression. However, this field has been hampered by the safety—graft vs. host disease (GVHD) being the most common catastrophic complications—and logistics of such a dual transplantation.

Earlier clinical trials used simultaneous bone marrow and kidney transplantation, initially from HLA-identical living donors, and later single haplotype-matched living donors (1). The results were highly encouraging, with several patients coming off immunosuppression within the first year of transplantation, but the major adverse effects included GVHD, “engraftment syndrome” with acute kidney injury, capillary leak syndrome, and development of new donor-specific antibodies upon withdrawal of immunosuppression. It was thought that some of these reactions resulted from the nonselective nature of the transplanted hematopoietic cells.

Over the years, investigators from the University of Louisville, led by Suzanne Ildstad, MD, a transplant surgeon, have developed a proprietary hematopoietic stem cells (HSC) product from the living kidney donor bone marrow with tolerogenic CD8+/TCR-–graft-facilitating cells, which is denoted FCRx. Central to the success of this product are “facilitating cells,” which resemble precursor plasmacytoid dendritic cells and are able to induce antigen-specific regulatory T cells in the recipient (Figure 1). These cells assist the HSC to engraft, proliferate, and subsequently induce chimerism in the recipient who received a kidney from the same donor.

This product was studied in a phase 2 clinical trial, the long-term follow-up of which is still ongoing, and the initial results from 31 patients with more than 12 months of follow-up have been reported (2). Of the 31 patients, durable (>12 months) chimerism developed in 23 patients, and 22 of them were able to be weaned from maintenance immunosuppression. The adverse effects mentioned above were noted to be uncommon in the study population. Importantly, GVHD occurred in only two individuals.

The regimen
The living kidney donor, who is typically HLA-mismatched with the recipient, is prepared at least 2 weeks before the date of the kidney transplantation. Granulocyte colony-stimulating factor is used for 4 to 5 days, and peripheral blood stem cells are procured by apheresis. By use of a proprietary process at a central location, the mature donor GVHD-producing cells are deleted and the HSC, facilitating cells, and progenitors are retained. The product, FCRx, is then cryopreserved and transported to the transplantation center.

The recipient is conditioned by a nonmyeloablative treatment, as shown in Figure 2, several days before transplantation and with a dose of cyclophosphamide after kidney transplantation. The living donor kidney transplantation is performed in the standard fashion along with the usual induction treatment. FCRx is infused intravenously on the day after kidney transplantation. Maintenance immunosuppression is provided with tacrolimus and mycophenolate mofetil at the usual dosing. At 6 months, peripheral blood is tested for T cell chimerism along with a protocol kidney biopsy to rule out acute rejection. If the recipient’s renal function is stable, no donor-specific antibodies are present, and if the chimerism is at or above 50%, mycophenolate mofetil is discontinued. Tacrolimus is slowly weaned during the following 3 to 6 months as well, as tolerated. At the time of the last reporting, 42 patients were enrolled into the phase 2 study, and 37 transplantsations had been performed (3).

On the basis of these results, a phase 3 clinical trial, FREEDOM-1, was launched in October 2019. This is a 2:1 randomized controlled trial recruiting 120 patients who will undergo mismatched living donor kidney transplantation and receive either the FCR001 (redefined FCRx for the purpose of this specific indication) treatment or standard of care. At present five transplantation centers are participating, and the primary endpoint is the proportion of recipients who are free from immunosuppression and without acute rejection at 24 months. The estimated study completion date is April 2025.

This study is the most exciting development to date in the field of immunologic tolerance induction and, if successful, will represent a paradigm shift in the practice of organ transplantation. The mechanisms of how and why FCRx is able to promote mixed chimerism are still being elucidated and will also be a subject of great interest.

Several other clinical trials using a similar principle but differently reconstituted bone marrow products are being done. The two most successful such trials are reported by investigators from Stanford University and Massachusetts General Hospital, both of which completed phase 2 trials with plans of starting phase 3 trials in the near future.

Uday Nori, MD, is associate professor of medicine and program director of the nephrology fellowship program at The Ohio State University Wexner Medical Center, Columbus, OH, and is a member of the Kidney News Editorial Board.

References

Figure 1. Facilitating cells interact with the HSC through numerous mechanisms to promote chimerism and tolerance

Figure 2. Algorithm for the non-myeloablative conditioning of the transplant recipient before and after the kidney transplant

Abbreviations: GVHD, graft vs. host disease; HSC, hematopoietic stem cells

Home Dialysis
By Ankur Shah

A top area to watch in 2020 is the new emphasis on home dialysis. On July 10, 2019, President Donald Trump signed an executive order launching Advancing American Kidney Health. Based on this executive order, the US Department of Health and Human Services (HHS) released three major goals to improve kidney health. The first goal is that 80% of incident kidney failure patients in 2025 receive a home modality of dialysis or a transplant. To facilitate this goal, mandatory and voluntary reimbursement models are being released. The mandatory model, ESRD Treatment Choices, will incentivize the provision of dialysis in the home.

In addition to the focus on home dialysis, HHS has also set goals of reducing the number of Americans reaching end stage kidney disease by 25% and doubling the number of kidneys available for transplant by 2030, and calls for a public awareness initiative to increase awareness of kidney disease for both patients and providers as well as for funding to support the development of an artificial kidney.

There is a large anticipated educational need to meet the lofty goals of 80% of patients receiving dialysis in the home setting or a kidney transplant. A recent survey of graduating nephrology fellows in the United States found that 40% of trainees would like to receive additional instruction during fellowship in peritoneal dialysis, and a 2010 survey of 133 early career nephrologists showed 45% did not feel competent in the management of peritoneal dialysis patients. A remarkable finding of a 2010 survey of nephrologists was that 93% would choose a home modality as their initial renal replacement therapy modality. Furthermore, many myths exist regarding selection of patients suitable for peritoneal dialysis despite literature disputing the myths, including that obesity, diabetes, and autosomal dominant polycystic kidney disease are contraindications.

In 2020, Kidney News will launch a new series, Peritoneal Dialysis 101, which is meant to serve as an introduction to peritoneal dialysis, the most prevalent form of home dialysis, for physicians. The series will include articles on the history of peritoneal dialysis, outcomes, debunking myths, and basics of prescribing, and will conclude with options for further education in home dialysis.

Suggested Reading

References

Shared-Care Dialysis Improves Patient Outcomes: Building the Evidence
By Martin Wilkie and Steve Ariss on behalf of the SHARED team, University of Sheffield, UK

All across medicine, there is strong evidence that people who understand and are engaged in their own healthcare have better outcomes. There are several reasons for this, including being able to make quality healthcare choices, knowing when to seek help, and knowing how to reduce the risk for the development of complications. The body of literature in this area is large; however, there has been high levels of patient engagement, and there has been considerable interest and investment in patient training to improve outcomes.

From a strategic point of view, healthcare organizations have recognized this and have prioritized patient training and self-efficacy as key objectives (2). Within kidney medicine, there is evidence of a link between health literacy and outcomes; a strong example is home dialysis, wherein people who are trained to undertake their own treatment do well (3, 4). A key question is how to reliably extend these opportunities to people who undergo in-center dialysis so that they can reap the potential benefits that come from greater self-efficacy.

One approach is to develop mechanisms that encourage people who undergo in-center dialysis to have the choice to learn and engage in tasks related to their own treatment. This is described as shared hemodialysis care (SHC). Home dialysis (HD) can be broken down into approximately 14 tasks, which range from easy to more complex (Figure 1) (5). The level and complexity of tasks an individual decides to learn is flexible, and the logical approach is to start with simple aspects before progressing to more complex tasks as confidence is gained. Benefits reported by patients include a greater sense of independence and control over their own condition and, for some, the opportunity to conduct independent dialysis (6).

It is therefore important to discover the best approaches to support the delivery of SHC and how they can best be measured. The key is to test metrics that can be used to assess individual progress and to demonstrate the level of engagement that is offered by providers. Until such measures are used routinely, it will not be possible to develop evidence-based mechanisms that create optimal opportunities for SHC.

In 2016, a quality improvement collaborative was established in England, supported by the Health Foundation, with the objective of scaling up SHC for patients in center-based HD (7). The work involved multidisciplinary teams that included patient partners from 12 kidney centers. It focused on patient and nurse education, and it incorporated quality improvement measures such as rapid tests of change and peer assistance to examine and share the most effective approaches to support the delivery of SHC and how they can best be measured. The key is to test metrics that can be used to assess individual progress and to demonstrate the level of engagement that is offered by providers. Until such measures are used routinely, it will not be possible to develop evidence-based mechanisms that create optimal opportunities for SHC.

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**Figure 1. Small steps (tasks) within shared care provides a framework to unlock potential.**

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**Endothelin Receptor Antagonism in CKD**

**SONAR and Beyond**

By Donald Kohan

On April 15, 2019, the results of the CRE-DENCE (1) and SONAR (2) trials were published. Both trials showed a 35% reduction in the relative risk of composite renal events in people with type 2 diabetes and kidney disease (DKD). Canagliflozin is now the first drug approved by the US Food and Drug Administration in almost two decades for slowing the progression of chronic kidney disease (CKD) in people with type 2 diabetes. By contrast, the future of endothelin receptor antagonists (ERAs) for treating DKD is uncertain. Various forums within the nephrology community have discussed aspects of atrasentan and SONAR; however, there is apparently no consensus opinion among nephrologists on what SONAR accomplished and the future of ERAs in diabetic or other forms of CKD.

SONAR was the first major ERA trial to incorporate an enrichment period: this involved all study participants receiving atrasentan for 6 weeks to identify individuals who might benefit (proteinuria reduction as a predictor of renoprotection) and in whom minimal side effects might occur (early ERA-induced fluid retention as a predictor of heart failure). Such an approach is highly relevant to the modern era of personalized medicine, whereby the goal is individualized therapy that is effective and safe. In addition, the enrichment period approach will permit correlation of initial drug response with systems biology (e.g., genomics, proteomics, metabolomics). Such analyses for SONAR will be forthcoming and may provide important insights into the biology of DKD.

There was a numerically higher incidence of heart failure events in the atrasentan treatment group in SONAR, although this did not achieve statistical significance and was much lower than in a previous trial of ERAs in DKD patients (3). This obviously indicates the need for continued vigilance for fluid retention, but is it the death knell for ERAs in DKD? Is the future of ERAs in DKD even more dismal, given the sponsor’s decision to prematurely stop SONAR? It should be noted that despite the sponsor’s actions, a strong renoprotective effect of atrasentan was observed. Further, given that atrasentan conferred renoprotection similar to that of canagliflozin, it begs the question whether combining canagliflozin or another sodium-glucose co-transporter 2 inhibitor (given their unique diuretic properties) and atrasentan (both on top of renin-angiotensin system [RAS] blockade) will yield additive or synergistic renoprotection in DKD while minimizing fluid retention. Hence, it is too soon to say what will happen with atrasentan in DKD; it would indeed be a shame to turn our backs at this point on what appears to be a highly renoprotective drug.

Moving beyond DKD, it is important for the kidney community to keep in mind that ERAs are being vigorously pursued as a treatment for a variety of kidney diseases, based on an abundance of preclinical data. Relevant kidney and/or hypertension clinical trials include the following:

- **Focal segmental glomerulosclerosis (FSGS).** The phase 2 DUET trial found that sparsentan, a combined ERA/angiotensin receptor blocker (ARB), reduced proteinuria by ~50% compared with ARB treatment alone in people with primary FSGS (4). On the basis of those studies, the phase 3 DUPLEX trial has been launched involving 500 FSGS patients with a primary endpoint of change in eGFR slope (NCT03941174).
- **IgA nephropathy.** The phase 3 PROTECT trial is examining the effect of sparsentan versus an ARB on proteinuria in 280 people with IgA nephropathy (NCT03762850).
- **Resistant hypertension.** The phase 3 PRECISION trial examines the effect of the ERA aprotinin (vs. placebo) on blood pressure (BP) reduction in 600 people with resistant hypertension (NCT03541174).
- **Uncontrolled hypertension and CKD.** The phase 3 INSPIRE-CKD trial will examine the effect of the ERA aprepitant (vs. placebo) on BP reduction in 200 people with stage 3–4 CKD.
- **Systemic sclerosis CKD.** The phase 2 ZEBRA trial will report shortly on the effect of the ERA rilonacept on renal functional outcomes in people with systemic sclerosis (NCT02047708).

- **Sickle cell nephropathy.** A recently completed phase I trial examined the effect of the ERA ambrisentan on albuminuria (NCT02712366). The initial findings suggest that in patients using RAS blockade, ambrisentan confers greater albuminuria reduction than does placebo.

To date, fluid retention–related adverse events have not been reported to be an issue in the above-mentioned non-DKD trials. It is notable that most of the patients in these non-DKD studies are less likely to have significant cardiovascular comorbidities than the patients in SONAR (the latter had a mean eGFR of ~43 mL/min per 1.73 m², and fluid retention or hypervolemia was present in 32.3% and 36.6% of the placebo and atrasentan groups, respectively). Thus, it is possible that ERA-induced significant adverse events related to fluid retention may prove to be less of an issue in patients with lower cardiovascular disease involvement.

In summary, I believe that the future holds much promise for the use of ERAs in CKD. Although we remain very mindful of their potential for fluid retention, we as a nephrology community must remain cognizant that this class of drugs has consistently reduced proteinuria, on top of RAS blockade, in the majority of CKD patients in whom they have been tried, and that the renoprotective effect of atrasentan in DKD parallels that of canagliflozin. Looking toward the future, there remain a wide variety of kidney diseases for which ERAs may exert a therapeutic benefit on top of RAS blockade, either as a single add-on agent or together with sodium-glucose co-transporter 2 inhibitors.

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**References**

By Sara Denicolò and Gert Mayer

Clonal Hematopoiesis of Indeterminate Potential (CHIP) A Novel Cardiovascular Risk Factor with Potential Relevance to Chronic Kidney Disease

Although different genes are associated with CHIP, mutations are most commonly found in DNMT3A, TET2, ASXL1, and JAK2 (4–8). In the absence of gene deletions or duplications, the VAF is proportional to the size of the mutated leukocyte clone: When assuming heterozygosity, a VAF of 5%, for instance, indicates that approximately 10% of all peripheral blood leukocytes are mutation carriers. CHIP is rare in individuals under the age of 40, but prevalence increases with every decade thereafter and may be as high as 20% in 70-year-olds (1, 2).

Although genes mutated in CHIP are also frequently mutated in hematologic malignancies such as acute myeloid leukemia and myelodysplastic syndrome, the progression rate from CHIP to acute myeloid leukemia or myelodysplastic syndrome is low (0.5% to 1% per year) and resembles the progression rate from monoclonal gammopathy of undetermined significance to multiple myeloma (5, 6). Nonetheless, the overall mortality in individuals with CHIP is significantly higher than in the age-matched general population, primarily as a result of increased cardiovascular events.

The association between CHIP and worse cardiovascular outcome was first described by Jaiswal et al. (6) in late 2014. While studying the occurrence of somatic mutations associated with hematologic malignancies in a large population without known hematologic disorders, the authors noted that all-cause mortality rates in individuals with detectable mutations greatly exceeded the incidence rates of hematologic malignancies. On closer analysis, an increased risk of coronary heart disease (hazard ratio, 2.0; 95% CI, 1.2–3.4) and stroke (hazard ratio, 2.6; 95% CI, 1.4–4.8) became apparent. In 2017, the association between CHIP and cardiovascular risk was confirmed in a second study that included data from four independent case-control cohorts (7). The risk of myocardial infarction was found to be two to four times higher among CHIP carriers, and CHIP was strongly associated with early-onset myocardial infarction. In 2018 and 2019, the presence or absence of CHIP was assessed in two populations with chronic ischemic heart failure and degenerative calcified aortic valve stenosis, respectively (8, 9). In both studies, individuals with detectable CHIP-associated mutations had a worse prognosis in terms of hospitalization and death. Among CHIP carriers, progression was further aggravated with increasing size of the mutated leukocyte clone (VAF) (7, 8).

Age appears to be the main predictor of CHIP. However, evidence suggests that CHIP is enriched in populations with type 2 diabetes, ischemic heart failure, or degenerative aortic valve stenosis (6, 8, 9).

Although causality between CHIP and poor cardiovascular outcome has not yet been unequivocally demonstrated, experimental data hint at endothelial inflammation as a possible mechanism (1, 2). It appears that clonally derived macrophages and monocytes promote atherosclerosis, vessel wall scelrosis, and tissue fibrosis by way of inflammatory stimuli. A simulation of a TET2 loss-of-function mutation in mice transplanted with TET2 knockout bone marrow revealed increased atherogenesis and also marked glomerulocidrosis in the kidney. TET2 knockout macrophages had increased RNA expression of inflammatory mediators such as IL-6 and IL-1β (7). Sano et al. (10) showed that mice with an inactivating mutation in TET2 or DNMT3a experienced more evident cardiac dysfunction along with cardiac and renal fibrosis after experimental challenge with angiotensin II. They further showed that mice with myeloid-restricted JAK2V617F expression had increased cardiac inflammation and dysfunction (11).

Chronic low-grade inflammation contributes to the development and progression of chronic kidney disease, especially in diabetes (12), and experimental data from animal models suggest kidney involvement with loss of TET2 and DNMT3 function (7, 10). Thus, it seems reasonable to assume that CHIP not only influences cardiovascular disease but also may have a negative impact on renal outcome. This hypothesis, however, has not yet been investigated and awaits future studies. CHIP is not yet routinely tested because knowledge is still emerging and no specific therapies are currently available.

CHI will become more prevalent as the population ages, and a better understanding of this condition is an important step toward individualized patient treatment.

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References
Hypoxia-Inducible Factor Stabilizers for Treating Anemia of CKD

By Edgar V. Lerma

Advancement in hypoxia-inducible factor (HIF) stabilizers for treating anemia of chronic kidney disease (CKD) is a prime area to watch in 2020.

Anemia is a major complication of CKD. Defining anemia as serum hemoglobin ≤12 g/dL in women and ≤13 g/dL in men, one study found that with an estimated 14% of the US adult population having CKD during 2007–2010, anemia was twice as prevalent in people with CKD (15.4%) compared with the general population (7.6%). Anemia prevalence increased with stage of CKD, from 8.4% at stage 1 to 53.4% at stage 5 (1). Among 22.8% of CKD patients with anemia who reported being treated for anemia within the previous 3 months, 14.6% were patients with CKD stages 1–2 and 26.4% were patients with stages 3–4.

Anemia of CKD has been known to be associated with poor outcomes, decreased quality of life, left ventricular hypertrophy (LVH), and increased risk of hospitalization. It is also an independent predictor of mortality.

Although anemia in CKD has been primarily attributed to decreased erythropoietin (EPO) production by the kidneys, it is recognized that there are other contributing factors (2), such as uric acid-induced inhibitors of erythropoiesis, disordered iron homeostasis (decreased iron reabsorption and release from the macrophages, increased production and decreased clearance of hepcidin, as well as blood (and iron) loss (Figure 1).

The main therapy consists of the use of erythropoiesis-stimulating agents (ESA) administered either intravenously (IV) or subcutaneously (SC) along with adjuvant iron therapy, given orally or intravenously. For this discussion, ESA refers to short-acting recombinant human erythropoietin (rHEPO; epoetin), medium-acting darbepoetin alfa, and long-acting epoetin beta.

Some known causes of hyporesponsiveness to ESA include iron deficiency, malnutrition-inflammation complex, hemoglobinological disorders or malignancy, secondary hyperparathyroidism, drugs (ACE inhibitors or ARBs), and inadequate dialysis.

Suboptimal response often leads to use of blood transfusions, which are not a preferred option, especially in that they may affect future kidney transplantation.

Three large randomized controlled trials (Table 1) have demonstrated that using ESA to raise hemoglobin levels in patients with CKD to the same range as healthy individuals has been associated with higher rates of cardiovascular events and/or mortality, compared to trying to achieve a lower hemoglobin target.

These studies raised serious concerns about ESA therapy and its safety. It is unclear whether these adverse effects were brought about by the high hemoglobin itself or by the use of high dosages of ESA.

Present in nearly all tissues, the hypoxia-inducible factor (HIF) is a heterodimer composed of HIF-α and HIF-β subunits. HIF-β is constitutively expressed, whereas HIF-α is modulated by oxygen tension via a family of HIF-prolyl hydroxylases (PHD) regulating its degradation by the proteasome. During hypoxia, HIF plays an important role in regulating the levels of EPO, glucose transporter-1, vascular endothelial growth factor (VEGF), and pyruvate dehydrogenase kinase 1 and 4. HIF stabilizers (also called PHIs, prolyl-hydroxylase inhibitors) are small-molecule oral agents resulting in the activation of HIF-mediated gene expression (3).

In a way, HIF action represents a physiological and natural adaptive mechanism of the body in response to low oxygen. Exposure to hypoxia stimulates the expression of various genes related to the hypoxia response, particularly those involved in red blood cell production, angiogenesis, and anaerobic metabolism (4). The HIF pathway also regulates iron homeostasis to meet the iron demands of erythropoiesis via direct and indirect mechanisms (increased transferrin, transferrin receptor, duodenal cytochrome B, divalent metal transporter-1, ceruloplasmin). The consequent normoxic stabilization of HIF-α leads to downstream pleiotropic effects, which in the pathological context of CKD promises to enhance erythropoiesis via an increase in endogenous EPO production and improved iron utilization (5).

Several notable phase 2 trials of various HIF stabilizers have been published recently, demonstrating efficacy in raising or maintaining Hgb levels with reasonable safety (Figures 2 and 3). With current guidelines recommending a relatively low hemoglobin target, it is likely that HIF stabilizers could potentially raise the hemoglobin target for patients with CKD safely to the same level as that of healthy individuals, because they increase endogenous EPO “physiologically,” compared to the mechanism of action of conventional ESA. Considering the pleiotropic effects of the PHD-HIF pathway, they could also confer other beneficial effects such as protection from obesity and metabolic abnormalities (4).

HIF stabilization is a novel treatment strategy that induces a physiological increase in endogenous EPO production and iron utilization efficiency (decreasing ferritin and hepcidin levels in non-dialysis-dependent patients with CKD). Clinical trials have demonstrated that these oral agents increase hemoglobin levels in both non-dialysis and dialysis patients.

One practical advantage with these new agents is that of oral administration, which avoids the pain and discomfort associated with injections. Interestingly, HIF stabilizers are also less expensive to produce than ESA because the manufacturing process relies on synthetic chemistry rather than recombinant DNA technology, there is also less need for sterile manufacturing conditions and no need for cold chain transport due to stability at room temperature (5). The absence of a protein structure also removes concerns regarding immunogenicity, a problem that was seen in epidemiological studies of ESA (5,8).

However, there are potential safety concerns, including angiogenesis and tumor growth, as well as effects on glucose metabolism, bone and cartilage growth (which are potential concerns in the pediatric population), and pulmonary hypertension.

During ASN Kidney Week 2019, two phase 3 randomized, open label, active-controlled studies of the efficacy and safety of the HIF stabilizer Roxadustat in the treatment of anemia in incident dialysis patients and dialysis-dependent CKD patients and one phase 3 randomized, double-blind, placebo controlled, international study of Roxadustat efficacy in patients with non-dialysis-dependent CKD and anemia were presented. In the incident dialysis study, the conclusions were as follows:

Efficacy
- Roxadustat was non-inferior and superior to epoetin alpha in hemoglobin change.
- Roxadustat was non-inferior to epoetin alpha in the proportion of subjects achieving a hemoglobin response.
- Roxadustat was non-inferior to epoetin alpha among patients who were iron depleted and/or inflamed at baseline.
- Roxadustat treatment reduces IV iron use while achieving similar levels of iron repletion.

Table 1. Large randomized studies of ESAs in patients with anemia of CKD

<table>
<thead>
<tr>
<th>ESA</th>
<th>CHOIR (US)</th>
<th>CREATE (Europe)</th>
<th>TREAT (international)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n = 1432</td>
<td>n = 603</td>
<td>n = 4038, Type 2 DM</td>
</tr>
<tr>
<td>Hgb target mg/dL</td>
<td>(13.5 vs. 11.3)</td>
<td>(13–15 vs. 10.5–1.5)</td>
<td>(13 vs. placebo control, ESA rescue for Hgb &lt; 9)</td>
</tr>
<tr>
<td>CV endpoints</td>
<td>Higher in high Hgb group</td>
<td>No difference</td>
<td>Higher stroke and lower coronary revascularization in high Hgb group</td>
</tr>
<tr>
<td>Progression of CKD</td>
<td>No difference</td>
<td>Faster in high Hgb group</td>
<td>No difference</td>
</tr>
<tr>
<td>Cancer deaths</td>
<td>Not noted</td>
<td>Not noted</td>
<td>Higher in high Hgb group (among patients with cancer)</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>No difference</td>
<td>Better in high Hgb group</td>
<td>Less fatigue in high Hgb group</td>
</tr>
</tbody>
</table>

Abbreviations: ESA = erythropoiesis-stimulating agent; DM = diabetes mellitus; Hgb = hemoglobin.
Hypoxia-Inducible Factor Stabilizers

Continued from page 15

Figure 2. Effects of Molidustat in the treatment of anemia in chronic kidney disease – DIALOGUE 1, 2, & 4 trials

<table>
<thead>
<tr>
<th>Methods</th>
<th>Intervention</th>
<th>Outcomes (Molidustat vs Control)</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>CKD patients with Anemia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 121</td>
<td>Darbepoetin</td>
<td>Final dose Molidustat</td>
<td>1.6 vs 0.2 g/dl (1.4, 1.8)</td>
</tr>
<tr>
<td>dialysis CKD</td>
<td></td>
<td>Phosphate</td>
<td></td>
</tr>
<tr>
<td>n = 124</td>
<td>Darbepoetin</td>
<td>Final dose Molidustat</td>
<td>0.5 vs 0.3 g/dl (0.3, 0.6)</td>
</tr>
<tr>
<td>Open Label</td>
<td>Phosphate</td>
<td>Double Blinded</td>
<td></td>
</tr>
<tr>
<td>Molidustat, Variable dose</td>
<td></td>
<td>Double Blinded</td>
<td></td>
</tr>
<tr>
<td>n = 199</td>
<td>Epopeitin</td>
<td>Final dose Molidustat</td>
<td>-0.7 vs -0.4 g/dl (0.4, 0.3)</td>
</tr>
<tr>
<td>ESKD + HD</td>
<td></td>
<td>Phosphate</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion: The overall phase 2 efficacy and safety profile of molidustat in patients with CKD and anemia warrants continued evaluation of molidustat in larger phase 3 studies.


Figure 3. Long-term efficacy and safety of Molidustat for anemia in chronic kidney disease: DIALOGUE extension studies

<table>
<thead>
<tr>
<th>Methods</th>
<th>Intervention</th>
<th>Outcomes (Molidustat vs Control)</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>16-week, Multicenter, Parallel-group, Randomized Controlled Phase 2b Trials</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 164</td>
<td>Darbepoetin</td>
<td>Mean ± SD Hb concentrations at baseline</td>
<td>85.7%</td>
</tr>
<tr>
<td>n = 156</td>
<td>Molidustat</td>
<td>11.08 ± 0.51</td>
<td>11.28 ± 0.55</td>
</tr>
<tr>
<td>n = 156</td>
<td></td>
<td>Mean ± SD blood Hb concentrations throughout the study</td>
<td>85.6%</td>
</tr>
<tr>
<td>n = 164</td>
<td></td>
<td>At least 1 adverse event</td>
<td></td>
</tr>
<tr>
<td>n = 88</td>
<td>Epopeitin</td>
<td>Mean ± 10.0 Hb concentrations at baseline</td>
<td>93.3%</td>
</tr>
<tr>
<td>n = 88</td>
<td>Molidustat</td>
<td>Mean ± 10.0 Hb concentrations at baseline</td>
<td>91.2%</td>
</tr>
</tbody>
</table>

Conclusion: Molidustat was well tolerated for up to 36 months and appears to be an effective alternative to darbepoetin and epoetin in the long-term management of anemia associated with CKD.


Figure 4. Roxadustat potential additional benefits in NDD

<table>
<thead>
<tr>
<th>Change in GFR from Baseline</th>
<th>Patients with eGFR ≥15 ml/min/1.73 m² (N=2438)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean LDL (mg/dl) over time up to Week 52</td>
<td></td>
</tr>
<tr>
<td>Treatment difference: P&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Mean LDL (mg/dl) over time up to Week 52

Safety

- The safety profile of Roxadustat in this study was consistent with results from prior Roxadustat studies.

In the Late Breaking and High Impact Clinical Trials Session at Kidney Week 2019, Robert Provenzano, MD, FASN, presented the “Pooled efficacy and CV safety results of Roxadustat in the treatment of anemia in CKD patients on and not on dialysis.”

He reported:

- Risks of major adverse cardiovascular events (MACE), MACE+, or all-cause mortality in Roxadustat patients were comparable to placebo in nondialysis-dependent patients.
- Risks of MACE and all-cause mortality in Roxadustat patients were not increased compared to epoetin alfa in dialysis-dependent patients.
- Roxadustat patients had a lower risk of MACE+ than epoetin alpha patients.
- Roxadustat patients had a 30% lower risk of MACE and 54% lower risk of MACE+ than epoetin alpha, with a trend toward lower all-cause mortality relative to epoetin alpha, in incident dialysis patients.
- Roxadustat also delayed deterioration of renal function in CKD 1.6 mL/min when compared to control and lowered cholesterol (Figure 4).

In the April 2019 issue of ASV Kidney News, Jay Wish, MD, wrote about “HIF Stabilizers: Will They Have a Place?” in the special section on “Anemia of CKD.” He states: “It is likely that HIF stabilizers will initially be favored in patients unable to reach target hemoglobin levels on high doses of ESA (deemed ‘ESA resistant’) and in non-dialysis-dependent patients who favor an oral drug over an injection.”

Now further along, we will soon see how HIF inhibitors actually impact anemia care in CKD patients.

Edgar V. Lerma, MD, is clinical professor of medicine in the nephrology section at the University of Illinois at Chicago College of Medicine in Oak Lawn, IL. He is a member of the Kidney News Editorial Board.

References

My Transplant Journey

The Executive Order on Advancing American Kidney Health calls for an increased focus on transplantation, including provisions to increase the availability of organs for transplant and support for living donors through compensation for costs such as lost wages and child and elder care expenses. For the next few months, the Kidney News series “My Transplant Journey” will feature perspectives on the patient experience with transplantation.

By Stuart Miller

Every morning people wake up and start their day. They take their kidney health for granted. I was one of those people. For me, that all changed in May 2008 when I received a diagnosis of IgA nephropathy.

I would like to share my transplantation journey for a few reasons: to encourage others to become more aware of their kidney health, to let other people with kidney failure know that there is hope for them, and last, to raise awareness of the need for organ donors and inspire others to become living donors.

Here is my story.

In July 1986 my wife, Carole, and I were living in Milwaukee. Just newly married, we decided we would apply for life insurance. I was denied coverage because I had a small amount of protein and blood in my urine. My physician suggested that I should have an intravenous pyelogram. When the results came back, I was told that the doctors could not see anything abnormal in my bladder or kidneys. The amount of protein in my blood was not abnormal, and my overall health was fine.

We moved a few times, and each time we moved I had a physical. The results were always the same. The doctors never seemed to be concerned.

In 1998 we moved again. I went to see my physician and had a routine physical. My blood pressure was 220/140 mm Hg, and I immediately received some drugs to reduce my blood pressure and was prescribed drugs to help maintain normal blood pressure. No formal testing was done on my kidneys, and there was no diagnosis of any kidney issues. It seems that my doctor missed some signs that my kidneys were not functioning properly, which was probably causing my high blood pressure. The symptoms were treated—but not the cause.

In early 2008 we moved again. My new physician performed a routine physical and noticed the blood and protein in my urine. He was the first doctor to tell me that this was not normal and that I needed to see a nephrologist. He thought I had a problem with my kidneys. I went through some routine tests. At that time my GFR was 56. My nephrologist told me that was not normal. However, the direct cause could be determined only by doing a kidney biopsy.

Because of the risk involved in the biopsy, I opted to continue to monitor my kidney function through laboratory tests instead of undergoing the biopsy. Over the next year, my kidney function continued to decline, and I was forced to have my first biopsy. The biopsy results revealed my IgA nephropathy.

Over the next years, we tried various treatments, including a pulse therapy of prednisone and heavy doses of fish oil. I made some changes to my diet in an effort to help take any additional strain off my kidneys. I was hoping that perhaps I was one of those patients who would stay in IgA nephropathy remission. But as my GFR continued to decline, I realized that would not be the case for me. In December 2017 we went to visit the Mayo Clinic in Jacksonville, FL, to see a nephrologist who was a specialist in IgA nephropathy. Ironically, my GFR that day turned out to be 21, which was the lowest it had been. I learned that I could now apply for a transplant.

At that time, I knew my life was going to change and we were looking at some difficult times ahead. I was lucky I had a good support network, starting with my wife, who was always there to support me mentally and physically.

Thomas Pearson, MD, was the first transplantation nephrologist we met. He warned me that transplantation was a treatment, not a cure. I applied to Emory University Hospital, and after about 5 months I was finally approved to become a transplant recipient. I wanted to take whatever steps I could take to try and find a living donor so I could avoid dialysis.

Sharing your story with friends and family to help find a living donor is a pretty humbling experience. It is not easy to ask someone to donate their kidney to help save your life. I tried many different options to help find a donor. We had some friends who graciously agreed to be tested, but none were approved as donors. Carole agreed to be tested. She went through the same tests that were performed on me, and it took about 4 months for the testing to be completed. The stress test revealed that she potentially could have an issue with her heart, and that she could not be approved as a donor unless she went through some additional testing. She had to have a heart catheterization to make sure her heart was working properly. The test was done, and the results were negative. She was approved as a donor, and now we could officially be listed in the paired exchange program. About 9 months later we were notified that a matching donor was found and that our surgeries were being scheduled.

On July 18, 2018, Carole had her kidney removed, and on July 19, 2018, I received my new kidney. After 3 days we arrived home together.

Thanks to our friends and family who were there to support us, we were able to spend our recovery days at home without any worries. The recovery went well for Carole. I had some challenges, including an acute rejection about 3 weeks after receiving my transplant. I was admitted back to the hospital to receive a thymoglobulin treatment. I was released, and my kidney seemed to be working well again. It took a while to recover from the treatment. Eventually, I started to feel better as the doctors adjusted my medications.

I have now been a little more than a year and a half since I received my transplant. There have been some ups and downs, but overall I am very lucky to have been able to receive my transplant and to be here to share my story. Over the past year I have learned a lot about IgA nephropathy, its causes, and potential treatments.

I would like to encourage readers in the medical professions to share as much information as you can with your patients. Learning more about their disease will help patients understand what their treatment options are and what they can do to help live with their disease.

Stuart Miller was diagnosed with IgA nephropathy in May 2008. Through lifestyle change and with good care from his doctor, Stuart was able to manage his IgA nephropathy until July 2018. Thanks to his wife Carole and the Paired Kidney Donor Exchange, Stuart was able to have a preemptive transplant at Emory University Hospital in Atlanta. Stuart and his wife own a wholesale home decor business. When he is not working, he enjoys spending time with friends and his two dogs (Theodore & Oliver), as well as cooking and following his favorite sports teams from his hometown, Boston. He is an ambassador for the American Association of Kidney Patients and an advocate for the National Kidney Foundation.
Cardiovascular and Chronic Kidney Diseases: Impact of Sex and Gender, Compounding Underdiagnosis, Atypical Presentation, Undertreatment, and Underrepresentation

By Manisha Singh

The fact that chronic kidney disease (CKD) and cardiovascular diseases (CVDs) are closely related would not surprise any healthcare professional. Of note, the data show that the primary cause of death resulting from CKD is a cardiovascular event and also that CKD is one of the important risk factors for CVD.

We have established data that CKD awareness and research are lagging despite the significant impact of this disease on patients and the healthcare system. CVD, traditionally thought to be a ‘male’ problem, is actually the main killer of older people of both sexes universally. In fact, each year CVD is the cause of more deaths in older women than in older men (7.4 million women over 60 years of age compared with 6.3 million men in 2004). In addition, CVDs are thought of as diseases of affluence, whereas in reality, cardiovascular mortality rates for older women are more than twice as high in low-income and middle-income countries as in high-income countries. In addition, women are less likely to seek medical help and therefore may not receive timely and appropriate care.

To make matters even more concerning is the lack of attention to sex and gender differences in the focus of research. This article attempts to assess the impact of sex and gender in both diseases and to highlight areas of gaps in research. We attempt to highlight sex and gender awareness and its relevance to designing appropriate trials, and to bring attention to strategies for increasing the inclusion of women as research participants going forward.

There is a scarcity of research in populations with coexisting CKD and CVD, specifically with equitable attention to sex and gender.

Terms

Sex refers to anatomic differentiation, resulting in a binary assignment at birth and leading to physiologic changes and secondary sexual characteristics implying the hormonal and physical changes that happen with biologic maturity. This is commonly a binary system, starting from the chromosomal differences (X and Y) and leading to internal gonadal developments and to external genitalia (male or female at birth). This system can have certain anomalies, leading to assign- ments of trustees. The impact of sexual differences on individuals with CKD and CVD includes genetic variations, hormonal differences, and the course of diseases affected by these differences, which have a direct impact on reproductive health, including pregnancy and childbirth in women and on erectile dysfunction in men.

Gender, by contrast, refers to the psychologic, social, and cultural identity that a person takes up while growing. It can also represent a cultural identity that a person takes up while growing. It can be the role of a man or a woman, and it can also represent a transgender person. The GLAAD (Gay and Lesbian Alliance Against Defamation) website explains these terms with the following words: “For transgender people, their own internal gender identity does not match the sex they were assigned at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices (nonbinary and/or genderqueer). Unlike gender expression, gender identity is not visible to others.” In 2016, about 1.4 million people identified as transgender in the United States.

Gender exposes the person to unique aspects of health-care, especially disparities and biases that have an impact on access to care. This makes understanding this aspect of a person’s life extremely important for healthcare professionals. The most vulnerable in this group, transgender people, like women, remain severely underrepresented in research. Aside from patient and provider biases from and against healthcare, the healthcare aspects also include the results of gender change surgeries, the effects of hormonal change, delayed di- agnosis, and a physicians’ discomfort regarding appropriate treatment strategies, not to mention communication blocks (e.g., how to refer to a transgender person) even from the most well-meaning physician. About 80% of the physicians in a survey at Johns Hopkins thought that patients would not want to talk about their sexual orientation, whereas only 10% of patients said they would refuse to answer that question. In this context, competence in transgender issues is important in the training of a physician. In the realm of CKD and CVD, the transgender group is high risk.

Diagnostics are affected because the reference ranges of all laboratory values are based on biologic sex, whereas there are significant gender-specific changes that happen when a transgender person is receiving therapy. In 2018, at the 70th Annual Scientific Meeting of the American Association for Clinical Chemistry, scientists presented data showing that 6 months of transgender hormone therapy will produce marked changes in the results of common laboratory tests. This team tracked the comprehensive metabolic panel, complete blood count, and lipid test results for 147 healthy transgender patients using hormone therapy over the course of 5 years and found that red blood cell and creatinine lev- els underwent the largest shifts when transgender individu- als started hormone therapy. These values stabilized after 6 months. In transgender women, plasma creatinine and creatinine levels increased and alkaline phosphatase decreased over years before returning to baseline.

The risk factors for CVD are expected to worsen in transgender persons receiving hormone therapy, including hypertension, diabetes, and hyperlipidemia, along with an increased risk for thromboembolic events. A seminal study in Circulation reported that the transgender population, except transgender women, had a higher reported history of myocar- dial infarction (MI), even after adjustment for cardiovas-

cular risk factors, although there was no increase in mortality. The diagnosis of CKD and ascertaining its risk factors present unique challenges, as mentioned above, because esti- mated GFR and creatinine measurements change on the ba- sis of sex and generation of creatinine, which is muscle mass dependent. With overlap of the CVD risk factors, there are additional concerns. The patient may end up having more conditions that are diagnostic criteria for recurrent acute kidney injury from obstructions (post- operative complication of urethral strictures), urinary tract infections, depression resulting from genetic body image changes, and poor access to unbiased care.

Conversely, in some cases providers are unable to move past gender identity and blame that for many of these pa- tients’ unrelated health concerns.

Unfortunately, and not unexpectedly, few data are available that focus on gender research, and all the studies identi- fied appear to be using sex and gender as interchangeable entities, limiting our review to binary gender difference. From here onward, the discussion is focused on binary sex difference.

Presentation, treatment, and outcomes

In patients with CKD and in women, “oligosymptomatic” presentation of acute coronary syndrome (ACS) is common. About 44% of patients with CKD grade 3a or higher ex- perience acute MI, presenting with the typical symptoms of chest, arm, shoulder, or neck pain, compared with 72% of patients with normal kidneys. Most patients with CKD pres- ent with fatigue and dyspnea. When that is compared with the traditional presentation of women with ACS, major con- founding and a potential for missed diagnosis exist. Women commonly present with unstable angina. ACS presentations are broad (atypical): fatigue; dyspnea; pain in the neck, jaw, or back; nocturnal dyspnea; nausea; indigestion; cough; pal- pitations; dizziness. Women also tend to have more Q wave abnormalities and to be about 10 years older at presentation.

Another concerning piece of data is that women are less likely to be referred for angiography and are less likely to receive fibrinolytic therapy; percutaneous coronary inter- vention, or coronary artery bypass surgery. The diagnosis of silent ACS, although it was present in a similar number of cases (27% in men, 26% in women) was significantly de- creased over years before returning to baseline.

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Impact

Population and epidemiology studies reveal that the primary cause of mortality for women is a cardiovascular event. The World Heart Federation reports that heart attacks claim the lives of 3.3 million women yearly; another 3.2 million women die of stroke, and 2.1 million women die of other CVDs. Diagnostic delays are common, especially because the presenting symptoms in women may be quite different from those in men. Women smokers have a higher risk than men smokers, and the same pattern is seen with weight, lipid profile, and diabetes prognosis. Women are also less likely to seek medical care, especially those living in rural areas, com- pounding the impact of disparities on access to healthcare.
Studies have consistently shown an increased risk of ischemic research. Despite this association between CKD and CVD, randomized greater risk for poor outcomes in patients with CVD. De- risk for CVD, stand to be underdiagnosed and undertreated, that women with CKD can be expected to have a very high risk for men.

The generalizability of research data to the population re-quires appropriate sex and gender representation. However, attention to the representation of women remains an area of concern in many trials. Even if women are well represented in numbers, the impact of the sex difference is rarely teased out from the data. In 2001, the US Food and Drug Administration (FDA) published the results of a retrospective assessment of the drugs withdrawn between 1997 and 2000 as a result of adverse effects. The majority (8 out of 10) were withdrawn because the drugs posed greater health risks to women than to men.

To extrapolate from this, it may not be incorrect to state that women with CKD can be expected to have a very high risk for CVD, stand to be underdiagnosed and undertreated, and are at an exceptionally high risk for ensuing complica-

Research

Studies have consistently shown an increased risk of ischemic heart disease, heart failure, and arrhythmias in patients with CKD. On the other hand, CKD confers a significantly greater risk for poor outcomes in patients with CVD. De- spite this association between CKD and CVD, randomized controlled trials investigating CVD have historically exclud- ed people with preexisting CKD. Of 12,794 studies that ap- pear on clinicaltrials.gov for CVD (studies that were active, recruiting, and not recruiting), only 2712 were focused on CKD, and only 412 were studies on CKD and CVD com-bined.

The global participation report by the FDA states that globally only 45% of participants in clinical trials are women (the United States leads with 49.1%).

From the 1977 FDA ban of women of childbearing po-tential from research (which was an attempt to protect the most vulnerable women after the thalidomide disaster) to re- versal of the policy in 1993, gender balance has been skewed against women in research participation. This is despite the fact that disease parity exists with worse outcome for women. A review article from the National Institutes of Health Of- fice of Research on Women’s Health indicated that women reported inconvenience related to securing transportation, along with the associated cost and time, limiting their abil- ity to participate in clinical research. Women also identified childcare commitments, in addition to transportation, as barriers to participation in multiple research studies. Given the above concerns, a broadening of trial eligibility and attempts to make it easier for women to participate are warranted in the design of new studies.

We conclude that there is a scarcity of research in popula-
tions with coexisting CKD and CVD, specifically with eq-
tuable attention to sex and gender. These subpopulations have high risks, present atypically, are at high risk for being underrepresented and undertreated, and face worse compli-
cations. We believe that physicians need deliberate training to diagnose, treat, and recruit for research with intentional inclusion and attention to these populations.

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ences (UAMS), VA, in Little Rock. She is also co-director, M2 renal Module, UAMS.

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Coronary Microvascular Dysfunction Is Linked to Cardiovascular Risk in CKD

In people with chronic kidney disease (CKD), the risk of cardiovascular events is independently related to coronary microvascular dysfunction—and not to estimated glomerular filtration rate (eGFR), according to a study by Narkavanishi S. Bajaj and colleagues in a recent issue of Circulation.

The longitudinal study included 352 patients re-ferred for stress myocardial perfusion positron emis-
sion tomography (PET) at the authors’ hospital from 2006 through 2016. Other evaluations included two-
dimensional echocardiography and serum creatinine measurement. Patients with overt obstructive coro-

nary artery disease were excluded from the analysis.

The patients’ median age was 55 years; 63% were women and 22% were black. Their median left ven-

tricular ejection fraction was 62% on echocardiogra-
phy and 59% on PET, and more than 70% had ab-

normal left ventricular remodeling. CKD was present in 35% of patients, who had a mean eGFR of 41.0 mL/min/1.73 m².

Those patients with stage 3 or higher CKD were more likely to have hypertension and diabetes, and they also had a lower body mass index. On PET, pa-

tients with CKD had lower stress myocardial blood

flow (1.7 versus 2.1 mL/min/g) and lower coronary flow reserve (1.5 versus 1.9). The authors considered these findings to represent coronary microvascular dysfunction. Both eGFR and coronary flow reserve were associated with diastolic and systolic echocardiographic indexes, as was the risk of adverse cardiov-

ascular events.

On multivariable analysis, however, coronary flow reserve was independently associated with cardiac me-

chanics and cardiovascular event risk whereas GFR was not. And on stratified analysis, a severely abnor-
mal coronary flow reserve of less than 1.5 was associat-
ed with a 1.61 adjusted hazard ratio for major adverse cardiovascular events.

In this study, coronary microvascular dysfunction was a significant mediator of the associations among eGFR, cardiac mechanics, and cardiovascular events. In fact, in fully adjusted models, coronary microvascu-
lar dysfunction accounted for 32% of the relationship between impaired renal function and major adverse cardiovascular events, the authors noted.

Even in the absence of overt coronary dis-
ease, patients with CKD are at elevated risk of cardiac dysfunction and cardiovascular events. Coronary mi-
crovascular dysfunction might help to explain the im-
paired cardiac function and increased cardiovascular risk associated with abnormal renal function, accord-
ing to the authors.

The new study suggests that coronary microvascu-
lar dysfunction is associated with cardiovascular risk in CKD patients without overt coronary artery dis-

ease and might mediate the effects of eGFR on cardiac function and cardiovascular events.

“The presence of coronary microvascular dysfunction signals the transition from physiological to patholo-

gical left ventricular remodeling that increases the risk of heart failure and death in patients with chronic kidney disease,” Bajaj and colleagues write.

 “[O]ur study raises the possibility that efforts to attenuate coronary microvascular disease could produce ben-
efits on myocardial dysfunction and cardiovascular events,” they state.

Among patients with even minimal perfusion defects on quantitative single-photon emission computerized tomography (SPECT), the impact on risk of major adverse cardiovascular events (MACE) is significantly higher in those with diabetes, reports a study in *Diabetes Care*.

Data were drawn from the international, observational REGistry of Fast Myocardial Perfusion Imaging With NExt generation SPECT (REFINE SPECT) study. In that study, patients with known or suspected coronary artery disease underwent quantititative myocardial perfusion imaging using cadmium zinc telluride cameras. From the overall study population of more than 20,000 participants, the researchers identified propensity score–matched groups of 2951 patients with or without diabetes.

Total perfusion defect (TPD) was classified as no deficit (0%), very minimal (0% to less than 1%), minimal (1% to less than 5%), mild (5% to less than 10%), and moderate to severe (greater than 10%). Associations between TPD category and risk of MACE—a composite of death from any cause, myocardial infarction, unstable angina, or late revascularization—were compared for those with diabetes and those without diabetes.

Even after matching, patients with diabetes had a higher rate of moderate to severe TPD: 7.6% versus 5.8%. Median follow-up was 4.6 years in the diabetic group and 4.7 years in the nondiabetic group. The overall rate of MACE was 16% in the patients with diabetes compared to 10% in matched patients without diabetes.

Across TPD categories, there was a significant interaction between diabetes and the risk of MACE. Risk increased progressively with each increasing TPD category, but the increases were consistently greater in those with diabetes. The difference was greatest at a TPD of greater than 10%; annualized MACE rate was 9.4% for patients with diabetes versus 5.8% for those without. For diabetic patients with a TPD of 0.5% to 3.0%, future MACE risk was the same as for nondiabetic patients with a TPD of 8% to 11%.

On Cox regression analysis, TPD was significantly associated with MACE risk, as were patient age and sex, body mass index, family history of coronary artery disease, and stress test type. In the group with no deficit (TPD of 0%), there was no difference in MACE risk between the diabetic and nondiabetic groups. However, for patients with a TPD of greater than 0%, risk was higher for those with diabetes: hazard ratio 1.70. Hazard ratios for diabetic versus nondiabetic patients were 1.68 at a TPD of 0% to less than 1%, 1.45 at a TPD of 1% to less than 5%, 1.56 at a TPD of 5% to less than 10%, and 2.35 at a TPD of greater than 10%.

Diabetes is associated with more rapid progression and a worse prognosis of cardiovascular disease. Visually assessed SPECT myocardial perfusion imaging is reported to have prognostic value in people with diabetes. The present study provides new information on the prognostic significance of quantitative SPECT defects assessed using next-generation fast myocardial perfusion imaging.

The results show that at every level of TPD greater than 0%, the risk of MACE is greater in patients with diabetes, compared to matched nondiabetic controls. The difference is such that diabetic patients with "minimal" ischemia have the same 5-year MACE risk as nondiabetic patients with "significant" ischemia. The authors note the high prevalence of mild stress perfusion myocardial abnormalities in their study: over half of patients had TPD above 0% but under 5%, the usual cutoff for an abnormal result [Han D, et al. Myocardial ischemic burden and differences in prognosis among patients with and without diabetes: results from the multicenter international REFINE SPECT Registry. 2019; DOI: 10.2337/dc19-1360].
Antibiotic Use Linked to Increased Risk of Kidney Stones

Women who take antibiotics for two months or longer are at increased risk of developing incident kidney stones later in life, suggests a study in American Journal of Kidney Diseases.

The researchers analyzed prospective data on female registered nurses enrolled in the Nurses’ Health Study (NHS) I and II cohorts. Among other medical history items, the women provided information on cumulative time they took antibiotics from age 20 to 39 and from age 40 to 49 (NHS II) or 40 to 59 (NHS I). Incident symptomatic kidney stones were elicited, along with further information about these episodes.

The analysis included 46,336 women from NHS I and 65,988 from NHS II. Associations between antibiotic use and urine composition were analyzed in 5010 participants for whom 24-hour urine collections were available.

Antibiotic use for two months or longer was reported by 4518 women in NHS I and for 7562 women in NHS II. Urinary tract infections were the reason for antibiotic prescriptions in 11% of participants in NHS I and 15% in NHS II.

At both age ranges studied, women using antibiotics for two months or longer were at higher risk of incident kidney stones. Pooled multivariable-adjusted hazard ratios were 2.48 in the 40- to 49/59-year group analysis and 1.36 in the 20- to 39-year group analysis. The association of antibiotic use with kidney stones was similar after exclusion of women reporting urinary tract infection at the time of stone diagnosis or as the reason for antibiotic use. Most urine parameters were similar between groups; participants taking antibiotics for two months or longer had slightly lower values for pH, calcium, and citrate.

Recent studies have suggested that the intestinal microbiome may affect the development of urinary stone disease, possibly by modulating oxalate absorption from the intestine. This raises the possibility that prolonged antibiotic use might increase the risk of stone formation.

The new findings suggest that women who take antibiotics for as little as two months during early adulthood and middle age are at higher subsequent risk of developing kidney stones. “Our data provide an additional reason to minimize the unnecessary use of antibiotics,” the researchers write.

They point out some limitations of their study, including the lack of information on types of antibiotics and the nonstandardized time between antibiotic use and urine sample collection [Ferrari PM, et al. Antibiotic use and risk of incident kidney stones in female nurses. Am J Kidney Dis 2019; 74:736-741].
I recently started practicing nephrology and wish to share a few reflections.

To start, when I am going about my duties during the week, I often begin thinking about my fellowship. My heart beats faster and I can’t keep myself from looking at the time. This is exactly what I used to do while on consult service as I tried to budget the time I had with the work yet to be done. I also remember the dark, small room, nestled between just a few other rooms on the bottom floor of the old hospital building, where we fellows used to end our long and exhausting days, wanting to make sure each of us had survived. I used to call that room the “cave” because when you are there, you are disconnected from the outside world. You cannot tell if it is day or night or dark or light outside. If we could only leave our pagers outside, the cave could be a paradise.

On first sight, the cave looks ugly and feels cold. But over time, you get used to the cave and the cave gets used to you. The longer you stay in the cave, the warmer it starts to feel.

There, I spent most of my time looking up charts, answering pages, and typing as fast as I could to finish my endless notes while arguing with residents over the phone that my kidney failure patient did not need urgent dialysis after receiving computed tomography of the chest with contrast.

I cried in the cave when my 35-year-old patient died in his wife’s arms after all the antibiotics under the sun failed to treat his hemodialysis catheter–related sepsis. I got excited in the cave when I was the first to hear from my dialysis patient that he had received his first call about an available deceased donor.

I read most of the Primer textbook in the cave when the days approached their end and my pager fell dead after a full day of buzzing and beeping. We used to hide in the cave and discuss our rare cases, laugh at jokes that did not sound as silly as they do now when I recall them, and brag about our success in diagnosing that tough case or getting the core from the second poke while doing a kidney biopsy.

In the cave, we used to support each other and remind ourselves there was “light at the end of the tunnel.” When I was a junior fellow, my senior’s job was to walk me through the tunnel and try to show me the light. Before I knew it, I found myself talking to my junior fellows about the tunnel and the light at the end.

The light at the end of the tunnel fairy tale became the happy ending to any conversations we started in the cave. I could not wait to leave the cave and see that light at the end of the tunnel one day. But that day felt like it would never come. By all objective indicators, I would never miss the cave when I got to the end of the tunnel and saw the light there.

Fellowship passed more quickly than I thought it would, and soon I graduated and started practicing on my own. For the first time, I came up with the plan and didn’t have to run it by my attending. That felt wrong, very wrong. What if my plan was incorrect? What if I was missing something?

As I muddled through, memories from my fellowship started to pop up in my mind: Dr. X once told me this, and I learned that from Dr. Y. I felt them around me in my mind. I heard them whispering in my ears to do this and check that. I felt like a baby taking the first step and walking away from their parents, thrilled about finally being independent but anxious about falling. I used to check my notes several times before I signed them. Gradually, I felt more comfortable and confident. I found myself talking like Dr. M, and telling my patients the same jokes as Dr. Z.

I started seeing that light at the end of the tunnel I’ve always looked forward to. But guess what? I really miss the cave.

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