Testing Treatments in Posttransplant Focal Segmental Glomerulosclerosis Recurrence

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In their recent editorial[1] accompanying a randomized controlled trial of bleselumab in patients with recurrent focal segmental glomerulosclerosis (rFSGS),[2] Mahgoub and Zand appropriately highlight the extraordinary challenges inherent to conducting rigorously designed clinical trials in rFSGS posttransplantation. The absence of universally accepted criteria for diagnosing primary FSGS and its recurrence, the rarity of recurrent cases, heterogeneity in the etiology of podocytopathy and posttransplant immunosuppression, and uncertainty regarding optimal clinical endpoints collectively render traditional trial designs exceptionally difficult.[1]

Within this context, the authors of the trial should be commended for completing a multicenter randomized study across 23 sites in Canada and the United States, enrolling 67 patients during 4 y.[2] Such an achievement is, in itself, notable in the rFSGS field. Although treatment with bleselumab was associated with a numerically lower incidence of rFSGS at 3 mo compared with standard of care (absolute reduction 12.7%), the difference did not reach statistical significance, with wide confidence intervals reflecting the unavoidable limitations imposed by sample size and the disease rarity and heterogeneity of cause.[2]

Importantly, the absence of a priori power calculation—unavoidable given the lack of reliable historical data—should not detract from the significance of this effort. Rather, this trial represents the first successfully completed randomized clinical study evaluating a novel therapeutic strategy in patients with primary FSGS at high risk of recurrence. In a field marked by repeated failed or aborted trials, this study establishes both feasibility and a benchmark for future investigations.

However, the key question is how the field should move forward. Enthusiasm for new randomized controlled trials in rFSGS has waned in recent years, largely due to repeated logistical failures and inconclusive results.[3] In this setting, carefully designed registry-based analyses may offer a complementary and, in some respects, more immediately informative approach. In the absence of clear guidelines, substantial practice variability exists across centers and individual physicians, creating a natural experiment that can be leveraged to generate comparative effectiveness and safety data.[4]

Indeed, analyses from large international registries, including our international TANGO cohort, have already provided important insights into recurrence risk stratification and safety/efficacy profile of various treatment approaches.[5] However, because recurrent FSGS is both rare and clinically severe, management remains highly heterogeneous. Therapeutic approaches often combine multiple interventions, including, among others, plasmapheresis and B-cell or plasma cell targeting therapies, with substantial variability in timing, dosing, and sequencing across centers. This heterogeneity limits comparability across studies and complicates the interpretation of treatment effects. We therefore advocate for the development of a shared, detailed, consensus-driven treatment protocol that can be implemented across centers worldwide. In parallel, incorporation of emerging research biomarkers, such as circulating anti-nephrin autoantibodies and other podocyte-directed immune signatures, may help refine risk stratification, enrich future trial populations, and advance the field toward mechanism-informed patient selection.

Iterative refinement of such a shared protocol, guided by serial comparative analyses, could progressively improve patient outcomes and generate higher-quality evidence than is currently achievable through fragmented single-center approaches. This strategy offers a pragmatic, yet scientifically rigorous pathway to advance the field.

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