

blood flow rate (Qb). To avoid an in-dialyzer hemoconcentration, a Qb between 300 and 400 ml/min was required to achieve the targeted convection volume of 6 L/h. However, in the vast majority of patients, these targets were clearly missed; the mean delivered convection volume was 20.7 L. In one-third of the study population, it was only 18 L or less. Thus, although not primarily intended by design, per-treatment and cumulative removal of larger solutes differed significantly among study participants. As pointed out by the authors, this appears to be a reflection of common practice, where it may be difficult to achieve the high Qb requirements because of inadequate vascular access.

The major impact of CONTRAST may be the recognition that dosing matters, not only in HD, but also in HDF. Because of a lack of clinical data, dosing of HDF has not been a matter of much debate; it still mainly relates to an arbitrarily prescribed absolute convection volume. Understanding that convective volume translates directly into uremic toxin mass removal, it is apparent that HDF dose needs to be better related to generation and distribution of those toxins. Uremic toxin generation, among other factors, depends on metabolic rate and visceral organ mass,<sup>8</sup> whereas toxin distribution is affected by total body water, protein binding, and intracellular accumulation. In the future, HDF dose should therefore be normalized to a body size–related factor such as body weight or body surface area. In addition, complete and regular delivery of the individually prescribed target dose should become priority in HDF, with treatment time being an important variable in cases where inadequate vascular access limits blood flow rates. As demonstrated by the CONTRAST trial, higher convection volumes may be difficult to achieve in the postdilution mode. These limitations may be overcome with the mixed dilution HDF mode, where the replacement fluid is infused both upstream and downstream of the dialyzer, and the ratio of upstream and downstream infusion rates varies to achieve the optimal compromise between maximizing clearance and avoiding the consequences of hemoconcentration.<sup>9</sup>

The results of the CONTRAST trial should not be a cause for discouragement but rather be understood as a wake-up call for the development of unified international definitions of HDF itself and its adequacy. After a long time in which an advantage of on-line HDF over conventional HD was somehow taken for granted, it is now becoming clear that, to achieve the potential benefits of better middle molecule removal, HDF needs to be applied in an educated and well defined manner. Ongoing studies in this field will help to define future treatment standards. On-line HDF is not a self-fulfilling prophecy; it must be used wisely.

## DISCLOSURES

None.

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See related article, “Effect of Online Hemodiafiltration on All-Cause Mortality and Cardiovascular Outcomes,” on pages 1087–1096.

## Rituximab in Steroid-Resistant Nephrotic Syndrome in Children: A (False) Glimmer of Hope?

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Idiopathic nephrotic syndrome in childhood is responsive to treatment with steroids in the majority of cases. Its main causes

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are minimal change nephropathy (MCNS) and focal segmental glomerulosclerosis (FSGS). Approximately 10%–15% of children with idiopathic nephrotic syndrome are steroid resistant.<sup>1</sup> Treatment of steroid-resistant nephrotic syndrome (SRNS) remains a challenge for pediatric nephrologists. Among available treatment options, calcineurin inhibitors (CNIs) are most successful in inducing remission in SRNS but have a significant burden of nephrotoxicity and prolonged duration of treatment.<sup>2</sup> High-dose intravenous steroids, mycophenolate mofetil, and alkylating agents have also been used with less success. Children who fail to respond to treatment progress to ESRD. Although children with FSGS have a worse prognosis, steroid responsiveness remains the best prognostic indicator for renal survival irrespective of histology.

The underlying pathogenic mechanism for nephrotic syndrome has traditionally focused on dysregulation of T cells, but there is increasing evidence for a role for B cells. The primary injury in nephrotic syndrome is at the level of the glomerular podocyte—this is likely from a soluble mediator such as a circulating permeability factor described in FSGS, which alters the glomerular filtration barrier or from mutations in genes that encode slit diaphragm proteins in the genetic forms of FSGS.<sup>3,4</sup> Anecdotal reports of the presence of hypogammaglobulinemia, response to immunoadsorption in recurrent FSGS, and response to levamisole and recently rituximab suggest a role for B cell involvement and/or aberrant B cell–T cell crosstalk.

Rituximab is a chimeric anti-CD20 monoclonal antibody, which is primarily approved for use in non-Hodgkin's lymphoma, chronic lymphoid leukemia, and rheumatoid arthritis and has recently been approved for use in granulomatosis with polyangiitis and microscopic polyangiitis. CD20 is a pan-B cell surface glycoprotein thought to be important in the activation of B lymphocytes.<sup>5</sup>

The exact mechanism by which rituximab would be effective in the treatment of nephrotic syndrome is unclear, but it has been proposed that induction of regulatory T cells may lead to a late effect on decreasing proteinuria long after completion of therapy.<sup>6,7</sup>

Since 2004, there have been several reports of the use of rituximab in steroid-dependent/frequently relapsing and steroid-resistant nephrotic syndrome.<sup>8–15</sup> These are comprised of case reports, case series, and a cohort study. These studies have reported remission in patients lasting for up to 12–16 months in steroid-dependent nephrotic syndrome (SDNS) patients. Results in SRNS and CNI-resistant patients have been less favorable but are still encouraging.<sup>12,14,15</sup>

In this issue of *JASN*, Magnasco *et al.*<sup>16</sup> report the results of the first randomized controlled trial of rituximab in children  $\leq 16$  years of age, with an estimated creatinine clearance  $>60$  ml/min per  $1.73$  m<sup>2</sup> with nephrotic syndrome resistant to steroids and CNIs for  $\geq 6$  months. Nephrotic syndrome was defined by either nephrotic range proteinuria ( $>40$  mg/m<sup>2</sup> per day) or lesser proteinuria in the presence of a low serum albumin. Included subjects had negative genetic testing for

*NPHS2* and *WT1*, no history of infantile onset of disease, and no serologic evidence of systemic autoimmune disease. The authors randomized a total of 31 subjects: 16 received two doses of rituximab ( $375$  mg/m<sup>2</sup>) at a weekly interval after a minimum of 6 months of steroid and CNI resistance, whereas the control group of 15 patients continued to receive prednisone and CNI therapy. Study facilitators collecting follow-up data were blinded to the treatment allocation. Children with delayed resistance, initial steroid responders who later developed  $\geq 6$  months of treatment resistance, were also included in the study but are represented equally in the two arms.

The current study was powered to detect a relatively large effect of 70% reduction in urinary protein at 3 months. Enrolled subjects had a mean age of 8 years, 1.5-year duration of disease, urinary protein excretion of  $2.7$  g/d per m<sup>2</sup>, and a mean serum albumin of  $2.3$  g/dl, which were comparable in the two groups. The authors performed intention-to-treat analysis. Three children each in the rituximab and control groups, all of who had delayed resistance to prior therapy, entered remission. No subjects with early resistance to therapy entered remission in either arm. Rituximab therapy did not reduce proteinuria in the overall treatment group. Although nonsignificant, there was a larger magnitude of reduction in proteinuria in the group that had been previously responsive to standard therapy in the past. CD20 counts remained low ( $<1\%$ ) during this time, and serum levels of rituximab indicated adequate therapeutic levels. The majority of children (61%) had FSGS on renal biopsy, but histology did not affect the outcome of rituximab treatment. Although the follow-up period of 3 months is short, most patients who respond to rituximab do so within that time, and the authors did not see any further change in proteinuria on additional monitoring for 3 months. Two patients treated with rituximab developed reactions with bronchospasm to rituximab or pretreatment, and treatment was stopped in the intervention arm.

The disappointing results of this study are in contrast to the cohort study of rituximab in SRNS (and SDNS) by Gulati *et al.*,<sup>17</sup> in which 9 of 33 (27%) children achieved complete remission at 6 months, which was sustained beyond 12 months in 7 children. There was a lack of response in 51.5% of patients, and the remaining achieved partial remission. There was no difference in response rate based on initial or late resistance or renal histology, although there was a trend toward better response in patients with MCNS. Four doses of rituximab at weekly intervals were used in SRNS patients. This latter study included patients with SDNS; 20 of 24 patients had sustained remission 12 months after receiving two doses of rituximab at weekly intervals.

Results from a questionnaire sent to members of the International Pediatric Nephrology Association on the use of rituximab in nephrotic syndrome reported data on 27 patients with SRNS, 12 (44%) of whom had a complete/partial remission.<sup>18</sup> There was no difference in response rates based on total rituximab dose, and some children without CD19 cell depletion responded to treatment. There was significant

variability in preceding treatment and dosing of rituximab in the 25 centers that reported on the outcome of patients.

A randomized controlled study by Ravani *et al.*<sup>19</sup> has also shown noninferiority of rituximab therapy in children with nephrotic syndrome who were resistant to only steroid therapy but dependent on both steroids and CNIs. In this trial, 27 patients were randomized to receive one to two doses of rituximab followed by withdrawal of prednisone and CNIs over 6 weeks, whereas 27 patients continued standard therapy with prednisone and CNIs. Remission was maintained at 3 months in the treatment group, despite reduction or withdrawal of prednisone and CNIs, with a 70% reduction in proteinuria in the treatment group compared with the controls.

Other reports of the use of rituximab in SRNS are anecdotal in one to five patients receiving one to four doses of the medication, with remission up to 3–15 months.<sup>12,14,15</sup>

Overall, the results of uncontrolled studies have shown a 40%–48% response rate in treatment-resistant nephrotic syndrome, with better outcomes in SDNS (up to 80% remission) and in recurrent nephrotic syndrome after renal transplant. Management of resistant nephrotic syndrome in childhood remains frustrating for patients, families, and pediatric nephrologists, and hence it is tempting to use a new therapy with a short duration of treatment and lack of nephrotoxicity. However, small sample size at individual centers and significant variability in approach to treatment makes it difficult to draw conclusions from uncontrolled studies of childhood nephrotic syndrome, which by itself is a heterogeneous disease.

The results of the controlled trial by Magnasco *et al.* should give reason for pause in our quest for newer and better treatments in SRNS until further data are available from larger trials of rituximab with longer periods of follow-up.

From this study and in the context of prior reports, rituximab may have a role in SDNS and CNI-dependent nephrotic syndrome in reducing exposure to and hence toxicity of these drugs. It may be more effective in reducing proteinuria in children who had prior response to standard therapy and later developed steroid resistance. Although the current trial was powered to only see a large effect in reduction of proteinuria, this trial suggests that, for early treatment-resistant nephrotic syndrome, rituximab therapy is unlikely to be successful. Although rituximab is generally well tolerated, it has serious side effects—mainly infusion-related hypotension, fever and rigors, serious infections, fatal lung fibrosis,<sup>20</sup> and progressive multifocal leukoencephalopathy (<http://www.fda.gov/Drugs/DrugSafety>). Additionally, it is an expensive treatment, with the cost of 500 mg of rituximab being approximately US\$8000. Therefore, clinicians caring for children with treatment-resistant nephrotic syndrome should carefully weigh the potential benefits of this treatment until further evidence is available for its efficacy.

Finally, this study points out the difficulty of studying treatment-resistant nephrotic syndrome in children. It is uncommon; therefore, multicenter collaboration is essential

to recruit an adequate number of subjects to address questions of treatment efficacy. Additionally, the disease itself is likely heterogeneous, leading to further difficulties in adequately powering a trial to assess treatment effects in subgroups of subjects. The question that remains to be answered is whether rituximab has a role in treatment of SDNS and late-resistant nephrotic syndrome to minimize toxicity of current therapy and improve outcome. Clearly further multicenter randomized controlled trials are necessary to further define the role of rituximab in nephrotic syndrome in children and to adequately test new therapies in the treatment of this frustrating disease, whose treatment continues to elude pediatric nephrologists and their affected patients.

## DISCLOSURES

None.

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See related article, "Rituximab in Children with Resistant Idiopathic Nephrotic Syndrome," on pages 1117–1124.