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A multicenter randomized trial indicates initial prednisolone treatment for childhood nephrotic syndrome for two months is not inferior to six-month treatment

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In this multicenter, open-label, randomized controlled trial, we determined whether 2-month prednisolone therapy for steroid-sensitive nephrotic syndrome was inferior or not to 6-month therapy despite significantly less steroid exposure. The primary end point was time from start of initial treatment to start of frequently relapsing nephrotic syndrome. The pre-specified non-inferiority margin was a hazard ratio of 1.3 with one-sided significance of 5%. We randomly assigned 255 children with an initial episode of steroid-sensitive nephrotic syndrome to either 2 - or 6-month treatment of which 246 were eligible for final analysis. The total prednisolone exposure counted both initial and relapse prednisolone treatment administered over 24 months. Median follow-up in months was 36.7 in the 2-month and 38.2 in the 6-month treatment group. Time to frequent relaps was similar in both groups; however, the median was reached only in the 6-month group (799 days). The hazard ratio was 0.86 (90% confidence interval, 0.64–1.16) and met the non-inferior margin. Time to first relapse was also similar in both groups: median day 242 (2-month) and 243 (6-month). Frequency and severity of adverse events were similar in both groups. Most adverse events were transient and occurred during initial or relapse therapy. Thus, 2 months of initial prednisolone therapy for steroid-sensitive nephrotic syndrome, despite less prednisolone exposure, is not inferior to 6 months of initial therapy in terms of time to onset of frequently relapsing nephrotic syndrome.

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[10]See appendix.

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Idiopathic nephrotic syndrome (NS) is a disorder affecting the kidneys that is mainly characterized by high excretion of protein in the urine. Pediatric idiopathic NS is understood to be the most common cause of primary glomerular diseases, and it frequently occurs in infants aged 2–6 years. Most patients are presumed to have minor glomerular abnormality. Cellular immunologic abnormalities are believed to contribute to the condition, although its pathology remains unknown. In Europe and the United States, two in 100,000 children will develop idiopathic NS in a single year.[1] An 8-week corticosteroid regimen is the standard initial treatment for children with idiopathic NS, as outlined by the International Study of Kidney Disease in Children (ISKDC).[2,3] Although corticosteroids induce the remission of proteinuria in more than 80% of children with idiopathic NS, ~60% undergo proteinuria relapse. Previous research has shown that a high number of children undergo frequent relapse, and corticosteroid toxicities occur after repeated therapy.[2,3] Although some controlled studies[4–7] and a meta-analysis[8] show that long-term corticosteroid treatment up to 7 months maximum leads to a longer sustained remission of NS than ISKDC-recommended administration, the optimum

dose and duration of initial therapy are still unknown. A Cochrane review concluded that a well-designed and adequately powered randomized controlled trial is required to establish the optimum dose and duration of treatment.[8] The purpose of this study is to investigate whether 2 months of initial prednisolone therapy (ISKDC regimen) is not inferior to 6 months of initial therapy with an increasing cumulative dose, and to compare adverse events between treatment regimens.

RESULTS

Patient population

The study was conducted from September 6, 2007 until February 8, 2013. Figure 1 shows the trial profile. We assessed 255 patients from 90 hospitals (61 general, 7 children's, and 22 university hospitals) for eligibility. We randomly assigned 128 patients to the 2-month prednisolone group and 127 patients to the 6-month prednisolone group. We excluded nine patients from the analysis: six did not receive trial medication because of either early relapse after remission during the initial 4-week prednisolone treatment, or withdrawn consent, and three were excluded owing to a lack of participant data. Thus, we analyzed data for 246 patients. Median follow-up was 36.7 months in the 2-month group (interquartile range 27.8–46.4 months) and 38.2 months in the 6-month group (interquartile range 28.6–48.5 months). There was no difference in characteristics between the two groups (Table 1).

Primary end point

The primary end point was defined as the duration from start of initial treatment to diagnosis of frequently relapsing nephrotic syndrome (FRNS), or 'time to FRNS'. By the end of the 24-month intervention period, we observed 54 events in the 2-month group (comprising 46 FRNS [definition 1, 28; definition 2, 18], and 8 requiring immunosuppressant administration) and 58 events in the 6-month group (comprising 45 FRNS [definition 1, 23; definition 2, 22], and 13 requiring immunosuppressant administration). Twenty-one patients required immunosuppressants owing to steroid-dependent or steroid-resistant relapse. Times to FRNS were similar in both groups: however, the median duration of time to FRNS was reached only in the 6-month group (at 799 days). The hazard ratio (HR) was 0.86 (90% confidence interval (CI), 0.64–1.16; Figure 2), and noninferiority of the 2-month group was confirmed significantly, with an HR margin of 1.3 ($P = 0.01$). Post-hoc analyses showed that age groups did not affect the median duration of time to FRNS. The HRs (95% CI) were 0.92 (0.59–1.45), 0.86 (0.41–1.84), and 0.74 (0.31–1.77) for the age groups 1–5 years, 6–10 years, and 11–15 years, respectively.

Secondary end points

Times to first relapse were similar in both groups: the median was 242 days and 243 days in the 2-month and 6-month treatment groups, respectively (HR = 0.97; 95% CI, 0.72–1.31; $P = 0.86$; Figure 3). The number of relapses per person-year during the trial intervention period was 1.25 times in the 2-month group and 1.33 times in the 6-month group, and the ratio was 0.94 (95% CI, 0.71–1.22; $P = 0.65$, Table 2). The median cumulative dose of prednisolone during the 2-year trial period in the 2-month group was also significantly lower than in the 6-month group (4621.9 [interquartile range = 2191.3–7472.5] vs. 6484.8 [interquartile range = 3701.0–9577.9], $P < 0.001$).

Adverse events

Frequency and severity of adverse events were similar in both groups (Table 3). Most adverse events were transient and occurred during initial therapy or relapse therapy. In our study, steroid dependency did not greatly affect the occurrence of adverse events. Two patients in the 2-month group had severe adverse events requiring hospitalization. One patient discontinued because of acute kidney failure during

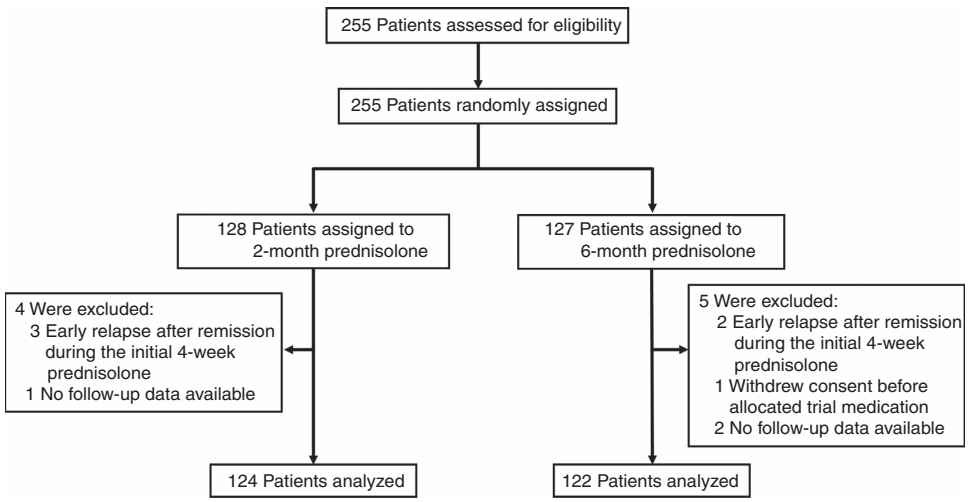

Figure 1 | Trial profile.