FSGS is the most common cause of nephrotic syndrome in the United States and a frequent cause of advancing kidney failure (1). It causes tremendous morbidity for patients, and is highly challenging to successfully treat. A significant part of the challenge is distinguishing patients with primary FSGS from those with other causes of this histologically defined lesion, as secondary causes have a different natural history and are unlikely to benefit from a standard approach with immunosuppressive therapy (2). Although several features favor a diagnosis of primary FSGS, including relatively rapid disease onset, presence of nephrotic syndrome, and diffuse foot process effacement, whereas other features suggest secondary FSGS (e.g., glomerulomegaly, known genetic mutations, obesity, and the presence of an alternate primary glomerular disease), the differentiation is still challenging.

Perhaps the most definitive distinguishing feature of primary FSGS is the relatively early and often devastating recurrence of proteinuria after kidney transplantation. Biopsies of transplanted kidneys at an early stage after FSGS recurrence typically show a podocytopathy, with variable foot process effacement but without demonstrable focal scars. As in primary FSGS affecting native kidneys, response to therapy for post-transplant FSGS is often poor, with only 40%–60% of patients achieving any response, and these responses are often incomplete and not sustained (2). Too many patients suffer graft failure and end up back on dialysis well before the expected $t_{1/2}$ of their transplant, facing a future of repeat kidney transplant with a very high, sometimes unacceptable risk of recurrence. It is absolutely essential to better understand this disease and the risk factors for post-transplant FSGS recurrence, and to identify better treatments.

Supporting this effort, Uffing et al. report their findings from a collaborative effort of an international network of transplant centers—The Post-Transplant Glomerular Disease (TANGO) project—to better define glomerular disease in the transplant population (3). For this report, 15 centers from Europe, South America, and the United States retrospectively examined the development of post-transplant FSGS among patients with native kidney biopsy-proven FSGS who had undergone a kidney transplant. Recurrent FSGS was defined as nephrotic-range proteinuria with biopsy features of recurrent FSGS. Among nearly 12,000 transplants (patients aged ≥16 years) over a 10-year period, they identified 253 patients with a history of FSGS, ultimately defining 176 as biopsy-proven primary FSGS. Fifty seven (32%) of these patients developed post-transplant FSGS over this time. The investigators then evaluated risk factors for, outcomes of, and treatments for post-transplant recurrent FSGS. Not surprisingly, FSGS recurrence had a detrimental effect on graft survival, with a nearly 5-fold increase in the risk of graft loss, although successfully treated patients who entered partial or complete remission experienced outcomes similar to those patients who did not relapse. Risks identified for recurrence included older age, white race, United States transplants, and lower body mass index. Interestingly, prior nephrectomy was also a significant risk for recurrence (as reported from other cohorts), but the number of participants is too small to draw definitive conclusions. Severe nephrosis from FSGS, which may also have conferred a higher risk for recurrence, might have been the indication for nephrectomy. As expected, those with prior transplant recurrence had a particularly high risk (50%) for recurrence in a subsequent transplant, and all five patients with recurrence in two prior transplants experienced recurrence with poor outcomes in their third transplant. There was a trend toward higher recurrence risk with living donor kidneys, but this risk was not significant in univariate or multivariable analyses. This finding is important, as some centers appear to shy away from using living donors for patients with FSGS, despite evidence demonstrating better outcomes with living donation for FSGS patients (4). Interestingly, no relation was found between time on dialysis or time from diagnosis to kidney failure and FSGS recurrence, both factors previously thought to have an effect on risk and, in turn, have influenced programs to probably unfairly delay transplants in patients with rapidly progressing FSGS.

The investigators also reviewed treatment practices and associated outcomes. For this analyses, an additional 18 patients (who did not fully meet their entry criteria but who were thought to have recurrent FSGS and reliable treatment data) were included, allowing the review of treatment in 75 patients. The majority were treated with apheresis (81%) on top of their ongoing immunosuppression and usually augmented steroids. Plasmapheresis treatment was associated
with remissions (complete or partial) in 57% of cases, although responses were mostly partial. Adding rituximab to plasmapheresis was associated with similar to slightly inferior outcomes to plasmapheresis alone (47% response), although we do not know if disease severity was similar. Other treatment regimens were too rarely used to accurately evaluate. Younger patients and women were more likely to experience remission. Time to relapse did not predict response to intervention.

Efforts such as these are critical and advance the field, but there is still much more to learn and do about the generally catastrophic problem of recurrent primary FSGS. Retrospective, observational studies of small numbers of patients cannot reliably inform us of true risks for recurrence or true utility of interventions. In primary FSGS in the native kidney, at least in adults, plasmapheresis is of uncertain value, and practitioners rely on steroids or calcineurin inhibitors to provide a roughly 30%–60% response rate (1). In the transplant kidney, apheresis use makes physiologic sense: remove the injurious, podocyte toxic factor from the blood before there is serious, irreversible structural damage. However, a prospective, randomized trial of apheresis versus placebo, in combination with standardized background immunosuppression, has never been conducted for either native kidney or post-transplant FSGS, and the effect of this intervention on long-term graft survival is especially unknown. We are left with uncertainty regarding the effectiveness of apheresis. It does not seem to be effective preventatively; however, reported response rates of 50%–90% are higher than expected with other approaches (30%–40%), making it a reasonable approach until more data become available (5). The same concern, of course, is true for even less regularly used interventions, such as high-dose cyclosporine, rituximab, adrenocorticotropic hormone, Liposorb columns, and others; each have case reports or small prospective studies suggesting efficacy, but are used in dynamic and unique settings, limiting the reproducibility and generalizability of these reports. As this is a rare disease, even larger collaborations than the one undertaken thus far by the TANGO investigators are required, and ultimately prospective studies must be done to inform best practices.

Fortunately, these collaborations are occurring in the general nephrology community, with the creation of increasingly large cohorts, such as those seen in the Nephrotic Syndrome Study Network (NEPTUNE) (6), Cure Glomerulopathy Study (CureGn) (7), and National Registry of Rare Kidney Diseases (RaDaR) (8) groups, designed to examine the natural history of FSGS (and other kidney diseases), understand its biology through the evaluation of biospecimens, and form cohorts for interventional studies. The TANGO investigators plan to organize and start this kind of international activity as well, which will be welcome. It is also a very optimistic time for clinical trials, where industry is now actively involved in rare glomerular disease research, including studies in patients with FSGS. Presently, more than 20 clinical trials for FSGS are reported on Clinicaltrials.gov, perhaps in part fueled by regulatory easing of the end points required to ultimately allow therapeutic drugs into practice. Ongoing studies are assessing a range of interventions: dietary modification, biologics, drugs targeting podocyte proteins and transporters, and even stem cell/hematopoietic cell infusions. Small studies are also underway in post-transplant FSGS with a goal to establish the role of novel therapies. However, it will be essential to assure that these therapies are applied to the right patient at the right time, utilizing reasonable outcomes to assess efficacy and safety (9).

Again, Uffing et al. (3) are to be congratulated for addressing this challenging and highly frustrating disease (or diseases) of post-transplant recurrent FSGS in a systemic and international manner. However, many challenges remain, including a great need to define the disease process more precisely and to test and hopefully establish more effective prevention and therapy for these patients.

Disclosures

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