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CLINICAL RESEARCH

# Effect of Telitacicept on Circulating Gd-IgA1 and IgA-Containing Immune Complexes in IgA Nephropathy



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**Introduction:** Telitacicept, a transmembrane activator and cyclophilin ligand interactor (TACI) fusion protein targeting B cell activating factor and a proliferation-inducing ligand (APRIL), has proven efficacy in treating Immunoglobulin A (IgA) nephropathy (IgAN). However, serum biomarkers that could predict the clinical response during the treatment remain unclear.

**Methods:** Plasma samples from 24 participants in the phase 2 clinical trial were collected at baseline and after 4, 12, and 24 weeks; with 8 participants in the placebo group, 9 in the 160 mg group, and 7 in the 240 mg group. We measured the levels of galactose-deficient-IgA1 (Gd-IgA1), IgA-containing immune complexes, C3a, C5a, and sC5b-9. The association between the changes in these markers and proteinuria reduction was analyzed.

**Results:** After 24 weeks of treatment, Gd-IgA1 decreased by 43.9% (95% confidence interval: 29.8%, 55.1%), IgG-IgA immune complex by 31.7% (14.4%, 45.5%), and poly-IgA immune complex by 41.3% (6.5%, 63.1%) in the 160 mg group; Gd-IgA1 decreased by 50.4% (38.6%, 59.9%), IgG-IgA immune complex decreased by 42.7% (29.5%, 53.4%), and poly-IgA immune complex decreased by 67.2% (48.5%,79.1%) in the 240 mg group. There were no significant changes in the circulatory C3a, C5a, or sC5b-9 levels during telitacicept treatment. Decreases in both plasma Gd-IgA1 and IgG-IgA or poly-IgA immune complexes were associated with proteinuria reduction. In turn, IgG-IgA or poly-IgA immune complexes showed a dose-dependent effect, consistent with proteinuria reduction during telitacicept treatment.

**Conclusion:** Telitacicept lowered both circulating Gd-IgA1 and IgA-containing immune complexes, whereas IgA immune complex levels were more consistent with decreased proteinuria.

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IgAN, also referred to as Berger's disease, is typified by the renal deposition of IgA immune complexes, thereby instigating an inflammatory response and the subsequent development of fibrotic lesions.[1] A "multi-hit" hypothesis has been postulated to explicate the intricate pathogenesis underlying IgAN. Gd-IgA1 is recognized by IgG or IgA autoantibodies as a self-antigen and is prone to self-aggregation into poly-IgA.[2,3] The formed IgA-containing immune complexes

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are subsequently deposited in the kidney, activating the complement and precipitating further renal pathology.[4]

Advancements in understanding the pathogenesis of this disease have paved the way for innovative therapeutic approaches. Notably, several agents targeting the B-cell pathway against Gd-IgA1 production have exhibited promising clinical efficacy. More specifically, the recently approved targeted-release formulation of oral budesonide (nefecon), the TACI fusion protein acting as a B cell activating factor and APRIL inhibitor (telitacicept and atacicept), as well as monoclonal antibodies against APRIL (Sibeprenlimab and BION-1301), have demonstrated their therapeutic potential in clinical trials.[5] Nevertheless, it remains to be determined whether plasma biomarkers, including Gd-IgA1 or IgA immune complexes, can serve as surrogate indicators for predicting clinical remission.

Telitacicept, an innovative fusion protein incorporating a TACI ligand-binding domain and a crystalline fragment of human IgG, possesses the capacity to neutralize B cell activating factor/APRIL and disrupt its interaction with TACI.[6,7] In a phase 2 clinical trial, 44 patients with IgAN were randomly assigned to receive either placebo, 160 mg, or 240 mg of telitacicept through weekly subcutaneous injections. Following a period of 24 weeks, it was observed that the administration of 240 mg telitacicept led to a substantial reduction of proteinuria by 49% and a notable impact on all classes of immunoglobulins.[8] The primary objective of our study was to explore the effect of telitacicept on the circulating levels of Gd-IgA1, IgA immune complexes, and complement activation fragments. In addition, we aimed to evaluate the correlation between the reduction of these biomarkers and proteinuria among patients diagnosed with IgAN.

## METHODS

### Study Protocol and Participants

The detailed protocol and findings of this study have been previously published (NCT04291781).[8] Briefly, the study enrolled patients with biopsy-confirmed diagnosis of IgAN, along with a proteinuria level exceeding 0.75 g/d and an estimated glomerular filtration rate greater than 35 ml/min per 1.73 $m^2$. Participants were randomized into placebo, 160 mg, and 240mg telitacicept. To conduct the exploratory biomarker analysis, plasma specimens were obtained from 24 patients during the randomization phase and at 4, 12, and 24 weeks following randomization. Blood samples were centrifuged and stored frozen (-80 °C) until measurements were performed.

### Measurement of Gd-IgA1 and Complement Activation Fragments

The Gd-IgA1 concentration was quantified using an enzyme-linked immunosorbent assay (ELISA) kit precoated with KM55 (IBL, Japan). Plasma specimens were diluted 200-fold with EIA buffer, and other procedures were performed in accordance with the manufacturer's instructions. Human EIA Kit (Quidel Corp., USA) was used to measure the C3a, C5a, and sC5b-9 levels. C3a was diluted 200-fold, C5a was diluted 20-fold, and sC5b-9 was diluted 10-fold.

### Measurement of Poly-IgA Immune Complex Concentrations

Plasma poly-IgA immune complex was detected using recombinant CD89 as a capture molecular probe, as described previously.[9] ELISA plates were coated with recombinant CD89 overnight at 4 °C. Plates were washed thrice with phosphate-buffered saline with Tween (PBST) and blocked with phosphate-buffered saline with Tween/1 % bovine serum albumin. Samples were diluted 1000-fold with phosphate-buffered saline with Tween/1% bovine serum albumin, incubated at 37 °C for 1 hour, and washed 4 times with phosphate-buffered saline with Tween, followed by incubation with antihuman IgA-HRP detection antibody at 37 °C for 1 hour. Detection was performed using a tetramethylbenzidine liquid substrate system, and the optical density was measured at 450 nm with wavelength correction at 630 nm. The ELISA kits used were commercially available (NephroPlex, Lujing Biotech, China).

### Measurement of IgA Immune Complexes by ELISA

Cross-capture ELISA was used to measure plasma IgG-IgA immune complex levels.[10] Rabbit antihuman IgG (H+L) (Abcam, Waltham, MA) was used as the capture antibody, and biotin-labeled mouse anti-human IgA1 antibody (Southern Biotech, Birmingham, AL) was used as the detection antibody.

### Statistical Analysis

An intention-to-treat analysis was performed, and all missing data were treated as missing without imputation. The level of biomarkers and 24–hour urinary protein were log-transformed before analysis. The changes in biomarkers of each group at 4, 12, and 24 weeks were estimated from the linear mixed model, with treatment group, time, log-transformed baseline biomarkers, and time-by-treatment group interaction as fixed effect, and individuals as random effects. To evaluate the association between the changes in biomarkers and proteinuria, we involved the log-

**Table 1.** Baseline characteristics of the participants

| Characteristics | Placebo $n = 8$ | 160 mg $n = 7$ | 240 mg $n = 9$ |
|---|---|---|---|
| Female, *n* (%) | 3 (37.5%) | 5 (71.4%) | 6 (66.7%) |
| Age, mean (SD), y | 35.8±4.3 | 38.1±10.2 | 40.0±8.8 |
| BMI, mean (SD) kg/m$^2$ | 26.8±5.3 | 25.6±5.1 | 24.2±3.8 |
| SBP, mean (SD), mm Hg | 112±7.6 | 115.4±17.5 | 120.4±8.6 |
| DBP, mean (SD), mm Hg | 72.4±4.6 | 77.9±9.1 | 79.7±7.2 |
| Urine protein, median (IQR), g/d | 1.78 (1.37–1.97) | 1.71 (1.15–1.96) | 1.26 (1.05–1.53) |
| eGFR, Median (IQR), ml/min per 1.73 m$^2$ | 91.2 (68.3–100.7) | 74.1 (62.7–94.2) | 62.6 (57.4–74.0) |
| IgA, mean (SD), g/l | 2.97±1.35 | 3.12±0.74 | 4.08±1.95 |
| IgG, mean (SD), g/l | 9.68±2.77 | 12.12±2.30 | 11.31±2.56 |
| IgM, mean (SD), g/l | 0.99±0.51 | 1.18±0.69 | 0.90±0.44 |
| C3a, mean (SD), ng/ml | 170.64±47.62 | 167.12±56.88 | 168.70±74.64 |
| C5a, mean (SD), ng/ml | 7.66±2.57 | 7.72±4.025 | 8.10±3.90 |
| sC5b-9, median (IQR), ng/ml | 232.52 (190.39–254.65) | 223.24 (149.12–258.75) | 194.08 (178.69–276.64) |
| Gd-IgA1, median (IQR), ng/ml | 5 721.3 (3 341.7–7 208.6) | 4 890.5 (4 289.8–64 66.4) | 5 137.7 (4 268.3–12 105.3) |
| Poly-IgA, median (IQR), mg/l | 90.11 (58.19–165.94) | 128.18 (60.76–197.82) | 132.26 (83.32–186.46) |
| IgG-IgA IC, median (IQR), AU/l | 5.19±2.57 | 3.32±0.52 | 5.54±2.60 |
| Urine protein after 24 weeks, median (IQR), g/d | 2.16 (0.805–2.62) | 0.83 (0.55–1.24) | 0.51 (0.47–0.748) |
| eGFR after 24 weeks, Median (IQR), ml/min per 1.73 m$^2$ | 79.6 (71.29–101.9) | 89.51 (61.61–108.12) | 68.33 (53.8–77.28) |

BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; Gd-IgA1, galactose-deficient IgA1; IC, immune complex; IQR, interquartile range; SBP, systolic blood pressure.

transformed biomarkers as the dependent variable, the log-transformed baseline biomarkers, 24-h urinary protein as fixed effects. All statistical analyses were performed using R 4.3.2 software (R Foundation for Statistical Computing, Vienna, Austria), and a $P$ value of $<0.05$ was considered statistically significant.

## RESULTS

### Demographic Information and Clinical Characteristics of Participants

Twenty-four patients with sequentially collected plasma specimens were included in this study. There were 8 participants in the placebo group, 9 in the 160 mg group, and 7 in the 240 mg group. One patient in the placebo group withdrew from the study in the 15th week. Table 1 outlines the baseline characteristics of the study participants. After 24 weeks of treatment, compared with the placebo group, proteinuria decreased by 32% (95% confidence interval: −12.1%, 58.7%) in the 160 mg group, and by 57.8% (32.3%, 73.7%) in the 240 mg group (Supplementary Figure S1).

### Percentage Change of the Biomarkers After Telitacicept Treatment

In Figure 1, we show the trajectories of the biomarkers after telitacicept treatment. At 24 weeks, compared with placebo group, plasma Gd-IgA1 levels were decreased by 43.9% (29.8%, 55.1%) in the 160 mg group and 50.4% (38.6%, 59.9%) in 240mg group (Figure 1a). During treatment, Gd-IgA1/total IgA remained stable (Figure 1b). An elevation in plasma recombinant CD89-captured poly-IgA immune complex was observed in the control group, with 41.3% (6.5%, 63.1%) reduction in the 160 mg group and 67.2% (48.5%, 79.1%) reduction in the 240 mg group at week 24 (Figure 1c). The IgG-IgA immune complexes showed a persistent, dose-dependent decrease (160 mg: 31.7% [14.4%, 45.5%] at week 24; 240mg: 42.7% [29.5%, 53.4%] at week 24) (Figure 1d). There was no difference in C3a, C5a, or sC5b-9 levels between the placebo and telitacicept groups at week 24 (Supplementary Figures S2–S4).

### Correlation Between the Change of Biomarkers and Proteinuria

Alterations in percentage change of the plasma levels of IgA, Gd-IgA1, poly-IgA immune complex, and IgG-IgA immune complex from baseline to each visit were correlated with changes in proteinuria throughout the follow-up period (Table 2). In addition, only poly-IgA or IgG-IgA immune complexes showed a greater reduction in the higher dose telitacicept groups, consistent with proteinuria reduction, whereas total IgA or Gd-IgA1 did not.

## DISCUSSION

Telitacicept and atacicept, as dual blockers of B cell activating factor and APRIL, exert inhibitory effects on the production of pathogenic antibodies by B cells and plasma cells.[11,12] Phase 2 clinical trials have both demonstrated their efficacy in lowering urinary protein and immunoglobulin levels among patients with IgAN.[8] In this study, we further showed that telitacicept decreased circulatory Gd-IgA1, IgG-IgA immune complex, and poly-IgA immune complex by

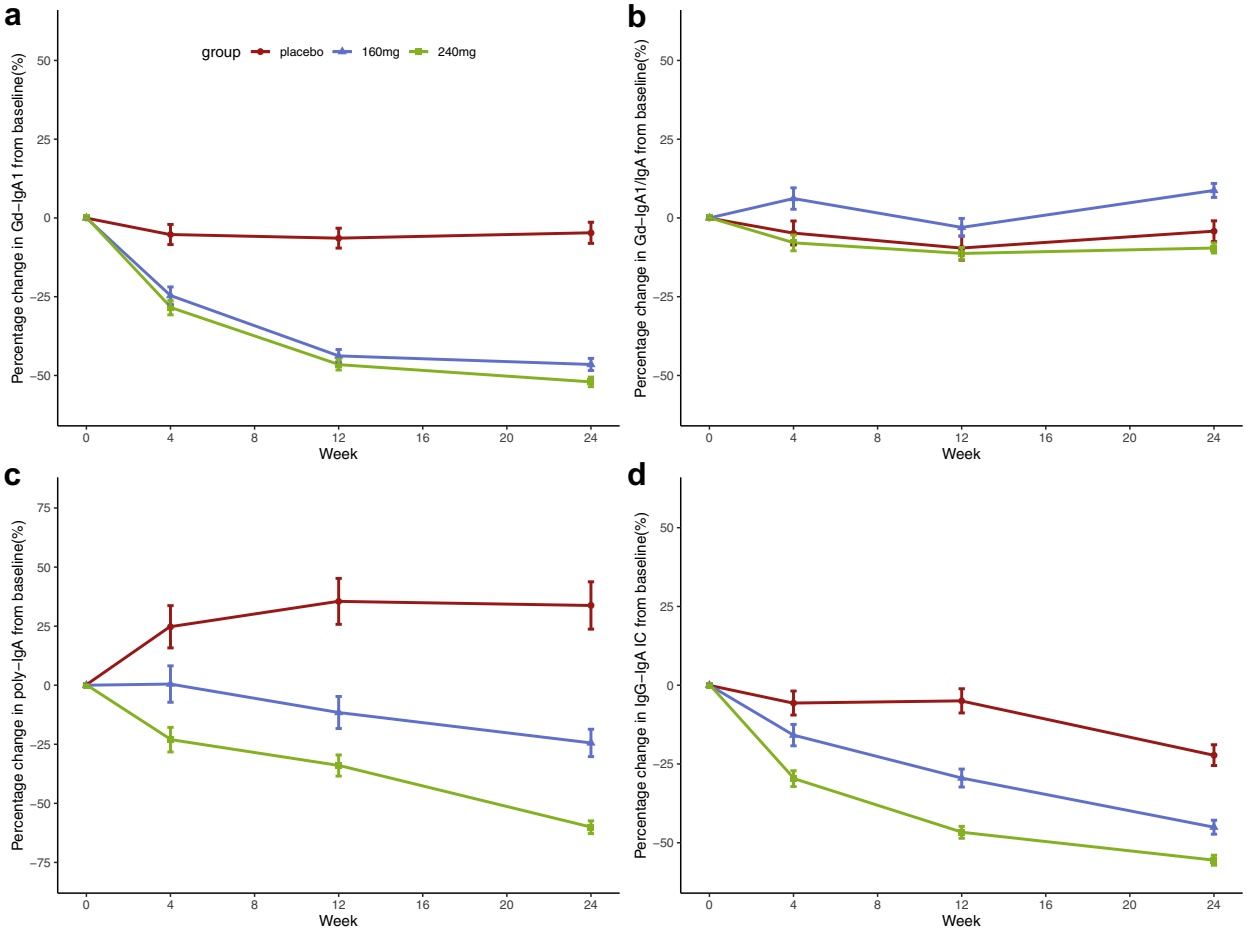


**Figure 1.** Percentage change in biomarkers from baseline. Percentage change in (a) Gd-IgA1, (b) Gd-IgA1/IgA, (c) poly-IgA immune complex, (d) IgG-IgA immune complex levels from baseline to week 24. Data are expressed as LS mean values (bars indicate the standard error of the LS mean). Gd- IgA1, galactose-deficient IgA1; IC, immune complex; IgA, Immunoglobulin A.

approximately 50%. Moreover, the reduction in Gd-IgA1 or IgA immune complexes correlated with a decline in proteinuria in IgAN, especially in the IgG-IgA or poly-IgA immune complexes. These findings support the potential utility of these biomarkers in predicting the likelihood of achieving clinical remission.

Several trials with agents targeting IgA production have demonstrated their clinical efficacy in proteinuria reduction and kidney protection. The promising results of recent trials on these drugs call for biomarkers to identify patients who may benefit from this treatment. In the phase 2 atacicept trial, the reduction in serum Gd-IgA1 levels was in parallel with that of proteinuria, regardless of whether patients received the 25 mg or 75 mg dose.[12] In the large NefIgAgard trial, nefecon reduced circulating Gd-IgA1 levels by 23.5%, associated with a 27% decrease in proteinuria.[13,14] In this trial, we confirm that a decrease in Gd-IgA1 and IgA immune complexes with telitacicept treatment was associated with clinical response. Interestingly, a higher dose of telitacicept induced greater proteinuria reduction, consistent with poly-IgA or IgG-IgA complex reduction, whereas no dose-dependent effect was observed for Gd-IgA1.

**Table 2.** Correlation between change in 24-hour urine protein and changes in biomarkers in Treatment groups

| Biomarkers | Coefficient | *P* value |
|---|---|---|
| Total IgA | 0.851 | <0.001 |
| Gd-IgA1 | 0.714 | <0.001 |
| poly-IgA immune complex | 0.522 | <0.001 |
| IgG-IgA immune complex | 0.844 | <0.001 |

Gd-IgA1, Galactose-deficient IgA1.

Sequential assessment of the circulating IgA immune complexes or Gd-IgA1 levels holds the potential to help predict responses to agents targeting B cells or IgA in the context of IgAN. This will be important for future precision management in IgAN. In the NefIgAard trial, a notable time lag of several months was observed between the initiation of nefecon therapy and the subsequent reduction in proteinuria.[14] Therefore, the early detection of IgA immune complexes or Gd-IgA1 levels reduction will help identifying patients who will benefit from such targeted therapies.

This study showed the effect of telitacicept on Gd-IgA1 and IgA immune complexes in IgAN and also identified potential biomarkers for predicting treatment response. However, there are still several key limitations. First, it was just an exploratory study conducted within the framework of a phase 2 trial, thus possessing a relatively small sample size. In addition, not all the randomized patients were included in the analysis due to the unavailability of blood samples, introducing the possibility of selection bias. Therefore, it is imperative to validate these findings through larger-scale studies. Second, the follow-up was short, with only a 24-week following period. Consequently, the evaluation of these biomarkers in relation to long-term kidney outcomes remains inconclusive.

In conclusion, we showed that telitacicept could reduce Gd-IgA1, poly-IgA immune complex, and IgG-IgA immune complex in patients with IgAN rather than C3a, C5a, and sC5b-9. The change of posttreatment IgA immune complexes including poly IgA and IgG-IgA immune complex rather than Gd-IgA1 is an indicator of the telitacicept response and may also be used with other agents that target B cells or Gd-IgA1 therapy.

## 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 and LL are sponsor employees, and they contributed to data collection and all necessary support. All other authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF).

**Figure S1.** Percentage change in 24-hour proteinuria from baseline.

**Figure S2.** Percentage change in complement activation fragments from baseline.

**Figure S3.** The absolute value of the biomarkers at each visit.

**Figure S4.** The percentage change of the biomarkers at each visit.

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