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Randomized Phase 2 Trial of Telitacicept in Patients With IgA Nephropathy With Persistent Proteinuria

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Introduction: To date, no specific therapies have been approved for immunoglobulin A nephropathy (IgAN) treatment. Telitacicept is a fusion protein composed of transmembrane activator and calcium-modulating cyclophilin ligand interactor and fragment crystallizable portion of immunoglobulin G (IgG), which neutralizes the B lymphocyte stimulator and a proliferation-inducing ligand.

Methods: This phase 2 randomized placebo-controlled trial aimed to evaluate the efficacy and safety of telitacicept in patients with IgAN. Participants with an estimated glomerular filtration rate (eGFR) >35 ml/min per 1.73 m^2 and proteinuria ≥0.75 g/d despite optimal supportive therapy, were randomized 1:1:1 to receive subcutaneous telitacicept 160 mg, telitacicept 240 mg, or placebo weekly for 24 weeks. The primary end point was the change in 24-hour proteinuria at week 24 from baseline.

Results: Forty-four participants were randomized into placebo ($n = 14$), telitacicept 160 mg ($n = 16$), and telitacicept 240 mg ($n = 14$) groups. Continuous reductions in serum IgA, IgG, and IgM levels were observed in the telitacicept group. Telitacicept 240 mg therapy reduced mean proteinuria by 49% from baseline (change in proteinuria vs. placebo, 0.88; 95% confidence interval, −1.57 to −0.20; $P = 0.013$), whereas telitacicept 160 mg reduced it by 25% (−0.29; 95% confidence interval, −0.95 to 0.37; $P = 0.389$). The eGFR remained stable over time. Adverse events (AEs) were similar in all groups. Treatment-emergent AEs were mild or moderate, and no severe AEs were reported.

Conclusion: Telitacicept treatment led to a clinically meaningful reduction in proteinuria in patients with IgAN in the present phase 2 clinical trial. This effect is indicative of a reduced risk for future kidney disease progression.

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IgAN is the most common form of primary glomerulonephritis worldwide. Persistent proteinuria, hypertension, impaired kidney function, and pathologic lesions are its strongest risk factors.[1] Supportive therapy, including blood pressure management, maximally

tolerated dose of renin-angiotensin-system inhibitors, lifestyle modification, and steroid administration to patients from high-risk populations, remain the main therapies. Despite treatment, up to 40% of affected individuals develop end-stage kidney disease. IgAN is among the most common causes of end-stage kidney disease in young adults, particularly those from the Asian and Pacific regions.[1–3]

IgAN is characterized by the deposition of IgA1 (in particular, galactose-deficient IgA1 [Gd-IgA1]) in the mesangial area of the glomeruli. In the circulation of most patients with IgAN, Gd-IgA1 and its corresponding IgG and/or IgA autoantibody levels increase with an increased risk of disease progression.[4,5] Although the exact pathogenesis of IgAN remains unclear, targeting Gd-IgA1 production and its autoantibodies seems to be a promising therapy for IgAN.[6–8] However, in a recent trial, B-cell-depleting therapy with rituximab failed to reduce proteinuria in IgAN, and serum levels of Gd-IgA1 and its antibodies did not decrease.[9] IgA production can be induced by T cell-dependent or T cell-independent pathways in the mucosa-associated lymphoid tissue and gut-associated lymphoid tissue.[10–12] T cell-dependent IgA production mainly occurs in lymphoid follicles of Peyer's patches.[13,14] In contrast, T cell-independent IgA class switching of B cells can occur in the lamina propria and is induced by various cytokines, primarily tumor necrosis factor ligand superfamily member 13 (APRIL), a proliferation-inducing ligand, and B cell activating factor (BAFF); also known as tumor necrosis factor superfamily member 13B.[15–17] Moreover, BAFF and APRIL reportedly promote the proliferation of human mesangial cells.[18] A humanized IgG2 monoclonal antibody that inhibits APRIL is being developed as a potential new treatment for IgAN.[19,20]

Telitacicept is a soluble fusion protein composed of transmembrane activator and calcium-modulating cyclophilin ligand interactor and fragment crystallizable domain of human IgG. A similar agent, atacicept, showed reduced proteinuria in IgAN.[21] Telitacicept is anticipated to interfere with abnormal B cell and plasma cell activation by antagonizing the interaction between BLyS or APRIL and their respective receptors on the surface of the B lymphocytes. On the basis of previous efficacy and safety data, telitacicept was approved in China for the treatment of patients with active systemic lupus erythematosus.[22–26] A phase 2 clinical trial was designed to assess the efficacy and safety of telitacicept for treating patients with primary IgAN.

METHODS

Trial Design

A phase 2 randomized double-blind placebo-controlled trial was conducted to compare telitacicept with placebo in terms of efficacy and safety in patients with IgAN who were already receiving supportive therapy, including optimal blood pressure control and full renin-angiotensin-system blockade. The study was performed at 21 sites in China from April 13, 2020, to May 20, 2021. The ethics committee of each participating center approved the protocol. This study was registered at clinicaltrials.gov (NCT04291781). Informed consent was obtained before all study procedures, and the study adhered to the Declaration of Helsinki. An independent data monitoring committee (DSMB) provided oversight.

Study Participants

The key inclusion criteria for this trial were as follows: biopsy-confirmed primary IgAN; 24-hour proteinuria excretion $\geq$0.75 g/d; and eGFR (calculated using the Chronic Kidney Disease Epidemiology Collaboration formula) $>$35 ml/min per 1.73 m^2. The exclusion criteria included a strong indication or contraindication for corticosteroid therapy based on the treating physician's judgment or the use of systemic immunosuppressive therapy in the previous 3 months. The inclusion and exclusion criteria are detailed in Supplementary Methods.

No significant change was made to the method after trial commencement, except for the rectified inclusion criteria because of slow enrollment. Key rectifications included changed proteinuria criteria from no less than 1.0 g/d to no less than 0.75 g/d, and decreased eGFR criteria from more than 45 ml/min per 1.73 m^2 to more than 35 ml/min per 1.73 m^2 (refer to Supplementary Methods).

Randomization and Study Procedures

Potentially eligible participants who had already received supportive therapy for at least 8 weeks entered a run-in period of 4 weeks, during which background therapy was optimized, including blood pressure control and maximal renin-angiotensin-system inhibitor therapy, to ensure a minimum of 3 months before randomization. Randomization was performed using a minimization algorithm, which was centrally generated and used by all centers. Eligible patients were centrally randomized 1:1:1 to the subcutaneous telitacicept 160 mg, 240 mg, and placebo groups stratified by proteinuria ($<$3 g/d or $\geq$3 g/d).

Patients were administered a placebo or telitacicept in different groups per week and assessed every 4

weeks during the 24-week treatment phase. By the end of the treatment phase, safety data were collected until 28 days after the last administration of the placebo or telitacicept. All study personnel and participants were blinded during the trial.

End Points

The primary end point was the mean change in 24-hour proteinuria from baseline over a 24-week medication period. We set multiple secondary end points, including changes in 24-hour proteinuria, eGFR, as well as IgA, IgG, and IgM levels. All indicators were determined once every 4 weeks during the treatment period.

The safety end point was the incidence of AEs. All AEs were reported and coded in a MedDRA (version 24.0) manner, from the signature of informed consent to the end of the 28-day follow-up after the last administration of placebo or telitacicept. No change in trial outcomes was observed after the trial commenced.

Statistical Analysis

An analysis of the full analysis set was reported. The primary end point, the mean change in 24-hour urinary protein from baseline, was analyzed over the 24-week treatment phase using analysis of covariance. The baseline 24-hour urinary protein level was the covariate. All analyses were conducted by analyzing all patients according to the group to which they were randomized, regardless of treatment adherence or protocol violations. Missing data were imputed using the last observation carried forward method. Analysis of variance and chi-squared tests were used to analyze other indicators. No formal sample size calculations were performed. We aimed to recruit 30 participants, and 14 eligible patients finished the run-in phase when reaching this target; finally, 44 were randomized. No interim analyses were performed. All analyses were performed using the SAS software, version 9.4(SAS Institute Inc., Cary, NC). Statistical analyses and randomization were performed using BioGuider Medical Technology Co., Ltd. Shanghai, China.

RESULTS

Enrollment and Follow-Up

Between April 2020 and October 2020, 66 eligible patients were screened, and 44 were randomized to the telitacicept 160 mg ($N = 16$), telitacicept 240 mg ($N = 14$), and placebo groups ($N = 14$) (Figure 1).

The baseline characteristics of the participants were similar across the randomized groups (Table 1). The mean age of the participants was 37 years, 48% were women, the mean body mass index was 25.7 kg/m^2, the mean baseline eGFR was 79.38 ml/min per 1.73 m^2, and the mean baseline 24-hour urinary protein level was 1.86 g/d. Four patients had diabetes, but no histologic findings of diabetic nephropathy were observed when they underwent renal biopsy.

Among the randomized participants, 42 (95.45%) completed the full treatment course. Two patients in the placebo group discontinued treatment prematurely because of local outbreaks of COVID-19, although none suffered from SARS-CoV-2.

Efficacy on Primary Outcomes

As shown in Figure 2a and b and Supplementary Table S1, at the end of the 24-week treatment, the 24-hour proteinuria of patients in the telitacicept 240 mg/week group decreased by 0.889 g/d (49%) from baseline (LS means difference [240 mg/wk vs. placebo] = −0.88; 95% confidence interval −1.57 to −0.20; $P = 0.013$), and a reduction of 0.316 g/d (25%) was observed in the 160 mg group (−0.29, 95% confidence interval: −0.95 to 0.37; $P = 0.389$). Excluding 4 patients with diabetes did not change the results.

Secondary Outcomes

eGFR remained stable in the telitacicept group during the treatment phase. The mean change in eGFR over 24 weeks is shown in Figure 3a and b and Supplementary Table S2. At week 24, the mean eGFR of patients in the telitacicept 240 mg group and 160 mg group increased by 2.34 and 4.32 ml/min per 1.73 m^2 compared with a decrease of 5.70 ml/min per 1.73 m^2 in the placebo group (P-values for the 240 mg or 160 mg vs. placebo groups = 0.015 and 0.002, respectively).

After 24 weeks of treatment, telitacicept in the 160 mg and 240 mg groups significantly decreased the serum levels of immunoglobulins, including IgA, IgG, and IgM, compared with those in the placebo group (Figure 4, Supplementary Figure S1). At week 24, the mean change in IgA level was −1.48 g/l (−45.75%) in the telitacicept 160 mg group and −1.60 g/l (−46.65%) in the telitacicept 240 mg group; the mean change in IgG level was −3.00 g/l (−26.16%) in the telitacicept 160 mg group and −2.56 g/l (−24.55%) in the telitacicept 240 mg group; the mean change in IgM level was −0.76 g/l (−64.28%) in the telitacicept 160 mg group and −0.62 g/l (−65.34%) in the telitacicept 240 mg group. The time courses of the blood pressure levels were similar among the 3 groups (Supplementary Figure S2).

Safety Outcomes

During treatment, no participants died, no events of kidney failure requiring kidney replacement therapy occurred, and no participants progressed to end-stage

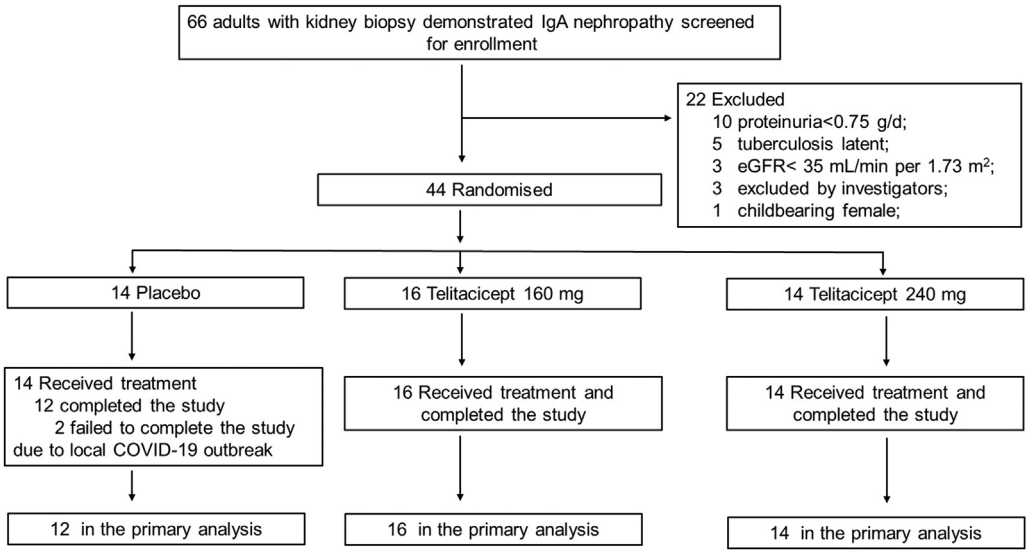

Figure 1. Participant enrollment, randomization, and follow-up. eGFR, estimated glomerular filtration rate.

renal disease. Three serious AEs (10%) were reported in the 2 telitacicept groups (2 in the high dose and 1 in the low dose group) versus 1 (7.1%) in the placebo group ($P = 0.718$) (Table 2). Among these events in the telitacicept groups, 2 (hospitalization for gastric polyps and epididymal cyst) were thought not to be related to study drug whereas 1 (severe injection site reaction) were thought by the investigators to be related to telitacicept treatment. Overall, the safety profile of telitacicept was similar to that of the placebo (Table 2). Injection site reactions were much more common in the telitacicept groups (19/30 [63.3%]) than in the placebo group (0/16 [0%]). None of the participants was treated with a reduced dose of telitacicept for low levels of plasma IgM. Anti-telitacicept antibodies were detected in 17 patients (56.7%) in the telitacicept groups in the 12th week and 20 patients (66.7%) in the 24th week.

DISCUSSION

In this double-blind clinical trial, we demonstrated for the first time that a 6-month course of supportive therapy with telitacicept significantly reduced proteinuria in patients with IgAN. This reduction was accompanied by a stable eGFR compared with a

Table 1. Baseline characteristics of participants

Characteristics	Placebo (n = 14)	Telitacicept 160 mg (n = 16)	Telitacicept 240 mg (n = 14)	All (n = 44)
Age, mean (SD), yr	38.3 (6.91)	35.9 (9.88)	36.8 (8.83)	37.0 (8.55)
Female sex, n (%)	4 (28.6)	8 (50.0)	9 (64.3)	21 (47.7)
Weight, mean (SD), kg	78.19 (16.56)	72.30 (18.19)	67.89 (15.78)	72.77 (17.06)
BMI, mean (SD) kg/m^2	26.29 (4.65)	25.98 (4.27)	24.93 (4.00)	25.74 (4.25)
Hypertension history, n (%)	6 (42.9)	7 (43.8)	8(57.1)	21 (47.7)
Blood pressure, mean (SD), mmHg				
Systolic	117.7 (11.78)	117.1 (12.83)	117.1 (10.03)	117.3 (11.39)
Diastolic	77.3 (10.19)	78.7 (8.41)	77.1 (7.67)	77.7 (8.62)
Past systemic corticosteroid therapy, n (%)	2 (14.3%)	4 (25.0%)	0 (0)	6 (13.6%)
Past other immunosuppressant therapy, n (%)	2(14.3)	4 (25.0)	5 (35.7)	11 (25.0%)
Diabetes mellitus	1 (7.1%)	1 (6.3%)	2 (14.3%)	4 (9.1%)
WBC, mean (SD), 10^9/l	6.24 (1.45)	6.77 (1.20)	6.17 (1.69)	-
Lymphocyte, mean (SD), 10^9/l	1.73 (0.42)	2.31 (0.58)	1.67 (0.49)	-
Time from diagnosis to start of treatment, median (IQR), days	1081.5 (873–2036)	1661.5(988–2818)	1618.5 (390–2203)	1563.5 (808–2238)
Urine protein, median (IQR), g/d	1.86 (1.57–2.36)	1.63 (1.29–2.41)	1.34 (1.14–2.01)	1.66 (1.22–2.28)
Number of patients with urine protein at baseline > 3 g/d, n (%)	1 (7.1%)	3 (18.8)	2 (14.3)	6 (13.6)
eGFR, median (IQR),				
ml/min /1.73 m^2	91.20 (67.73–108.83)	71.67 (58.83–93.42)	70.17 (57.43–94.94)	75.01 (59.09–94.94)
IgA, median (IQR), g/l	3.02 (2.26–3.83)	2.94 (2.80–3.62)	3.61 (2.01–4.14)	3.02 (2.39–3.88)
IgG, median (IQR), g/l	9.33 (8.30–11.14)	11.14 (10.04–12.60)	10.65 (8.65–12.51)	10.75 (9.06–12.00)
IgM, median (IQR), g/l	0.91 (0.63–1.07)	1.06 (0.8–1.35)	0.77 (0.67–0.94)	0.89 (0.68–1.22)

BMI, body mass index; eGFR, estimated glomerular filtration rate; IQR interquartile range; SD, standard deviation; WBC, white blood cell.

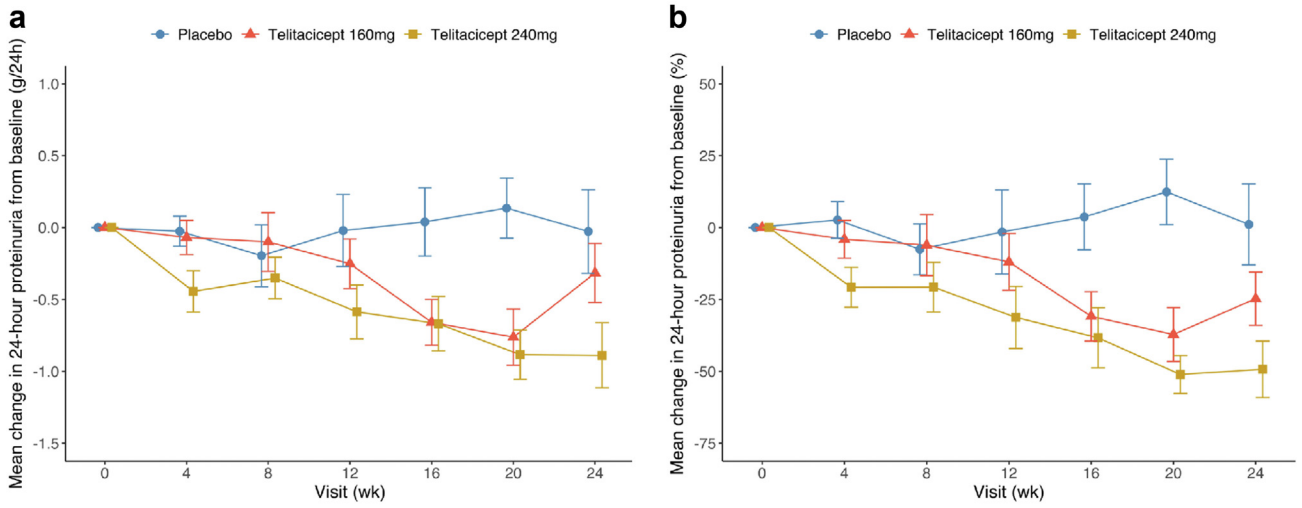

Figure 2. Mean changes in proteinuria from baseline. Data are expressed as mean values (bars indicate the standard error of the mean). (a) Absolute mean changes in 24-hour proteinuria from baseline in patients receiving placebo or telitacicept (160 mg/week or 240 mg/week) at each visit. (b) Mean change (%) in 24-hour proteinuria from baseline in patients receiving placebo or telitacicept (160 mg/week or 240 mg/week) at each visit.

sustained decrease in eGFR in the placebo group. Although more patients reported a high frequency of injection site reactions, there was no increase in the risk of serious AEs, including infections, in patients treated with telitacicept.

Although IgAN was described more than 50 years ago, there is still an ongoing need for effective and safe therapy.[27] The central pathogenic feature of IgAN is the formation of circulating IgA-containing immune complexes, mainly poorly galactosylated IgA1, which has the propensity to deposit in the kidneys and trigger glomerular inflammation and tubulointerstitial scarring.[5] A targeted-release formulation of budesonide (TRF-budesonide) has recently been approved for the treatment of IgAN. This formulation moderately reduces proteinuria in patients with IgAN by down-regulating pathogenic IgA production in Peyer's GALT Field patches.[28] Telitacicept is a transmembrane activator and calcium-modulating cyclophilin ligand interactor-fragment crystallizable fusion protein that targets BLyS and APRIL, neutralizing their interactions with all BLyS receptors on B cells and plasma cells.[22] In this study, we demonstrated that telitacicept significantly reduced serum IgA and proteinuria levels to almost half their original levels in the high-dose group. Telitacicept has the potential to become a disease-

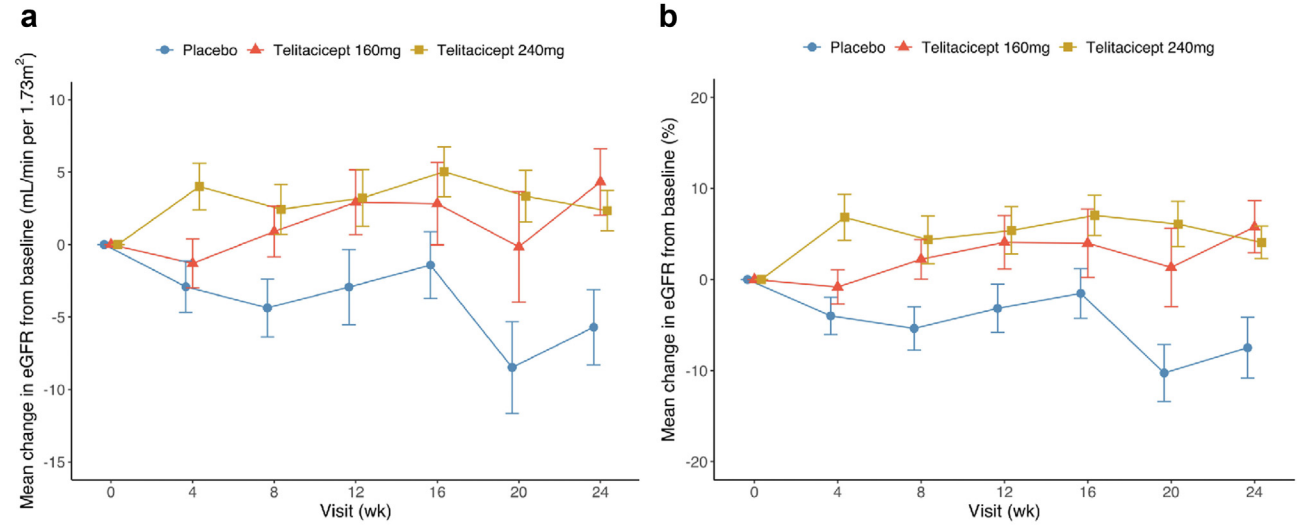

Figure 3. Mean changes in eGFR from baseline. Data are expressed as mean values (bars indicate the standard error of the mean). (a) Absolute mean changes in eGFR from baseline in patients receiving placebo or telitacicept (160 or 240 mg/week) at each visit. (b) Mean change (%) in eGFR from baseline in patients receiving placebo or telitacicept (160 or 240 mg/week) at each visit. eGFR indicates the estimated glomerular filtration rate calculated using CKD-EPI. CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate.

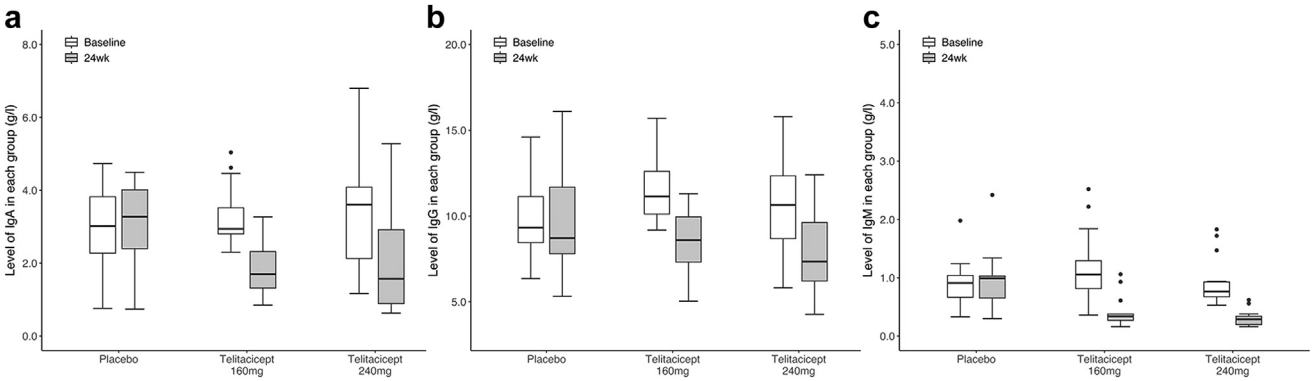

Figure 4. Median and IQR of immunoglobulins among patients before and after treatment. Data are expressed as median and IQR. (a) Absolute values of IgA in patients receiving placebo or telitacicept (160 mg/week or 240 mg/week) at baseline and week 24. (b) Absolute values of IgG in patients receiving placebo or telitacicept (160 mg/week or 240 mg/week) at baseline and week 24. (c) Absolute values of IgM in patients receiving placebo or telitacicept (160 mg/week or 240 mg/week) at baseline and week 24. IgA, immunoglobulin A; IgM, immunoglobulin M; IgG, immunoglobulin G; IQR, interquartile range.

specific treatment for patients with IgAN who are at high risk of disease progression. Recent early-stage trials of APRIL-neutralizing IgG monoclonal antibody or atacicept also suggest reducing proteinuria in IgAN.[21] The most frequently observed AE was related to injection site reaction, and there was no increased risk of serious AEs. Although serum immunoglobulin levels, including those of IgA, IgG, and IgM, were significantly decreased, we did not observe an increased risk of infection compared to that in the placebo group. In a larger lupus trial with 249 participants, telitacicept therapy did not increase the risk of AEs or serious AEs. The safety and tolerability demonstrated in this study, especially the low risk of infection, are important features of a potential therapy for IgAN, because patients often require repeated dosing to achieve meaningful and sustained responses.

This study had several limitations. First, owing to the short-term follow-up period, we could not evaluate the efficacy of telitacicept in long-term kidney function. Some confounders, such as body weight or body mass index, were not balanced among the 3 groups; with a high proportion of females, low body mass index patients and a bit more patients with immunosuppression medication history in the high-dose groups leading to higher dose of telitacicept per kilogram of body weight. The slightly faster decline of eGFR in the placebo group was possibly because of the small sample size. A long-term and larger phase 3 trial is needed to confirm the efficacy of telitacicept on kidney function decline. In addition, the effect of telitacicept on circulating Gd-IgA1 or IgA1 complexes, which is associated with the development of or kidney progression in IgAN, needs further evaluation.[5,29–32] Second, the inconsistency of results, such as the nondose-dependent variation of serum IgA, IgG or IgM, and better proteinuria reduction in higher dose group, was possibly because of the small sample size, with only 14 or 16 participants in each group. Third, pathologic data were not collected, and the evaluation of the risk of the participants was limited. Finally, supportive therapy was optimized for at least 3 to 6 months, according to the guidelines, before randomization.

In conclusion, in this phase 2 trial, we showed that telitacicept reduced proteinuria in patients with IgAN with a safety profile. This effect is indicative of a reduced risk for future kidney disease progression.

Table 2. AE that occurred in at least 2 subjects in any group

Events, *n* (%)	Placebo (*n* = 14)	Telitacicept 160 mg (*n* = 16)	Telitacicept 240 mg (*n* = 14)
AE, *n* (%)	12 (85.7)	15 (93.8)	13 (92.9)
Serious AE, *n* (%)	1 (7.1)	1 (6.3)	2 (14.3)
AE resulting in reduction or temporary discontinuation of study agents, *n* (%)	1 (7.1)	1 (6.3)	3 (21.4)
AE resulting in discontinuation of study agents, *n* (%)	0 (0)	0 (0)	0 (0)
AE resulting in death, *n* (%)	0 (0)	0 (0)	0 (0)
Injection site reactions, *n* (%)	0 (0)	9 (56.3)	10 (71.4)
Blood IgG decreased, *n* (%)	1 (7.1)	5 (31.3)	4 (28.6)
Blood IgM decreased, *n* (%)	0 (0)	5 (31.3)	5 (35.7)
Hyperuricemia, *n* (%)	2 (14.3)	3 (18.8)	1 (7.1)
Upper respiratory tract infection, *n* (%)	6 (42.9)	5 (31.3)	6 (42.9)

AE, adverse events.

DISCLOSURE

HZ has received consultancy for steering committee roles from Novartis, Omeros, Calliditas, Chinook, and Otsuka. JF is a sponsor stakeholder. JL reported receiving fees for advisory or scientific presentations from Chinook Therapeutics, KBP Bioscience, Alebund Pharmaceuticals, or SanReno Therapeutics outside the submitted work. WW, LL, and WJ are sponsor employees, and they contributed to data collection and all necessary support. All other authors have no competing interests.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1. Median and IQR of immunoglobulins among patients at each visit (g/l).

Figure S2. Blood Pressure at each visit (mm Hg).

Supplementary Table 1. Mean proteinuria at each visit (g/24 h).

Supplementary Table 2. Mean eGFR at each visit (mL/min /1.73 m^2).

Supplementary Table 3. Number of patients with hypogammaglobulinemia at each visit.

Supplementary Methods.

Consort Statement.

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