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EDITORIAL COMMENTARY

Should we consider MMF therapy after rituximab for nephrotic syndrome?

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Abstract The management of steroid-dependent nephrotic syndrome, especially in patients who have failed to respond to cytotoxic drugs, such as cyclophosphamide, remains challenging. Rituximab represents a new (off-label) therapeutic option. In a significant portion of patients, it has a short serum half-life following the recovery of CD20-positive cells. The addition of mycophenolate mofetil (MMF) as a maintenance therapy is also an attractive option, but one which requires testing in a prospective randomized clinical trial with therapeutic drug monitoring and mechanistic ancillary studies.

Keywords Rituximab · Steroid-dependent nephrotic syndrome · Evidence-based treatment · MMF

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Introduction

The treatment of childhood nephrotic syndrome (NS) is more evidence-based than most other pediatric nephrology conditions. Publication of the International Study of Kidney Disease in Children (ISKDC) study, which demonstrated a high prevalence of minimal change disease in children with NS and a good response to steroids in minimal change disease, has led to initial corticosteroid treatment as the standard therapy, with renal biopsy only performed in the case of steroid unresponsiveness [1]. There is high-level evidence for the benefits of extending initial steroid therapy to longer than 4 weeks of prednisone therapy at 60 mg/m^2/day, which results in a reduced number of subsequent relapses after initial remission. Therefore, in children with frequently relapsing or steroid-dependent NS, prednisone at 60 mg/m^2/day for 6 weeks followed by 40 mg/m^2/every second day for an additional 6 weeks is recommended [2]. Disappointingly, only a minority of North American pediatric nephrologists adhere to these recommendations, as shown in a recent survey [3]. For steroid-resistant NS, there is evidence from three randomized placebo-controlled clinical trials, two of which included children, which demonstrates that cyclosporine is the therapy of choice [4, 5]. In frequently relapsing or steroid-dependent NS, alkylating agents, such as cyclophosphamide and chlorambucil, achieve longer cumulative remission [6].

The choice of therapy in children who do not respond well to these therapies is challenging. The recommendations for this group of patients are not well-defined. This lack of evidence-based approach is possibly driven by concerns about the toxicities resulting from the long-term use of cyclosporine and alkylating agents [7]. Long-term

steroid-toxicity is also responsible for this continued search for alternative therapies. Immunomodulating therapy with levamisole has been found to be effective in frequently relapsing cases; however, its restricted availability and inadequate effectiveness in steroid-dependent NS have limited its use [8]. Over the last few years, therapy with mycophenolate mofetil (MMF) has become an attractive alternative to alkylating agents and cyclosporine in the management of frequently relapsing and steroid-dependent NS [9]. Unfortunately, the results of a recent randomized controlled clinical trial comparing a cyclosporine-based therapy for steroid-resistant NS versus MMF in combination with oral dexamethasone were disappointing [10].

Rituximab

The new kid on the block is rituximab. To the best of our knowledge, the first report of rituximab use in children stems from Benz et al. in 2004 [11]. These authors describe an adolescent with NS and 35 relapses who developed idiopathic thrombocytopenic purpura (ITP) that was refractory to steroids and intravenous immunoglobulins. Not only did the ITP respond to rituximab, but the patient suffered no further relapse of his NS. More observational evidence favoring a therapeutic potential of this B-cell depleting monoclonal antibody against CD20 originates from case reports on the use of rituximab for post-transplant lymphoproliferative disease (PTLD) that resulted in the remission of relapsing NS in the graft [12]. François et al. [13] were the first to suggest that B cells may be involved in the pathophysiology of NS, possibly by regulating T-cell function. The first larger series on the use of rituximab in patients with steroid-dependent NS was published in 2008 in *Pediatric Nephrology* [14]. In 19 of the 22 patients enrolled in this trial, other immunosuppressive agents could be withdrawn; however, there was a high rate of relapses once the CD19 and CD20 counts returned to normal. To avoid underreporting, an even larger case series was initiated from the Great Ormond Street group, and an overall beneficial effect was noted with rituximab use, albeit with significant variability with regards to preceding therapies and rituximab dosing [15]. However, the paper also demonstrated that we need more prospective data, including a dose-finding study, to determine the appropriate administration of rituximab in patients with refractory NS.

The benefits of rituximab in patients with steroid-resistant NS who fail to respond to conventional treatments have been encouraging [16]. Despite their initial response, rituximab responders remain prone to relapse when the CD19 count returns to normal, necessitating repeat rituximab use. A new concept propounded to maintain the remission without repeat rituximab use is the addition of MMF to the therapeutic regimen after the initial rituximab response [17]. This concept has a mechanistic rationale considering the similarity in B cell targeting by rituximab and MMF, although it has never been evaluated in a larger case series.

MMF after rituximab

In this context, we are delighted to read the article by Ito et al. [18] in this issue of *Pediatric Nephrology* in which the authors describe their prospective study involving nine patients with steroid-dependent NS who entered remission after rituximab therapy and subsequently received MMF as additional therapy. The results from this cohort were compared with a historical control of seven patients who received rituximab without additional MMF. In the historical cohort, only one patient remained in remission over 1 year follow-up, whereas six patients in the MMF group did not suffer any relapse. The historical control group in this study had a somewhat lower success rate of cumulative sustained remission than that of another previous report [19]. In this latter study, the authors included patients who did not benefit from conventional immunosuppressive therapies. Seven patients received cyclophosphamide, although none received additional chlorambucil. The cumulative dose of cyclophosphamide was not provided; evidence-based dosing would require 12 weeks at 2 mg/kg for a cumulative dose of 168 mg/kg in the case of steroid dependent NS [6]. All patients received cyclosporine. Nine patients in the MMF group and six of the seven patients in the control group received mizoribine without success. MMF was given at a fixed dose of 27.7 mg/kg (1000–1200 mg/m^2), which is similar to the dose received by renal transplant patients, but no pharmacokinetic monitoring was performed. Considering the substantial inter- and intra-patient variability of mycophenolic acid (MPA, the active metabolite of MMF) exposure [20, 21], it is conceivable that therapeutic drug monitoring would have further increased the number of patients in remission. In our limited experience with MMF therapy in steroid-resistant NS and focal segmental glomerulosclerosis, MPA trough levels of >1.5 mg/L or an MPA area under the time–concentration curve (AUC) of >30 mg h/L is required to maintain remission [17]. Nonetheless, the study of Ito et al. expands the body of evidence generated by individual case reports indicating that the addition of MMF to the therapeutic regimen after rituximab may provide an effective tool to prevent further relapses once the CD19/CD20 count returns to normal [18]. This is an important development in view of the substantial cost of rituximab therapy (in Canada the commercial acquisition cost of Rituxan (HLR) for 500 mg/50 ml vial is $2,390.11 as of April 27th, 2011) and the concerns that repeated rituximab administration may not be without significant risks. Ardelean et al. [22] reported severe ulcerative colitis

after rituximab therapy, and Kamei et al. [23] reported severe respiratory symptoms with the infusion of rituximab. The most severe adverse event associated with rituximab is fatal pulmonary fibrosis [24]. In one of our patients who received a total of eight doses of rituximab, followed by MMF [17], we observed persistent agammaglobulinemia that has persisted for more than 2 years, requiring ongoing intravenous immunoglobulin infusions. Considering the unpredictability and seriousness of adverse events after rituximab therapy, MMF therapy represents an attractive therapeutic option with a relatively milder side effect profile [21].

So, what can we learn from the carefully conducted study of Ito et al. [18]? One important message is that the current recommendations lack firm evidence on the management of steroid-dependent and steroid non-responsive NS in children, who generally do not respond well to alkylating agents, cyclosporine, and MMF, all of which have significant toxicities. The small sample size at individual centers is the main hindrance in developing clear recommendations in this group of nephrotic children. The absence of clear guidelines results in many different center-specific approaches. MacHardy et al. [3] demonstrated the variable approach very well. The solution lies in collaboration and in the culture of randomized controlled clinical trials. Appropriately powered, multi-center randomized controlled trials are the way to go for the required answers. An even broader question is whether there is a need to stratify the choice of therapy in nephrotic children with multiple relapses or steroid resistance. This is a clinically relevant question considering the observed variability in therapeutic response and adverse effect occurrence in individual patients. Long-term nephrotoxicity from cyclosporine is always an anxiety-provoking concern for the parents and physicians. The undersigned call for the initiation of a randomized controlled clinical trial in children with steroid-dependent NS who failed the recommended cyclophosphamide therapy, comparing cyclosporine in one arm and rituximab followed by MMF in the other arm. Thanks to support from the National Institutes of health (NIH) and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), a randomized controlled clinical trial comparing cyclosporine and MMF combined with oral dexamethasone was conducted. Given the much higher proportion of children with steroid-dependent rather than steroid-resistant NS, we should be able to complete such a trial. Therapeutic drug monitoring of MPA must be included in such trials.

Conclusion

The study of Ito et al. [18] demonstrated a more favorable proportion of steroid-dependent NS patients with sustained remission with a therapeutic regimen of ribuximab followed by MMF, especially when MMF therapy was initiated after the recovery of the CD19/CD20 counts. While promising, the continued off-label use of rituximab should be subject to appropriately powered prospective randomized clinical trials.

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