Clinical Trials in FSGS: Past Challenges and New Trial Designs

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My goal today will be to help you think a bit about our overarching goal, which is to think about the right therapy for the right patient at the right time. This is important in nephrotic syndrome and in focal segmental glomerulosclerosis (FSGS) because the patient is not the same entity on day one of the disease as compared with the day that they are approaching futility or essentially terminal kidney failure. As patients move progressively toward kidney failure, the timing of our interventions matters a great deal. In the next 25 minutes or so, we are going to talk about the FSGS population, lessons learned from past trials, and trial design considerations that may be helpful as we think about moving forward.

FSGS occurs in all ages. So why in the world is a pediatric nephrologist standing in front of you today? Because the disease occurs in all ages, it is important that we think about the lifespan of the disorder. Indeed, I have run clinical trials on individuals with FSGS across all ages. In work by our group, we showed poor kidney survival with resistant FSGS in a pediatric population.[1] Notably, 47% of children with FSGS did not achieve any remission.[1] Within 4 years, only 9 of 28 children had avoided dialysis, in other words, 68% of the children who did not achieve remission suffered kidney failure within 4 years of being diagnosed with FSGS.

The same is true for adults with FSGS, as shown by Troyanov et al.[2] Patients who are unable to achieve remission, either partial or complete proteinuria remission, have a high risk of renal failure. In a study of an adult FSGS population, of 85 patients who had not achieved remission, only 6 had avoided dialysis within 10 years of diagnosis.[2] In the same study population, 50% had experienced kidney failure within 4 years and a staggering 93% of patients were on dialysis within 10 years from their diagnosis with FSGS.[2] Taken together, these data support the conclusion that children and adults really react quite the same way with this disease. In addition, it is important to recognize that in these academic registries, we find that 47% of children and 38% of adults do not respond to therapy, inclusive of all available therapies in their clinical environment. These numbers help us understand the magnitude of the unmet need.

The outcomes in children and adults with FSGS also have been elucidated further, specifically with regard to their response to initial therapy with a course of corticosteroids. What happens to these patients if they do not respond to corticosteroids? Does their phenotype or their characteristics help us understand their risk? Recent data have suggested that 50% of patients with severe nephrotic syndrome, with proteinuria greater than 6 g/g and creatinine and hypoalbuminemia of approximately 1.5 mg/dL, progress to renal failure at 1,000 days after diagnosis.[3]

However, there is a differential response to available treatments in this population, which brings up the issue of patient heterogeneity. Let us consider three randomized clinical trials using calcineurin inhibitors (Fig. 1). They were conducted in India,[4] Toronto,[5,6] and North America.[7–9] In aggregate, we note that complete and partial remission was extremely different between these studies. Eighty-two percent of patients were able to reach proteinuria remission in India, 72% in Toronto, and only 46% in North America. What was different about the studies? First, the duration of therapy was different, with the North American study actually having the longest exposure in that trial design, and the worst outcome for proteinuria control. Therefore, we conclude that longer therapy does not equate to better outcomes. The country or the environment clearly was different as well, and the populations were different in terms of age differences. In the India study, the population was exclusively pediatric, in Toronto it was all adults, and in the North American study it was a combination of children and adults.

Ancestry also may be important, and historically we have thought about this as a race effect in FSGS, with African Americans having worse outcomes. However, through work by Jeffrey Kopp, Martin Pollak and many others in this room, we have identified the APOL1 risk haplotype, and so now we can talk about APOL1 risk

	Treatment Duration	N	CR+PR
India	6 mos	124	82%
Toronto	6 mos	49	72%
N. America	12 mos	138	46%

Lessons learned from these studies:

- **Duration of therapy (longer therapy ≠ better outcome)**
- **Country (Environment)**
- **Population (Age; Ancestry; Other)**

Figure 1. Different response rates in SR-FSGS clinical trials of calcineurin inhibitors. Data from Gulati et al,[4] Cattran et al,[6] and Hogg et al.[9]

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haplotype as opposed to African American race.[10] What we found in this group was that individuals who had the high-risk APOL1 risk alleles had a lower opportunity for complete remission and a greater likelihood of loss of kidney function. Therefore, when we think back to the North American trial (Fig. 1) and we consider APOL1 status and patient heterogeneity, it is helpful to recognize that 38% of those patients were of African American ancestry, which was not the case in the India and Toronto cohorts (Fig. 1).

In summary, our work thus far has shown that FSGS is a disease of all ages. In academic registries, approximately 40% of patients are treatment resistant. Severe nephrotic syndrome after initial steroid therapy portends a poor prognosis, and APOL1 risk alleles portend a poor prognosis. These lessons we now have learned have implications for future study designs in this disease.

What are the lessons learned from past trials? The North American FSGS trial was a National Institutes of Health (NIH)-sponsored, randomized controlled trial using a parallel design. The question was which agent was able to provide better control of proteinuria during the 12 months of the trial, comparing two therapeutic arms. One arm included mycophenolate mofetil (MMF) and dexamethasone, and the other arm was a standard therapy of cyclosporine. All patients were on angiotensin-converting enzyme inhibitors and a low dose of prednisone on alternate days. This appears to be an odd choice now, but it was anchored on a past clinical trial by Cattran et al.[11] Here is a lesson learned: sometimes we replicate study designs because that seems to have been standard in previous trials. However, if these trial designs do not reflect clinical practice, then one should think carefully about these types of choices going into the design.

The FSGS trial was designed to determine whether one study arm was better than another. It also addressed the specific question regarding steroid dose. To enter into this trial, a patient needed to have had at least 4 weeks of corticosteroids. This time frame may have been considered insufficient, but it was reflective of what happens in the clinic and how we clinically define steroid resistance. From a randomization perspective, everyone in the MMF arm also received high-dose dexamethasone for 6 months. Perhaps the trial should have been powered to determine whether more dexamethasone or more oral corticosteroids were needed to achieve remission. Notably, the midpoint of the trial was defined as the time to evaluate patients for response to therapy: patients who did not have at least a complete or partial remission of proteinuria with preserved kidney function were to withdraw from the trial at this time. This was an important design consideration in a trial seeking its primary outcome at 52 weeks, with a withdrawal of therapy possible at 26 weeks. One then should be able to also explore the outcomes of withdrawal of therapy, which became the secondary end point. Ultimately, this FSGS study taught us that in the North American FSGS population, in this trial, less than 50% of patients had a proteinuria remission, either complete or partial. My response to that is that it really was not very good for what we consider standard therapy.

Another lesson from the FSGS trial is that with 138 patients enrolled, the minimal detectable difference between the two arms was 15.8%, thus defined as not different. In the end, neither one of these therapeutic options would be desirable in conversation with our patients because none of us would like to say "I am going to provide you with treatment options. They have some toxicities. You have less than a 50% chance to have a good response."

Another important lesson from the FSGS study concerns the midpoint analysis at 26 weeks. The vast majority of individuals who were going to fail therapy failed at 26 weeks, showing us that those patients who had at least a partial remission by that time were the patients who tended to ultimately stay in reasonable control. This leads us to the conclusion that a 26-week window actually is long enough to test the efficacy of antiproteinuric therapy.

In 2010, the Institute of Medicine (IOM) released a report aimed at a review of cancer centers, and part of their review was to consider clinical trial infrastructure. Indeed, one of the most important lessons learned from the North America FSGS trial was that it took a lot of effort to build the infrastructure for the trial to be up and off the ground and to make it work. As we think about deploying new trials and how to move trials from target and into the field, bringing up and tearing down an infrastructure for every trial is exceedingly inefficient. The IOM recognized the same problem in cancer center clinical trial networks. Therefore, with input from cancer centers and the National Cancer Institute, one of the IOM recommendations was to maintain a robust clinical trials network, to improve the speed and efficiency of trial design, to launch and conduct trials, and to help optimize the translation of scientific innovations, indeed, to be ready to act on innovations, and to select, prioritize, support, and complete clinical trials, expanding the participation of both patients and physicians. Often we think about targets and drugs, scientists and clinical trialists, but we should not lose the glue that holds all of that together, or the reason why we actually design trials: our patients and their clinicians must be on board as well. This is how we actually can become successful in our clinical trial conduct and completion.

The FONT network is a *National Institute of Diabetes and Digestive and Kidney* Diseases/NIH-funded clinical trials network that we in nephrology created, not because of the IOM report, but because it was collectively obvious to everyone that a clinical trials network would make everything a lot easier. In fact, in the midst of the NIH trial design development, we noticed that many patients who already had failed calcineurin inhibitors could not be