function and time to clinical progression included the rate of decline in kidney function and time to clinical progression events, including hypertension and pain. At the end of the 3-year study, the annual increase in total kidney volume (2.8 percent for tolvaptan versus 5.51 percent for placebo) and the slope of renal function decline (−2.61 [mg/mL]/year for tolvaptan versus −3.81 [mg/mL]/year for placebo) were significantly reduced in the tolvaptan group (both p < 0.001). Patients taking tolvaptan also demonstrated significant reductions in risk for secondary end points including worsening kidney function (61 percent) and pain requiring intervention (36 percent).

"The trial results show that Tolvaptan, given over 3 years, slowed the increase in kidney volume and the decline in kidney function," said Torres. "If these results are sustained beyond 3 years, tolvaptan would substantially extend the time before patients with ADPKD would need renal replacement therapy; Kidney pain, hematuria, and urinary tract infections, complications associated with ADPKD, occurred less frequently in the patients treated with tolvaptan compared to those treated with placebo. By reducing the rate of these complications, tolvaptan may lead to an improvement in quality of life."

Yet Torres cautions that tolvaptan is not without risks. "The most common adverse effects were anticipated and related to high urine output with more frequent voiding. Unexpected liver test abnormalities were observed in approximately 5 percent of patients and led to the discontinuation of tolvaptan in 1.8 percent of the patients." Adverse events led to a higher discontinuation rate in the tolvaptan group (23 percent) than in the placebo arm (14 percent).

"Although tolvaptan is already approved for treatment of other medical conditions, it is not approved for the treatment of ADPKD. The doses of tolvaptan used in the TEMPO trial were higher than used in previous studies of other diseases," Torres said. "In addition, ADPKD patients are a unique patient population. Further analysis of the benefits and risks of this potential therapy will need to be performed by the sponsor (Otsuka Pharmaceuticals) and regulatory agencies. Therefore, although the results are encouraging, at the present time, patients with ADPKD should not be treated with tolvaptan outside of approved research studies."

Terry Watnick, MD, of the University of Maryland School of Medicine and an investigator in the TEMPO trial, found the results of the trial’s primary end point very encouraging. But Watnick added that "it is still important that we control blood pressure and other cardiovascular risk factors in ADPKD patients since this population may still require renal replacement therapy. While tolvaptan may delay disease progression, it will not completely prevent or reverse established disease based on the data presented."

There are other important questions with respect to tolvaptan that remain to be answered, Watnick said. For example she wondered if tolvaptan would be more beneficial if the drug was initiated earlier in the course of disease when patients had fewer cysts or smaller kidneys. In addition, the applicability of treatment in patients with milder disease severity, or the consequences of longer-term drug administration remain to be defined. She also pointed to a need for more basic research into the mechanisms underlying ADPKD pathogenesis. "Blocking the V2 receptor improves the disease course, but it doesn’t completely stop progression. ADPKD is a complicated disorder, and the PKD community has invested a lot in research over the past 15 years. The signaling pathways involved in cyst formation are complex, and we still don’t know everything we need to know about this disease. Blocking the V2 receptor provides one therapeutic approach, but I believe that there is likely to be others."

References


Renal Replacement Therapy: Cautiously Expanding the Donor Pool and Disparities in Transplant Access for Children

Two studies presented at Kidney Week 2012 offer a cross-section of the state of renal replacement therapy in the United States. The first study demonstrated that living kidney donors with prediabetes did not experience an increased risk for developing diabetes over a mean follow-up of 10 years. It indicates that the living kidney donor pool may be cautiously expanded to include prediabetic individuals, which could contribute to a reduction in the duration patients spend waiting for kidney transplants. The second study confirmed that minority children with kidney disease face disparities in access to renal replacement therapy, especially preemptive transplantation, compared to whites. Although transplantation is the preferred treatment option for children with ESRD, white children were four times more likely to receive a transplant as their initial renal replacement treatment compared with black children. Both studies reflect the complex situation that patients with kidney disease encounter when selecting renal replacement options, and identify knowledge gaps for future research that could contribute to improved decision making and outcomes.

Cautiously expanding the living kidney donor pool

Potential living donors receive extensive screening before being approved for kidney donation, and a diagnosis of prediabetes (defined as impaired fasting glucose level of 100–125 mg/dL) may prevent some from donating a kidney. Current clinical guidelines lack consensus on the suitability for donation of individuals with prediabetes, which by current estimates may include as much as 35 percent of the U.S. population. To determine if the condition is truly a contraindication for donation, Sindhu Chandran, MD, of the University of California, San Francisco, and colleagues studied a single-center cohort of living kidney donors who were prediabetic at the time of donation and who agreed to a clinical follow-up after their operation (1).

Thirty-five donors who had a fasting glucose level ≥100 mg/dL at time of donation underwent a telephone interview and laboratory testing. At the time the study was conducted, the mean duration between donation and follow-up was 10.2 years (range 5.1–15.9 years). Results revealed four donors (11.4 percent) had progressed to diabetes, two
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donors (5.7 percent) had microalbuminuria, and kidney function was well preserved in all donors (mean eGFR 68.9 mL/min/1.73 m²). In addition, 66 percent of prediabetic donors reverted to normal glycemic levels, which Chandran noted was higher than the commonly cited rate of approximately 25 percent.

However, the reversion rate varies depending on factors such as race, family history, and obesity, and because donors are screened for these they are healthier than the average population,” Chandran said. “Also, the majority of our donors were white (75 percent) so it is perhaps not surprising.”

“Studies such as these can be controversial,” said William Harmon, MD, of Boston Children’s Hospital and Harvard Medical School, who was not involved in either study. “The major issue for living donation is that you never want to put the donor at risk for the recipient. As we’ve expanded the donor pool to include people with mild hypertension or those with a history of kidney stones, you always worry that as you expand the pool farther that we’re going to see more morbidity and mortality, which then gets to be counterproductive.” But he added the study “is good news and it will allow some other programs to say that being prediabetic is probably not a contraindication to donation.”

Although the results appear to be encouraging, what further data are needed to convince physicians to change their practice patterns and consider expanding the donor pool to include donors with prediabetes?

“This data would preferably have larger numbers of patients (to ensure major events aren’t missed); more minorities, including blacks and Hispanics because they are at higher risk; more transplant centers, to ensure that center-specific practice patterns (such as being too selective) aren’t influencing outcomes; and finally a control group,” Chandran said. “The ideal controls would be prediabetics who ended up not donating for nonmedical reasons, but because this is impracticable the next best thing would be to compare them to similar patients with normal blood glucose who donated at the same time. We have already enrolled such controls and are working on data analysis.”

Harmon added that generating consensus for clinical guidelines to assess the risk of donor pool expansion requires studies like Chandran’s. But he pointed to a bigger problem. “The bottom line is we need more information on more donors,” he said. “Living kidney donation programs are supposed to send data at certain intervals post-transplant, yet it’s difficult to get those data because donors tend not to return because they’re not sick and don’t want to take the time. Switzerland has long-term data on their living kidney donors because laboratory tests are covered by national health system and information gathered via their primary care physicians, yet similar testing in the United States could be denied by insurance or physicians may be penalized financially for ordering the test. Our system is not very friendly for getting data for otherwise healthy people.”

Chandran echoed Harmon’s concerns, noting currently there are no good established data sources for living donors to verify her research. “There are two current NIH-sponsored cohorts—ALTOLD, with follow-up of 56 months, and RELIVE, which was just completed in June 2012,” she said. A registry of living donors could address this gap, but she said that cost and willingness of donors to participate remain barriers to establishing such a registry. New policies enacted by the United Network for Organ Sharing in November 2012 that require a mandatory 2-year follow-up of all donors may help address the gap in donor data.

Disparities in renal replacement options for minority children

Health care disparities have been less well documented in the U.S. pediatric population than in adults. Previous studies have shown that black children are more likely to receive hemodialysis instead of peritoneal dialysis as their initial renal replacement therapy compared with white children, yet there...
have been few investigations regarding the preferred treatment for ESRD—preemptive transplantation. To determine if children experienced racial and ethnic disparities in renal replacement options and to determine the factors behind such disparities, Roshan George of Emory University School of Medicine and Children's Healthcare of Atlanta and her co-workers examined a pediatric and adolescent cohort (<20 years of age) from the United States Renal Data System (USRDS) who initiated renal replacement therapy between January 2005 and September 2009 (2).

Of 5623 patients included in the study, 45.3 percent were white, 30.3 percent were black, and 26.4 percent were Hispanic. The results, though as expected, were stark: the percentage of black children receiving preemptive transplants was one-fourth and the percentage of Hispanic children was one-half that of white children who underwent preemptive transplantation. Hemodialysis was the renal replacement for a majority of blacks (70.8 percent) and Hispanics (60 percent) as well as whites (49.1 percent).

Yet the rates of white children initiating peritoneal dialysis (32.4 percent) or receiving preemptive transplantation (18.6 percent) were higher than in the other groups. Adjusting for demographic, clinical, and socioeconomic differences attenuated the differences in renal replacement therapy for Hispanics, yet when compared with hemodialysis, black children still had a 75 percent lower chance for preemptive transplantation than white children. Examining rates of pre-ESRD access to a nephrologist also revealed significant differences between black and Hispanic children when compared with whites.

“The study is important because typically children have safety nets in terms of prejudice and poverty,” said Harmon. “You would hope that what’s true for adults, where socioeconomic disparities may account for differences in care, wouldn’t apply to children. Showing that these things are true in children is an important finding, and shows that we still have a way to go in terms of the transplant process.”

The results mirrored those in the incident adult population, said George, who noted that black adults are more likely to initiate therapy with hemodialysis and face delays in getting on a transplant wait list.

“It is true that there is a very big disparity between whites and blacks in terms of how soon they get on the waiting list,” Harmon said. “Until recently, physicians would place their patients on the waiting list way before they needed a transplant and keep them inactive where they could still accumulate waiting time points, whereas blacks often wouldn’t get on until after they had started dialysis, and even then there be a long delay in terms of giving them the opportunity to get on the transplant list.

“Some of this has been ameliorated by recent movements to not count waiting time until the patient is either on dialysis or has a GFR <20 mL/min/1.73 m²,” Harmon said. “But once on the list, the time to transplant for blacks doesn’t seem to be as affected because the listing criteria are clear.”

George concluded that further research examining patient and physician perspectives when choosing renal replacement options could be helpful in resolving disparities and determining unmeasured factors that typically are not captured in most data sources.

References
2. George RP et al. Racial disparities in renal replacement therapy in the pediatric end stage renal disease population. (Abstract)