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Improving the evidence for the management of childhood nephrotic syndrome

Brendan D. Crawford[1] and Debbie S. Gipson[1]

Management of idiopathic nephrotic syndrome in children is based on a series of clinical trials. The trial by Sinha and colleagues in this issue is 1 of many needed to improve the evidence base for induction and maintenance therapies in this population. While key questions remain about identifying the appropriate therapy for each patient, clinical trials provide an opportunity to extend evidence-based practice that minimizes toxicity and optimizes patient health.

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Presently there are no well-validated biomarkers available to classify treatment responsivity or prognosis *a priori* in children with nephrotic syndrome (NS). As of 2017, response to corticosteroid therapy remains the best prognostic marker for childhood nephrotic syndrome.[1] Steroid-resistant nephrotic syndrome (SRNS) may occur with initial steroid therapy or as a late event months to years after initial steroid sensitivity. Significant morbidity, including progressive decline of kidney function, is well-documented in childhood SRNS.

The optimal SRNS treatment regimen remains unclear and may indeed vary at the patient level.[2] Progress in the generation of evidence to guide treatment recommendations are best supported by a strategic portfolio of well-designed clinical trials. Few randomized controlled trials (RCTs) have been completed to compare alternative therapies to maximize disease control and minimize toxicity. In a 2012 issue of this journal, Gulati and colleagues at All India Institute of Medical Sciences published a prospective, randomized, multicenter trial demonstrating superiority of tacrolimus over cyclophosphamide for treatment of SRNS.[3] The worse efficacy and cyclophosphamide-associated toxicity profile (e.g., bone marrow suppression, gonadal toxicity, and malignancy) provide rationale for the preferred use of calcineurin inhibitors (CNIs) for SRNS and help to refine pediatric standards of care for SRNS.

Current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend CNIs as the first-line treatment for childhood SRNS, based on cumulative evidence from several RCTs demonstrating high likelihood of achieving either partial or complete remission.[4] While the KDIGO guidelines recommended a minimum treatment with CNIs of 1 year, the ideal duration of treatment remains unknown. The side effects of CNIs including nephrotoxicity, hypertension, cosmetic effects, and glucose intolerance justify ongoing interest in minimizing CNI exposure. Conversely, some patients and their clinicians opt to prolong therapy with CNIs to maintain proteinuria remission. Thus, further investigation is warranted to determine the optimal duration of CNI treatment or whether alternative agents with better side effect profiles can maintain sustained remission.

The antimetabolite mycophenolate mofetil (MMF) has a better kidney safety profile than CNIs and has been used extensively for SSNS. However, based on a study of children and adults with steroid-resistant focal segmental glomerulosclerosis, MMF with high-dose dexamethasone was only able to achieve complete or partial proteinuria remission in 33% of patients, compared with the 48% of CNI-treated patients.[5]

The induction of remission and maintenance of remission must be considered with separate treatment goals, and studies evaluating remission maintenance are lacking. To date, there have been no large RCTs comparing the role of tacrolimus and MMF as it pertains to disease control (sustained remission) and toxicity (frequency of adverse effects) in patients who have already achieved a CNI-induced remission.

In this issue, Sinha and colleagues (2017)[6] present their findings from the first prospective, open-label, randomized, multicenter trial of MMF versus tacrolimus in children with SRNS following remission with tacrolimus therapy. Patients aged 1 to 18 years with initial or late steroid resistance, partial or complete proteinuria remission with tacrolimus and enalapril, histology of minimal change disease or focal

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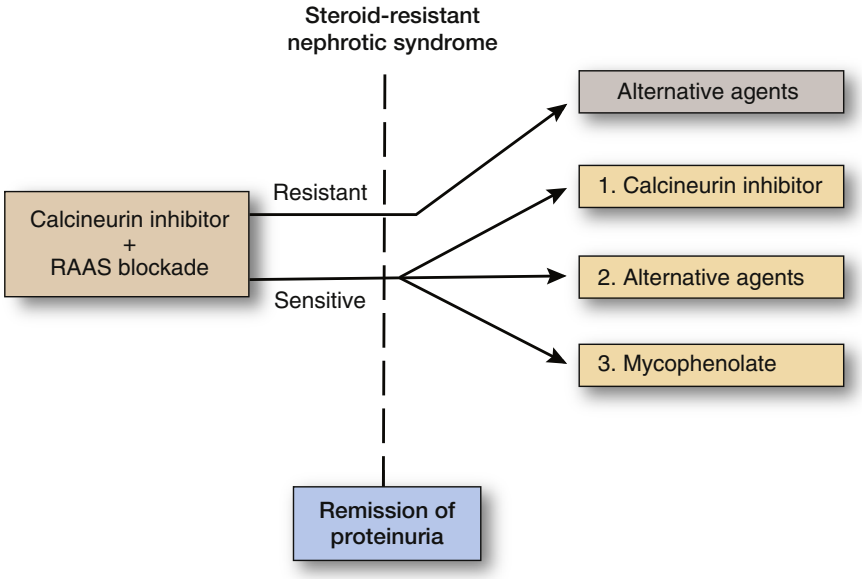

Figure 1 | An algorithm for managing steroid-resistant, calcineurin inhibitor–sensitive nephrotic syndrome in children supports the continued use of calcineurin inhibitors for 18 months in the absence of dose-limiting toxicities. The comparatively poor efficacy of mycophenolate demonstrated by Sinha *et al.*[6] supports a need for future investigations of alternate therapies for children with nephrotic syndrome.

segmental glomerulosclerosis were randomized to receive 12 additional months of open-label tacrolimus or MMF. The primary endpoint was the proportion of patients with favorable outcome, defined as partial or complete remission. A favorable outcome was more common with tacrolimus compared with MMF, to a degree that the study enrollment was halted at the interim analysis. In total, 60 patients were randomized, with the percentage of favorable outcome reported with tacrolimus (90.3%) far exceeding that with MMF (44.8%). Frequent relapses were also more common with MMF than tacrolimus (35.7% vs. 9.7%). Based on interim analysis, the authors conclude that a switch from tacrolimus to MMF after 6 months of tacrolimus therapy fails to maintain remission in tacrolimus-sensitive SRNS. This study supports a recommendation to continue tacrolimus rather than switch to MMF in children with tacrolimus-sensitive SRNS in India. Short-term safety with an 18-month total tacrolimus treatment phase was demonstrated.

Numerous questions still remain. First, it is unclear whether patients with late steroid resistance have a different pathophysiology, necessitating unique treatment protocols. In 2013, the US-led Midwest Pediatric Nephrology Consortium reported the findings of a retrospective review of NS patients with late steroid resistance, indicating variability in second-line agent use but with majority of patients with late steroid resistance achieving complete or partial remission.[7] In the current study, the authors included patients with either early or late steroid resistance, with equal portions in each treatment arm. Subgroup analysis in the Sinha *et al.* trial suggest that patients with initial SRNS were more likely to achieve a sustained remission (34.4 vs. 64.3%) than late resistance.[6] Future trials are needed to define optimal treatment regimens for children with late steroid resistance.

In this study by Sinha *et al.*, only tacrolimus drug levels were monitored with drug dose adjustment to ensure target levels were achieved.[6] Increasingly, mycophenolate pharmacokinetics with level-defined drug dosing are included in the management of children with NS.[8] In a randomized trial comparing cyclosporine versus MMF in frequently relapsing NS, *post hoc* analyses showed similar relapse rates between study arms when comparing patients with therapeutic mycophenolate levels with those with therapeutic cyclosporine levels.[9] Future studies of MMF in SRNS will need to incorporate MMF therapeutic drug level–based dosing to reduce the likelihood of systematic bias.

Replication studies in patients of other ancestries are recommended to assess the generalizability of single-country findings to children from other international regions and ancestries. Finally, the issue of long-term safety of tacrolimus as well as other nephrotic syndrome therapies used as single, combination, or sequential therapies remains an open question.

In summary, management of nephrotic syndrome in children is based on a series of clinical trials. The trial by Sinha and colleagues[6] is 1 of many needed to improve our evidence base for induction and maintenance therapies. Figure 1 shows the incorporation of this trial's results into a treatment algorithm for children in India with steroid-resistant, calcineurin-sensitive NS. While key questions remain about the identification of the right therapy for the right patient, well-designed, well-executed original and replication clinical trials provide an opportunity to extend evidence-based practice into the clinical environment that minimizes toxicity and optimizes patient health.

DISCLOSURE

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Reading the tree leaves—how to enrich clinical trials of diabetic kidney disease

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Most participants selected for clinical trials of renoprotective drugs do not reach approved endpoints; thus, large trials or prolonged follow-up are needed to achieve adequate statistical power. Yamanouchi *et al.* used a classification and regression trees analysis to enrich enrollment criterion for patients at the highest risk of reaching these outcomes. Their findings suggest a greater role for newly identified biomarkers of diabetic kidney disease in the selection of participants for clinical trials.

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Despite improvements in treatment, diabetic kidney disease (DKD) remains the leading cause of end-stage renal disease (ESRD) in much of the world; new medicines are urgently needed to reduce ESRD incidence. But to receive regulatory approval for DKD treatment, new medicines should have efficacy beyond established treatments in reducing ESRD and other late-stage events such as doubled serum creatinine levels or death. Accordingly, if we continue to select participants for clinical trials using traditional risk factors for DKD progression, future renoprotective trials will need to be larger or longer, or both, than those conducted in the past, adversely affecting both trial cost and feasibility. Enriching clinical trials to selectively enroll those at highest risk of progression may offer a viable and lower cost alternative.

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In this issue of *Kidney International*, Yamanouchi *et al.*[1] describe an approach to optimize the enrollment criteria for phase III clinical trials using the classification and regression tree analysis, a machine-learning method designed for creating simple rules to identify patients who are at a high risk for a particular outcome. The investigators used extensive data on the natural history of DKD of patients with either type 1 or type 2 diabetes who were receiving care at the Joslin Diabetes Center to identify optimal prognostic criteria for rapid DKD progression. All participants had chronic kidney disease (stage 3 or 4), history of elevated albuminuria, and up to 15 years of follow-up data. A composite endpoint was defined that included ESRD, >40% decline in estimated glomerular filtration rate, or death unrelated to ESRD. Using a time frame of 3 years, which is typical for DKD clinical trials, 222 cases met the composite endpoint: 134 and 88 in the type 1 and type 2 diabetes cohorts, respectively.

The classification and regression tree analysis was limited to eight measures: 4 clinical risk factors (age, sex, systolic blood pressure, and hemoglobin A1c), 2 established biomarkers (estimated glomerular filtration rate and albumin:creatinine ratio), and 2 novel serum biomarkers (tumor necrosis factor receptor [TNFR] 1 and 2 concentrations). Using the type 1 diabetes cohort for development and the type 2 diabetes cohort for validation, only serum TNFR1 and albumin:creatinine ratio were needed to optimize the discrimination between cases and noncases. Subjects at the highest risk of progression were defined based on serum TNFR1 levels of >4.3 ng/ml or combined serum TNFR1 levels of 2.9 to 4.3 ng/ml and albumin:creatinine ratio of >1.9 g/g. This model performed well in both type 1 and type 2 diabetes cohorts, despite their different clinical characteristics, and greatly increased the prognostic value of the enrollment criteria relative to traditional risk factors alone. It was also encouraging to see that the model performed better