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Randomized Controlled Trial of Corticosteroid Tapering in Steroid-Sensitive Podocytopathy

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Introduction: Corticosteroids remain the cornerstone of therapy for podocytopathies, including minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS), in both adults and children. However, the optimal duration of steroid tapering after remission is uncertain, and current guidelines generally recommend a prolonged taper. In this study, we compared a 2-month taper with a 4-month taper of corticosteroids in adults with steroid-sensitive podocytopathy.

Methods: This was a randomized, parallel-group, active-controlled, noninferiority clinical trial that enrolled adults with steroid-sensitive podocytopathy who achieved clinical remission. Patients with active viral infections or recent use of other immunosuppressive therapies were excluded. After achieving remission, participants were randomized to 1 of the 2 following predefined tapering regimens: a short course (oral prednisolone tapered over 2-months) or a standard course (oral prednisolone tapered over 4-months). The primary outcome was relapse-free remission at 12-months from the initiation of tapering.

Results: Of the 118 patients screened for the study, 94 were randomized—49 to the short-course arm and 45 to the standard-course arm. The targeted sample size of 114 patients was not met. Relapse-free remission at 12-months was achieved in 63.3% of patients in the short-course group and 57.8% in the standard-course group, meeting the prespecified criteria for noninferiority (absolute difference 5.5%; lower bound of the confidence interval [CI]: -14.3%; 1-sided *P*-value for noninferiority = 0.001). Adverse events occurred in 12 (24.5%) patients in the short-course group and 24 (53.3%) in the standard-course group ($P = 0.003$).

Conclusion: These findings suggest that a shorter course of corticosteroid tapering is noninferior to a prolonged taper in preventing relapses in adults with steroid-sensitive podocytopathy, with a lower incidence of adverse events.

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Corticosteroids remain the cornerstone of treatment for podocytopathy, which includes MCD and FSGS in both adults and children.[1] The Kidney Disease: Improving Global Outcomes guidelines recommend corticosteroids as first-line therapy for nephrotic syndrome.[1] In adults, after remission is achieved, oral prednisolone is gradually tapered and discontinued to reduce the risk of relapse.

In the pediatric population in the treatment naïve phenotype, at least 3 randomized studies have shown no significant difference in relapse rates between shorter and longer tapering schedules.[2-4] Importantly, shorter courses of corticosteroids were associated with fewer steroid-related adverse effects and a lower incidence of infections. The clinical advantage of reducing steroid exposure by giving a short-course therapy has also been established in the infrequently relapsing nephrotic syndrome in the pediatric population.[5] Despite the guidelines suggesting gradual taper of corticosteroids in adults, in real-world practice, considerable variation exists in tapering strategies, largely driven by concerns regarding the safety profile of prolonged corticosteroid exposure and the high cumulative steroid dose associated with extended tapering.

Given that many patients require repeated courses of corticosteroids to achieve remission, cumulative steroid exposure remains a critical concern. Despite podocytopathy being the commonest cause of nephrotic syndrome in adults,[6] no randomized controlled trial has systematically compared relapse rates between short and prolonged corticosteroid tapering regimens in this population. Accordingly, we hypothesize that a shorter corticosteroid taper (2 months) following remission induction in adult podocytopathy (FSGS + MCD) is noninferior to a standard taper (4 months) in preventing relapses, while offering the potential advantage of reduced cumulative steroid exposure and lower treatment-related toxicity.

METHODS

Study Design and Setting

This study was a randomized, parallel-group, active-controlled clinical trial conducted at the Postgraduate Institute of Medical Education and Research, Chandigarh, and the Army Hospital (Research and Referral), New Delhi between May 2021 to December 2025 (Patient enrolment was done between May 2021 and May 2023), including follow-up. The trial was initiated after obtaining approval from the institute ethics committee of the coordinating center and registration with the Clinical Trials Registry-India (START trial, CTRI/2021/04/032484). Enrollment at the centers commenced only after approval from their respective institutional ethics committees.

Participants

Adult patients with nephrotic syndrome because of MCD and FSGS (steroid sensitive phenotypes) were screened for eligibility. Inclusion criteria were as follows: age >18 years, nephrotic syndrome (newly diagnosed and infrequently relapsing phenotype as per the Kidney Disease: Improving Global Outcomes criteria and biopsy-proven MCD or FSGS disease confirmed by light microscopy, immunofluorescence, and/or electron microscopy), and achieved proteinuria remission (proteinuria less than 500 mg/d) with oral prednisolone alone. Exclusion Criteria—Hepatitis B, hepatitis C, or HIV-I/II infection, before exposure to corticosteroids in last 12 months or other immunosuppressive agents for any indication within the past 12 months, persistent renal dysfunction despite remission of proteinuria, history of diabetes mellitus, abnormal liver function tests, history of steroid intolerance or history of intolerance before randomization, active urinary sediment (> 5 red blood cells/high-power field in unspun urine), antinuclear antibody positivity, and suspected secondary causes of nephrotic syndrome like drug-induced MCD (e.g., analgesic- or omeprazole-associated). Patients fulfilling all inclusion and exclusion criteria were enrolled after obtaining written informed consent.

Randomization and Allocation Concealment

After achieving remission, participants were randomized to 1 of 2 steroid tapering regimens. Randomization was performed centrally at the coordinating center using a computer-generated random sequence. The study was open-label, and neither participants nor treating nephrologists were blinded to treatment allocation. Allocation concealment was ensured using sequentially numbered, sealed opaque envelopes. The individual responsible for generating the randomization sequence was not involved in patient care or outcome assessment.

Interventions

All participants initially received oral prednisolone at a dose of 1 mg/kg/d, for a maximum duration of 8 weeks. Patients were assessed for remission at 4, 6, and 8 weeks after initiation of therapy. Upon achieving remission, participants were randomized to 1 of the following 2 predefined steroid tapering regimens: short course—oral prednisolone tapered over 2 months and standard course—oral prednisolone tapered over 4 months (Supplementary Table S1).

After completion of steroid therapy, patients were followed monthly for 2 months, then every 2 months till month 6, then every 3 months till month 12, and then 6-monthly assessments. Assessments included 24-hour urinary protein excretion, serum creatinine, and serum albumin levels. All participants received loop diuretics (torsemide or furosemide) for edema management, as clinically indicated during relapses. All patients received angiotensin converting enzyme

inhibitor or angiotensin receptor blocker, oral calcium supplements, along with vitamin D replacement until completion of steroid therapy. Subsequent relapses were treated with steroids and/or steroid sparing immunosuppression as clinically indicated.

Outcomes

The primary outcome was relapse-free remission at the end of 12 months of randomization. Secondary outcomes included the time to first relapse, relapse-free remission in the MCD and FSGS subgroups, as well as in treatment-naïve and infrequently relapsing patients, relapse-free remission at the last follow-up, cumulative prednisolone dose, and safety profile.

Definitions

Nephrotic syndrome was defined as urinary protein excretion > 3.5 g/d or > 2 g/d in the presence of serum albumin < 2.5 g/dl and hyperlipidemia.[7] Remission at randomization was defined as proteinuria < 0.5 g/d. Relapse was defined as recurrence of nephrotic syndrome after achieving remission. Relapse-free remission was defined as patients who did not have relapse of nephrotic syndrome in the specified time period.

Sample Size

Assuming a relapse-free remission rate of 70% in both groups and an absolute noninferiority margin of -25%, with 80% power and a 1-sided alpha of 0.025, 53 participants were required per group (106 total). Allowing for 5% attrition, the target enrollment was increased to 57 participants per group (114 in total). A noninferiority margin of -25% was prespecified based on the current evidence.[8-10] Currently, there are no randomized controlled trials comparing the corticosteroid tapering in adult podocytopathy precluding the use of classical fixed margin method. A few studies report a relapse rate of 50% to 75% in adult MCD and 36% to 57% in steroid-responsive FSGS even with prolonged corticosteroid tapers.[8-13] The margin was hence selected as a trade-off between the largest acceptable reduction in relapse-free remission accounting for anticipated advantages of reduced corticosteroid exposure ($\sim$ 50% reduction) in a clinical entity where corticosteroids continue to remain the primary therapy for the last 5 decades. The primary analysis was performed in the intention-to-treat (ITT) population, with a per-protocol (PP) analysis conducted as supportive. Noninferiority was considered established only if supported by both ITT and PP analyses.

Although the planned sample size was 114 patients, only 94 participants were ultimately enrolled. Recruitment was adversely affected by the COVID-19 pandemic, which led to prolonged interruptions in outpatient services, reduced referral volumes, delayed diagnostic evaluations including kidney biopsies, and constraints on clinical research operations. Given these limitations, enrollment was closed prematurely after inclusion of 94 eligible patients.

Statistical Analysis

Both ITT and PP analyses were performed. The ITT population included all randomized patients and served as the primary analysis set. For the ITT analysis, in patients lost to follow-up, a sensitivity analysis was performed with missing 12-month outcomes in patients lost to follow-up imputed as relapses. The PP population included patients who received the assigned steroid regimen without dose reduction and had evaluable primary outcome data; patients with dose reductions, major protocol deviations, or incomplete follow-up were excluded. PP assessment was performed for the primary outcome, corticosteroid dosing, and adverse events.

Relapse-free remission at 12 months was compared using the chi-square test, with results expressed as absolute risk differences and 1-sided 97.5% confidence interval (CI). Noninferiority was prespecified for only relapse-free remission at 12 months, and all other assessments were exploratory in nature. Noninferiority was assessed on the absolute risk difference scale using a 1-sided Newcombe-Wilson test at a significance level of 0.025. The null hypothesis was that the risk difference (short-course minus standard-course) was less than or equal to the prespecified noninferiority margin of -25%. Noninferiority was concluded if the lower bound of the one-sided 97.5% CI exceeded -25% (both ITT and PP). All other outcomes were considered exploratory and expressed as 95% 2-sided CI. Normally distributed variables are presented as mean $\pm$ SD, and non-normally distributed variables as median with interquartile range (IQR). Continuous variables were compared using the Student's t test or the Mann-Whitney U test, as appropriate. Time to first relapse was analyzed using Kaplan–Meier curves and compared with the log-rank test, with hazard ratios estimated using Cox proportional hazards models. Safety outcomes were summarized descriptively, with group comparisons using chi-square or Fisher's exact tests. A P-value of < 0.05 was considered statistically significant. Analyses were performed using R and GraphPad Prism version 10.

RESULTS

During the study period, 118 patients were screened, of whom 94 fulfilled all inclusion and exclusion criteria and were randomized, with 45 assigned to the standard-duration steroid regimen and 49 to the

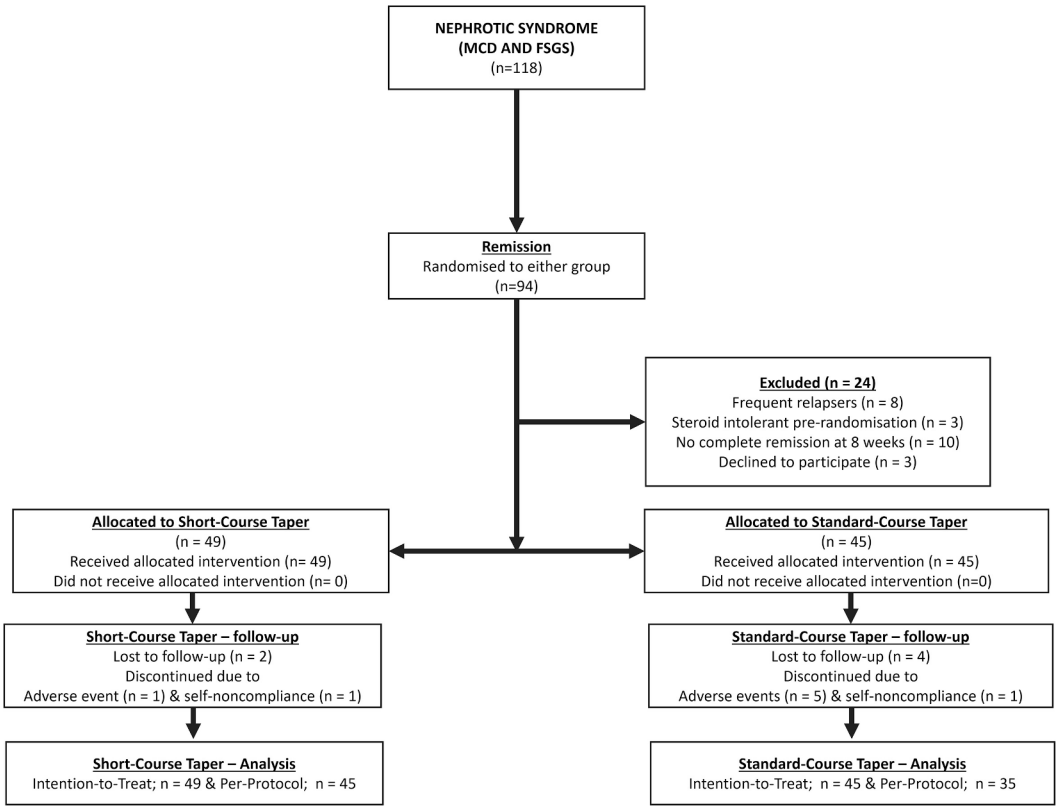


Figure 1. Study flow diagram. FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease.

short-duration regimen (Figure 1). The mean age of the study population was 31.9 ± 11.1 years, and the cohort included 57 (60.6%) male and 37 (39.4%) female patients. MCD and FSGS were reported in 48 (51.1%) and 46 (48.9%) patients, respectively.

Overall, 52 (55.3%) patients were treatment-naïve, whereas 42 (44.7%) had infrequently relapsing disease. At presentation with nephrotic syndrome, the median proteinuria was 6.0 (IQR: 3.8–9.7) g/day, median serum albumin was 2.1 (IQR: 1.8–2.5) g/dl, and median serum creatinine was 0.8 (IQR: 0.6–1.01) mg/dl. At the time of randomization, median proteinuria had decreased to 0.2 (IQR: 0.1–0.4) g/day, median serum albumin increased to 3.7 (IQR: 3.5–4.0) g/dl, and median serum creatinine was 0.7 (IQR: 0.6–0.9) mg/dl. The median time to remission from initiation of prednisolone was 38 (IQR: 29–52) days overall, 41 (IQR: 30–56) days in the short-course group, and 36 (IQR: 28–47) days in the standard-course group.

The most common comorbidities included obesity/overweight, pre-existing hypertension, and seizure disorder, present in 5.3%, 5.3%, and 2.1% of patients, respectively. Overall, 6 patients (6.4%) were lost to follow-up before completing 12 months after randomization, including 4 patients (8.9%) in the standard-course group and 2 patients (4.1%) in the short-course group. Baseline characteristics by treatment group are summarized in Table 1.

Primary Outcome

In the ITT population, relapse-free remission at 12 months was achieved in 63.3% (31/49) and 57.8% (26/45) of patients in the short-course and standard-course groups, respectively. On sensitivity analysis, with 6 participants with missing 12-month outcomes (2 in the short-course group and 4 in the standard-course group) were imputed as relapses. The absolute risk difference was 5.5% (lower bound of the confidence interval was -14.3%). The lower bound of the confidence interval remained above the prespecified noninferiority margin of -25%, demonstrating noninferiority (1-sided $P = 0.001$; log-rank $P = 0.90$; Figure 2). In the PP analysis, relapse-free remission at 12 months occurred in 30 of 45 patients (66.7%) in the short-course group and in 24 of 35 patients (68.6%) in the standard-course group, yielding an absolute risk difference of -1.9% with a lower bound of the confidence interval of −22.6%. The lower bound of the confidence interval remained above the prespecified noninferiority margin of -25%, supporting noninferiority of the short-course regimen (1-sided $P = 0.014$).

Secondary Outcomes

Cause of Nephrotic Syndrome

Among the patients with MCD ($n = 48$), relapse-free remission at 12 months was achieved in 75% (21/28)

Table 1. Baseline parameters

Parameter	Total ($N = 94$)	Short course ($n = 49$)	Standard course ($n = 45$)
Age, yrs, mean ± SD	31.9 ± 11.1	30.3 ± 10.6	33.7 ± 11.6
Male sex, *n* (%)	57 (60.6)	32 (65.3)	25 (55.6)
Body mass index (kg/m^2) median (IQR)	24.8 (24.3–26.0)	24.8 (24.4–26.1)	24.6 (24.2–26.0)
Treatment-naive (%)	52 (55.3)	28 (57.1)	24 (53.3)
Infrequent relapsing, *n* (%)	42 (44.7)	21 (42.9)	21 (46.7)
Any comorbidity	19 (20.2)	9 (16.3)	10 (22.2)
Obesity / Overweight, *n* (%)	5 (5.3)	1 (2.0)	4 (8.9)
Hypertension, *n* (%)	5 (5.3)	2 (4.1)	3 (6.7)
Other comorbidities[a], *n* (%)	11 (11.7)	5 (10.2)	6 (13.3)
Biopsy diagnosis			
MCD, *n* (%)	48 (51.1)	28 (57.1)	20 (44.4)
FSGS, *n* (%)	46 (48.9)	21 (42.9)	25 (55.6)
Baseline			
Proteinuria (g/d)	6 (3.8–9.7)	6 (4.0–9.9)	5.6 (3.4–9.6)
Baseline serum creatinine (mg/dl)	0.8 (0.6–1.0)	0.8 (0.6–1.0)	0.8 (0.5–1.1)
Baseline serum albumin (g/dl)	2.1 (1.8–2.5)	2.1 (1.7–2.6)	2.1 (1.8–2.5)
At randomization			
Proteinuria (g/d)	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.2 (0.1–0.4)
Serum creatinine (mg/dl)	0.7 (0.6–0.9)	0.7 (0.6–0.9)	0.8 (0.6–0.9)
Serum albumin (g/dl)	3.7 (3.5–4.0)	3.8 (3.5–3.9)	3.7 (3.5–4.1)
Cumulative steroid dose pre-randomization, mg prednisolone equivalents	2375 (1597–3210)	2400 (1800–3030)	2250 (1530–3360)

FSGS, focal segmental glomerulosclerosis; IQR, interquartile range; MCD, minimal change disease.
[a]Other comorbidities included leiomyoma uterus ($n = 1$), deep vein thrombosis ($n = 1$), seizure disorder ($n = 2$), nonalcoholic fatty liver disease ($n = 1$), hemorrhoids ($n = 1$), renal stone disease ($n = 1$), atopic disease ($n = 1$), neurofibromatosis ($n = 1$), and hypothyroidism ($n = 1$). Each patient was counted once.

of patients in the short-course group and 55% (11/20) in the standard-course group, corresponding to an absolute risk difference of 20.0% (95% CI: -6.6% to 44.2%; $P = 0.22$).Among patients with FSGS ($n = 46$), relapse-free remission at 12 months occurred in 47.6% (10/21) of patients receiving the short-course regimen and in 60% (15/25) receiving the standard-course regimen, yielding an absolute risk difference of -12.4% (95% CI:-37.8% to 15.4%; $P = 0.4$).

Treatment-Naïve or Relapsing Disease

Among treatment-naïve patients, relapse-free remission at 12 months was achieved in 60.7% (17/28) of patients in the short-course group and 54.2% (13/24) in the standard-course group, yielding an absolute risk difference of 6.5% (95% CI:-19.1% to 31.3%; $P = 0.63$). Among patients with a history of relapse at baseline, relapse-free remission at 12 months occurred in 66.7% (14/21) in short course group and 62% (13/21)

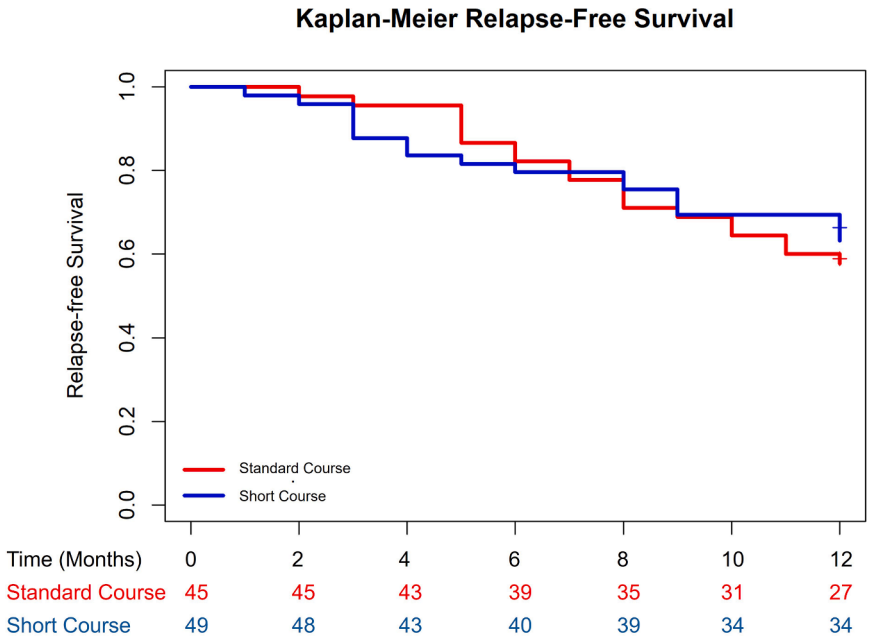


Figure 2. Kaplan-Meier estimates of relapse-free remission after randomization.

in standard course group, corresponding to an absolute risk difference of 4.8% (95% CI: -24% to 32.8%; $P = 0.75$).

Last Follow-Up

At the last follow-up (36 months), relapse-free remission was observed in 38.8% (19/49) patients in the short-course group and 44.4% (20/45) patients in the standard-course group, corresponding to an absolute risk difference of −5.7% (95% CI: −32.4% to 21.8%; $P = 0.58$).

Time to Relapse

Among patients who experienced a relapse, time to relapse was 12 months (IQR 4.0–17.5) in the short-course group and 10 months (IQR 5–15) in the standard-course group ($P = 0.56$).

Corticosteroid Exposure

In the ITT, the cumulative median dose of prednisolone post randomization was 1750 mg (1592–2205) and 3430 mg (3080–4390) in the short course and standard course, respectively ($P < 0.001$). In the PP analysis, the cumulative median dose of prednisolone post-randomization was 2310 (IQR: 1575–3185) mg and 4620 (IQR: 3150–6370) mg in the short course and standard course, respectively ($P < 0.001$).

There was no difference in the efficacy between nonprespecified group defined by baseline sex (male or female), age (32 years or > 32 years), nature of the kidney disease (FSGS or MCD) and phenotype of the disease (treatment naïve or relapsing disease; Figure 3).

Safety Profile

Adverse events occurred in 24 of 45 patients (53.3%) in the standard-course group and 12 of 49 patients (24.5%) in the short-course group (risk ratio: 0.46; 95% log-transformed CI: 0.26–0.81; $P = 0.003$). In the PP analysis, adverse events were observed in 11 of 45 patients (24.4%) in the short-course group compared with 19 of 35 patients (54.3%) in the standard-course group (risk ratio: 0.45; 95% log-transformed CI: 0.25–0.82; $P = 0.006$). Two patients, both in the short course group developed serious infectious requiring hospitalization (renal abscess, severe COVID-19 infection in 1 patient each). Steroid-related metabolic and musculoskeletal adverse events, were all more frequent in the standard-course group. At the 1-year follow-up, although the standard-course group showed a numerically higher median body mass index of 25.1 (24.6–25.7) compared with 24.9 (24.4–25.2) in the short-course group, the difference was not statistically significant ($P = 0.51$). The details are shown in Table 2.

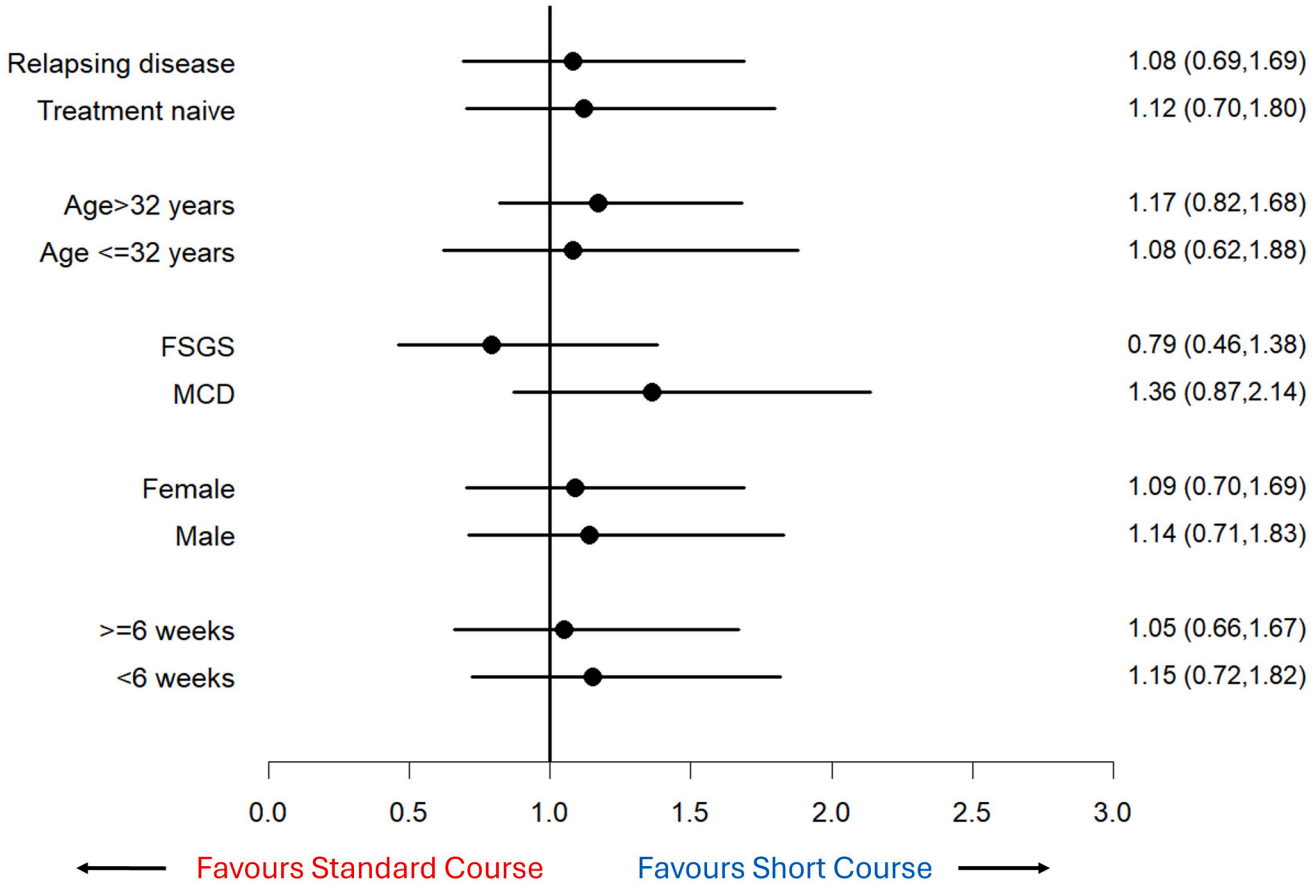


Figure 3. Subgroup analysis of relapse risk according to baseline characteristics. FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease.

Table 2. Safety profile

Outcome	Short course group ($n = 49$)	Standard course group ($n = 45$)
≥ 1 adverse event	12 (24.5%)	24 (53.3%)
≥ 1 serious adverse event (SAE)	4 (8.2%)	8 (17.8%)
Steroid-induced dysglycemia	0 (0%)	4 (8.9%)
Cosmetic issues[a]	2 (4.1%)	7 (15.5%)
Arthralgia/myalgia	1 (2.0%)	6 (13.3%)
Steroid-induced myopathy	1 (2.0%)	2 (4.4%)
Upper or lower respiratory tract infection	2 (4.1%)	1 (2.2%)
Varicella zoster infection	0 (0%)	1 (2.2%)
Fungal infection (tinea)	0 (0%)	3 (6.7%)
Bacterial vaginosis	0 (0%)	1 (2.2%)
Acute gastroenteritis	1 (2.0%)	1 (2.2%)
Infected dental caries	0 (0%)	1 (2.2%)
Any nonserious infection	3 (6.1%)	8 (17.8%)
Gastritis	2 (4.1%)	1 (2.2%)
Avascular necrosis of the hip	1 (2.0%)	1 (2.2%)
Severe COVID-19 infection requiring hospitalization	1 (2.0%)	0 (0%)
Renal abscesses with pyelonephritis	1 (2.0%)	0 (0%)
Steroid-induced psychiatric disorder	0 (0%)	2 (4.4%)
Progression of kidney disease	1 (2.0%)	0 (0%)

[a]Necessitating interventions:
1. Analysis shown for the intention-to-treat (ITT) population.
2. Patients could experience more than one adverse event and were therefore counted once per adverse-event category, not once overall.
3. Serious adverse events (SAEs) were defined as events resulting in hospitalization, life-threatening illness, permanent organ damage, necessitating treatment interruption or protocol deviation. SAEs in the short course group included progression to end stage kidney disease (ESKD) (1 patient), renal abscess (1 patient), steroid induced myopathy/arthralgia necessitating protocol deviation (1 patient), avascular necrosis of the hip and severe COVID-19 infection requiring admission (both in the same patient). SAEs in the standard course group included steroid induced myopathy/arthralgia necessitating protocol deviation (3 patients), psychiatric disturbances (2 patients), hemorrhoidal bleed requiring blood transfusion (1 patient), avascular necrosis of the hip (1 patient).
4. Lower respiratory tract infections and varicella zoster infections did not require hospitalization and were classified as nonserious adverse events.
Protocol deviations occurred in 2 patients in the short-course group (1 because of adverse events and 1 because of self-noncompliance) and in 6 patients in the standard-course group, the majority of which were attributable to steroid-related adverse events (5 of 6), with one deviation because of self-noncompliance. This excludes 2 and 4 patients in the short-course and standard-course arms who were lost to follow-up.

DISCUSSION

In this randomized trial involving adults with steroid-sensitive podocytopathy, we demonstrate that a shortened corticosteroid taper of 2 months following remission induction is noninferior to a conventional 4-month taper in preventing relapse at 12 months.

Corticosteroids are the cornerstone of therapy for MCD and FSGS; however, the optimal duration of steroid tapering after remission remains uncertain in adults.[1] Current guideline recommendations advocate gradual tapering over 6 months, largely extrapolated from pediatric experience and expert consensus rather than robust adult randomized data. Several retrospective studies from the United States, Europe, and China have reported high relapse rates in adults with MCD treated with corticosteroids.[8-10] In a study from Japan, 35 patients received a short course of oral prednisolone (total duration approximately 3–4 months) and were compared with controls treated according to the conventional tapering schedule. The short-course group experienced earlier relapses than the standard-taper group (adjusted hazard ratio: 2.45; 95% CI: 1.51–3.97; $P < 0.001$). However, the incidence of frequently relapsing disease did not differ significantly between the 2 groups.[14] In a study by Waldman *et al.*[9] involving 95 patients, 73% experienced a relapse of nephrotic syndrome after a median follow-up of 139 weeks. Fenton *et al.*[8] ($n = 78$) reported relapses in 61% of patients at a median follow-up of 72 months. Similarly, Maas *et al.*[15] ($n = 125$) observed a relapse rate of 54% after a median duration of 59 months, whereas Szeto *et al.*[10] ($n = 340$) reported a relapse rate of 38% over a median follow-up of 175 months. In addition, the authors from the Toronto registry reported a relapse rate of 57% among patients with FSGS and hypoalbuminemia, with a median time to relapse of 7 months.[16] Collectively, these data underscore the substantial burden of relapses in adult MCD despite reasonable corticosteroid exposure. In the pediatric populations, multiple randomized clinical trials have shown no reduction in relapse rates with prolonged steroid courses, while consistently demonstrating higher toxicity with longer exposure. In the study by Sinha *et al.*,[4] which included 181 cases, the median relapse rates were 1.54 and 1.26 episodes in the 3- and 6-month groups, respectively. In another study by Yoshikawa *et al.*,[2] 255 children with nephrotic syndrome were randomized to receive a 2-month and a 6-month taper of corticosteroids. At the end of 2 years, 54 and 58 episodes of nephrotic relapse were documented in the 2-month and 6-month groups, respectively. In a study from the UK, including 237 patients with the first episode of childhood onset nephrotic syndrome, were randomized to receive 8 weeks versus 16 weeks taper.[3] The time to first relapse was comparable, and the incidence of frequently relapsing nephrotic syndrome was noted in 53% and 50% in the 8-week and 16-week groups, respectively. In this study, there was no significant difference in the remission rates between the short-course and standard-course corticosteroid tapering. At the last follow-up, close to 50% of the patients relapsed in both groups, highlighting the fact that long duration of therapy does not reliably prevent relapse, but inevitably increases cumulative steroid exposure.

Subgroup analyses of the histological pattern revealed broadly consistent patterns, though these findings should be interpreted cautiously. Among patients with MCD, relapse-free remission rates favored the short-course regimen, whereas in FSGS, outcomes favored the standard-course regimen; these differences were not statistically significant. Importantly, the

study was not powered to detect histology-specific differences. Accordingly, these observations should therefore be considered hypothesis-generating rather than definitive and underscore the need for larger, stratified trials in these specific clinical conditions. Similarly, when stratified by clinical phenotype, relapse-free remission rates were comparable between treatment-naïve patients and those with infrequently relapsing disease across both tapering strategies. Although limited by inadequate statistical power, patients with infrequently relapsing did not appear to derive additional protection from prolonged tapering, reinforcing the notion that relapse propensity may reflect intrinsic disease biology rather than taper duration alone. These findings support the applicability of a shorter taper across common adult podocytopathy phenotypes encountered in clinical practice.

The safety profile observed in this study is directionally consistent with the dose considerations. Patients in the standard-course group had a higher incidence of adverse events, which aligns with the notion of higher complications with a larger dose of corticosteroids. The incidence of serious adverse events was not statistically significant; this may be attributed to the younger age of the cohort (< 35 years), prophylactic antibiotic therapy, and heightened sensitivity to infection prevention during the immediate COVID-19 pandemic. The finding is consistent with the report by Webb *et al.*[3] (17% vs. 25%), Yoshikawa *et al.*[2] and Sinha *et al.*[4] Although there were no excess signals regarding serious adverse events in the standard course group as compared with the short course group, we believe that the larger dose would have a more subclinical and long-term effects on all the organ systems of the body.

A major strength of the short-course strategy was the marked reduction in cumulative corticosteroid exposure. This difference is clinically meaningful. Adults with podocytopathy frequently experience multiple relapses over their lifetime, often requiring repeated courses of high-dose corticosteroids. In many resource-limited settings, corticosteroids continue to remain the mainstay of therapy, both for induction and for infrequent relapsing episodes. Even modest reductions in exposure during each treatment episode may translate into substantial long-term benefits by mitigating steroid-associated diabetes, weight gain, osteoporosis, avascular necrosis, and cardiovascular risk. In this context, a shorter taper offers a tangible steroid-sparing advantage without compromising efficacy.

This study has several strengths, including its randomized design, pragmatic tapering regimens reflective of real-world practice, and the use of both ITT and PP analyses to support noninferiority. However, certain limitations merit acknowledgement. Recruitment was curtailed prematurely because of the COVID-19 pandemic, resulting in fewer recruited subjects than initially planned, and an observed statistical power of approximately 75% for the primary end point and higher-than-expected relapse rates, indicating residual uncertainty; and a clinically meaningful difference cannot be confidently excluded. In addition, the observed relapse-free remission rate in the standard-course group (57.8%) was lower than anticipated at the time of sample size estimation, further reducing the effective power of the study. The width of the confidence intervals should therefore be interpreted in the context of this reduced sample size. The study was conducted at 2 centers, potentially limiting generalizability, and was open-label. The open-label design may introduce performance bias and a Hawthorne-type effect. In addition, the trial was not powered for subgroup analyses by histology or phenotype, dysglycemia not defined based on HbA1c measurements to objectively quantify steroid-induced dysglycemia and longer-term outcomes beyond the first year could not be fully assessed in all cases. Finally, as with most noninferiority trials, the findings should be interpreted with caution and ideally validated in broader, real-world settings before definitive conclusions are drawn.

In conclusion, this randomized trial provides evidence that a 2-month steroid taper is an effective and potentially safer alternative to prolonged tapering in adults with steroid-sensitive podocytopathy. Larger multicenter trials with longer follow-up are warranted to confirm these findings and to refine steroid-sparing approaches in adult nephrotic syndrome.

DISCLOSURE

VJ reports consulting fees and honoraria from Bayer, AstraZeneca, Boehringer Ingelheim, Baxter, Vera, Visterra, Otsuka, Novartis, Timberlyne, Biogen, Chinook, and Alpine, with all payments made to his institution under organizational policy. All other authors declared no competing interests.

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DATA AVAILABILITY STATEMENT

The data underlying this study contain de-identified participant information and is not publicly available

because of institutional ethics protocol. Data will be provided to researchers whose proposed use has been approved by an independent review committee and after obtaining a no-objection certificate from the PGIMER ethics committee. Data requests should be submitted to the corresponding author, RR (drraja1980@gmail.com).

AUTHOR CONTRIBUTIONS

AP, JB, VS, PMD, and TS contributed to data collection, analysis, and manuscript drafting. VK and RN provided randomization allotment. MR, HSK, and VJ supervised methodology. RR designed and supervised the study, and finalized the manuscript.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this manuscript, the authors used ChatGPT5.2 for only language editing and readability. The authors reviewed and edited the content as needed and take full responsibility for the final content.

SUPPLEMENTARY MATERIAL

Supplementary file (PDF)

Table S1. Steroid Taper protocol.

CONSORT Checklist.

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