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The Efficacy and Safety of Reduced-Dose Oral Methylprednisolone in High-Risk Immunoglobulin A Nephropathy

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Introduction: The therapeutic effects of steroids in immunoglobulin A nephropathy (IgAN) global (TESTING) study reported that methylprednisolone reduces the risk of major kidney events in individuals with IgAN at high risk of disease progression compared to supportive care alone but is associated with increased serious adverse events (SAEs) primarily with full-dose therapy. The risk benefit balance of the reduced-dose methylprednisolone regimen is examined in this prespecified analysis of the reduced-dose cohort of the TESTING trial.

Methods: Between 2017 and 2019, patients with IgAN, proteinuria ≥1 g/d despite 3 months of renin-angiotensin-system blockade and estimated glomerular filtration rate (eGFR) 30 to 120 ml/min per 1.73 m^2 were randomized to reduced-dose methylprednisolone 0.4 mg/kg/d or placebo. The primary outcome was a composite of a 40% eGFR decline, kidney failure, or death due to kidney disease.

Results: A total of 241 participants were randomized and followed-up with for a median of 2.5 years (mean age: 37 years; baseline eGFR: 65 ml/min per 1.73 m^2; proteinuria: 2.48 g/d). Methylprednisolone was associated with fewer primary outcome events compared to placebo (7/121 vs. 22/120; hazard ratio [HR]: 0.24; 95% confidence interval [CI]: 0.10–0.58, $P = 0.002$), lowered proteinuria, and reduced eGFR rate of decline from baseline. The mean difference between methylprednisolone and placebo in proteinuria and eGFR from baseline was −1.15 g/d and 7.9 ml/min per 1.73 m^2 ($P < 0.001$) at 12 months, respectively; however, these benefits were lost over time. There were 7 versus 3 SAEs in the methylprednisolone versus placebo group (HR: 1.97; 95% CI: 0.49–7.90), including 5 versus 2 infections.

Conclusion: Reduced-dose methylprednisolone is effective in improving kidney outcomes in high risk IgAN; however, it is associated with a modestly higher number of SAEs compared to placebo.

Kidney Int Rep (2024) **9,** 2168–2179; https://doi.org/10.1016/j.ekir.2024.03.032
KEYWORDS: corticosteroids; glomerulonephritis; IgA nephropathy

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IgAN is the most prevalent primary glomerular disease worldwide.[1] Nontargeted supportive management, including optimal renin-angiotensin system blockade has been the cornerstone of IgAN management. Although this approach is effective in delaying kidney events, the risk of kidney failure prevails with up to 50% of adults with IgAN reaching kidney failure requiring dialysis or transplantation within 10 to 30 years of diagnosis.[2,3]

It is increasingly understood that an immune-mediated multi-hit mechanism incites kidney injury in IgAN, which lends plausibility to the role of immunosuppressive therapy.[4] Current clinical guidelines suggest consideration of a course of corticosteroids in a selected

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Received 20 February 2024; revised 19 March 2024; accepted 25 March 2024; published online 3 April 2024

cohort of high risk patients who have greater than 1 g/d of proteinuria despite maximal supportive care.[5] These recommendations are based on moderate certainty evidence and there has been equipoise regarding the net therapeutic effect of corticosteroids in IgAN.

The TESTING study is the largest randomized controlled trial to assess the effect of corticosteroids in IgAN to date.[6] During the study, an excess number of SAEs was observed, thus an interim analysis was conducted, which showed methylprednisolone 0.6 to 0.8 mg/kg/d was associated with 4-fold increased SAEs, but may improve kidney outcomes.[7] Recruitment was paused, and protocol amendments were enacted to include a reduction in methylprednisolone dose to 0.4 mg/kg/d (maximum 32 mg/d). The combined full-dose and reduced-dose TESTING study was reported in 2022 and found that 6 to 9 months of oral methylprednisolone was effective in reducing kidney events compared to placebo across the overall trial population.[6] However, this was associated with increased SAEs, particularly with higher doses. Subgroup analyses found no difference in the magnitude of benefit between the full-dose and reduced-dose methylprednisolone cohort, with fewer SAEs reported in the latter.

Whereas other drugs that target specific immunological and hemodynamic pathways in IgAN are being studied in trials, systemic corticosteroids are currently the only immunosuppressant agents in widespread use worldwide, including low resource settings. Therefore, it is important to define the balance of risks versus benefits of the reduced-dose regimen to inform the safe use of corticosteroids in clinical practice. Here, we report the prespecified secondary analysis of the TESTING study to assess the efficacy and safety of the reduced-dose oral methylprednisolone regimen, compared to placebo, in people with IgAN at a high risk of kidney function decline.

METHODS

Study Design and Participants

The study design, oversight, and eligibility criteria of this randomized, double blind, placebo controlled, international multicenter clinical trial have previously been described in detail.[6,8] The reduced-dose study was conducted in Australia, Canada, China (including Hong Kong), India, and Malaysia. Recruitment commenced in March 2017, the final participant was randomized in November 2019, and the final follow-up visit was in June 2021.

Eligible individuals for this cohort included those aged at least 18 years with primary IgAN confirmed on kidney biopsy, an eGFR between 30 and 120 ml/min per 1.73 m^2 (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula) and a 24-hour urinary protein excretion greater than or equal to 1 g/d while receiving maximum tolerated renin-angiotensin system blockade. Individuals with a strong indication or contraindication for immunosuppressive therapy as determined by the treating physician, a history of systemic immunosuppressive therapy in the preceding year, uncontrolled hypertension, unstable kidney function, and secondary IgAN were excluded.

Study Procedures

Eligible participants entered a run-in period of 4 to 12 weeks and received optimal supportive care with maximally tolerated renin-angiotensin system inhibitor therapy for a minimum of 12 weeks. Those with persistent proteinuria of greater than 1 g/d and demonstrated treatment adherence were randomized to oral methylprednisolone or matching placebo in a 1:1 ratio. Participants in the intervention arm received 0.4 mg/kg/d of oral methylprednisolone at a maximum dose of 32 mg/d for 2 months, followed by a tapering regimen of 4 mg/d each month for a total duration of 6 to 9 months. Antibiotic prophylaxis for *Pneumocystis jirovecii* pneumonia, as per local practice, was administered during the initial 12 weeks of therapy when the treatment dose was the highest. Supportive background therapy was continued throughout the study period. Study visits were conducted monthly for the first 3 months and every 3 months thereafter until the study completion date.

Outcomes

The primary end point for the entire study was a composite of the first occurrence of a sustained 40% reduction in eGFR from baseline (based on consecutive serum creatinine readings at least 30 days apart, or the last available result), kidney failure requiring kidney replacement therapy including transplantation or dialysis, or death due to kidney disease. Additional prespecified primary outcomes for the reduced-dose study included the mean change in proteinuria and eGFR from baseline at 6 and 12 months of treatment. The secondary end points were the composite of a sustained eGFR reduction of each of 30%, 40%, and 50%, with kidney failure, or death due to any cause; individual components of the primary and secondary composite outcomes; proteinuria reduction determined by the time-averaged mean proteinuria; and average annual eGFR slope.

Safety outcomes included the total number of SAEs, serious infection requiring hospitalization, new onset diabetes mellitus, gastrointestinal hemorrhage requiring hospitalization, clinically evident fracture or

osteonecrosis, and cardiovascular events. Cardiovascular events were defined as a composite of myocardial infarction, stroke, heart failure requiring hospitalization, and death due to cardiovascular disease.

Statistical Analysis

The study was event driven, as determined by the original study protocol. Additional prespecified sample size calculations were conducted for this cohort to detect a 0.50 g/d difference from baseline proteinuria at 6 months with 90% power and a 5 ml/min per 1.73 m^2 difference from baseline eGFR at 6 months with 80% power. Data were censored when a participant died from nonkidney causes, was lost to follow-up, withdrew from the study, or at the end of the study follow-up period. Data from all randomized participants were included according to the intention-to-treat principle. The detailed statistical analysis plan has been published previously.[6]

A Cox proportional hazard frailty model adjusted for baseline proteinuria, baseline eGFR, and endocapillary hypercellularity score on biopsy as prespecified fixed covariates; and site as a random effect was used to estimate the HR and 95% CI comparing methylprednisolone to placebo for the primary composite end point and all secondary end points of a time-to-event nature. Heterogeneity across subgroups was tested for the primary composite end point using predefined groups, including baseline proteinuria (<3 g/d vs. ≥3 g/d); baseline kidney function (eGFR <50 ml/min per 1.73 m^2 vs. ≥50 ml/min per 1.73 m^2), baseline histological lesion scoring (presence or absence of endocapillary proliferation as per the Oxford classification [E1 vs. E0])[9]; race (Chinese vs. non-Chinese); age (<50 years vs. ≥50 years) and time between randomization and kidney biopsy (<1 year vs. ≥1 year). An adjusted Poisson model using the same covariates as for the Cox model was used to estimate the adjusted annual event rates and absolute risk differences per 100-person years.

The changes in proteinuria and eGFR from baseline were analyzed using a linear mixed model with the baseline measurement, treatment group, and stratification variables as fixed effects as per the analysis of the primary composite outcome. The effect of the treatment was assessed as the adjusted mean difference and its 95% CI. Individual time-averaged proteinuria was calculated as a weighted average of all available proteinuria measurements for each participant and compared using *t* test. The rate of eGFR decline (ml/min per 1.73 m^2 per year) for each individual was calculated from the slope of a linear regression model of all eGFR over time, and the mean rate of decline for each group was compared using *t* test. Sensitivity analyses were conducted excluding eGFR values when participants were exposed to higher doses of methylprednisolone in the first 3 and 6 months of the treatment course to negate the short-term catabolic effects of corticosteroids. Additional exploratory analyses were conducted to assess the effects of methylprednisolone on annual eGFR slope over 3 years by fitting a 2-slope mixed effects linear spline model with a knot at 3 months. The mean total slope was computed as a combination of the short-term (0–3 months) and long-term (3 months–3 years) slopes.

SAEs were summarized as the number of total events and the number of participants experiencing at least 1 event. An adjusted Poisson model was used to estimate the number needed to treat to prevent 1 kidney event and to cause 1 SAE over 2.5 years from the absolute risk difference per 100-person years.

All *P*-values were 2-sided, and *P*-values less than 0.05 were considered to indicate statistical significance. Analyses were performed using SAS software (version 9.4; SAS Institute) and R (version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

A total of 427 potentially eligible participants were screened across 42 sites in China, Australia, India, Canada, and Malaysia. Of these, 241 participants were included in the study, with a median follow-up period of 2.5 years. One hundred twenty-one were randomized to reduced-dose oral methylprednisolone, and 120 were randomized to placebo (Figure 1). Of the participants, 225 (93%) received *Pneumocystis jirovecii* pneumonia prophylaxis. The baseline characteristics were similar across both groups (Table 1). Overall, the mean age was 36.7 years, 102 participants (42%) were female, 113 participants (47%) were recruited from sites based outside of China, and 17 (7%) were Caucasian. The mean baseline eGFR and 24-hour urinary protein excretion were 65.0 ml/min per 1.73 m^2 and 2.48 g/d, respectively.

Primary and Secondary Composite Outcomes

The primary composite outcome occurred less frequently in the methylprednisolone arm than in the placebo arm (7/121 [6%] vs. 22/120 [18%]; HR [95% CI]: 0.24 [0.10–0.58]; $P = 0.002$) (Figure 2 and Table 2). No significant heterogeneity was found in the effect of treatment on the primary composite outcome across all subgroups (Figure 3). The effects of methylprednisolone on the secondary composite and component outcomes were similar to the findings for the primary composite outcome (Table 2). In total, there were 3 of 121 (2%) compared to 10 of 120 (8%) participants with

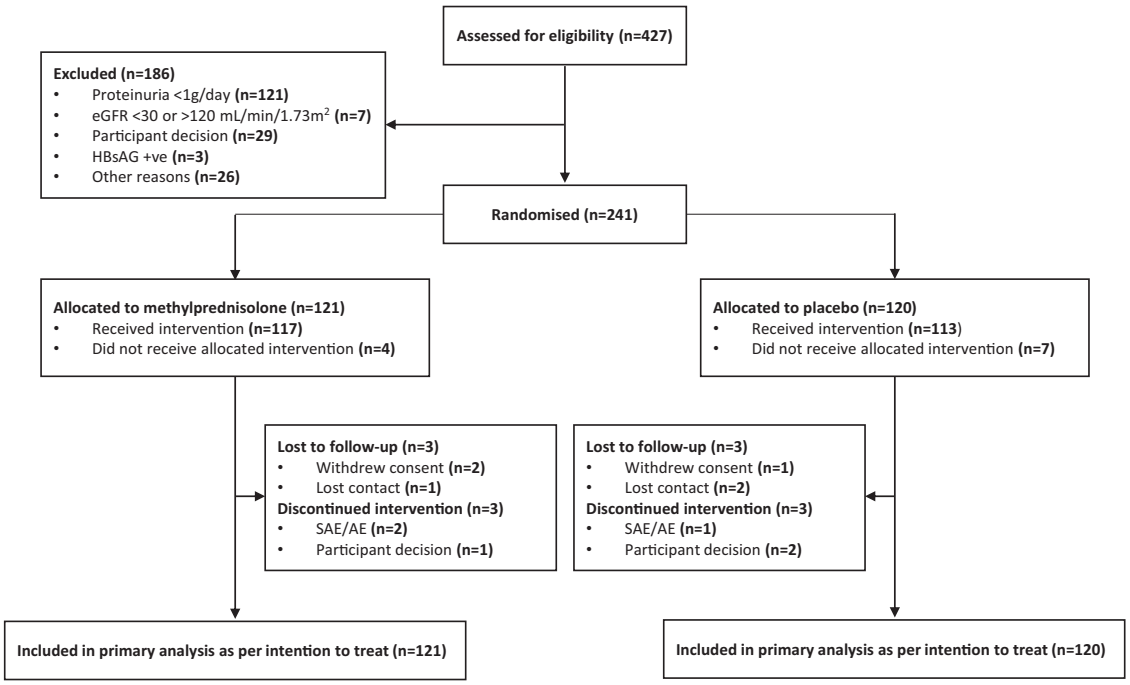

Figure 1. Flow diagram of participants in the reduced-dose TESTING study. eGFR, estimated glomerular filtration rate; HBsAG +ve, Hepatitis B surface antigen positive; SAE, serious adverse event; AE, adverse event.

kidney failure events in the methylprednisolone and placebo arms, respectively (HR [95% CI]: 0.26 [0.07–1.03]; $P = 0.056$). There were no deaths due to kidney failure across the 2 groups, and 1 death in the methylprednisolone group.

Effect on Proteinuria and eGFR

The mean change in proteinuria from baseline was 1.15 g/d lower (50.4% reduction) in the methylprednisolone group compared to 0.03 g/d lower in the placebo group at 6 months, with a mean difference of 1.14 g/d (95% CI: 0.48–1.80; $P = 0.002$) (Table 3 and Figure 4). The results at 12 months were similar, with a mean difference of 1.15 g/d (95% CI: 0.62–1.68; $P < 0.001$) between the 2 groups (methylprednisolone: 1.01 g/d lower [45.8% reduction], placebo: 0.10 g/d higher). Overall, the mean difference in the time-averaged 24-hour proteinuria between the methylprednisolone (1.58 g/d) and the placebo (2.41 g/d) arms was 0.83 g/d lower (95% CI: 0.48–1.25; $P < 0.001$) (Supplementary Figure S1). The proteinuria lowering effect was predominantly noted in the first 12 months and was lost over time, with no apparent between group difference seen by 4 years of follow-up.

With methylprednisolone, there was an increase in eGFR from baseline of 4.7 ml/min per 1.73 m^2 and 5.0 ml/min per 1.73 m^2 at 6 and 12 months respectively, compared to a decrease of 3.2 ml/min per 1.73 m^2 and 3.0 ml/min per 1.73 m^2 with placebo (Table 3 and Figure 5). The mean differences between the 2 arms were 7.6 ml/min per 1.73 m^2 at 6 months (95% CI: 3.8–11.4; $P < 0.001$) and 7.9 ml/min at 12 months (95% CI: 4.3–11.5; $P < 0.001$). Overall, the mean annual eGFR slope of decline was −0.7 ml/min per 1.73 m^2 per year in the methylprednisolone arm and −3.0 ml/min per 1.73 m^2 per year in the placebo arm (mean difference [95% CI]: 2.3 ml/min per 1.73 m^2 per year [−0.0 to 4.6]; $P = 0.05$) (Supplementary Figure S2). Sensitivity analyses conducted by excluding values during the first 3 and 6 months of treatment found a mean difference between the 2 groups of 2.9 ml/min per 1.73 m^2 (95% CI: 0.6–5.2; $P = 0.01$) and 2.9 ml/min per 1.73 m^2 (95% CI: 0.6–5.1; $P = 0.01$) per year respectively. The mean between-group difference in total eGFR slope over 3 years using a linear spline model was 2.9 ml/min per 1.73 m^2 per year (95% CI: 0.6–5.2; $P = 0.01$).

Safety

There were 7 SAEs in the methylprednisolone group compared to 3 SAEs in the placebo group (7 vs. 3; HR: 1.97; 95% CI: 0.49–7.90; $P = 0.34$) (Supplementary Tables S1 and S2). The number of participants who reported at least 1 SAE were 6 (5%) in the methylprednisolone group and 3 (2%) in the placebo group (Table 4). Five participants in the methylprednisolone arm (4%) experienced severe infection requiring hospitalization compared to 2 (2%) in the placebo arm. No participants developed *Pneumocystis jirovecii* pneumonia. Two participants (2%) developed new onset diabetes following methylprednisolone therapy. The single death in the methylprednisolone group was related to serious infection. There were no major

Table 1. Baseline characteristics of all participants in the reduced-dose TESTING study

Parameter	Reduced-dose methylprednisolone (*N* = 121)	Placebo (*N* = 120)
Age, mean (SD), yr	36.7 (10.74)	36.6 (10.81)
Sex, *n* (%)		
Female	52 (43.0)	50 (41.7)
Male	69 (57.0)	70 (58.3)
Race, *n* (%)[a]		
Caucasian/European	8 (6.6)	9 (7.5)
Chinese	65 (53.7)	63 (52.5)
South Asian	30 (24.8)	33 (27.5)
South-East Asian	17 (14.0)	13 (10.8)
Japanese	0 (0.0)	1 (0.8)
Other Eastern Asian	1 (0.8)	0 (0.0)
Mixed	0 (0.0)	1 (0.8)
BMI, mean (SD)	25.4 (4.8)	26.1 (5.0)
Smoking history, *n* (%)		
Previous	15 (12.4)	7 (5.8)
Current	9 (7.4)	12 (10.0)
Medical history, *n* (%)		
Hypertension	57 (47.1)	61 (50.8)
Tonsillectomy	1 (0.8)	0 (0.0)
Macrohematuria	15 (12.4)	14 (11.7)
Previous corticosteroids	13 (10.7)	7 (5.8)
Previous other immunosuppressant	9 (7.4)	6 (5.0)
Diabetes mellitus	6 (5.0)	7 (5.8)
Coronary heart disease	2 (1.7)	0 (0.0)
Stroke	1 (0.8)	1 (0.8)
Family history of IgA nephropathy	1 (0.8)	4/120 (3.3)
Baseline eGFR, mean (SD), ml/min per 1.73 m^2	63.4 (22.1)	66.6 (24.9)
Baseline proteinuria, mean (SD), g/24 h	2.38 (1.41)	2.58 (2.09)
Time since renal biopsy, median (IQR), mo	5 (3–18)	6 (4–27)
Histology, no./total no. (%)[b]		
Mesangial hypercellularity (M1)	71/120 (59.2)	73/118 (61.9)
Endocapillary hypercellularity (E1)	29/121 (24.0)	25/120 (20.8)
Segmental glomerulosclerosis (S1)	78/120 (65.0)	75/118 (63.6)
Tubular atrophy/interstitial fibrosis (T)		
T0: 0–25%	72/120 (60.0)	75/118 (63.6)
T1: 26–50%	34/120 (28.3)	35/118 (29.7)
T2: > 50%	14/120 (11.7)	8/118 (6.8)

BMI, body mass index; eGFR, estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula).
[a]Race was self-reported by participants
[b]Histological findings were scored as per the Oxford Classification MEST scoring system.

cardiovascular events, fractures, or gastrointestinal bleed in either group during the study.

Number Needed to Treat

At 2.5 years, the numbers needed to treat to prevent 1 primary composite outcome and to prevent 1 kidney failure event were 6 (95% CI: 4.6–8.9) and 16.7 (95% CI: 10.7–38.0), respectively. The number needed to treat to cause harm in 1 person was 41 (95% CI: −116.1 to 17.4).

DISCUSSION

This prespecified analysis of the TESTING study found that a reduced-dose oral methylprednisolone regimen

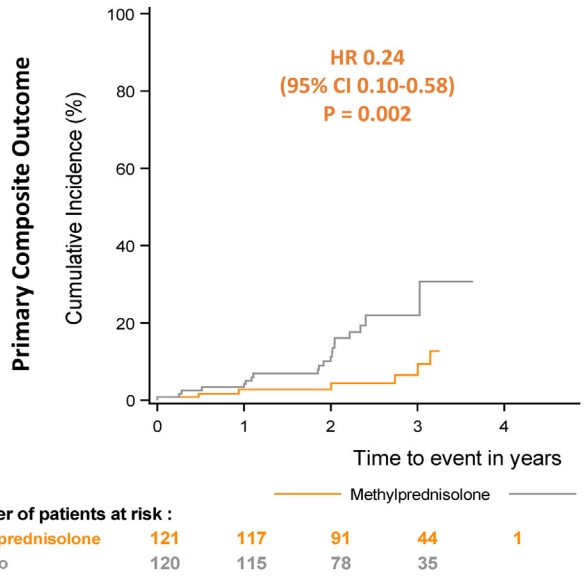

Figure 2. Time from randomization to first primary composite outcome in patients with high-risk IgA nephropathy treated with reduced-dose methylprednisolone. Primary composite outcome (40% reduction in eGFR, kidney failure, or death due to kidney disease) for all randomized participants over a median follow-up period of 2.5 years. Hazard ratios were estimated using a Cox proportional hazards model, adjusted for site, baseline proteinuria, baseline eGFR, and endocapillary hypercellularity score on kidney biopsy. The *P*-value was estimated using a log rank test. Analyses were censored at the date when patients died, were lost to follow-up, or withdrew from the study or at the end of study visit, whichever occurred first. CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

of 0.4 mg/kg/d (maximum 32 mg/d) tapered over 6 to 9 months was associated with a 76% reduction in risk of the primary composite kidney outcome compared to supportive care alone, with consistent relative effects across the all-composite and component outcomes. There was also a greater reduction in proteinuria and a slower rate of eGFR decline from baseline with methylprednisolone compared to placebo at 6 and 12 months. An increased number of SAEs was observed in methylprednisolone treated participants, predominantly related to infection. However, the study was underpowered to detect a significant difference between the 2 arms.

Current international guidelines on corticosteroid use in IgAN are based on moderate quality evidence.[5] The steroid based regimens implemented in previous clinical trials have widely varied with inconsistent results[10-14] leading to a lack of clear guidance about corticosteroid dose and duration in individuals with IgAN at high risk of disease progression. Specifically, there has been no conclusive evidence to support the use of lower corticosteroid doses less than or equivalent to oral prednisolone 30 mg daily.[15] The findings from the reduced-dose TESTING study suggest that the kidney benefits seen with reduced-dose methylprednisolone, equivalent to a

Table 2. Primary and secondary outcomes for the treatment effect of reduced-dose oral methylprednisolone compared to placebo in high-risk IgA nephropathy

Outcome	Reduced-dose methylprednisolone ($N = 121$)		Placebo ($N = 120$)			
	No. events (%)	Annual event rate[a] (95% CI) %	No. events (%)	Annual event rate[a] (95% CI) %	Hazard ratio (95% CI)	*P*-value
Primary composite outcome	7 (5.8)	2.2 (1.1–4.6)	22 (18.3)	7.1 (4.6–10.9)	0.24 (0.10–0.58)	0.002
30% eGFR reduction, kidney failure or all-cause death	11 (9.1)	3.5 (2.0–6.4)	25 (20.8)	8.4 (5.6–12.7)	0.33 (0.15–0.70)	0.004
40% eGFR reduction, kidney failure or all-cause death	8 (6.6)	2.5 (1.3–5.1)	22 (18.3)	7.1 (4.6–10.9)	0.27 (0.11–0.61)	0.003
50% eGFR reduction, kidney failure or all cause death	7 (5.8)	2.2 (1.0–4.6)	17 (14.2)	5.2 (3.1–8.6)	0.30 (0.11–0.77)	0.013
Kidney failure	3 (2.5)	0.9 (0.3–2.9)	10 (8.3)	2.7 (1.3–5.3)	0.26 (0.07–1.03)	0.056
Death due to any cause[b]	1 (0.8)	0.3 (0.0–2.2)	0 (0)	0.0 (0.0–0.0)	N/A	N/A
30% eGFR reduction	9 (7.4)	2.9 (1.5–5.5)	22 (18.3)	8.1 (5.3–12.3)	0.29 (0.13–0.66)	0.003
40% eGFR reduction	6 (5)	1.9 (0.9–4.2)	19 (15.8)	6.7 (4.3–10.5)	0.22 (0.08–0.56)	0.002
50% eGFR reduction	5 (4.1)	1.6 (0.7–3.8)	12 (10)	4.2 (2.4–7.3)	0.30 (0.10–0.88)	0.029

CI, confidence interval; eGFR, estimated glomerular filtration rate.
[a]Annual event rate reported per 100-person years.
[b]Too few events to derive hazard ratio, confidence intervals and *P*-value. No reported deaths due to kidney failure.
Hazard ratios were estimated using a Cox proportional hazard frailty model and annual event rates were estimated using a Poisson model. All analyses were adjusted for baseline proteinuria, baseline eGFR, and endocapillary hypercellularity score on biopsy as fixed covariates and site as a random effect.

maximum oral prednisolone dose of 40 mg daily, are consistent with the benefits of full-dose therapy, despite a shorter follow-up period for the reduced-dose cohort.[6,7] In addition, 47% of participants in the reduced-dose cohort were from outside of China compared to 5% in the full-dose cohort. The results from this multiethnic cohort increase the generalizability of this study and further reiterates the role of corticosteroid therapy in high risk IgAN (Figure 3). Additional differences in baseline characteristics included a higher

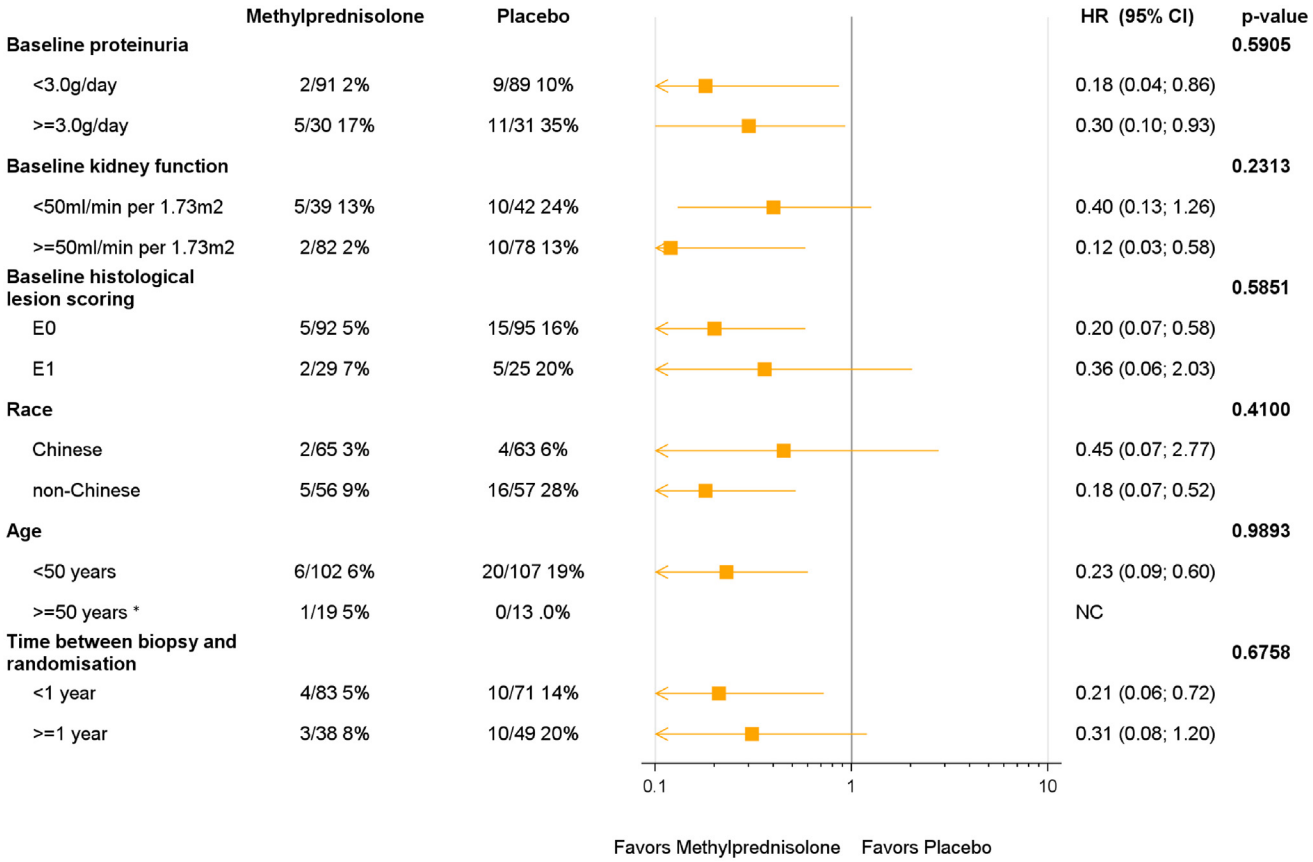

Figure 3. Subgroup analysis of the primary outcome in the study of reduced-dose methylprednisolone in high-risk IgA nephropathy. Hazard ratios and confidence intervals were estimated using a Cox proportional hazards model adjusted for site, baseline proteinuria, baseline eGFR, and endocapillary hypercellularity score on kidney biopsy. Interaction *P*-values between the trial group and subgroup variable showed no heterogeneity across all subgroups. Inadequate events to derive estimates of effect and confidence intervals. eGFR, estimated glomerular filtration rate.

Table 3. Effect of reduced-dose methylprednisolone compared to placebo on proteinuria and eGFR in high-risk IgA nephropathy

Outcome	Reduced-dose methylprednisolone	Placebo	Mean difference (95% CI)	*P*-value
Proteinuria (g/d)				
Baseline (SD)	2.38 (1.41)	2.58 (2.09)		
Change from baseline				
At 6 mo	−1.15	−0.03	−1.14 (−1.80 to 0.48)	0.002
At 12 mo	−1.01	0.10	−1.15 (−1.68 to −0.62)	<0.001
Time averaged	1.58	2.41	−0.83 (−1.25 to −0.40)	<0.001
eGFR (ml/min per 1.73 m^2)				
Baseline (SD)	63.4 (22.1)	66.6 (24.9)		
Change from baseline				
At 6 mo	4.7	−3.2	7.6 (3.8–11.4)	<0.001
At 12 mo	5.0	−3.0	7.9 (4.3–11.5)	<0.001
Annual decline (ml/min per 1.73 m^2/yr)				
Overall	−0.7	−3.0	2.3 (−0.03 to 4.6)	0.054
Excluding values from mo 1 and 3[a]	−0.6	−2.2	2.9 (0.6–5.2)	0.01
Excluding values from mo 1, 3 and 6[a]	−0.2	−1.8	2.9 (0.6–5.1)	0.01

CI, confidence interval; eGFR, estimated glomerular filtration rate.
[a]Sensitivity analyses conducted for annual rate of eGFR decline by excluding eGFR values during high exposure treatment.
Changes in proteinuria and eGFR from baseline were analyzed using a linear mixed model with the baseline measurement, treatment group and stratification variables as fixed effects. Individual time-averaged proteinuria was calculated as a weighted-average of all available proteinuria measurements for each participant. Rate of eGFR decline (ml/min per 1.73 m^2 per year) was calculated from the slope of a linear regression model of all eGFR over time. All results are expressed as mean values unless otherwise specified.

mean eGFR, longer duration from kidney biopsy, and less tubular atrophy and fibrosis on histology in the reduced-dose cohort, with subgroup analyses showing no significant heterogeneity in treatment effect based on eGFR or duration from biopsy.

The well-known side effect profile of systemic corticosteroids has frequently resulted in reluctance to treat by both clinicians and patients. SAEs, predominantly infection-related hospitalization and complications, were significantly higher with methylprednisolone compared to placebo in the full-dose TESTING study, resulting in a temporary halt in recruitment.[7] This analysis suggests that a lower cumulative dose of methylprednisolone and adding

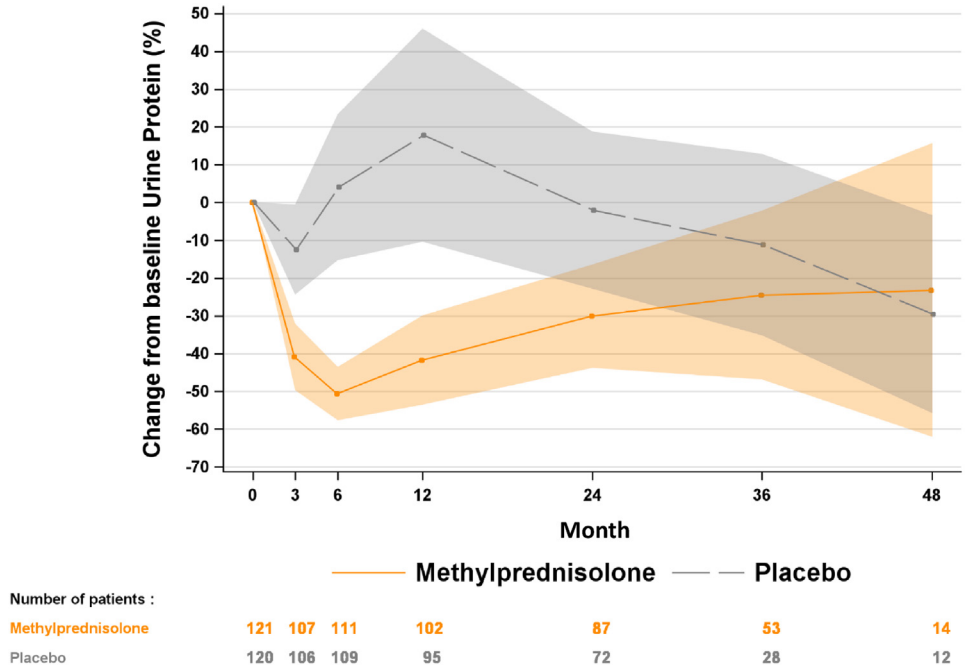

Figure 4. Effect of reduced-dose methylprednisolone in high-risk IgA nephropathy on proteinuria from baseline over time. Mean relative change from baseline 24-hour urinary protein excretion over time as a percentage with 95% confidence intervals analyzed using a linear mixed model with the baseline measurement, treatment group, and stratification variables as per the analysis of the primary composite outcome. All analyses were conducted with untransformed proteinuria values. The mean absolute change from baseline proteinuria in g/24 h over time is shown in Supplementary Figure 1A. The overall mean 24-hour proteinuria values plotted over time for each treatment arm are shown in Supplementary Figure 1B.

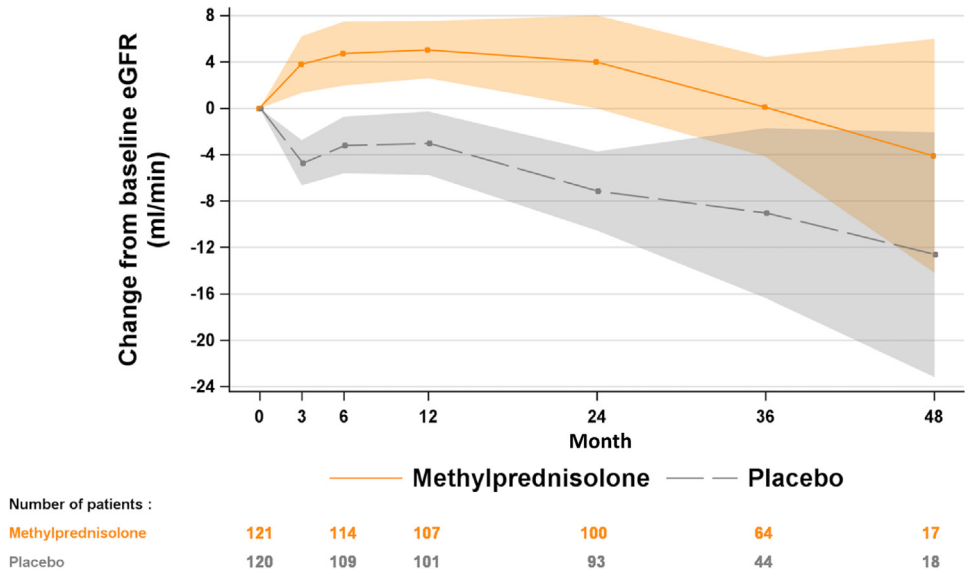

Figure 5. Effect of reduced-dose methylprednisolone in high-risk IgA nephropathy on eGFR from baseline over time. Mean absolute change from baseline eGFR over time in ml/min per 1.73 m^2 with 95% confidence intervals analyzed using a linear mixed model with the baseline measurement, treatment group, and stratification variables as per the analysis of the primary composite outcome. The mean relative change from baseline eGFR as a percentage over time is shown in Supplementary Figure 2A. The overall mean eGFR values plotted over time for each treatment arm are shown in Supplementary Figure 2B. eGFR, estimated glomerular filtration rate.

Pneumocystis jirovecii pneumonia prophylaxis can safely mitigate much of the excess risk of infection–related adverse events with a lower absolute risk of SAEs compared to a full-dose regimen. Despite this, the total number of SAEs reported with reduced-dose methylprednisolone was higher than the number reported with placebo and included 1 death. The impact of nonserious steroid-related side effects such as weight gain, mood disturbance, and skin changes on patient-perceived tolerability is more challenging to quantify and was not reported in this study; however it should be regarded as an important aspect in the treatment decision making process.[16] The potential risks should continue to be considered and discussed with patients; and there is still a need for safer, better tolerated, and preferably more targeted, immunosuppressive therapeutic agents in the management of IgAN. Several clinical trials studying the effects of steroid-sparing immunomodulatory agents with various targets such as the complement system, A proliferation inducing ligand, and B cell activating factor have been published. Recently, the ENVISION study reported that 12 months of treatment with sibeprenlimab, a monoclonal antibody that binds to and neutralizes A proliferation inducing ligand, reduced proteinuria in IgAN compared to placebo, with no difference in the risk of adverse events, including infection.[17] In another phase 2 trial, telitacicept, a dual B-lymphocyte stimulator/A proliferation inducing ligand inhibitor, was shown to reduce proteinuria in patients with IgAN at 24 weeks of treatment, with a similar safety profile compared to placebo.[18] Longer phase 3 trials are currently underway.[19]

Table 4. Serious adverse events with reduced-dose methylprednisolone or placebo in patients with high-risk IgA nephropathy

Serious adverse events (SAEs)	Reduced-dose methylprednisolone (N = 121)	Placebo (N = 120)	P-value
Total number of SAEs	7	3	
Patients with at least 1 SAE, *n* (%)	6 (5.0%)	3 (2.5%)	0.50
Resulted in death[a]	1 (0.8%)	0 (0.0%)	1.00
Hospitalization/prolongation of hospitalization	6 (5.0%)	3 (2.5%)	0.50
Special interest per protocol, *n* (%)			
Severe infection requiring hospitalization	5 (4.1%)	2 (1.7%)	0.45
Gastrointestinal bleed	0 (0.0%)	0 (0.0%)	
New onset diabetes mellitus	2 (1.7%)	0 (0.0%)	0.50
Fracture or osteonecrosis	0 (0.0%)	0 (0.0%)	
Major cardiovascular events	0 (0.0%)	0 (0.0%)	

SAE, serious adverse event.
[a]One death due to infection in the reduced-dose methylprednisolone arm.

Proteinuria reduction at 9 months has been identified as a reliable surrogate end point to predict a treatment's effect on progression to kidney failure in IgAN.[20] This has been a transformative advancement in clinical trials for IgAN because sample sizes can be reduced due to the continuous end points, and the time-to-event for traditional end points, such as the composite primary outcome in the TESTING study, is often long, requiring protracted study durations before confirming the efficacy of a drug. There was a 45.8% reduction in proteinuria from baseline with reduced-

dose methylprednisolone at 12 months, with the treatment effects becoming less pronounced by 24 months and a convergence in the methylprednisolone and placebo arms by 48 months. Potential reasons to account for the demonstrated loss of proteinuria-lowering effects over time include the median follow-up period of 2.5 years, resulting in a relatively small number of participants included beyond 36 months, the underlying mechanism of action of methylprednisolone, and the short-term course of treatment. It could be postulated that suppressing the active inflammatory process early in the disease course improves kidney outcomes, although it remains uncertain whether these effects are temporary and highlights the need for further effective agents in the long-term. Despite this, the reduced-dose TESTING study demonstrated a clear reduction in hard kidney end points, including kidney failure on follow-up and reflects the correlation between an early reduction in proteinuria with long-term kidney benefits in IgAN.[21] At present, there are no data to support the efficacy of repeated courses of corticosteroids; and the long-term metabolic, cardiovascular, and infective side effects are likely to offset any benefits. Targeted release formulation budesonide, which localizes drug release to the distal ileum is anticipated to have a superior safety profile than systemic corticosteroids.[22] Based on the primary end point of a reduction in proteinuria at 9 months of treatment compared to placebo in the NefIgArd trial,[23] targeted release formulation budesonide received accelerated US Food and Drug Administration approval for use in IgAN. The full 2-year study findings have since shown that it also reduces the rate of eGFR decline compared to placebo by 2.95 ml/min per 1.73 m^2 per year, which is comparable to the benefits seen with reduced-dose methylprednisolone.[24] The NefIgArd study was not powered for hard kidney end points and as such, it is not known whether these results will translate into fewer kidney events such as kidney failure and maintain favorable safety outcomes on longer term follow-up.

Nonimmunosuppressive agents with hemodynamic benefits have also been shown to be effective in improving kidney outcomes in IgAN. A prespecified analysis of the Dapagliflozin And Prevention of Adverse Outcomes Chronic Kidney Disease study found that dapagliflozin, a sodium glucose cotransporter 2 inhibitor, reduced the risk of disease progression in IgAN compared to placebo with a favorable safety profile.[25] There were no participants receiving sodium glucose cotransporter 2 inhibitors during the TESTING trial because the study was conducted before the era of these now widely prescribed agents. Recently, the PROTECT study reported 24-month data showing significant reduction in proteinuria with sparsentan, a dual endothelin angiotensin receptor antagonist, compared to placebo and that it was well-tolerated, with favorable signals in eGFR slope.[26] However, the effect on eGFR slope was modest compared to the larger reduction in proteinuria, emphasizing the need for confirmatory data on eGFR outcomes. This was a strength of the TESTING study which was powered for eGFR and hard kidney outcomes. The role and effects of such non-immunosuppressive agents versus corticosteroids in IgAN remain unclear, with no head-to-head comparison or combination studies completed to date.

The Dapagliflozin And Prevention of Adverse Outcomes Chronic Kidney Disease and PROTECT studies included fewer participants from Asian backgrounds, with lower baseline eGFR and proteinuria compared to the reduced-dose TESTING cohort. Regional and racial variations have been linked to kidney progression and outcomes in IgAN, with those of Pacific Asian background being at risk of faster eGFR decline.[27] Certain therapies found to be exclusively beneficial in specific population groups have been outlined in international guidelines, including tonsillectomy for Japanese patients and mycophenolate mofetil in Chinese patients,[5] but the impact of race on corticosteroid response remains uncertain. Given that the underlying pathophysiology of IgAN involves an immune-mediated component, it could be postulated that those with an aggressive disease process and active histological lesions may demonstrate a greater response to immunosuppression. However, this has not been confirmed.

There are limitations to this study. First, there was a modest number of kidney failure events and SAEs in this cohort, leading to low power in detecting differences between the intervention arms. Second, the follow-up period at a median of 2.5 years was relatively short for the reduced-dose cohort compared to the 6.1 years for the full-dose cohort. This was by design because the reduced-dose protocol was implemented after an interim analysis of the TESTING study. Longer term follow-up in the posttrial observational TESTING-ON study is currently underway to determine whether these kidney benefits are sustained over time. Third, although the proportion of Chinese versus non-Chinese participants was comparable, the majority were still of Asian origin, who are demonstrated to exhibit more aggressive disease and a less favorable prognosis compared to their Caucasian counterparts. Subgroup analysis found no differential effect in Chinese compared to non-Chinese participants; however, the effect among other ethnicities was not able to be reliably tested, with only a small number of Caucasian participants. Finally, the TESTING study was not

powered to compare the full-dose and reduced-dose cohorts; thus, though numerically there were more SAEs and primary outcome events with the former cohort, this analysis alone cannot determine whether the latter was superior.

The recent advances in therapeutic agents potentially herald a new era for IgAN management. However, novel agents are expensive and inaccessible for many populations, particularly those from low middle-income countries. On the other hand, corticosteroids are included in the World Health Organization model list of essential medicines (2021) and are universally accessible and affordable.[28] Criticisms for the use of corticosteroids in IgAN include treatment-related side effects and their perceived loss of proteinuria-lowering benefits over time, yet the short study period of 2 years or less across most novel agents must also be considered. For a condition that places a significant burden of disease worldwide, including in low middle income countries, an effective, inexpensive, and readily available treatment option with an acceptable safety profile is paramount, highlighting the global importance of this analysis, and its immediate applicability.

In conclusion, the reduced-dose TESTING study demonstrates that a 6 to 9 month reduced-dose methylprednisolone regimen is associated with improved kidney outcomes and a delay in the progression toward kidney failure for individuals with high risk IgAN already established on maximal supportive care. However, some increased risk of SAEs likely remains, albeit at a lower rate than with the full-dose regimen.

APPENDIX

List of Collaborative Group Authors from the TESTING Trial Steering Committee

Adeera Levin, Daniel Cattran, David W Johnson, David Wheeler, Jürgen Floege, Mark Woodward, Meg Jardine, Ming-hui Zhao, Rajiv Agarwal, Richard Glassock, Tak Mao Chan, Yangfeng Wu, and Zhihong Liu.

DISCLOSURE

DK is a recipient of the Royal Australasian College of Physicians Jacquot Research Entry Scholarship. JL reported receiving grants from the China National Funds for Distinguished Young Scientists and the National Key Research and Development Program of China during the conduct of the study; and personal fees from Chinook Therapeutics and KBP Bioscience outside the submitted work. MH reported receiving grants from the Canadian Institute for Health Research; study drugs from Pfizer during the conduct of the study; and grants from Calliditas for a study in IgA, from Ionis for a study in IgA, from Pfizer for a study in focal segmental glomerulosclerosis, and from Roche for a study in preeclampsia outside the submitted work; and being the medical lead for glomerulonephritis for the Ontario Renal Network. VJ has received grant funding from GSK, Baxter Healthcare, and Biocon; and honoraria from Bayer, AstraZeneca, Novartis, Vera, Chinook, Otsuka, Omeros, Boehringer Ingelheim, NephroPlus, and Zydus Cadilla, under the policy of all honoraria being paid to the organization. HR reported receiving grants from Kidney Foundation of Canada and the Canadian Institutes of Health Research and is the director of the Glomerulonephritis Fellowship funded by the Louise Fast Foundation. She has received fees for Steering Committee roles, consulting, scientific presentations, and/or advisory board attendance from Calliditas, Omeros, Alnylam, Chinook (Novartis), Otsuka, Pfizer, Eledon, and Travere outside the submitted work. SB reported receiving investigator-initiated grants from Novartis and Alexion. He has received fees for steering committee roles, consulting, scientific presentations, and/or advisory board attendance from Roche, Vera, BioCryst, BeiGene, Novartis, MorphoSys, Pfizer, HIBio, Travere, and Eledon. HZ reported receiving personal fees related to steering committee roles from Novartis, Omeros, Calliditas, Chinook, and Otsuka; and grants and funding from Pfizer during the conduct of the study. VP is employed by UNSW Sydney and serves as a Board Director for St. Vincent's Health Australia, and several Medical Research Institutes. He has received honoraria for steering committee roles, scientific presentations, and/or advisory board attendance from Abbvie, Amgen, Astra Zeneca, Bayer, Baxter, Boehringer Ingelheim, Chinook, Durect, Eli Lilly, Gilead, GSK, Janssen, Merck, Mitsubishi Tanabe, Mundipharma, Novartis, Novo Nordisk, Otsuka, Pharmalink, Pfizer, Reata, Travere, Relypsa, Roche, Sanofi, Servier, and Tricida. MGW has received fees for advisory boards, steering committee roles, or scientific presentations from Travere, Baxter, Amgen, Abbvie, Chinook, Dimerix, Ostuka, GlaxoSmithKline, and CSL-Behring. All the authors declared no competing interests.

ACKNOWLEDGEMENTS

The TESTING trial was funded by the Australian National Health and Medical Research Council, National High Level Hospital Clinical Research Funding High Quality Clinical Research Project of Peking University First Hospital (2022CR81), Chinese Academy of Medical Sciences Innovation Fund for Medical Science (2019-I2M-5-046), China National Funds for Distinguished Young Scientists (81925006), National Key Research and Development Program of China (2018YFC1314004), and the Canadian Institutes for Health Research (MOP126078) and had study drug and initial funding ($75,000) provided by Pfizer. TESTING is an investigator-initiated trial funded by Peking University First Hospital, China for all China sites; CIHR

grant MOP126078 for sites in Canada, and NHRMC Project grant APP1042474 for central coordination and the remaining sites in the other participating countries. The authors acknowledge the TESTING trial steering committee and all participants, investigators, sites staff and operation staff who have contributed to the TESTING study.

DATA AVAILABILITY STATEMENT

Data access can be requested from Vlado Perkovic via the email: vlado.perkovic@unsw.edu.au. Once the data access is granted, data can be accessed via a secured environment hosted by the George Institute for Global Health, Australia. Reprint of the Statistical analysis plan can be accessed via https://osf.io/d7qrw/.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

CONSORT Checklist.

Figure S1. Effect of reduced-dose methylprednisolone in high risk IgA nephropathy on proteinuria over time.

Figure S2. Effect of reduced-dose methylprednisolone in high risk IgA nephropathy on eGFR over time.

Table S1. Comparison of safety data between reduced-dose methylprednisolone, full-dose methylprednisolone, and targeted-release formulation budesonide in patients with high risk IgA nephropathy.

Table S2. List of all serious adverse events reported in the reduced-dose methylprednisolone and placebo arms.

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