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See related articles, “Loss of Properdin Exacerbates C3 Glomerulopathy Resulting from Factor H Deficiency,” and “Combination of Factor H Mutation and Properdin Deficiency Causes Severe C3 Glomerulonephritis,” on pages 43–52 and 53–65, respectively.

Corticosteroid Therapy for Steroid-Sensitive Nephrotic Syndrome in Children: Dose or Duration?

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Idiopathic nephrotic syndrome, although a rare disease, is the most common primary glomerular disease among children. It causes substantial morbidity because it typically runs a relapsing course punctuated with prolonged periods of corticosteroids and other immunosuppressive medication. It affects about 2 children per 100,000 aged <16 years in Europe and North America,¹ with higher rates reported among children from the Indian subcontinent.²

Approximately 80% of children achieve complete remission with 4 weeks of corticosteroid therapy after their first presentation and are considered to have steroid-sensitive nephrotic syndrome (SSNS),^{3,4} but a similar proportion relapse ≥ 1 times.^{3,4} Among children who relapse, about 50% will relapse frequently (defined by the International Study of Kidney Disease in Children [ISKDC] as ≥ 2 relapses within 6 months of initial response, or ≥ 4 relapses in any 12-month period⁵) or will have a steroid-dependent disease (defined by Arbeitsgemeinschaft für Pädiatrische Nephrologie [APN] as ≥ 2 consecutive relapses either during corticosteroid therapy or within 2 weeks of ceasing it⁶). Despite relapses, most children continue to be steroid responsive, maintain normal kidney function, and ultimately, will be cured as they age into adolescence and early adult life.⁴

Over 40 years ago, the ISKDC proposed a regimen for the initial episode of SSNS, which comprised 60 mg/m² per day of prednisolone for 4 weeks followed by 40 mg/m² administered on 3 of 7 days⁵ for a further 4 weeks. Subsequently, a randomized trial coordinated by the APN demonstrated that alternate-day prednisolone was more effective in maintaining remission than prednisolone given on consecutive days.⁷ Most pediatric nephrologists adopted a regimen of daily prednisolone for 4 weeks followed by 4 weeks of alternate-day prednisolone as their standard regimen for the treatment of the first episode of SSNS.

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Because of the high relapse rate with this regimen, several trials have evaluated whether extending the duration of prednisolone therapy would result in fewer children relapsing and developing frequently relapsing nephrotic syndrome (FRNS). In a systematic review, data from six randomized controlled trials (RCTs) show that compared with 8 weeks of initial therapy, increasing the duration of prednisolone to ≥ 3 months reduced the risk of relapse over the following 12–24 months by 30% (relative risk [RR], 0.70; 95% confidence intervals [CI], 0.58–0.84) and the number of children with FRNS by 37% (RR, 0.63; 95% CI, 0.46–0.84).⁸ A meta-analysis of four RCTs demonstrates that compared with 3 months, 6 months of prednisolone reduced the risk of relapse by 12–24 months by 43% (RR, 0.57; 95% CI, 0.45–0.71) and the number of children with FRNS by 45% (RR, 0.55; 95% CI, 0.39–0.80). However, increased duration of prednisolone also resulted in an increased total dose of prednisolone, so it remained unclear whether the benefit resulted from the increased duration or the total dose of prednisolone. Regression analysis suggested that an increased duration, rather than dose, was the most influential variable; however, because it was a nonrandomized comparison, the potential existed for confounding by design.

In this issue of *JASN*, Teeninga *et al.*⁹ report the results of a placebo-controlled, parallel group trial in which 150 children aged between 9 months and 17 years with their first episode of idiopathic nephrotic syndrome were randomized at diagnosis to receive 12 weeks of prednisolone followed by 12 weeks of placebo (74 children) or 24 weeks of prednisolone (76 children), with the dosage regimens designed to provide the same total dose of prednisolone in both groups. The primary outcome was the number of children who developed FRNS, with the secondary outcomes being the number with relapse and the adverse events seen. Twenty-four children (12 children from each treatment group) were excluded from the analysis because of primary steroid resistance (11 children) or withdrawal of consent for the study (13 children). There was no significant difference in the number of children who developed FRNS between treatment groups, whether FRNS was defined according to strict ISKDC criteria (45% versus 50%) or using clinical extended criteria (50% versus 59%). Similarly, there was no significant difference in the number of children with any relapse (77% versus 80%). Adverse effects (hypertension, ophthalmologic complications, moon face, striae, viral and bacterial infections), growth rates, bone mineral densities, and behavioral scores did not differ significantly between treatment groups. The authors conclude that extending the duration of prednisolone therapy without increasing the total dose did not improve outcomes in children with their first episode of SSNS.

The major strength of this study is its methodologic rigor. Participants were recruited from 60 general hospitals and 9 tertiary centers and represented about half of all children diagnosed with idiopathic nephrotic syndrome in the Netherlands during the study period. Participants were enrolled and followed-up using processes that limited selection, performance, detection, attrition, and selective reporting bias. In contrast, among the 10

RCTs included in meta-analyses examining extended duration or increased dose regimens,⁸ 5 studies did not demonstrate adequate allocation concealment, none were blinded, and follow-up was incomplete or participants were inappropriately withdrawn from analysis in 7 studies. Inadequate allocation concealment and lack of blinding are typically associated with overestimation of the benefit of an intervention.¹⁰

Possible weaknesses of this study relate to the definition of the primary outcome, to the postrandomization withdrawals, and to inadequate power. The definition of the primary outcome event of FRNS was based initially on the ISKDC definition (strict FRNS), which is difficult to apply during extended-duration prednisolone regimens, because it does not account for relapses during the initial course of therapy. Consequently, the authors added a third criterion in which FRNS was diagnosed based on the clinical decision to use additional immunosuppressive therapy (clinical FRNS). However, analyses using either the ISKDC definition or the extended definition found no significant differences in the incidence of FRNS between treatment groups indicating that different outcome definitions did not influence the results. Twenty-four children were withdrawn after randomization because of steroid resistance (7%) or withdrawal of consent (9%). This may have been prevented with randomization occurring once remission had been achieved. However, given that such postrandomization exclusions were nondifferential, it is unlikely that such exclusions would bias the study; rather, they would just reduce power. Based on 80% power to detect a 20% reduction in the cumulative incidence of FRNS, enrollment and analysis of 72 children in each study arm were required. However, fewer children were enrolled and the study demonstrated no significant differences in the outcome of clinical FRNS (difference at 1 year, 5.0%; 95% CI, –9.1, 19.1). Nevertheless, the authors reasonably conclude that a significant benefit of the 24-week regimen over the 12-week regimen was unlikely because using the 24-week regimen would provide at best only a 9.1% benefit at 1 year and a 5.7% benefit at 5 years based on the 95% CIs around between-group differences.

Although this trial has demonstrated no benefit of extended duration of prednisolone using the same total dose, controversy remains over the most effective duration and dose of prednisolone for the initial episode of SSNS. Recent guidelines suggest 12 weeks,^{11,12} ≥ 12 weeks,¹³ or 18 weeks¹⁴ of prednisolone with total doses of prednisolone exceeding that given in the 8-week regimen. Searches of clinical trial registries identified that two well designed placebo-controlled trials comparing extended duration prednisolone (with a higher total prednisolone dose) with short duration are in progress. In the Prednisolone in Nephrotic Syndrome (PREDNOS) trial in the United Kingdom (EudraCT number 2010-022489-29), which commenced in 2011, children are randomized after achieving remission with 4 weeks of daily prednisolone to receive either 4 weeks of alternate-day prednisolone followed by 12 weeks of placebo or to receive 16 weeks of alternate-day prednisolone with tapering of the dose. Participants are being followed for

24 months. In the second trial in India (CTRI/2010/091/001095), which commenced in 2010, children are randomized to 12 weeks of prednisolone (6 weeks daily, 6 weeks alternate days) followed by placebo for 12 weeks, or to 12 weeks of prednisolone followed by 12 weeks of tapering doses of prednisolone. Participants are followed for 12 months from the end of therapy. These studies should determine whether increasing the total dose of prednisolone results in improved outcomes in the initial episode of SSNS.

DISCLOSURES

None.

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