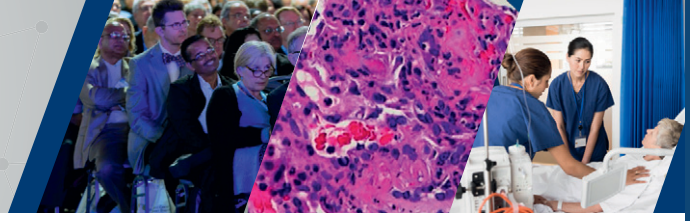

How I Treat Steroid-Sensitive Nephrotic Syndrome in Children

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CJASN 17: 1685–1687, 2022. doi: https://doi.org/10.2215/CJN.05200422

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Introduction

Steroid-sensitive nephrotic syndrome represents the most frequent pediatric glomerular disease (1), persisting into adulthood in approximately 30% of patients (2). Most frequently, steroid-sensitive nephrotic syndrome is not a severe condition, not leading to kidney failure and eventually achieving permanent remission (3). Only 1%–2% of patients develop secondary steroid resistance (1). Within this relatively benign spectrum, however, is a tremendous degree of heterogeneity, ranging from children who experience only one or two episodes despite no treatment to children who relapse persistently despite multiple steroid-sparing immunosuppressive agents (1). After steroid sensitivity (remission of proteinuria within 4–6 weeks of standard prednisone treatment) has been established at disease onset, there are no further reliable early prognostic markers. Children who are younger and children who take longer to achieve remission at the first episode tend to have a more difficult disease course, but the specificity of the "time to remission" indicator is not sufficient to adapt treatment. Classification of disease severity is on the basis of frequency of relapses and on whether a relapse occurs during or in close proximity to prednisone treatment, defined as steroid dependency (1). Given that treatment affects relapse rate, it is essential that all patients receive the same regimen at onset to allow for correct classification. Evidence-based guidelines indicate the optimal approach to the initial episode (4).

Clinical Case

A 15-year-old girl presented with steroid-sensitive nephrotic syndrome at age 5. She responded in 11 days to a standard 8-week induction treatment with prednisone: 4 weeks at 60 mg/m^2 per day and 4 weeks at 40 mg/m^2 on alternate days. She experienced a first relapse 5 weeks after prednisone discontinuation, which was treated with 60 mg/m^2 per day until 4 days after remission, followed by 4 weeks at 40 mg/m^2 on alternate days, and subsequently with low-dose prednisone (±0.5 mg/kg) on alternate days for 2.5 years except for a few weeks when prednisone was increased to daily doses during intercurrent illness. During this time, she had only one relapse. After stopping maintenance treatment with low-dose prednisone, she relapsed rapidly twice and was maintained successfully in remission with cyclosporin A for 2.5 years. Cyclosporin A was stopped to avoid calcineurin-related kidney parenchyma toxicity. Discontinuation of such treatment was followed by three relapses in 8 months, with proteinuria presenting even during prednisone therapy (*i.e.*, steroid dependency). She was started on mycophenolate mofetil (MMF) at the standard dose (1200 mg/m^2 per day in two divided doses) while prednisone was rapidly tapered and discontinued, but she relapsed after 6 weeks. She received a first course of rituximab (375 mg/m^2) at age 11.5 years. Since then, she has experienced four relapses and received three additional infusions of rituximab. The first two additional doses of rituximab were given after relapsing, whereas the last dose was given following CD19-positive B cell reconstitution 6 months after the previous dose. After the third dose of rituximab, treatment with MMF was restarted and maintained. Adherence has not been optimal in the last years, particularly regarding oral prednisone administration and regular dipstick performance. She has hypertension (arterial blood pressure ≥95th percentile per sex, age, and height), height is at the 25° percentile despite genetic target being the 50°–75° percentile, and weight is at the 75° percentile with regular menstrual cycles. Ophthalmologic and skeletal evaluations show no evidence of cataract and normal bone mineral density (lumbar *Z* score: −0.3). Currently, the patient is treated with MMF monotherapy at a standard dose of 1 g twice per day. The last rituximab dose was given 3 months ago, and the patient has been relapse free for 9 months.

Discussion

More than 70 years since being introduced for steroid-sensitive nephrotic syndrome, steroids remain the cornerstone of treatment. Usually, the severity of steroid-sensitive nephrotic syndrome tends to decrease with age. However, as this case illustrates, some patients have a more erratic course. Our personal clinical experience suggests that in patients with frequent relapses, the wider the interval is made between

relapses by correct therapeutic management, the lower the chances of frequent relapse become. Alternate-day urinary monitoring with dipsticks is advisable in remission. When prolonged (>6 months) remission is achieved, monitoring may be reduced to twice a week, provided it is intensified during febrile illnesses.

What Is the Aim of Treatment in Steroid-Sensitive Nephrotic Syndrome?

When frequent relapse or steroid dependence develops, patients require the introduction of steroid-sparing agents, such as levamisole, MMF, calcineurin inhibitors, cyclophosphamide, or rituximab (4). Some children may attain prolonged remission using low-dose alternate-day prednisone, which usually does not cause significant side effects. With the exception of a minority of patients treated with cyclophosphamide, rituximab, or tacrolimus, current therapies are not disease modifying (4). Therefore, treatment is primarily aimed at reaching the age of permanent remission while minimizing prednisone and other immunosuppressive agent–related toxicity.

What Rationale Should Guide Prednisone Therapy?

The determining factors of prednisone-related toxicity are still not completely identified (5). Clearly, the propensity to develop side effects varies from patient to patient (5). Overall, the cumulative prednisone dose correlates more with long-term side effects than the intensity of short-term treatment. Therefore, the optimal steroid regimen represents a compromise aimed at treating relapses with enough prednisone to reduce relapse rate while avoiding an excessive increase of the cumulative prednisone dose. With a similar rationale, low-dose maintenance prednisone should be prescribed only if the steroid-sparing effect resulting from relapse prevention exceeds the increase in the cumulative dose resulting from long-term prednisone use. In general, this occurs if patients relapse once or twice per year. An ocular examination and a DEXA may be appropriate when prednisone use is extended >12 consecutive months (6). Every child with steroid-sensitive nephrotic syndrome should be critically evaluated every 6 months, and ongoing treatment, in the absence of relapses, should be reduced or discontinued at least annually. Increasing oral prednisone from alternate days to daily during intercurrent illness to avoid relapses has been advocated in the recent Kidney Disease Improving Global Outcomes guidelines on the basis of several studies (4). However, a recent clinical trial has challenged this approach (7). Children were randomized 1:1 to receive either placebo or a standard dose of daily oral prednisone for 6 days at the onset of an upper respiratory tract infection. No difference was found in terms of the number of relapses occurring within 14 days. Special consideration in terms of steroid toxicity must be given to the peripubertal phase, when steroid sparing becomes particularly important to preserve the linear growth spurt and the attainment of target height.

What Rationale Should Guide the Use of Steroid-Sparing Therapies?

Even after prednisone therapy has been optimized, approximately half of patients require, at some point of their disease course, treatment with steroid-sparing agents to avoid excessive steroid toxicity. Levamisole is a cheap and effective option, particularly for frequently relapsing forms, as well as cyclophosphamide (4). In the case above, cyclosporin A was initially used, but it was stopped after 2.5 years to avoid nephrotoxicity, which is greater with longer duration of exposure to calcineurin inhibitors (8). We usually do not prescribe cyclosporin A for >3 years, unless patients have very severe disease requiring combined therapy with different immunosuppressive agents, and we try to maintain 2-hour postdose levels below 600 ng/ml because higher levels tend to be associated with higher risk of nephrotoxicity (8). At this point, both MMF and rituximab represented reasonable therapeutic options. It would be incorrect to assume that in this child, MMF was not effective. MMF is not a rapidly acting drug and requires a few (6–8) weeks to become fully effective. During this time period, especially if relapses are occurring at close intervals, prednisone should not be tapered rapidly. Moreover, metabolism of MMF is highly variable, and efficacy is dependent on adequate AUC levels rather than on dosing per body surface area (9). In this patient, dosing the MMF AUC would have been important to verify whether the prescribed dose was sufficient. This adolescent had not achieved the goal of adequate disease control and avoidance of treatment-related morbidity, despite the use of multiple approaches. At this point, she was a good candidate for treatment with rituximab, which is particularly advantageous in prolonged forms of steroid-sensitive nephrotic syndrome with poor adherence. Prior to retreatment, a re-evaluation of B cell numbers and circulating total Ig and specific Ig levels is warranted because treatment with rituximab may be associated with hypogammaglobulinemia (4). Patients should be vaccinated against hepatitis B and hepatitis B titers, and HBsAg should be checked before infusing rituximab (4). Monitoring CD19 B cells helps guide retreatment, but memory B cells are a more reliable marker (10). Recent evidence (11) indicates that in complicated forms of steroid-sensitive nephrotic syndrome, the use of a second oral immunosuppressive agent postrituximab, preferably MMF, may be necessary to maintain remission off prednisone, the top priority of management.

Steroid-sensitive nephrotic syndrome is a disease spectrum with an array of therapeutic options and a relative paucity of high-quality data to guide decision making. Extensive experience and open discussions with patients and caregivers are the basis for tailored and effective management. An awareness of the fact that treatment morbidity may overtake relapse-related morbidity should lead to the prudent use of prolonged immunosuppression, starting with prednisone minimization.

Disclosures

F. Emma reports consultancy agreements with Kyowa Kirin and Otsuka Pharmaceutical; honoraria from Avrobio, Chiesi Pharmaceuticals, Kyowa Kirin, Orphan Europe, and Recordati Rare Diseases; and an advisory or leadership role for Otsuka Pharmaceuticals (safety board for pediatric trials). M. Vivarelli reports consultancy agreements with Alexion Pharmaceuticals, Apellis Pharmaceuticals, BioCryst Pharmaceuticals, Novartis Pharmaceuticals, Roche Pharmaceuticals, and Travere Pharmaceuticals; research funding from Alexion Pharmaceuticals (for participation in clinical studies), Bayer,

Chemocentrix, and Novartis (for participation in clinical studies); serves on the editorial boards of *Frontiers in Pediatrics–Pediatric Nephrology*, *Kidney International*, and *Pediatric Nephrology*; and serves as chair of the European Rare Kidney Diseases Network Working Group on Immune Glomerulopathies, chair of the Scientific Committee for the 2022 European Society of Pediatric Nephrology meeting, chair of the European Society of Pediatric Nephrology Working Group on Glomerular Disease, chair of the Kidney Disease Improving Global Outcomes Controversy Meeting on Complement in Kidney Diseases, and cochair of the National Kidney Foundation white paper on atypical hemolytic uremic syndrome nomenclature.

Funding

None.

Author Contributions

F. Emma and M. Vivarelli conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

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Published online ahead of print. Publication date available at www.cjasn.org.